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Can Systemic Inflammatory Indices Be Useful in Hypertensive Disorders of Pregnancy?

Gebeliğin Hipertansif Hastalıklarında Sistemik İnflamatuar İndeksler Faydalı Olabilir mi?

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ABSTRACT

Aim: This study aimed to assess the utility of systemic inflammatory indices in predicting and determining the prognosis of hypertensive disorders during pregnancy

Materials and Methods: This cross-sectional and retrospective single-center study involved 101 preeclampsia patients and 203 healthy pregnant women as the control group. Laboratory parameters were evaluated during the first trimester, at the time of diagnosis, and prior to delivery. The indices were calculated using laboratory values: PLR (platelet/lymphocyte), APRI (AST/platelet), SII (neutrophil × platelet / lymphocyte), and SIRI (neutrophil × monocyte / lymphocyte). Subgroup analyses were performed for early- and late-onset preeclampsia, severe and non-severe preeclampsia, and HELLP syndrome.

Results: Indices calculated during the first trimester were insufficient to predict preeclampsia, severe preeclampsia, early-onset preeclampsia, and HELLP syndrome. Although indices obtained at the time of diagnosis were also limited in predicting poor outcomes, PLR was lower in the preeclamptic group at diagnosis due to changes in lymphocyte counts. APRI was significantly higher in preeclamptic pregnancies, severe preeclampsia, early-onset preeclampsia, and HELLP syndrome prior to delivery ($p<0.001$). Additionally, among patients with HELLP syndrome, a significant increase in SIRI and a decrease in PLR levels were observed before delivery.

Conclusion: Among the inflammatory indices examined, APRI showed a significant elevation prior to delivery in cases of early-onset preeclampsia, severe preeclampsia, and HELLP syndrome. Moreover, in patients diagnosed with HELLP, SIRI increased while PLR decreased significantly. These findings suggest that a late-onset inflammatory response may be linked to increased severity of hypertensive pregnancy disorders.

Keywords: Preeclampsia, inflammation, HELLP, APRI

ÖZ

Amaç: Bu çalışmanın amacı, sistemik inflamatuar indekslerin gebeliğin hipertansif hastalıklarının prediksiyonu ve prognozu açısından faydalı olup olmadığını araştırmaktır.

Gereç ve Yöntemler: Bu kesitsel ve retrospektif tek merkezli çalışma, 101 preeklampsi hastası ve 203 sağlıklı hamile kadından oluşmaktadır. Laboratuvar parametreleri, ilk trimesterde, tanı anında ve doğumdan önce olmak üzere üç ayrı dönemde değerlendirilmiştir. PLR (trombosit/lenfosit), APRI (AST/trombosit), SII (nötrofil x trombosit / lenfosit) ve SIRI (nötrofil x monosit / lenfosit) indeksleri hesaplanmıştır. Bu indeksler ayrıca erken ve geç başlangıçlı preeklampsi, şiddetli ve şiddetli olmayan preeklampsi ile HELLP sendromunu içeren alt gruplarda analiz edilmiştir.

Bulgular: İlk trimesterde hesaplanan tüm indeksler, preeklampsi, şiddetli preeklampsi, erken başlangıçlı preeklampsi ve HELLP sendromunu predikte etme konusunda yetersiz kalmıştır. Tanı anında hesaplanan indeksler de kötü prognozu öngörmede etkili olmamış, ancak PLR'nin preeklamptik grupta kontrol grubuna göre daha düşük olduğu saptanmıştır. Bu farklılık lenfosit değerlerindeki değişikliklerden kaynaklanmıştır. Doğum öncesi dönemde ise APRI hem preeklamptik gebelerde hem şiddetli ve erken başlangıçlı preeklampside hem de HELLP sendromunda anlamlı şekilde yüksek bulunmuştur ($p<0,001$). HELLP sendromu teşhisi alan hastalarda doğum öncesinde SIRI anlamlı olarak artarken, PLR azalmıştır.

Sonuç: İncelenen inflamatuar indeksler arasında, özellikle doğum öncesi dönemde hesaplanan APRI'nin erken başlangıçlı preeklampsi, şiddetli preeklampsi ve HELLP sendromu olgularında anlamlı şekilde yükseldiği saptanmıştır. Ayrıca, HELLP tanısı alan hastalarda SIRI artmış, PLR ise anlamlı düzeyde azalmıştır. Bu bulgular, geç inflamatuar yanıtın gebeliğin hipertansif hastalıklarının şiddetiyle ilişkili olabileceğini düşündürmektedir.

Anahtar Kelimeler: Preeklampsi, inflamasyon, HELLP, APRI

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INTRODUCTION

Preeclampsia is a hypertensive disorder of pregnancy that can lead to serious maternal and fetal complications with multisystem organ involvement. It complicates 2-8% of pregnancies worldwide (1).

Preeclampsia is diagnosed when hypertension develops after the 20th week of gestation and is accompanied by evidence of end-organ dysfunction. Identified risk factors are nulliparity, multiple pregnancies, advanced maternal age, pregnancy with assisted reproductive techniques, maternal comorbidities, obesity (especially pregestational body mass index (BMI) > 30), a history of preeclampsia in the mother and sister, and a previous history of preeclampsia or abruption (2). Although its etiology is still not fully understood, insufficient trophoblast invasion, abnormal placentation, abnormal release of angiogenic factors, and the development of ischemia, inflammation, and atherosclerosis have been implicated (3).

The systemic immune inflammation index (SII) and systemic inflammation response index (SIRI) are calculated based on hemogram parameters, which are important mortality markers in cardiovascular diseases and COVID-19 patients (4). The use of systemic immune inflammation index (SII) (neutrophil x platelet/lymphocyte), systemic inflammation response index (SIRI) (neutrophil x monocyte/lymphocyte), and platelet-to-lymphocyte ratio (PLR) indices in predicting preeclampsia has been investigated in some studies considering that preeclampsia is an inflammatory process (5). APRI (AST/platelet) is considered a highly sensitive marker used to predict the degree of liver fibrosis and its progression to cirrhosis (6). Recent studies have reported that it is superior to liver transaminases in predicting HELLP syndrome (7).

In this study, we aimed to investigate how APRI, SIRI, PLR and SII indices changed at the time of diagnosis and before delivery in pregnant women diagnosed with preeclampsia and whether the first trimester indices of the same patients can predict early-onset preeclampsia, severe preeclampsia and progression to HELLP syndrome.

MATERIAL AND METHODS

This retrospective, cross-sectional study was conducted at Ankara Bilkent City Hospital Perinatology Clinic. In this study, 101 patients with preeclampsia as the study group and 203 healthy pregnant women as the control group were included between December 2022 and November 2023. The control group consisted of normotensive pregnant women with similar demographic characteristics. Adolescent pregnancies, maternal age>45 years and pregnant women with chronic systemic diseases were excluded. Demographic data, laboratory parameters, gestational age at diagnosis and delivery were retrieved from the hospital's electronic medical records. This study was approved by the "Institutional Review Board of the University of Health Sciences Turkey, Ankara Bilkent City Hospital Ethics Committee" (approval number: E2-23-4881), according to the Helsinki Declarations.

Pregnancy-induced hypertension is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, measured at least 4 hours apart after 20 weeks of gestation. Severe preeclampsia is defined as systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg and proteinuria (≥ 300 mg in 24-hour urine, ≥ +2 with dipstick test, urine protein/creatinine ratio in spot urine ≥ 0.3) or end-organ damage [thrombocytopenia (<100,000/dl), serum creatinine level above 1.1 mg/dl or doubling of serum concentration, doubling of liver transaminases, pulmonary edema, new-onset headache unresponsive to medication, visual symptoms] (2). Early-onset preeclampsia is defined as the onset of the disease before 34 gestational weeks (8). HELLP syndrome is characterized by thrombocytopenia, elevated liver enzymes, and hemolysis (9). The patients were categorized according to the defined diagnostic criteria. Laboratory parameters were studied in three different periods. The patients' complete blood count and biochemical parameters were obtained from the records in the first trimester, at the time of diagnosis and before delivery. Patients were analyzed for the following indices: PLR (platelet to lymphocyte count ratio), APRI (AST to platelet count ratio), SII (neutrophilxplatelet/lymphocyte), and SIRI (neutrophilxmonocyte/lymphocyte). Thereafter, study and control groups were compared for the mentioned parameters at different times. Additionally, preeclampsia groups were divided into subgroups as follows: preeclampsia with/without severe features, early/late-onset preeclampsia and preeclampsia with/without HELLP syndrome. A subgroup analysis was also performed for the comparison of SII, SIRI, PLR and APRI in the first trimester, at time of diagnosis and before delivery.

The statistical analyses were conducted using IBM Inc., Armonk, NY, USA's Statistical Package for the Social Sciences, version 26. Normality was assessed using the Shapiro–Wilk test, and the results indicated that the indexes did not follow a normal distribution. Median and minimum-maximum values were utilized to present descriptive statistics. The other data showed normal distribution, and these data were presented as mean and standard deviation. The Mann-Whitney U was used to compare the parameters between the groups according to distribution. Statistical significance was defined as a two-tailed P value of 0.05 with a 95% confidence interval.

RESULTS

This study included 101 women with preeclampsia and 203 healthy pregnant women as the control group. Of the preeclampsia group, 40 had severe preeclampsia, 61 had non-severe preeclampsia, and 28 were diagnosed with HELLP syndrome. Maternal demographic characteristics and obstetric history are shown in Table 1. When the control and preeclamptic patient groups were compared during the first trimester, at the time of diagnosis, and before delivery, although there was no difference in systemic indices in the first trimester, PLR was lower at the time of diagnosis while platelet count was at normal values. The corresponding data are shown in Table 2. Although PLR was lower in the severe preeclampsia and HELLP groups, no significant difference was observed in the first trimester. Furthermore, in the first trimester, SIRI, SII, and APRI did not differ significantly in the severe preeclampsia and HELLP groups. The corresponding data are shown in Table 3.

In the early-onset preeclampsia group, APRI was significantly higher compared with the late-onset group, and APRI was also higher in the severe preeclampsia group and HELLP group before delivery. SIRI and PLR indices were significantly higher in the HELLP group compared to preeclamptic and healthy pregnant women, but no significant difference was found for SII prior to delivery.

DISCUSSION

The main findings of the present study revealed that SII, SIRI, PLR and APRI indices calculated in the first trimester were insufficient in predicting preeclampsia, severe preeclampsia, early-onset preeclampsia, and HELLP syndrome. Although the indices calculated at the time of diagnosis were also inadequate in predicting poor prognosis, the PLR was found to be lower in the preeclamptic group at the time of diagnosis compared to the control group. This difference has emerged due to changes in lymphocyte counts. However, the APRI calculated in the pre-delivery period was found to be significantly higher in preeclamptic pregnancies, severe preeclampsia, early-onset preeclampsia, and HELLP syndrome. Moreover, SIRI, PLR, and APRI levels differed between the HELLP group and the non-HELLP group only before delivery.

Preeclampsia is an important obstetric pathology characterized by hypertension and multisystemic organ involvement. It is also a significant cause of fetal-maternal morbidity and mortality in the world. Many theories have been put forward in its etiology. It has been implicated in the pathophysiology of placental ischemia, which develops as a result of inadequate cytotrophoblastic invasion, inadequate compliance of spiral arteries, endothelial activation and development of atherosclerosis, intravascular inflammation,

Table 1. Maternal demographic characteristics

Variable	Control Group (n=203)	Preeclampsia Group (n=101)	P-value
Maternal age	28.4±5.2	30.8±5.6	**0.001**
Gravida	2.2±1.2	2.8±1.8	0.242
Parity	1.1±1	1.1±1.1	0.573

*All variables were presented as means and standard deviations.

Table 2. Comparison of laboratory values of the control group and the preeclamptic group in three different periods of pregnancy

Variable	Control Group (First Trimester)	Preeclampsia Group (1st Trimester)	P-value (First Trimester)	Control Group (At Diagnosis)	Preeclampsia Group (At Diagnosis)	P-value (At Diagnosis)	Control Group (Prior to Delivery)	Preeclampsia Group (Prior to Delivery)	P-value (Prior to Delivery)
Hemoglobin (g/dL)	12±1.1	12.4±1.2	**0.004**	11.6±1.1	12±1.1	**0.002**	11.8±1.27	11.9±1.44	0.307
Platelet (/mm³)	262280±55234	282720±75569	0.131	240060±66941	248670±94165	0.722	244160±69824	242010±120315	0.119
Wbc (/mm³)	8471±2165	9096±2485	0.082	9535±2064	11147±2974	**<0.001**	10457±2871	12084±3912	0.047
Monocyte (/mm³)	0.46±0.17	0.55±0.22	**0.004**	0.49±1.1	0.52±0.2	0.335	0.52±0.16	0.57±0.28	0.403
Neutrophil (/mm³)	7.22±1.98	7.56±1.22	0.112	7.15±1.85	8.28±2.92	0.011	7.89±2.6	9.21±4	0.303
Lymphocyte (/mm³)	1.88±0.57	1.90±0.59	0.812	1.71±0.5	2.07±0.67	**<0.001**	1.85±0.53	1.88±0.86	0.585
AST (IU/L)	16.7±5	18.3±11	0.945	19.3±6	22.8±9.6	**0.015**	19.8±5.7	60.2±101	**0.001**
ALT (IU/L)	16.7±9.5	19.9±17.1	0.895	15±7.1	19±14	**0.003**	14.9±9.8	56±98	**0.001**
Creatinine (ml/dk)	0.5±0.1	0.6±0.1	**0.035**	0.6±1.3	1.1±3	**<0.001**	0.5±0.09	0.66±0.26	**<0.001**

*All variables were presented as means and standard deviations. WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3. Comparison of indices with control and preeclamptic groups and between subgroups at 3 different times during pregnancy

Period	Indices	Preeclampsia	Control	P value
First trimester				
	SIRI	1.5 (1.2)	1.3 (1)	0.069
	SII	777 (572)	793 (536)	0.481
	PLR	134 (59)	131 (63)	0.751
	APRI	0.06 (0.03)	0.06(0.03)	0.307
At the time of diagnosis				
	SIRI	1.95 (1.5)	2 (1.29)	0.678
	SII	904 (778)	956 (541)	0.519
	PLR	123 (59)	139 (56)	**0.005**
	APRI	0.09 (0.08)	0.08 (0.04)	0.062
Prior to delivery				
	SIRI	2.3 (2.3)	2.05 (1.25)	0.916
	SII	994 (852)	988 (592)	0.343
	PLR	126(73)	131(57)	0.06
	APRI	0.11 (0.17)	0.07 (0.04)	**0.001**
		Early-onset preeclampsia	**Late-onset preeclampsia**	
First trimester				
	SIRI	1.51 (1.13)	1.49 (1.28)	0.414
	SII	877 (653)	772 (408)	0.334
	PLR	150 (69)	124 (50)	0.745
	APRI	0.06 (0.03)	0.05 (0.03)	0.179
At the time of diagnosis				
	SIRI	1.96 (1.02)	1.85 (1.02)	**0.046**
	SII	904 (897)	1110 (549)	0.097
	PLR	121 (70)	133 (44)	0.719
	APRI	0.09 (0.08)	0.06 (0.09)	0.312
Prior to delivery				
	SIRI	2.45 (2.59)	2.09 (2.04)	0.389
	SII	1008 (881)	994 (1321)	0.143
	PLR	120 (73)	130 (88)	0.594
	APRI	0.15 (0.3)	0.07 (0.11)	**<0.001**
		Severe preeclampsia	**Non-severe preeclampsia**	
First trimester				
	SIRI	1.47 (1.34)	1.63 (1.1)	0.685
	SII	859 (622)	772 (624)	0.685
	PLR	150 (64)	124 (73)	0.201
	APRI	0.06 (0.04)	0.05 (0.02)	0.369
At the time of diagnosis				
	SIRI	1.96 (1.4)	1.8 (1.7)	0.379
	SII	904 (704)	998 (952)	0.787
	PLR	123 (58)	123 (69)	0.720
	APRI	0.09 (0.08)	0.09 (0.11)	0.370
Prior to delivery				
	SIRI	2.9 (2.5)	2.8 (2.7)	0.461
	SII	994 (884)	971 (1645)	0.257
	PLR	123 (65)	133 (92)	**0.027**
	APRI	0.17 (0.44)	0.08 (0.11)	**<0.001**
		HELLP	**Non-HELLP**	
First trimester				
	SIRI	1.52 (2)	1.44 (1.06)	0.176
	SII	891 (575)	787 (545)	0.975
	PLR	127 (65)	133 (62)	0.532
	APRI	0.07 (0.05)	0.06 (0.03)	0.878
At the time of diagnosis				
	SIRI	1.8 (1.7)	1.96 (1.34)	0.381
	SII	878 (653)	955 (675)	0.717
	PLR	98.9 (62.7)	133 (64)	0.077
	APRI	0.12 (0.05)	0.08 (0.05)	0.152
Prior to delivery				
	SIRI	3.88 (4.2)	2.08 (1.55)	**0.024**
	SII	740 (1459)	1008 (675)	0.082
	PLR	82 (118)	130 (62)	**<0.001**
	APRI	1.28 (1.98)	0.08 (0.07)	**<0.001**

* All variables were presented as medians and interquartile ranges. SII, systemic immune inflammation index; SIRI, systemic inflammation response index; PLR, platelet-to-lymphocyte ratio; APRI, alanine aminotransferase-to-platelet ratio; HELLP, hemolysis, elevated liver enzymes and low platelets.

thrombosis and decreased placental blood flow as a result of spiral artery occlusion (3). However, the pathophysiology of preeclampsia is highly complex, and the main pathways behind this deadly pregnancy-specific syndrome have not been clarified yet.

When APRI, SIRI, PLR and SII parameters were calculated for the time of diagnosis, the PLR index was found to be significantly lower in the preeclamptic group at the time of diagnosis due to the presence of lymphocytosis. However, most of the patients had normal platelet counts and higher APRI values prior to delivery in the preeclampsia group, resulting from the higher AST levels rather than the platelet count. Although platelets have many functions in the immune response of the patients, findings from this study indicated that platelet counts did not differ over time between the groups. On the other hand, there are publications in the literature reporting altered maternal platelet levels in the first trimester for preeclampsia cases (10).

When literature was analyzed in a study published in 2008, the cytokine-dependent immune interaction between platelets and lymphocytes was called heterotypic cross-talk, and it was stated that this interaction has great importance in thrombosis, atherogenesis and inflammation (11).

In a study conducted by Yucel et al. with the participation of 82 severe-preeclamptic, 27 non-severe-preeclamptic and 110 healthy pregnant women, PLR was found to be significantly lower in the severe-preeclamptic group. However, this study was conducted with pregnant women hospitalized for delivery (12). In another study designed with 824 pregnant women hospitalized for delivery, PLR was found to be statistically significantly lower when the severe-preeclamptic group, non-severe preeclamptic group and control group were compared (13).

Although the PLR index was found to be lower in the preeclamptic group at the time of diagnosis compared to the control group in this study, it was not found to be effective in predicting severe preeclampsia. Since most of the studies in the literature were conducted at the time of delivery, the PLR was calculated at the time of delivery, and it was significantly lower in the severe preeclamptic group compared with the non-severe preeclamptic group. However, since this difference emerges at delivery, cell-based inflammatory indices may have limited predictive value in predicting and prognosing preeclampsia. Yet, changes observed prior to delivery may help clarify the immune-mediated mechanisms underlying preeclampsia.

When the studies investigating first-trimester PLR for prediction of preeclampsia in the literature were examined, Gezer et al. found that PLR was higher in the preeclamptic group in the first trimester

(14). However, Sisti et al. found no significant change in first-trimester PLR for prediction of HELLP in another study (15).

When first-trimester PLR was calculated, no significant difference was observed between the control and preeclamptic groups. The first trimester PLR was unable to predict severe pre-eclampsia. First-trimester PLR was higher in patients with early-onset pre-eclampsia but not statistically significant (p-value 0.06). In addition, PLR was insufficient to predict HELLP syndrome in our study.

SIRI, SII and APRI, have been investigated to determine the prediction of HELLP syndrome and pre-eclampsia in the first trimester. SIRI and SII were investigated at the time of delivery and in the first trimester in the study by Ipek et al. SIRI was found to be high at the time of delivery, but none of the indices have been successful in predicting HELLP syndrome in the first trimester (15). In another study by Seyhanli et al., first-trimester SIRI was found to be statistically significantly higher in preeclamptic patients, but no significant change was shown for SII (5). Li et al. reported that APRI was an important marker of progression to HELLP syndrome with a sensitivity of 90% and specificity of 97% in a study including pregnant women with gestational hypertension and HELLP syndrome (16). In another study, APRI was found to be significantly higher in severe preeclampsia compared to non-severe preeclampsia, gestational hypertension and the control group. In the same study, APRI values at 20 weeks of gestation were reported to be successful in predicting severe pre-eclampsia (17).

Therefore, we investigated these new markers, SIRI, SII and APRI, for prediction and severity of preeclampsia. APRI, SII and SIRI calculated at the time of diagnosis were not statistically significantly different between the preeclamptic group and the control group, between the early-onset preeclamptic group and the late-onset preeclamptic group and between the severe preeclamptic group and the non-severe preeclamptic group. There was also no statistically significant difference in the first-trimester indices of these patients. However, when analyzing the APRI values at the time of delivery, APRI was significantly higher in both the severe preeclampsia and the early-onset preeclampsia groups.

We found that APRI was statistically significantly higher only at the time of delivery. As expected, APRI was also significantly higher in the HELLP group at the time of delivery, but APRI values calculated at the time of diagnosis were insufficient to predict HELLP. These findings can be attributed to the relatively limited number of cases and the retrospective design of the study.

This research has some limitations. The restricted number of patients diagnosed with HELLP syndrome may have limited the statistical power for subgroup analysis and restricted the generalizability of the findings. Secondly, although ROC curve studies were performed to evaluate the discriminative capacity of inflammatory indices, the resulting AUC values were insufficient to demonstrate diagnostic efficacy. Consequently, the cutoff values obtained from these studies were not included in the results

Eventually, there are controversial findings in the literature regarding the utility of novel inflammatory indices in preeclampsia most probably due to the heterogeneity of the studies. While some researchers found promising findings for prediction and management of pregnant women with preeclampsia, others do not report significant benefits. It is important to note that preeclampsia is a complex and multifactorial condition, and it is not possible to just use a simple index to provide optimal health care for women. A management protocol that includes medical history, risk factors, previous obstetric experiences, clinical findings, and novel methods like inflammatory indices may be a guide for clinicians to achieve favorable perinatal outcomes.

CONCLUSIONS

The inflammatory indices evaluated in this study appear to have limited value in predicting preeclampsia and its prognosis. However, significant inflammatory changes seem to occur before delivery in the study population. This result suggests that a systemic inflammatory response may occur late and could indicate a risk of poor clinical outcomes. We suggest that inflammatory indices derived from accessible, cost-effective, and reproducible tests may support early diagnosis and prognosis, provided that further studies are conducted in larger populations.

Ethics Committee Approval: This study was approved by the "Institutional Review Board of the University of Health Sciences Turkey, Ankara Bilkent City Hospital Ethics Committee" (approval number: E2-23-4881), according to the Helsinki Declarations.

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