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The predictive role of inflammatory biomarkers based on first trimester complete blood count parameters for the risk of HELLP syndrome: A case-control study

HELLP sendromu riski için ilk trimester tam kan sayımı parametrelerine dayalı inflamatuar biyobelirteçlerin öngörücü rolü: Bir vaka-kontrol çalışması

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ABSTRACT

Aim: To conclude the predictive role of inflammatory biomarkers based on first trimester complete blood count parameters for the risk of HELLP syndrome.

Materials and Methods: This case-control study was included 45 of 73 pregnant women with HELLP syndrome. Clinical data and laboratory results were retrieved by medical and hospital records. We compared the inflammatory biomarkers based on first trimester complete blood count parameters for the risk of HELLP syndrome.

Results: We recruited 45 cases (pregnant women with HELLP syndrome) and 45 controls (healthy pregnant women), matched for body mass index, gravidity, parity and gestational week. The lymphocyte, platelets - lymphocyte ratio, neutrophil - lymphocyte ratio and systemic inflammation index values were statistically significant between the groups in the first trimester blood test results. There was no significant difference in systemic inflammation response index and pan-immune inflammation value between groups in the first trimester blood test results.

Conclusions: The main problem with HELLP syndrome is that it does not occur all at once, but that there is a certain inflammatory process. We can relate this process to the inflammatory parameters in the first trimester. Although this study does not aim to use the inflammatory markers for the diagnosis and treatment of HELLP syndrome, inflammatory parameters can be a trigger for the development of HELLP syndrome. However, none of the investigated indices proved to be an effective predictor in the first trimester. Nevertheless, simple and non-invasive predictive indices can be valuable tools for the prediction and management of HELLP syndrome.

Keywords: HELLP syndrome; lymphocyte; platelet; pregnancy; systemic inflammation response index

ÖZ

Amaç: İlk trimester tam kan sayımı parametrelerine dayanan inflamatuar biyobelirteçlerin HELLP sendromu riski için öngörücü rolünü sonuçlandırmak.

Gereç ve Yöntemler: Bu vaka-kontrol çalışmasına HELLP sendromu olan 73 gebeden 45'i dahil edildi. Klinik veriler ve laboratuvar sonuçları tıbbi ve hastane kayıtlarından elde edildi. HELLP sendromu riski için ilk trimester tam kan sayımı parametrelerine dayanan inflamatuar biyobelirteçleri karşılaştırdık.

Bulgular: Vücut kitle indeksi, gravidite, parite ve gebelik haftası açısından eşleştirilmiş 45 vaka (HELLP sendromlu gebe kadınlar) ve 45 kontrol (sağlıklı gebe kadınlar) alındı. İlk trimester kan testi sonuçlarında lenfosit, trombosit - lenfosit oranı, nötrofil - lenfosit oranı ve sistemik inflamasyon indeksi değerleri gruplar arasında istatistiksel olarak anlamlıydı. İlk trimester kan testi sonuçlarında sistemik inflamasyon yanıt indeksi ve pan-immün inflamasyon değerinde gruplar arasında anlamlı bir fark yoktu.

Sonuçlar: HELLP sendromu ile ilgili temel sorun, bir anda ortaya çıkmaması, ancak belirli bir inflamatuar sürecin olmasıdır. Bu süreci ilk trimesterdeki inflamatuar parametrelerle ilişkilendirebiliriz. Bu çalışma HELLP sendromunun tanı ve tedavisi için inflamatuar belirteçleri kullanmayı amaçlamasa da, inflamatuar parametreler HELLP sendromunun gelişimi için tetikleyici olabilir. Bununla birlikte, incelenen indekslerin hiçbirinin ilk trimesterde etkili bir belirleyici olduğu kanıtlanmamıştır. Bununla birlikte, basit ve invazif olmayan öngörücü endeksler, HELLP sendromunun öngörülmesi ve yönetimi için değerli araçlar olabilir.

Anahtar Kelimeler: HELLP sendromu; lenfosit; trombosit; gebelik; sistemik inflamasyon yanıt indeksi

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INTRODUCTION

HELLP syndrome with hemolysis -H-, elevated liver enzymes -EL- and low platelets -LP-, which is thought to be part of the pre-eclampsia spectrum, can occur in 0.5-0.9% of all pregnancies and in 10-20% of those with severe pre-eclampsia (1).

HELLP syndrome is a rare pregnancy-related condition that can be detected by simple blood and urine tests and is often associated with cerebral edema and multiple organ failure (2,3). The maternal and fetal mortality rate can reach 23.1% - 56.9% (4). As mentioned above, it is characterized by microangiopathic hemolysis, elevated liver enzymes and low platelet counts and is associated with severe clinical complications leading to maternal end-organ failure and even death (5). Patients often complain of abdominal pain, nausea and vomiting, which can worsen within a few hours (6). Patients may also have elevated blood pressure and proteinuria (6). The most feared complications of HELLP syndrome are cerebral hemorrhage and liver rupture (6).

Since the first description of HELLP syndrome in 1982, the diagnosis and treatment of this syndrome has been the subject of controversy. The difficulty with this syndrome is that there are no standardized diagnostic criteria and tests for prediction (5). In addition, HELLP syndrome is often difficult to distinguish from other pregnancy-related conditions and can lead to increased mortality. Although patients have elevated liver enzymes and low platelet, predictive tests with high sensitivity and specificity are currently being sought (5). The exact pathological mechanisms involved in the development of HELLP syndrome have never been fully elucidated. What is known is that there is widespread endothelial cell damage, particularly in the liver, leading to hemolysis, schistocytes and Burr cells and limited vascular involvement (7). In addition, activated platelets attach to damaged vascular endothelial cells, leading to platelet consumption (7). It is still controversial whether HELLP syndrome is a severe form of pre-eclampsia or a disease in its own right (8,9). The laboratory tests and clinical picture of pre-eclampsia and HELLP syndrome are different (6,8,9). In HELLP syndrome, the inflammatory reaction is more pronounced and mainly affects the liver and the coagulation system (8,9). However, the role and contribution of inflammation to neutrophil activation and endothelial dysfunction during the development of HELLP syndrome has been largely overlooked. One study found that the inflammatory marker neutrophil/lymphocyte ratio (NLR) was higher and platelet/lymphocyte ratio (PLR) was lower in women with HELLP syndrome (9). NLR and PLR have traditionally been used in various fields of medicine (10). Nowadays, however, it is becoming increasingly important to use a combination of these inflammatory markers (10-13).

In this study, the parameters of the complete blood count (CBC) in the 1st trimester in pregnant women with HELLP syndrome are evaluated, the Systemic Immune Inflammation Index (SII), the Systemic Inflammation Response Index (SIRI) and the Pan-Immune Inflammation Value (PIV) are calculated and it is investigated whether there is a correlation between these values and HELLP syndrome and whether they can be used to predict HELLP syndrome in early pregnancy.

MATERIAL AND METHODS

This case-control study was conducted retrospectively at the Obstetrics and Perinatology Clinics of an Education and Training Hospital between January 1, 2015 to January 1, 2022. This study was performed in accordance with the principles of the Helsinki Declaration, and it was approved by the local ethics committee (with the number: 05/29; April, 2022).

Inclusion and Exclusion Criteria

Singleton pregnancies with HELLP syndrome as study group and healthy singleton pregnancies with spontaneous labor as control group were included in the study.

Known maternal infections (acute or chronic), use of corticosteroids before the 20th week of pregnancy, hematologic diseases (idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hematologic malignancies, etc.), chronic systemic diseases that may alter CBC (lupus, renal or hepatic dysfunction, rheumatoid arthritis, asthma, etc.), pregnancies with known chromosomal abnormalities or congenital malformations were excluded from the study.

Data

The study required a sample of 45 pregnant women with HELLP syndrome for the study group and 45 healthy pregnant women for the control group. The study included a total of 90 pregnant women.

The data required for this study were obtained retrospectively from patient files and hospital records. For this purpose, data such as age, gravidity, parity, number of abortions, previous pregnancy history, body mass index, ultrasound findings, any concomitant diseases, information on previous operations, 1st trimester CBC parameters, routine biochemical findings, complete urinalysis, blood values on admission to the clinic (in third trimester), outcome of the current pregnancy and whether pregnancy complications occurred were used.

Study Design

Singleton pregnant women with HELLP syndrome who were cared for in the perinatology clinic and whose pregnancy ended in the

same clinic were included in the study group (Group I). Healthy singleton pregnant women with spontaneous labor who were cared for in the obstetric clinic and whose pregnancy ended in the same clinic were included in the control group (Group II). We planned to form the control group by randomization from pregnant women population who meet the exclusion criteria. We planned to perform the randomization in chronological order by including in the control group the pregnant women who were admitted to the hospital immediately after the patient from the study group was admitted to the hospital, were in the same week, and met the exclusion criteria.

We examined inflammatory biomarkers at the first trimester's routine CBC test (NEUT, PLT, MONO and LYM) of both groups to calculate SIRI (NEUT x MONO / LYM); SII (NEUT × PLT / LYM) and PIV (NEUT x PLT x MONO / LYM) (11-13). The SIRI, SII and PIV values of both groups were compared.

Laboratory analysis of blood samples and diagnosis of HELLP syndrome

The CBC parameters were analyzed with the Advia® 120 Hematology System (Siemens Healthcare Diagnostics Inc., Deerfield, Illinois) and the biochemical parameters with the Advia® 2400 Clinical Chemistry System (Siemens, Tarrytown, NY, USA). The diagnosis of HELLP syndrome was made on the basis of the criteria of the American College of Obstetricians and Gynecologists (14).

Statistical Analyses

The statistical analysis procedures were performed using Jamovi, an open statistical software, to analyze the data. The normal distribution of the variables was assessed using visual representations (histogram, probability plots) and analytical techniques (Kolmogrov-Simirnov/Shapiro-Wilk test). A Levene test was performed to assess the homogeneity of variance. The descriptive analysis included the presentation of mean values and standard deviations for variables that follow a normal distribution. A comparison of these factors between the groups was performed using a t-test for independent samples. Descriptive analysis for the non-normally distributed numerical data was performed using medians and quartiles (Q1-Q3). Comparisons of these factors between groups were performed using Mann-Whitney U-tests. Descriptive analysis for the categorical variables was performed using frequencies and percentages. Statistical analysis of relationships between categorical variables was performed using either the chi-square test or Fisher's exact test (in cases where the assumptions of the chi-square test are not applicable due to low expected cell counts). The capacity of various parameters that can be used to predict HELLP syndrome, were analyzed using ROC (Receiver Operating Characteristics) curve analysis. When a significant cut-off value was observed, the sensitivity, specificity, AUC (Area Under Curve) value, positive likelihood ratio and negative likelihood ratio were presented. ROC curves and areas under curve of these parameters were compared among themselves. A p-value below 0.05 was considered to indicate a statistically significant result.

RESULTS

In the present study, 45 of 73 pregnant women who were admitted to perinatology clinics with suspected HELLP syndrome between 2015 and 2022 and whose final diagnosis was HELLP syndrome formed the study group (Group I) and 45 pregnant women who were enrolled in the study according to the randomization system formed the control group (Group II) (Figure 1). There was no significant difference between the groups in terms of gravidity,

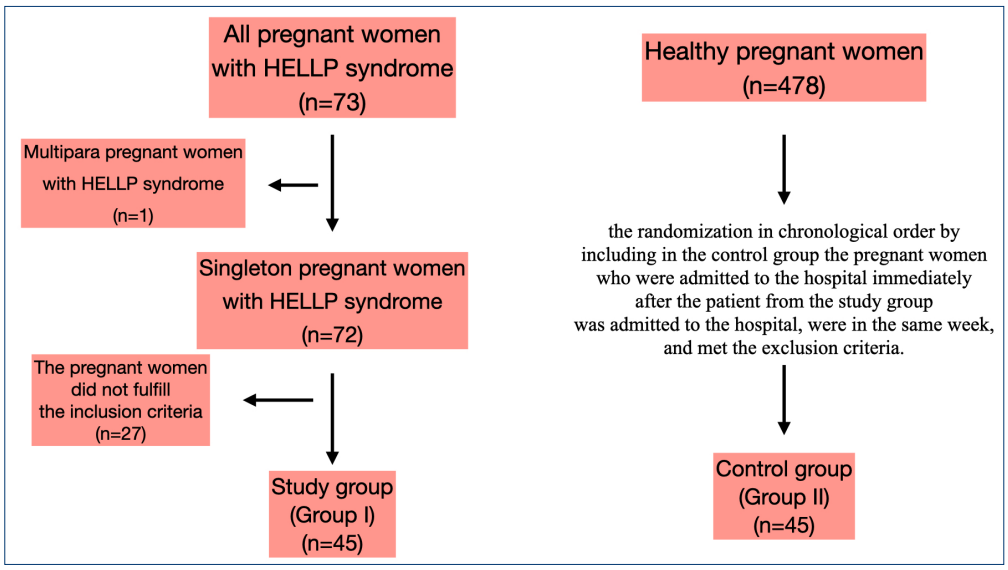

Figure 1. Flow-chart of the participants

parity, miscarriage and gestational week (admission to the clinic) (p> 0.05). Maternal age was higher in group I than in group II (p=0.001) (Table I).

The comparison of the inflammatory ratios and other blood parameters between the groups is shown in Table 2. The lymphocyte (LYM), platelets (PLT) - LYM ratio (PLR), neutrophil (NEUT) - LYM ratio (NLR) and SII values were statistically significant (p<0.05) between the groups in the first trimester blood test results. There was no significant difference in SIRI and PIV values between groups in the first trimester blood test results. These comparisons of all blood parameters between groups are shown in Table II.

NLR, PLR, SII and LYM have discriminatory properties for the prediction of HELLP syndrome in the ROC analysis of first trimester blood parameters and indices with statistical significance between

Table 1. Demographic and clinical characteristics of the study population

Variable	Group I (n=45)	Group II (n=45)	p
Age (years)	30 (27-34.5)	26 (24-29)	**0.001**
BMI (kg/m^2)	30 ± 4.3	29 ± 4.7	0.348
Gravidity (n)	2 (1-3)	2 (1-3)	0.475
Parity (n)	1 (0-1)	1 (0-2)	0.403
Miscarriage (n)	0 (0-0.5)	0 (0-1)	0.646
Gestational week (Admission to clinics)	33 (28-35)	32 (29-35)	0.891

BMI: body-mass index; n: numbers.
Data are expressed as median (Q1-Q3) and mean ± standard deviation.
A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

Table 2. Comparison of blood parameters, complete blood count-derived ratios between groups

Variable	Group I	Group II	p
First trimester blood parameters			
Neut (10^3/µL)	5.56 ± 2.16	5.51 ± 1.32	0.911
Lym (10^3/µL)	2.26 (1.62 - 2.50)	1.67 (1.33 - 2.26)	**0.044**
Mono (10^3/µL)	0.46 ± 0.16	0.44 ± 0.12	0.593
Plt (10^3/µL)	212.0 (165.5 - 295.2)	255.0 (218.5 -288.0)	0.137
WBC (10^9/L)	8.69 (6.68 -10.49)	8.11 (6.77 -9.18)	0.274
Hgb (g/dL)	12.9 (12 - 13.5)	12.5 (11.8 - 13.1)	0.208
NLR	2.46 (1.75 - 3.21)	3.18 (2.42 - 4.14)	**0.044**
PLR	111.9 (78.5 - 132.5)	142. 1 (114.9 - 181.9)	**0.007**
SII (10^3/µL)	543.29 (415.77 - 674.05)	757.62 (607.69 -106.46)	**0.002**
SIRI (10^3/µL)	1.15 (0.61 - 1.62)	1.25 (0.95 - 2.06)	0.308
PIV (10^6/µL2)	253.90 (129.41 - 392.63)	326.35 (230.38 - 446.80)	0.131
Third trimester blood parameters (blood values on admission to the clinic)			
Neut (10^3/µL)	10.02 (7.48 -14.23)	6.19 (5.42 - 6.79)	**<0.001**
Lym (10^3/µL)	1.50 (1.11 - 2.25)	1.63 (1.42 - 1.97)	0.351
Mono (10^3/µL)	0.45 (0.35 - 0.69)	0.51 (0.44 - 0.62)	0.142
Plt (10^3/µL)	92.0 (72.0 - 132.0)	222.0 (187.0 - 259.0)	**<0.001**
NLR	5.65 (3.27 - 11.78)	3.79 (2.84 - 4.39)	**<0.001**
PLR	61.54 (37.48 - 105.18)	128.75 (109.05 - 167.45)	**<0.001**
AST (U/L)	91 (53.50 - 191)	12 (8 - 15)	**<0.001**
ALT (U/L)	94 (30 - 150)	14 (11 - 17)	**<0.001**
SII (10^3/µL)	536.92 (285.23 - 123.95)	770.24 (610.42 - 102.92)	0.086
SIRI (10^3/µL)	2.82 (1.73 - 5.05)	1.84 (1.38 - 2.58)	**0.002**
PIV (10^6/µL2)	281.33 (140.83 - 639.19)	462.09 (271.81 - 560.56)	0.060

ALT: alanine transaminase; AST: aspartate aminotransferase; Hgb: hemoglobin; Hct: hematocrit; Lym: lymphocyte; MCV: mean corpuscular volume; Mono: monocyte; Neut: neutrophil; NLR, neutrophil-to-lymphocyte ratio; PIV: pan-immune inflammation score; Plt: platelet; PLR, platelet-to-lymphocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammatory response index; WBC: white blood cell
Data are expressed as median (Q1-Q3) and mean mean ± standard deviation. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

groups for the differential diagnosis in patients with suspected HELLP syndrome. The SII has the highest area under curve (AUC) value (AUC:0.720, cut-off: ≤ 676, p <0.001, sensitivity:78%, specificity:64%). The AUC values, the cut-off values, the CI 95%, sensitivity and the specificity of the statistically significant parameters are shown in Table III and Figure 2. The p-values showing the superiority of these parameters for use in the first trimester prediction of HELLP syndrome are shown in Table IV. None of the parameters listed in Table IV proved to be better than the other.

For the pregnant women in the study group whose blood values were analyzed in the first trimester, the changes in demographic or blood values, the changes in the parameters used to determine the risk of HELLP syndrome, and the data on the pregnant women's risk of developing HELLP syndrome are shown in Table V. Increases in LYM and PLR are considered protective factors, while increases in maternal age and NLR are considered risk factors. Each 1 year increase in maternal age increases the risk of HELLP syndrome by 1.1 times.

Table 3. ROC curve analysis for various parameters that can be used to predict HELLP syndrome

Variable	AUC	CI 95%	p	Cut-off value	Sensitivity (%)	Specificity (%)	+ LHR	- LHR
SII (103/µL)	0.642	0.598-0.822	**<0.01**	≤676	78	64	2.16	0.34
				≤512	40	90	1.85	0.46
NLR	0.642	0.517-0.755	**0.044**	≤2.87	71	61	3.37	0.78
				≤1.75	28	90	2.64	0.82
PLR	0.689	0.565 – 0.796	**0.005**	≤132.75	78	61	2.01	0.59
				≤91.2	38	90	4.50	0.36
LYM (103/µL)	0.632	0.517-0.755	**0.037**	>2.22	53	75	2.12	0.63
				>2.73	19	90	3.37	0.86

AUC: area under curve; CI: confidence interval; LHR: likelihood ratio; LYM: lymphocyte; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index.
A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

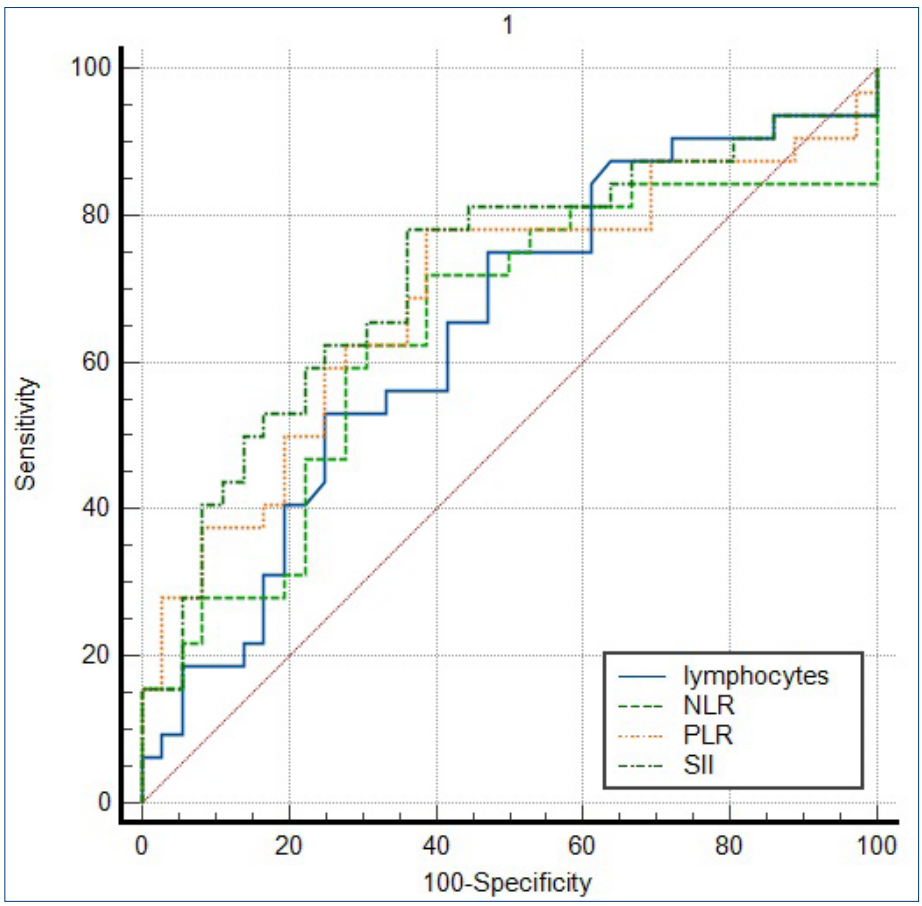

Figure 2. ROC curve for the variables

Table 4. ROC curve analysis for various parameters that can be used to predict HELLP syndrome

Variable	WBC	Neut	NLR	PLR	PLT	SIRI
WBC		0.952	**0.056**	0.827	**0.513**	**<0.001**
Neut	0.952		0.011	0.853	0.501	**<0.001**
NLR	**0.056**	**0.011**		0.285	**0.031**	0.201
PLR	0.827	0.853	**0.285**		0.141	0.083
PLT	0.513	0.501	**0.031**	**0.141**		**0.002**
SIRI	**<0.001**	**<0.001**	0.201	**0.083**	**0.002**	

NEUT: neutrophil; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT: platelet; ROC: receiver operating characteristic; SIRI: systemic inflammatory response index; WBC: white blood cell.

Table 5. Regression models for HELLP syndrome

Variables	OR (95%CI)	p value
Age	1.10 (1.0 – 1.21)	**0.033**
LYM	1.00 (1.00 – 1.00)	0.095
NLR	0.80 (0.56 – 1.15)	0.230
PLR	0.99 (0.98 – 1.00)	**0.031**
PLR / 10	0.89 (0.79 – 0.99)	**0.031**
SII	1.00 (1.00 – 1.00)	0.140

CI: confidence interval; LYM: lymphocyte; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratio; PLR: platelet-to-lymphocyte ratio; SII, systemic immune-inflammatory index. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

DISCUSSION

The study investigated the inflammatory biomarkers and inflammatory ratios based on the first trimester CBC in the prediction of HELLP syndrome. According to the results, a higher maternal age and a higher NLR value from the first trimester to the week of delivery are considered risk factors for HELLP syndrome. Additionally, logistic regression analysis clearly showed that a decreased LYM level and a higher maternal age are independent risk factors for the development of HELLP syndrome.

The underlying pathophysiological mechanism of HELLP syndrome is not yet fully understood (15). However, it may be associated with conditions such as placental origin, autoimmunity, mutations in the coagulation factor V gene and fatty acid oxidation disorders (15). Following an unexplained spasm of the small blood vessels of the maternal system, the red blood cells are compressed and ruptured as they travel through these vessels, resulting in hemolysis (16); hypoxia and tissue ischemia due to vasospasm and hemolysis result in damage to major organs, liver enzymes are released after liver injury, leading to an increase in liver enzymes (15,17); exposure to collagen tissue after endothelial cell injury leads to platelet activation, aggregation and excessive consumption, which in turn leads to a decrease in PLT count (18). Also, it is already known that the pathophysiological changes of HELLP syndrome in the maternal body are particularly similar to those of severe pre-eclampsia (15,16,19). Some studies have shown that inflammation is one of the causes of the pathophysiological changes underlying HELLP syndrome. In a study that demonstrated the relationship between inflammation and HELLP syndrome, it was assumed that the development of HELLP syndrome is associated with an even stronger endovascular inflammatory reaction than in pre-eclampsia (20). In another study, in the context of HELLP syndrome and the inflammatory process, it was found that the expression of ''for cluster of differentiation" (CD) markers on polymorphonuclear leukocytes (PML) leads to a change that resembles the inflammatory response and that the up-regulation of CD11b to bind to PLT Factor 4 leads to the formation of PLT-PML complexes (21). These aggregates lead to an increase in thrombotic microangiopathies with further tissue damage and thrombocytopenia (21). This reciprocal effect of platelets and leukocytes has been shown to play an important role in HELLP syndrome (21). However, the technical challenges associated with the use of these antigens and their high cost limit their widespread use in practice. Therefore, a clinically useful and cost-effective predictive test is needed to identify individuals at risk for HELLP syndrome. First trimester prediction of HELLP syndrome has already been established based on maternal characteristics, ultrasound findings and biochemical markers [pregnancy-associated protein-A (PAPP-A), free β-human chorionic gonadotropin, and placental growth factor (PLGF)] (1). In English-language medical research, SII, SIRI and PIV together have

not yet been studied as inflammatory biochemical markers for the prediction of HELLP syndrome.

There are some studies that use inflammatory markers on outcomes of pregnancies with maternal systemic diseases (22,23) and also some studies that use inflammatory markers or aspartate aminotransferase to PLT ratio index (APRI) score to predict HELLP syndrome (24,25). Sahin et al (22) investigated inflammatory markers in the prediction of composite adverse outcomes in pregnant women with systemic lupus erythematosus (SLE). They showed that SII, SIRI, and NLR may be used to predict adverse pregnancy outcomes in pregnant women with SLE (22). Another study by Sahin et al (23) SII, SIRI, and NLR may be used to predict adverse pregnancy outcomes in pregnant women with Familial Mediterranean fever. Ipek et al (24) investigated the predictive role of some inflammatory markers for the risk of HELLP syndrome. The study showed that none of the investigated indices was found effective in the first trimester in the prediction (24). Tolunay et al (25) investigated the efficiency of the APRI score in predicting HELLP syndrome in the first trimester. The study concluded that there is a correlation between APRI levels in the first trimester and the prediction of HELLP syndrome, which can develop in the later weeks of pregnancy (25).

In the present study, we evaluate the predictive role of inflammatory biomarkers based on first trimester CBC parameters for the risk of HELLP syndrome. The results of the present study show that an increase in LYM and PLR is considered a protective factor, whereas an increase in maternal age and NLR is considered a risk factor. For every 1-year increase in maternal age, the risk of HELLP syndrome increases 1.1-fold. However, when we analyzed the results in detail, we found that the most important determining factor for the HELLP syndrome was the number of LYM (which is the main component in all inflammatory ratios). This was because the number of LYMs decreased dramatically in pregnant women who developed HELLP syndrome.

In conclusion, the main problem with HELLP syndrome is that it does not occur all at once, but that there is a certain inflammatory process. We can relate this process to the inflammatory parameters in the first trimester. Although this study does not aim to use the inflammatory markers for the diagnosis and treatment of HELLP syndrome, inflammatory parameters can be a trigger for the development of HELLP syndrome. However, none of the investigated indices (SIRI, PIV and SII) proved to be an effective predictor in the first trimester. Nevertheless, simple and non-invasive predictive indices can be valuable tools for the prediction and management of HELLP syndrome. We believe that randomized, controlled and multicenter studies are needed for this purpose.

The strengths and limitations

The study was conducted in a large tertiary referral center where the same algorithms and treatment modalities were used for HELLP syndrome is the strength of the study. But the study had a retrospective design, so it has some limitations due to its nature. This is because we were missing some of the participants' data/information. The lack of a power analysis is also an inherent limitation of the study.

Ethics Committee Approval

This study was performed in accordance with the principles of the Helsinki Declaration, and it was approved by the local ethics committee (with the number: 05/29; April, 2022).

Competing interests

The authors declare that they have no competing interests.

Funding Statement

There is no financial disclosure to be made for this study.

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Authors' contributions

Conceptualization, S.O., F.B.F and S.S.; methodology, S.O., F.B.F, Y.A.R, and S.T.S.; software, D.K. and A.K.; validation, S.O., S.S. and Y.A.R; formal analysis, S.S. and S.T.S.; investigation, S.O., F.B.F. and M.L.D.; resources, A.K.; data curation, D.K. and A.K.; writing—original draft preparation, F.B.F. and S.O.; writing—review and editing, S.S. and S.C.; visualization, S.O., S.C., M.L.D. and Y.U-E.; supervision, Y.E-U.; project administration, S.O. and Y.E-U. All authors have read and agreed to the published version of the manuscript.

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