J Surg Med. 2021;5(12):1202-1205.
DOI: 10.28982/josam.1008359

Journal of Surgery and Medicine
e-ISSN=2602-2079

The predictive role of neutrophil-lymphocyte ratio, platelet lymphocyte ratio, and other complete blood count parameters in eclampsia and HELLP syndrome

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Ethics Committee Approval
Bursa Yüksek Ihtisas Training and Research Hospital Ethics Committee approved the study with numbered 2011-KAEK-25 2021/03-06. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 November 28

Abstract

Background/Aim: Previous studies declared the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, and other routine complete blood count (CBC) components as sensitive preeclampsia biomarkers. We speculated that the same associations existed with eclampsia and HELLP syndrome.
Methods: This retrospective case-control study was conducted on 120 pregnant women between the ages of 18 and 40 years. Forty-nine patients with HELLP syndrome, 40 patients with eclampsia/preeclampsia, and 40 healthy pregnant women were included in the study. All groups were evaluated in terms of clinical characteristics and first-trimester hematological parameters. The primary outcomes were neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and the secondary results were hemoglobin, red blood distribution width, mean platelet volume, platelet count, neutrophil count, and lymphocyte count.
Results: The median gestational age was 34 weeks (ranging between 23 and 41), with a median birth weight of 2300 grams. The median NLR was 3.9 (1.3-25.1), and the median PLR was 113.6 (20.7-693). The NLR and PLR values were significantly different between the three groups (P=0.014, P=0.002, respectively). NLR was different between normotensive and eclamptic pregnant women. PLR values were higher in normotensive pregnant women than in pregnant women with a history of HELLP. The median red cell distribution width was 44.6 in normotensive women, 41.5 in women with eclampsia, and 44.3 in women with a history of HELLP (P=0.017).
Conclusion: TLR value was higher in pregnant women who had eclampsia. Platelet count and MPV were significantly lower in the HELLP group.

Keywords: Eclampsia, HELLP syndrome, Neutrophil-lymphocyte ratio (NLR), Platelet-lymphocyte ratio (PLR)

How to cite: Bayram F, Karaşin SS. The predictive role of neutrophil-lymphocyte ratio, platelet lymphocyte ratio, and other complete blood count parameters in eclampsia and HELLP syndrome. J Surg Med. 2021;5(12):1202-1205.

Introduction

Pregnancy-induced hypertensive (PIH) disorders include chronic hypertension, gestational hypertension, preeclampsia, severe preeclampsia and hemolysis, high liver enzymes and low platelet (HELLP) syndrome, and eclampsia. Hypertensive disorders of pregnancy occur in 5-11% of all pregnancies [1]. Preeclampsia (PE) is a pregnancy-specific disease characterized by arterial hypertension and significant proteinuria after 20 weeks of gestation. It complicates approximately 2-8% of pregnancies worldwide [2, 3].

Preeclampsia is a multifactorial obstetric pathology with high morbidity and mortality rates, the pathogenesis of which has not been clearly clarified. There is insufficient placentation due to the absence of trophoblastic invasion, which causes placental hypoxia followed by proinflammatory cytokine secretion, increased neutrophil counts, thrombocyte activation, systemic inflammation and endothelial dysfunction [4].

Eclampsia, the major neurological complication of preeclampsia, is defined as a convulsive episode or any other sign of altered consciousness that occurs in the setting of preeclampsia and cannot be attributed to any pre-existing neurological condition [5]. We hypothesized that there is a similar relationship in the pathogenesis between PE and eclampsia in the first trimester of pregnancy.

HELLP syndrome was first reported by Weinstein in 1982 as hemolysis (H), elevated liver enzymes (EL) and low platelet count (LP) in the third trimester of pregnancy [6]. The presence of hemolysis and microangiopathy is one of the basic criteria of the HELLP syndrome triad, seen in 80-85% of these patients. The incidence of HELLP syndrome is 0.1-0.8%, and it occurs after the 20th week of pregnancy [7]. Although the exact etiopathogenesis is not known, genetic predisposition, abnormal placentation, immunological pathologies, and maternal vascular endothelial dysfunction may play a role. Seventy percent of the cases were detected in the antenatal period, and 30% were detected postpartum (usually in the first 48 hours). There is still debate about whether HELLP is a severe form of preeclampsia or a separate condition [8].

HELLP syndrome is part of the hypertensive disorders of pregnancy, but the inflammatory reaction is more intense than in preeclampsia, and the immune system specifically attacks the liver and coagulation cascade [9]. In addition, while hypertension is the definitive diagnostic criterion in preeclampsia, it is not always present in HELLP syndrome [8–10].

There are no known diagnostic markers that can predict the development of HELLP syndrome or eclampsia in the early trimester of pregnancy. Recently, neutrophil-to-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were recognized as novel markers of systemic inflammation. It is also noteworthy that these indices obtained from peripheral blood cells are easily measurable and accessible. There are many studies that found the rate of NLR and PLR in the first trimester to be higher in preeclampsia than in healthy pregnancies [11, 12].

However, there is limited data in the literature regarding the effectiveness of these markers in HELLP syndrome and eclampsia. Currently, the predictive roles of NLR, PLR and other hemogram parameters in HELLP and eclampsia are still unclear. This study aims to determine the predictive value of routine hemogram parameters in the first trimester for early diagnosis of HELLP syndrome and eclampsia.

Materials and methods

This retrospective case-control study was conducted in Bursa Yüksek İhtisas Training and Research hospital. For sample calculation, the study "Neutrophil-to-lymphocyte ratio and platelet indices in pre-eclampsia" (DOI: 10.1002/ijgo.12701) was used [13]. As a result of the sample calculation made according to the Neutrophil/Lymphocyte Ratio parameter in Table 2 of this study, a total of 130 volunteers were needed for 95% confidence interval, 0.05 type 1 error, 0.44 effect size and 80% power. A total of 129 pregnant women between the ages of 18 and 40 years, who delivered in our obstetrics clinic were included in the study. Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee approved the study numbered 2011-KAEK-25 2021/03-06. The patients had visited our obstetrics department in the first trimester (between 7 to 14 weeks of gestation) of their pregnancy and undergone a routine complete blood count (CBC) test. The participants were divided into three groups: There were 49 patients with HELLP syndrome, 40 patients with eclampsia/preeclampsia and 40 healthy pregnant women. All groups were evaluated in terms of clinical characteristics and first trimester hematological parameters.

American College of Obstetrics and Gynecology 2013 guidelines were used to diagnose HELLP and eclampsia [2]. HELLP syndrome indicated the presence of thrombocytopenia (<150,000/mm3), hepatic dysfunction (aspartate aminotransferase (AST) >40 IU/L, alanine aminotransferase (ALT) >40 IU/L, or both, and lactate dehydrogenase (LDH) level >600 IU/L), and hemolysis (increased LDH level, progressive anemia) [14].

PE was diagnosed with the following criteria: Systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg on two occasions at least 4 hours apart and proteinuria (>0.3 g per day) after the 20th gestation week. Eclampsia was defined as the presence of new-onset grand mal seizures in a woman with preeclampsia. The control group included healthy pregnant women with matching gestational age. Women with a history of membrane rupture, anemia, infection, multiple pregnancy, history of drug use or systemic disease (such as diabetes mellitus, thyroid disorders, chronic hypertension, cardiac disease, collagen vascular disease, epilepsy and hypercoagulopathy) were excluded from the study.

The noted demographic and clinical information included age, body mass index (BMI), gravidity, parity, race, birthweight, gestational age at delivery, and gestational age at CBC collection. Venous blood samples were drawn into 2 mL EDTA tubes. CBC values were analyzed with the automated hematology analyzer (ABX Micros ES 60; Horiba Medical, Kyoto Japan). The main outcomes were NLR, PLR and MLR, and the secondary outcomes were hemoglobin, RDW, MPV, platelet count, neutrophil, and lymphocyte values.

Statistical analysis

Windows-based SPSS 24.0 program was used (SPSS Inc., USA) for statistical analyses. We used visual (histograms, probability plots) and analytical methods (Shapiro-Wilk's test

and Kolmogorov Smirnov tests.) to determine whether the variables were normally distributed. Variables were descriptively specified as mean (standard deviation) (X(SD)), median (minimum-maximum (min-max)), frequency (n) and percentage (%). One-way ANOVA compared the normally distributed data and the Kruskal Wallis test was used to compare the non-normally distributed variables. Post-hoc Tukey test was used for the binary analysis of significant results. A value of $P<0.05$ was considered statistically significant.

Results

In this retrospective study, we analyzed 89 pregnant women diagnosed with eclampsia and HELLP in the last 3 years (2018-2021) and 40 pregnant randomized women with normal pregnancies.

The demographic and obstetric characteristics of the patients are shown in Table 1. The median age of the patients was 28 (17-43) years. The median gestational age was 34 weeks (ranging between 23 and 41) with a median birth weight of 2300 grams. The median systolic and diastolic blood pressure values were 140 mmHg and 90 mmHg, respectively. The mean hemoglobin value was 12 (1.5) g/dl, the mean platelet value was 218 in the microliter. The median NLR was 3.9 (1.3-25.1) and the median PLR was 113.6 (20.7-693). The rest of the analysis is shown in Table 1.

Table 1: Demographic and obstetric characteristics of the patients

Characteristics (n=94)	Mean (standard deviation)* Median (Minimum – maximum)
Age (years)	28 (17-43)
Gravidity	2 (1-6)
Parity	1 (0-5)
BMI (kg/m^2)	29.3 (21.4-46.6)
Gestational age (weeks)	34 (23-41)
Birth weight (gr)	2300 (475-4500)
APGAR 1st min.	8 (0-9)
APGAR 5th min.	10 (0-10)
Systole (mmHg))	140 (100-240)
Diastole (mmHg)	90 (60-120)
Dipstick proteinuria	1 (0-3)
Hemoglobin (g/dl)*	12 (1.5)*
Neutrophil (10^6/ml)	8000 (2150-24000)
Lymphocyte (10^6/ml)	1970 (400-5080)
Platelets (mcl)*	218 (73.1)*
Monocyte (10^6/ml)	500 (50-1600)
Neutrophil/Lymphocyte ratio	3.9 (1.3-25.1)
Platelet/Lymphocyte ratio	113.6 (20.7-693)
Monocyte/Lymphocyte ratio	4.9 (0.4-9.1)
Mean platelet volume (fl)	10.5 (6.6-16.4)
Red cell distribution width (%)	43.7 (12.6-72.4)
Diagnosis (n, %)	Normal pregnancy (40, %31) Eclampsia (40, %31) HELLP (49, %38)

gr: gram, kg: kilogram, mcl: microliter, fl: femtolitre, min: minute, n: frequency, %: percentage. Descriptive analyses were presented using mean (X(SD)) and median (min-max) for normally distributed* and non-normally distributed data, respectively

The analysis results of the maternal and fetal characteristics of all 3 groups are detailed in Table 2. The median ages of normotensive and eclampsia groups were 26 years, and that of the HELLP group was 30 years. The median gestational age of Groups 1, 2 and 3 were 38 weeks, 32 weeks, and 33 weeks, respectively ($p<0.05$). The median birth weights in the same order were 3300 grams, 1690 grams, and 1600 grams ($p<0.05$). Infants' 1st and 5th minute APGAR scores, mothers' systolic and diastolic blood pressures, and dipstick protein values also significantly differed between the three groups (Table 2).

Table 2: Comparison of maternal and fetal characteristics

RF	Group 1 (n=40) X (SD)/Median (min–max)	Group 2 (n=40) X (SD)/Median (min–max)	Group 3 (n=49) X (SD)/Median (min–max)	*P*-value
Age (years)	26 (19-40)	26 (17-43)	30 (19-41)	0.066
Gravidity	2 (1-6)	1 (1-6)	2 (1-6)	0.005
Parity	2 (1-5)	1 (0-5)	1 (1-5)	<0.001
BMI (kg/m^2)	29.3 (23.4-36)	28.5 (21.4-40)	30.4 (21-8-46.6)	0.230
Gestational age (weeks)	38 (34-41)	32 (24-41)	33 (23-40)	<0.001
Birth weight (gr)	3300 (2380-4070)	1690 (500-3480)	1600 (475-4500)	<0.001
APGAR 1st min.	9 (5-9)	8 (0-9)	8 (0-9)	<0.001
APGAR 5th min.	10 (9-10)	9 (0-10)	9 (0-10)	<0.001
Systole (mmHg)	110 (100-120)	150 (100-240)	150 (130-220)	<0.001
Diastole (mmHg)	70 (60-80)	100 (80-120)	90 (80-110)	<0.001
Dipstick proteinuria	0 (0-1)	2 (0-3)	3 (0-3)	<0.001

gr: gram, kg: kilogram, min: minimum, max: maximum. Descriptive analyses were presented using mean (X(SD)) and median (min-max) for normally distributed* and non-normally distributed variables, respectively. $P<0.05$ was considered significant for Kruskal Wallis and one way ANOVA tests

Table 3 shows the laboratory parameters of all groups. The median neutrophil counts in the normotensive, eclampsia and HELLP groups were 6830 (2630-11950) (10^6/ml), 9715 (2150-24000) (10^6/ml), and 8040 (3400-22500) (10^6/ml), respectively ($P<0.001$). The NLR and PLR values were significantly different between three groups ($P=0.014$, $P=0.002$, respectively). Post-hoc analyses were performed to evaluate the groups that created the difference. Accordingly, NLR significantly differed between the normotensive and the eclamptic pregnant women. The median NLR values in the first and second groups were 3.3 (1.3-6.3), and 4.3 (1.3-25.1), respectively ($P=0.007$). PLR values significantly differed between the normotensive pregnant women and those with a history of HELLP (128.3 (75.5-693) vs. 100.6 (20.7-280) ($P=0.026$), respectively) (Table 3).

Table 3: Comparison of laboratory parameters

RF	Group 1 (n=40) X (SD)/Median (min–max)	Group 2 (n=40) X (SD)/Median (min–max)	Group 3 (n=49) X (SD)/Median (min–max)	*P*-value
Hemoglobin (g/dl)*	11.7 (1.2)	11.7 (1.6)	12.5 (1.6)	0.026
Neutrophil (10^6/ml)	6830 (2630-11950)	9715 (2150-24000)	8040 (3400-22500)	<0.001
Lymphocyte (10^6/ml)	1925 (1000-5080)	2090 (700-4200)	1920 (400-4670)	0.892
Platelets (mcl)*	234.9 (64.6)	228.6 (74.2)	195.5 (75.5)	0.021
Monocyte (10^6/ml)	460 (240-1240)	520 (100-1000)	530 (50-1600)	0.289
Neutrophil/Lymphocyte ratio	3.3 (1.3-6.3)	4.3 (1.3-25.1)	3.9 (1.5-17.3)	0.014
Platelet/Lymphocyte ratio	128.3 (75.5-693)	107.9 (44.2-644)	100.6 (20.7-280)	0.002
Monocyte/Lymphocyte ratio	5 (3.2-7.9)	5.2 (0.4-7.6)	4.7 (0.6-9.1)	0.619
Mean platelet volume (fl)	10 (7.9-16.4)	10 (6.6-12.4)	11.3 (7.1-15.9)	<0.001
Red cell distribution width (%)	44.6 (36-72.4)	41.5 (12.6-64)	44.3 (13.2-69.6)	0.017
Post-Hoc analyze		*P*-value * Group 1 vs. 2	*P*-value * Group 1 vs. 3	*P*-value * Group 2 vs. 3
Hemoglobin (g/dl)*		0.999	0.052	0.057
Neutrophil (10^6/ml)		<0.001	0.047	0.020
Platelets (mcl)*		0.918	0.029	0.080
Neutrophil/Lymphocyte ratio		0.007	0.168	0.324
Platelet/Lymphocyte ratio		0.336	0.026	0.492
Mean platelet volume (fl)		0.782	0.001	<0.001
Red cell distribution width (%)		0.001	0.500	0.025

gr: gram, dl: deciliter, min: minimum, max: maximum. Descriptive analyses were presented using mean (X(SD)) and median (min-max) for normally distributed* and non-normally distributed variables, respectively. $P<0.05$ was considered significant for Kruskal Wallis and one way ANOVA tests. The Tukey test was used for the double group comparison of the results that were significant in multiple analysis. Homogeneity of variances was evaluated with Levene's test.

The median red cell distribution width was 44.6 in normotensive women, 41.5 in women with eclampsia, and 44.3 in women with a history of HELLP ($P=0.017$). The first and the second groups ($P=0.001$), and the second and the third groups significantly differed from one another ($P=0.025$) (Table 3).

Discussion

Preeclampsia indicates either new-onset hypertension and significant end-organ dysfunction (with or without proteinuria) occurring in a previously normotensive woman after 20 weeks of gestation. HELLP is the acronym that suggests a syndrome in pregnant women characterized by hemolysis with a microangiopathic blood smear, elevated liver enzymes, and a low platelet count [15].

In this study, both NLR and PLR were significantly different between three groups. Post-hoc analysis revealed that the NLR differed between the normal pregnant women and those with preeclampsia, while PLR differed between the normal pregnant women and those with HELLP. Hemoglobin, Neutrophil, Mean Platelet Volume and Red Cell Distribution Width were also significantly different between the three groups. Lymphocyte and Monocyte/Lymphocyte ratio were similar.

Although the standard course of pregnancy is associated with oxidative stress, factors such as vascular endothelial damage, placental ischemia, oxidative damage, coagulation anomalies, inflammation are predisposing factors to preeclampsia [16].

Hyperactivation of inflammatory cells in preeclampsia causes inflammatory cytokines and autoantibodies to be released and higher superoxide production, resulting in endothelial dysfunction [4]. The NLR, PLR, and other routine CBC components are sensitive early markers of preeclampsia and other inflammatory obstetric conditions. Gogoi et al. [13] found that NLR, PLR, RDW, and MPV values were all higher in women with pre- eclampsia compared to healthy pregnant women. Sachan et al. [17] showed that first-trimester NLR could predict preeclampsia and severe preeclampsia in the third trimester. Mannaertset et al. [12] found that NLR was higher, and PLR was lower in preeclamptic patients compared to healthy controls. On the other hand, Sisti et al. [18] did not report a direct association of NLR, PLR, and other complete blood parameters with HELLP syndrome.

Measuring NLR and PLR is easy and inexpensive. These markers were studied in inflammatory disorders such as diabetes mellitus, coronary artery disease, ulcerative colitis, and cancer [19]. Since NLR and PLR suggest the presence of an increased inflammatory state, they can be used to predict preeclampsia [13, 18].

PLR plays a role in cytokine-dependent immune response and is associated with severe ischemia, end-organ damage, and preeclampsia. Raised C-reactive protein and impaired flow-mediated vasodilation precede preeclampsia [20].

In this study, NLR was significantly higher in pregnant women diagnosed with eclampsia compared to the normotensive control group. However, PLR did not differ between the normotensive group and pregnant women with eclampsia. In women who developed HELLP findings, NLR did not differ significantly compared to the eclampsia group. Of course, considering the low platelet count, which is one of the HELLP diagnostic criteria, PLR was significantly lower in those with HELLP than in normotensive pregnant women. Although RDW was reportedly associated with preeclampsia in some studies, we found that the RDW value was significantly higher among normotensive pregnant women than in pregnant women with eclampsia [13, 21]. The reason for the increase in RDW levels in preeclampsia has not been fully determined in these studies.

The main limitation of this study is the lack of a comparison group of preeclamptic patients and the small sample size. This study should be performed in a large geographical area, with more patients. In addition, the correlation with other radiological and biochemical markers was not researched in this study.

One of the strengths of our study is the evaluation of pregnant groups diagnosed with HELLP syndrome and eclampsia. We were able to characterize two hypertensive diseases that threaten maternal and fetal life and observe the difference between healthy controls and hypertensive pregnant patients.

Conclusion

This study found that NLR was higher in pregnant women with eclampsia. Platelet count and MPV were significantly lower in the HELLP group. NLR and PLR may be useful in predicting the risk of eclampsia prenatally or during delivery. Multicenter studies with large numbers of patients and long-term follow-up are needed to confirm these findings.

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