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The predictive value of total leukocyte count and leukocyte differential for severe preeclampsia

Halenur Bozdağ[1], Ergül Demirçivi Bör[1], Esra Akdeniz[2]

[1]*Clinic of Obstetrics and Gynecology, Göztepe Training and Research Hospital, Istanbul Medeniyet University, Istanbul, Turkey*
[2]*Department of Biostatistics, Faculty of Medicine, Marmara University, Istanbul, Turkey*

Abstract

Objective: We aimed to evaluate the leukocyte, neutrophil, lymphocyte, monocyte counts and the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio levels in pregnant women with preeclampsia (PE) compared with matched normal pregnant women and to assess whether there is a relation between severity of preeclampsia and these hematological parameters.

Methods: A retrospective, descriptive, cross-sectional study was performed in 186 women: 72 healthy pregnant women and 114 women with PE [severe group (n=41) and without severe clinical features group (mild PE; n=73)]. The clinical and hemodynamic status and the laboratory parameters of patients were obtained from medical records. The predictive value of total leukocyte and neutrophil count, MPV, NLR and PLR for the severity of preeclampsia was assessed by using a receiver operator characteristic-area under the curve (ROC-AUC).

Results: There were no significant differences between patients with PE and healthy pregnant women with regard to maternal age; however, patients with PE exhibited significantly higher blood pressure and proteinuria levels and significantly lower gestational age at delivery. Median leukocyte count was found to be significantly higher in mild and severe preeclampsia compared with healthy pregnant women (9450/μL) and significantly higher in severe PE (12,100/μL) than in mild PE (11,450/μL). Median neutrophil and lymphocyte counts were significantly higher in severe PE group than healthy pregnant women. Leukocyte count was found to be related to the presence of severe preeclampsia at admission to hospital (OR: 1.0002, 95% CI: 1.0001–1.0003; p=0.0001). The total leukocyte count had a poor predictive value for severe preeclampsia with an ROC-AUC with 0.696 (p= 0.0001; the sensitivity and specificity were 65.9% and 65.5%, respectively). The maximum sensitivity and specificity cut-off point was found to be 0.191 (pointed number of leukocytes 10,890/μL). ROC-AUC of the neutrophil count, MPV, NLR and PLR for severe preeclampsia were 0.632, 0.564, 0.534 and 0.588, respectively.

Conclusion: Leukocyte count is significantly increased in women with preeclampsia compared to healthy pregnant women. The predictive value of total leukocyte count for severe preeclampsia is poor. The neutrophil count, MPV, NLR and PLR have poor predictive value for severe preeclampsia.

Keywords: Preeclampsia, leukocyte, leukocyte differentials, complete blood count, pregnancy.

Özet: Toplam lökosit sayısının ve lökosit değer farkının şiddetli preeklampsiye yönelik kestirim değeri

Amaç: Çalışmamızda, eşleşen normal gebelerle karşılaştırarak preeklampsili (PE) gebelerde lökosit, nötrofil, lenfosit, monosit sayılarını ve nötrofil/lenfosit oranını, trombosit/lenfosit oranı seviyelerini incelemeyi ve preeklampsinin şiddeti ile bu hematolojik parametreler arasında bir ilişki olup olmadığını değerlendirmeyi amaçladık.

Yöntem: Retrospektif, tanımlayıcı, kesitsel çalışma 186 kadın üzerinde gerçekleştirilmiş olup, bunların 72'si sağlıklı gebe ve 114'ü ise preeklampsili gebe idi [şiddetli grup (n=41) ve şiddetli klinik özellikleri olmayan grup (hafif PE; n=73)]. Hastaların klinik ve hemodinamik durumu ve laboratuvar parametreleri tıbbi kayıtlardan alındı. Toplam lökosit ve nötrofil sayısı, MPV, NLR ve PLR'nin preeklampsi şiddetine yönelik kestirim değeri, karar vericinin etkinliği - eğri altındaki alan (ROC-AUC) kullanılarak değerlendirildi.

Bulgular: Preeklampsi hastaları ile sağlıklı gebeler arasında maternal yaş bakımından anlamlı fark yoktu; ancak PE hastaları anlamlı derecede daha yüksek kan basıncı ve proteinüri seviyeleri ile doğum esnasında anlamlı derecede daha düşük gebelik yaşına sahipti. Medyan lökosit sayısı, sağlıklı gebelerle kıyaslandığında hafif ve şiddetli preeklampsi olgularında anlamlı derecede (9450/μL) ve şiddetli PE olgularında (12.100/μL) hafif PE olgularından (11.450/μL) anlamlı derecede daha yüksekti. Medyan nötrofil ve lenfosit sayıları, sağlıklı gebelere kıyasla şiddetli PE grubunda anlamlı derecede daha yüksekti. Lökosit sayısının, hastaneye başvuru esnasında şiddetli preeklampsi varlığı ile ilişki olduğu bulundu (Risk Oranı: 1.0002, %95 GA: 1.0001– 1.0003; p=0.0001). Toplam lökosit sayısı, 0.696'lık ROC-AUC ile şiddetli preeklampsi için düşük kestirim değerine sahipti (p=0.0001; duyarlılık ve özgüllük sırasıyla %65.9 ve %65.5 idi). Maksimum duyarlılık ve özgüllük eşik değeri 0.191 olarak bulundu (tam lökosit sayısı: 10.890/μL). Nötrofil sayısı, MPV, NLR ve PLR'nin şiddetli preeklampsiye yönelik ROC-AUC değeri sırasıyla 0.632, 0.564, 0.534 ve 0.588 idi.

Sonuç: Lökosit sayısı, sağlıklı gebelere kıyasla preeklampsili kadınlarda anlamlı derecede artmaktadır. Toplam lökosit sayısının şiddetli preeklampsiye yönelik kestirim değeri düşüktür. Nötrofil sayısı, MPV, NLR ve PLR şiddetli preeklampsi için düşük kestirim değerine sahiptir.

Anahtar sözcükler: Preeklampsi, lökosit, lökosit değer farkları, tam kan sayımı, gebelik.

Correspondence: Ergül Demirçivi Bör, MD. Clinic of Obst. & Gyn., Göztepe T&R Hospital, Istanbul Medeniyet University, Istanbul, Turkey. e-mail: drergul@yahoo.com

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Introduction

Preeclampsia (PE) is a placental and systemic disorder characterized by a high degree of systemic inflammation, compared with normal pregnancy. It is also an important cause of maternal and perinatal morbidity and mortality. Clinical symptoms such as hypertension and proteinuria occur after 20 weeks of gestation.[1] The pathological changes causing the symptoms are not clearly understood. However, it is supposed to begin with the failure of extravillous trophoblast cells invasion into maternal spiral arteries.[2] This process causes placental hypoxia and triggers the increase in the lipid peroxidation, leukocyte activation and stimulation of proinflammatory cytokines. Activated leukocytes release several substances, which may affect vascular tone directly by contracting smooth muscle and indirectly by inactivating endothelium-derived relaxing factor.[3] Interactions among the activated leukocytes,[4] syncytiotrophoblast[5] microvillus membrane, platelets and vascular endothelium also contribute to the vascular injury in the pregnancy-associated hypertension disorder.[6]

Total leukocyte and leukocyte differential counts are well known inflammatory biomarkers. They have prognostic value for several inflammatory conditions.[7] Mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) could be obtained from simplifying a complete blood count (CBC). CBC parameters as well as several acute phase reactants[8] and activated innate immune cells[9–12] have been studied in patients with PE for the prediction of disease severity and this contributes towards the understanding of the pathogenesis of PE.

Serious complications of preeclampsia including maternal, neonatal mortality are related with severity of disease. Prediction of severe preeclampsia at the first admission with an easily accessible method would optimize both the management of women with preeclampsia and the use of resources and reduce the poor consequences of disease. In this study, we aimed to investigate the predictive power of leukocyte, leukocyte differentials count, NLR and PLR levels for severe preeclampsia.

Methods

The study was designed as a retrospective, descriptive, cross-sectional study. The study population included 72 healthy pregnant women (control group) and 114 women with PE (preeclampsia group) admitted to the obstetrics ward at our hospital.

Patient with PE were further categorized into severe group (n=41) and without severe clinical features (mild PE) group (n=73), based on the severity of the clinical symptoms. Women who had diabetes mellitus, gestational diabetes, coagulation disorders, renal diseases, chronic hypertension, vascular complications and any fetal malformations were excluded from this study. The Institution's medical ethics committee approved the study protocols.

The diagnosis of PE was established according to the guidelines of the American Congress of Obstetricians and Gynecologists (ACOG) (2013).[13] High blood pressure was defined as systolic blood pressure (SBP) ≥140 mmHg and/ or diastolic blood pressure (DBP) ≥90 mmHg on at least two measurements at least 4 hours apart. Proteinuria was defined as a dipstick reading ≥1+. According to the guidelines of ACOG, severe PE was defined as SBP ≥160 mmHg or DBP ≥110 mmHg, thrombocytopenia (platelet count <100,000/μL), renal insufficiency (serum creatinine concentration >1.1 mg/dL), impaired liver function (elevated liver enzymes to twice of normal concentration, associated with epigastric or right upper-quadrant pain), pulmonary edema, new-onset cerebral or visual disturbance.

After admission to the hospital, close monitoring of the women with PE was performed with serial assessment of maternal symptoms and fetal movement along with serial measurements of blood pressure (BP). Women with PE having a persistent BP levels of 150 mmHg systolic or 100 mmHg diastolic or both were treated with antihypertensive medications. The intrapartum-postpartum regimen of magnesium sulphate was started in women with severe PE to prevent the development of eclampsia.

Maternal age, gestational age, laboratory findings such as CBC, aspartate transaminase (AST) and alanine transaminase (ALT) levels and the level of urinary protein with dipstick at the time of admission were obtained from patients' medical records. Urinary protein was tested using a urine dipstick. Detectable urinary protein was defined as >1+ by dipstick and recorded as its folds. Neonatal outcomes were defined as Apgar scores at the 1st–5th min of life, birth weight, need for admission to neonatal intensive care unit (NICU) and neonatal death.

All blood samples were drawn from a brachial vein into sterile EDTA tubes. CBC was automatically analyzed (with ABBOT CELL-DYN 3700 blood count equipment) within 30 min. The number of leukocytes (1000/μL) and its differentials as neutrophils (1000/μL), lymphocytes (1000/μL) and monocytes (1000/μL) and platelets (1000/μL) were recorded. NLR and PLR were calculated using these parameters. Hemoglobin levels (g/dL) and MPV obtained from the patient's whole blood count were also recorded.

Statistical analyses were performed using R Statistical Software (www.r-project.org) a free software environment for statistical computing and graphics. Baseline characteristics of the groups were presented as median, interquartile range (IQR), minimum and maximum values. The Shapiro-Wilk's test, boxplots, PP and QQ plots were used to analyze the data distribution. Baseline characteristics, age, clinical and laboratory variables excluding spot urine proteinuria were compared by Kruskal-Wallis test and the associated p values were given. Dunn's multiple comparison test was used after significant Kruskal-Wallis tests. Dunn's test function in FAS package of R statistical program is used for multiple comparisons. The p-values adjusted with Holm correction were given. Spot urine proteinuria between mild and severe preeclampsia groups was compared using Mann-Whitney U test.

Correlations of proteinuria and leukocyte, neutrophil, MPV, PLR NLR were assessed by Spearman's rank correlation test. The association between stages of preeclampsia and admission to NICU and perinatal mortality were tested using Fisher's exact test. Receiver operating curve (ROC) analyses were construed to evaluate diagnostic performances and to determine the optimal cut-off values for leukocyte and neutrophil biomarkers in preeclampsia patients. Youden's index (maximum sensitivity + specificity – 1) was used as an optimization criterion for cut-off values. The area under the receiver operating characteristic (ROC) curves was used to assess the discriminative ability of leukocyte and neutrophil for severe preeclampsia. Epi and verification packages were used for ROC curve estimations. The p-value produced for AUC is related to the Mann-Whitney U statistics. For all analyses, the p-value of $p<0.05$ was considered statistically significant.

Results

There was no significant difference in maternal age across three groups. Significant differences were noticed in the severe PE group such as increase in systolic and diastolic BPs, AST, ALT and proteinuria levels, and also decrease in gestational age at delivery. **Table 1** shows the demographic and clinical data of study population and neonatal outcomes of the study groups.

The results for comparison of CBC parameters in normal pregnant controls and in women with mild and severe PE are presented in **Table 1**. Leukocyte count was found significantly different among the three groups. Severe PE group had the highest median leukocyte count (12,100×1000 /μL). Neutrophil and lymphocyte counts were found significantly different among the control and PE groups. There was a significant association at admission to NICU, perinatal mortality in group of PE (mild and severe) with p values of 0.031 and 0.028 respectively. Admission to NICU and mortality percentages were significantly higher for severe PE group than mild PE group. The significant differences in **Table 1** were followed with pairwise comparisons and results were also presented in **Table 2**.

In this study, logistic regression analysis was used to identify the risk factors for the presence of severe PE during hospital admission. We found that in the reduced model, total leukocyte count has a statistically significant relationship with severe PE at the time of admission to the hospital ($p<0.0001$).

We also analyzed the performance of CBC parameters, MPV, NLR, and PLR in predicting the severity of PE using ROC curves and comparing with AUC. An AUC of >0.7 was considered the minimum to indicate as adequately. The performance associated with these parameters were considered from fair ($0.5<AUC\leq0.7$) to good ($0.7<AUC\leq0.9$).

The total leukocyte count has a poor predictive value for severe PE with an AUC of 0.696 ($p=0.0001$); the sensitivity and specificity were 65.9% and 65.5%, respectively. The maximum sensitivity and specificity cut-off point was at 0.191 [pointed number of leukocytes= 10,890 (1000/μL)] (**Fig. 1**). The neutrophil count, MPV, NLR and PLR have very fair predictive values for severe PE with AUC of 0.632, 0.564, 0.534 and 0.588, respectively (**Fig. 2**).

Table 1. Characteristics of healthy pregnant, mild and severe preeclampsia groups.

		Healthy (n=72) Median (IQR)	Mild PE (n=73) Median (IQR)	Severe PE (n=41) Median (IQR)	p-value
Age, year		29.3 (8.25)	30 (9)	27.9 (9)	0.1747
Gestational age, week		39 (1)	37 (4)	34 (6)	<0.001*
SBP, mm Hg		110 (20)	160 (30)	160 (30)	<0.001*
DBP, mm Hg		70 (10)	100 (10)	100 (10)	<0.001*
ALT, U/L		10.5 (6.3)	14 (8)	15 (19)	<0.001*
AST, U/L		17.5 (7.9)	22 (11)	30 (17)	<0.001*
Spot urine protein (+)		(-)	2 (1)	3 (1)	<0.001*
Hemoglobin (g/dl)		11.5 (2.1)	12 (1.2)	12 (2)	0.066
Platelets (1×10³/µL)		200.5 (61.3)	214 (102)	201 (80)	0.218
Total leukocyte count (1×10³/µL)		9450 (2725)	11.450 (3900)	12.100 (5100)	<0.001*
Differential (1×10³/µL)	Neutrophils	6.9 (2.97)	8.1 (3.70)	8.3 (5.80)	<0.001*
	Lymphocytes	1.9 (0.53)	2 (1)	2.3 (1.4)	0.03
	Monocytes	0.6 (0.20)	0.6 (0.2)	0.6 (0.4)	0.368
MPV (fl)		8.85 (3.25)	10 (1.6)	10 (2)	0.064
NLR		3.7 (2.2)	3.72 (1.99)	3.94 (3.81)	0.689
PLR		106.3 (63.66)	102.9 (52.1)	98.2 (62.7)	0.19

Continuous variables were presented as median (IQR); categorical variables were presented as number (%). **ALT:** alanine transaminase; **AST:** aspartate transaminase; **DBP:** diastolic blood pressure; **IQR:** interquartile range; **MPV:** mean platelet volume; **NICU:** neonatal intensive care unit; **NLR:** neutrophil-lymphocyte ratio; **PE:** preeclampsia; **PLR:** platelet-lymphocyte ratio; **SBP:** systolic blood pressure. *p<0.05

Discussion

Early detection and prediction of severe PE has gathered the attention of many researchers who have aimed to protect the mother and the baby from the detrimental effects of PE. They have performed several studies using clinical and laboratory predictors.[10] The diagnostic value of CBC parameters has been emphasized in inflammatory diseases (i.e. diabetes mellitus, coronary artery disease, ulcerative colitis and cancers).[11] These parameters are also reported as sensitive markers of inflammation.[12] However, the correlation between the severity of PE and the several complete blood count parameters has continued to be debatable.

Table 2. Comparison of complete blood parameters among groups.

		Healthy (n=72) Median (IQR)	Mild PE (n=73) Median (IQR)	Severe PE (n=41) Median (IQR)	p-value
Hemoglobin (g/dl)		11.5 (2.1)	12 (1.2)	12 (2)	0.066
Platelets (1×10³/µL)		200.5 (61.3)	214 (102)	201 (80)	0.218
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	Lymphocytes	1.9 (0.53)	2 (1)	2.3 (1.4)	0.03
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PLR		106.3 (63.66)	102.9 (52.1)	98.2 (62.7)	0.19

IQR: interquartile range; **MPV:** mean platelet volume; **NLR:** neutrophil-lymphocyte ratio; **PLR:** platelet-lymphocyte ratio. *p<0.05

In this study, we aimed to investigate the relationship between CBC parameters and the severity of PE and to determine the predictive power of each parameter of CBC for predicting the severity of disease.[14] Our results showed that the leukocyte count was significantly increased in women with mild and severe PE compared with healthy pregnant control women. The leukocyte count for severe PE was significantly higher than that for mild PE. These findings support a study performed by Özdemirci et al. and Ozkaya et al., who reported leukocyte count above 16,000/μL is an independent predictor of severe PE.[15,16] In another study, it was reported that there were statistically increased leukocyte and neutrophil counts in healthy pregnant women and women with PE compared with non-pregnant women. But these parameters could not be considered specific for PE or normal pregnancy.[17]

Immune system is greatly affected by physiology of pregnancy and is mainly characterized by increasing activation of peripheral blood leukocytes.[18] Preeclamptic condition is an exacerbation of this situation due to the lack of maintenance of control pathways like membrane glutathione activity as observed in normal pregnancy. The other characteristics of systemic inflammation in PE are the lack of symmetry in distribution of T lymphocyte subgroups and predominance of Th1-type immunity. Furthermore, the placental hypoxia resulting from uteroplacental arterial invasion insufficiency triggers the release of inflammatory stimuli (i.e. lipid peroxidation, leukocyte activation and increase in proinflammatory cytokine production) into the maternal circulation and contributes to systemic inflammation in PE.[6,19]

In pregnant women, leukocytosis is mainly due to increase in the neutrophil count.[20] Increase in the cortisol level triggers the mobilization of the leukocyte pool, and increase in the concentration of granulocyte-macrophage colony stimulating factor may also contribute to the increase in white blood cell count.[21] We focused on the differential of total leukocyte count (i.e. neutrophil, lymphocyte and monocyte) and found that these leukocyte differentials were significantly increased in severe PE group as compared with healthy pregnant group. Especially there was a significant increase in neutrophil counts in severe PE compared with the control group. But, this increase was not observed in mild PE and severe PE groups. These results correlate with the study findings revealed by Canzoneri et al.[20] Another study has demonstrated that there was an increase in neutrophil activation and production of superoxide in PE compared to normal pregnancy, and emphasized that the products of this activation play an important role in giving rise to endothelial damage and dysfunction.[18]

We also compared the MPV, NLR and PLR between normal healthy pregnancy and preeclamptic pregnancy, but the results did not reveal any significant differences between these two groups. We found that the increase in leukocyte and neutrophil counts are associated with severity of PE. The predictive value of total leukocyte count among with PE neutrophil count, MPV, NLR and PLR were found uncorrelated for severe PE and Mihu et al. have reported significant increase in leukocyte and neutrophil count in PE pregnancy and also emphasized that these parameters were

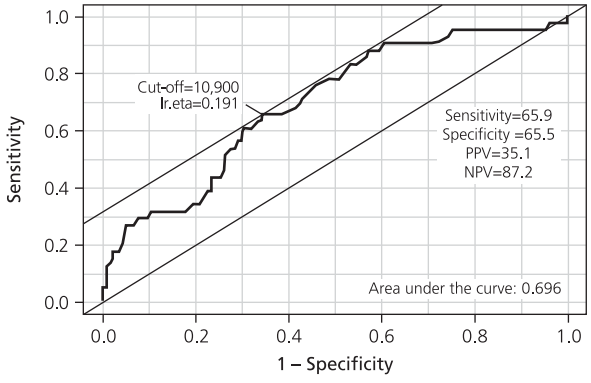

Fig. 1. ROC curve to predict severe preeclampsia based on leukocyte.

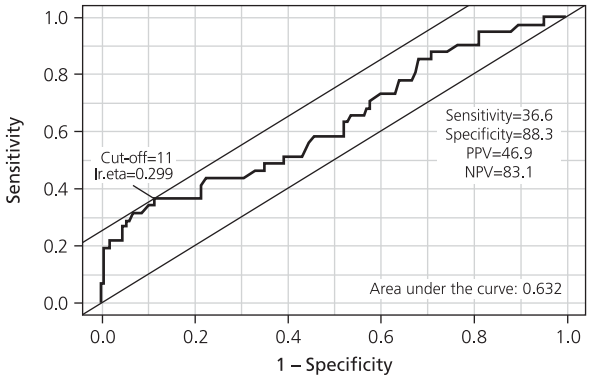

Fig. 2. ROC curve to predict severe preeclampsia based on maternal blood neutrophil count.

not specific for the preeclamptic women.[17] In several studies, NLR was reported to be significantly higher in PE than healthy pregnant women.[10,11,19,21,22] On the other hand, opposite results were noticed about using of NLR as a marker to predict the severity of PE.[10,11,23]

The relation between MPV and severity of PE is another debatable issue. In our study, there were no significant differences in the PE subgroups as compared with the healthy pregnant group. Some previous reports have claimed similar results as our study that PE does not affect MPV.[22,24–26] Yavuzcan et al. have reported that there is no statistically significant difference between the PE group and control group in terms of MPV and PLR.[22] Toptas et al. noticed that NLR and PLR are not significantly changed between these groups.[24] However, Ozdemirci et al., reported that MPV was higher in the PE group as compared with the control subgroups[15] and could be used as a predictive marker for severe PE.

Regarding neonatal status at birth, we found that gestational age, birth weight and Apgar score were significantly lower in severe PE group compared to mild PE and healthy pregnant groups. But, we did not compare these three groups in terms of NICU admission and neonatal mortality due to missing data in healthy pregnant group. However, these parameters were found significantly higher in severe PE group than in mild PE group. We found the demographic data correlated with the literature[27] and neonatal outcomes also correlated with the reviewed literature.[28,29]

Conclusion

In conclusion, the idea that CBC can predict the inflammatory state and severity of PE is extremely attractive but lacks in reproducibility and validity. Further studies are needed to find powerful predictive parameters for severity of PE to reduce maternal and neonatal morbidity and mortality.

Conflicts of Interest: No conflicts declared.

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