Mean Platelet Volume and Neutrophil Lymphocyte Ratio as New Markers of Preeclampsia Severity

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ABSTRACT

Introduction: This study was undertaken to examine the role of hematological parameters in predicting the severity of hypertension in pre-eclamptic women.

Patients and Methods: Two hundred sixty-one pre-eclamptic women and fifty-one women with normal pregnancy were included in the study. The severity of preeclampsia was classified as mild or severe.

Results: Compared to post-delivery period, pre-eclamptic females had lower platelet count, raised mean platelet volume and raised neutrophil lymphocyte ratio ($p< 0.001$, $p< 0.001$, $p< 0.001$, respectively). Multiple linear regression analysis showed an independent correlation between the severity of hypertension and mean platelet volume as well as the neutrophil lymphocyte ratio ($\beta= 0.25$, $p< 0.001$; $\beta= 0.31$, $p< 0.001$, respectively).

Conclusion: Both mean platelet volume and neutrophil lymphocyte ratio emerged as independent predictors of the severity of hypertension in preeclampsia.

Key Words: Preeclampsia; mean platelet volume; neutrophil lymphocyte ratio; hypertension

Ortalama Trombosit Hacmi ve Nötrofil Lenfosit Oranı: Preeklampsinin Ciddiyetinin Yeni Belirteçleri

ÖZET

Giriş: Bu çalışmada, hematolojik parametrelerin ölçümleri ile preeklamptik kadınlarda hipertansiyon şiddetini tahmin etmenin mümkün olup olmadığını araştırdık.

Hastalar ve Yöntem: İki yüz altmış bir preeklamptik ve 51 normal gebe kadın çalışmaya alındı. Preeklampsi olguları hafif ve ağır preeklampsi olarak sınıflandırıldı.

Bulgular: Doğum sonrası sonuçlar karşılaştırıldığında, preeklamptik kadınların trombosit sayıları düşük, ortalama trombosit hacimleri ve nötrofil lenfosit oranları yüksekti (sırasıyla; $p< 0.001$, $p< 0.001$ ve $p< 0.001$). Çoklu lineer regresyon analizinde, ortalama trombosit hacmi ve nötrofil lenfosit oranı hipertansiyon şiddeti ile bağımsız bir şekilde korelasyon gösterdi (sırasıyla; $\beta= 0.25$, $p< 0.001$ ve $\beta= 0.31$, $p< 0.001$).

Sonuç: Hem ortalama trombosit hacmi hemde nötrofil lenfosit oranı preeklamptik gebelerde hipertansiyonun şiddetini öngörmede bağımsız birer belirleyici olarak kullanılabilir.

Anahtar Kelimeler: Preeklampsi; ortalama trombosit hacmi; nötrofil lenfosit oranı; hipertansiyon

INTRODUCTION

Preeclampsia (PE), a complication occurring in the second or third trimester of pregnancy, affects approximately 7-10% of pregnant women. This condition characterized by the development of hypertension (HT) may lead to maternal and fetal adverse consequences[1,2]. Major pathophysiological processes include the alterations in hemostatic system, such as the endothelial cell damage, platelet activation and enhanced intravascular thrombin generation[3]. Also, increased platelet size is common in preeclampsia and other pathophysiological changes are generally preceded by a fall in the platelet count[4,5]. Similarly, association exists between the platelet density and reactivity, such that high-density platelets are more reactive than low-density platelets[6].

Despite previous studies showing an association between hematological parameters and PE, the relationship between the severity of hypertension and hematologic parameters in preeclamptic women has not been thoroughly studied[7,8].

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This study was undertaken to investigate the relationship between the severity of hypertension (HT) and hematologic parameters in preeclamptic women that can be measured by a simple complete blood count.

PATIENTS and METHODS

This study was conducted with the inclusion of consecutive patients who were followed up for newly diagnosed PE at Dicle University Medical Faculty Hospital between May 2006 and May 2013. Preeclampsia was defined as the new onset of hypertension characterized by systolic blood pressure ≥ 140 mmHg or diastolic ≥ 90 mmHg at bed rest on at least two occasions 6 hours apart, combined with proteinuria ≥ 0.3 gr/24 hour, after the 20th week of pregnancy. A random urine protein determination of 30 mg/dL or 1 + on dipstick was considered suggestive of, but not diagnostic for pre-eclampsia.

Patients were categorized as those with mild or severe PE. Preeclampsia was considered severe if any of the following criteria was met: systolic blood pressure ≥ 160 mmHg or diastolic ≥ 110 mmHg, or proteinuria ≥ 5 g/24 h (or ≥ 3 + on dipstick). Control group (n= 51) comprised women with non-preeclamptic healthy pregnancies. Patients with diabetes mellitus, history of hypertension, renal disorder, chronic systemic disease, placenta previa, abruptio placenta, polyhydramnios, multiple pregnancy, major fetal anomaly, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), and maternal or fetal infection were excluded from the study.

Automated blood counter Cell-Dyn 4000 (Abbott Diagnostics, Santa Clara, CA, USA) was used to measure the complete blood count parameters. Biochemical parameters were determined by Abbott Architect c16000 (Abbott Park, Illinois, USA) chemistry analyzer. The study has been carried out in accordance with the Declaration of Helsinki (2008) of the World Medical Association and approved by the Ethics Committee of Dicle University Medical Faculty.

Statistical Analysis

All data collected were stored in a computerized database. To evaluate the differences between the two groups, "t test: two sample-test assuming different variances" was used. The Pearson correlation test was used to determine the correlations between the parameters tested. Independent relationships between the severity of HT and hematological parameters were assessed by backward stepwise multiple linear regression analysis, through the inclusion of the parameters associated with severity of HT in bivariate analysis. Standardized β regression coefficients and their significance from multiple linear regression analysis were reported. The SPSS 13.0 computer program was used for statistical analyses. A p value less than 0.05 was considered statistically significant.

RESULTS

The result of hematological parameters tested in patient and control groups are presented as mean ± SD values in tables. A total of 312 women met the study inclusion criteria. Demographic characteristics and the results of biochemical parameters are shown in Table 1. Patients with mild or severe PE were not significantly different from controls in terms of age, number of pregnancies, and biochemical test results, while the difference in blood pressure was significant (p< 0.001).

The results for complete blood count are summarized in Table 2. There were no significant differences in red blood cell (RBC), hemoglobin, hematocrit, red cell distribution width, mean cell volume, mean cell hemoglobin and mean cell hemoglobin concentration between the three groups. However, white blood

Table 1. Demographic characteristics and biochemical parameters among the patients

	Control (n= 51)	Mild PE (n= 151)	Severe PE (n= 110)
Age (years)	30 ± 7	31.5 ± 7	31.7 ± 7
NP (n)	4 ± 2.7	4.4 ± 3.2	4.6 ± 3.2
BP (mmHg)	115 ± 5 / 75 ± 5	145 ± 7 / 90 ± 3*	158 ± 13 / 102 ± 5*,**
Glucose (mg/dL)	82 ± 43	89 ± 29	92 ± 34
BUN (mg/dL)	22 ± 9	21 ± 10	23 ± 9
Kreatin (mg/dL)	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.1
AST (U/L)	30 ± 18	34 ± 21	42 ± 30
ALT (U/L)	25 ± 12	29 ± 16	31 ± 22
LDH (U/L)	321 ± 88	344 ± 112	375 ± 134
T. Bilirubin (mg/dL)	0.4 ± 0.1	0.5 ± 0.3	0.6 ± 0.3
T. Protein (g/dL)	6.8 ± 2.5	6.4 ± 3.3	6.5 ± 3.3
Albumin (g/dL)	2.4 ± 0.4	2.4 ± 0.3	2.3 ± 0.4

NP: Number of pregnancies, BP: Blood pressure, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, BUN: Blood urea nitrogen, PE: Preeclampsia.
Values are expressed as numbers of subjects, percentages, and means ± SD *p< 0.001 vs. control group; **p< 0.001 vs. Mild PE.

Table 2. Complete blood count in patient and control groups

	Control (n= 51)	Mild PE (n= 151)	Severe PE (n= 110)
WBC ($\times 10^9$/L)	9.7 ± 3	12.5 ± 3.5*	12.7 ± 3.6*
RBC ($\times 10^{12}$/L)	4.3 ± 0.5	4.1 ± 0.5	4.1 ± 0.6
Haemoglobin (g/dL)	12 ± 1.4	11.5 ± 1.8	11.3 ± 1.7
Haematocrit (%)	35 ± 4	34 ± 5	34 ± 5
PLT ($\times 10^9$/L)	262 ± 67	237 ± 79*	213 ± 76*,**
RDW (%)	17.3 ± 2.9	17.8 ± 2.5	17.7 ± 2.8
MCV (fL)	85.7 ± 7	84.4 ± 7.3	83.5 ± 7
MCH (pg)	28.5 ± 2.8	28 ± 3	28 ± 2.8
MCHC (g/dL)	33.2 ± 1.5	33.1 ± 1.3	33.3 ± 1.1
MPV (fL)	7.5 ± 0.5	8.5 ± 1.5*	9.2 ± 1.5*,**
Neu (%)	61.8 ± 5	77.6 ± 9*	80.5 ± 8*,**
Lym (%)	29.3 ± 4	17.1 ± 8*	15.5 ± 7*,**
Neu/Lym	4.5 ± 1.5	6.2 ± 4*	7.5 ± 5*,**

WBC: White blood cell count, RBC: Red blood cell count, PLT: Platelet count, RDW: Red cell distribution width, MCV: Mean cell volume, MCH: Mean cell hemoglobin, MCHC: Mean cell hemoglobin concentration, MPV: Mean platelet volume, Neu: Neutrophil count, Lym: Lymphocyte count, Neu/Lym: Neutrophil lymphocyte ratio, PE: Preeclampsia.
Values are expressed as numbers of subjects, percent ages, and means ± SD *p< 0.001 vs. control group; **p< 0.01 vs. Mild PE.

cell count (WBC), mean platelet volume (MPV), neutrophil count and neutrophil lymphocyte ratio (NLR) were significantly higher in mild and severe PE groups than in controls (p< 0.001, p< 0.001, p< 0.001, and p< 0.001, respectively) in addition to a significantly lower platelet and lymphocyte counts among mild or severe PE patents (p< 0.001, p< 0.001, respectively). In addition, the platelet and lymphocyte counts were significantly lower (p< 0.01, p< 0.01, respectively), and MPV, neutrophil count, and NLR were significantly higher among severe PE patients in comparison with patients with mild PE (p< 0.01, p< 0.01, p< 0.01, respectively). For the overall group of pregnant women, correlations were observed between systolic blood pressure and age, number of pregnancies, total protein, WBC, RBC, hemoglobin, platelet count, MPV, neutrophil count, lymphocyte count, and NLR [r= 0.17, p< 0.01; r= 0.12, p< 0.05; r= -0.14, p< 0.01; r= 0.19, p< 0.001; r= -0.12, p< 0.01; r= -0.12, p< 0.01; r= -0.20, p< 0.001; r= 0.30, p< 0.001; r= 0.46, p< 0.001; r= -0.46, p< 0.001; r= 0.21, p< 0.001, respectively]. Similarly, the diastolic blood pressure correlated with glucose, total protein, WBC, platelet count, MPV, neutrophil count, lymphocyte count and NLR [r=0.11, p< 0.05; r= -0.11, p< 0.05; r= 0.23, p< 0.001; r= -0.21, p< 0.001; r= 0.30, p< 0.001; r= 0.44, p< 0.001; r= -0.44, p< 0.001; r= 0.18, p< 0.001, respectively] (Table 3).

Multiple linear regression analysis showed an independent correlation between the severity of hypertension and MPV as well as the NLR [β = 0.25, p< 0.001; β= 0.65, p< 0.001; β= -0.71, P< 0.001; β= 0.31, p< 0.001, respectively] (Table 3).

DISCUSSION

To the best of our knowledge, this is the first report in the literature to evaluate the association between the severity of PE and hematologic parameters in preeclamptic patients. The main findings of this study suggest that (i) MPV increases with the severity of PE, (ii) neutrophil count increases, but lymphocyte count decreases with the severity of PE (iii) NLR increases with the severity of PE, (iv) and also these exhibit an independent correlation with the severity of PE (Figure 1).

Increased platelet activity is associated with increased platelet volume. Large platelets that contain more dense granules are metabolically and enzymatically more active than small platelets[9].

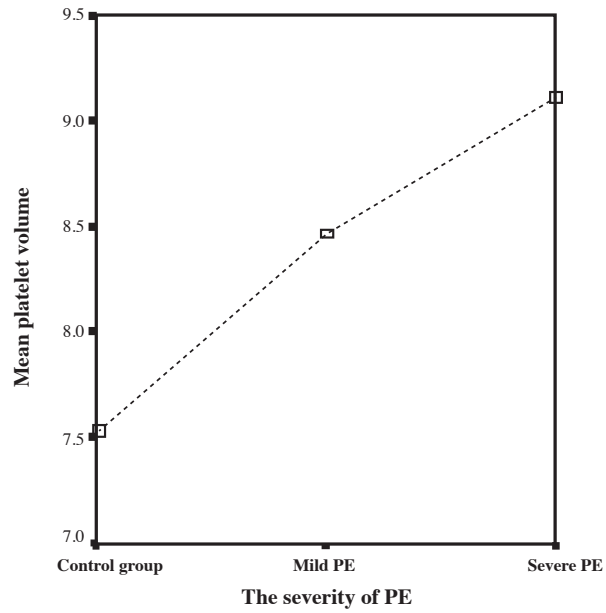

Figure 1. Association between the severity of PE and mean platelet volume.

Table 3. Pearson correlation and linear regression analysis

	Pearson's correlation coefficient (Systol)	Pearson's correlation coefficient (Diastol)	Standardized β regression coefficients
Age (years)	0.17**	0.06	
NP (n)	0.12*	0.04	
Glucose (mg/dL)	0.05	0.11*	
BUN (mg/dL)	0.07	0.08	
Kreatin (mg/dL)	0.004	0.03	
AST (U/L)	0.04	0.06	
ALT (U/L)	0.02	0.03	
LDH (U/L)	0.09	0.09	
T.Bilirubin (mg/dL)	0.06	0.06	
T.Protein (g/dL)	-0.14**	-0.11*	
Albumin (g/dL)	-0.11	-0.10	
WBC ($\times 10^9$/L)	0.19***	0.23***	
RBC ($\times 10^{12}$/L)	-0.12*	-0.05	
Haemoglobin (g/dL)	-0.12*	-0.03	
Haematocrit (%)	-0.10	-0.05	
PTL ($\times 10^9$/L)	-0.20***	-0.21***	
RDW (%)	0.073	-0.003	
MCV (fL)	-0.09	-0.09	
MCH (pg)	-0.08	-0.03	
MCHC(g/dL)	0.02	-0.09	
MPV (fL)	0.30***	0.30***	0.25***
Neu(%)	0.46***	0.44***	0.65***
Lym(%)	-0.46***	-0.44***	-0.71 ***
Neu/Lym	0.21***	0.18***	0.31***

NP: Number of pregnancies, BP: Blood pressure, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, BUN: Blood urea nitrogen, WBC: White blood cell, RBC: Red blood cell, PLT: Platelet count, RDW: Red cell distribution width, MCV: Mean cell volume, MCH: Mean cell hemoglobin, MCHC: Mean Cell hemoglobin concentration, MPV: Mean platelet volume, Neu: Neutrophil count, Lym: Lymphocyte count, Neu/Lym: Neutrophil lymphocyte ratio, HT: Hypertension. *p< 0.05, **p< 0.01, ***p< 0.001.

MPV, a determinant of platelet activation, has been recognized as an independent risk factor in HT and PE[8,10,11]. Impaired platelet activation, both in the form of decreased platelet count and increased MPV, were associated with severity of HT in patients with PE in our study. Similar to our observations, Dundar et al. and Jaremo et al. reported a significant relationship between MPV and PE[7,8]. Although the rapid turnover of platelets has been put forward as an explanation for this decrease in platelet count and increase in MPV, that study had a small sample size and did not investigate NLR.

Walker et al. found no significant differences in this regard among a group of pregnant women developing HT who were categorized into three groups based on the diastolic blood pressure value, while they observed a significant increase in MPV at least 1 week before HT became clinically apparent[12]. Makuyana et al. observed no significant differences with respect to hematological parameters in 38 preeclamptic and 72 non-preeclamptic women[13]. Ceyhan et al. reported comparable platelet counts and MPV among 56 preeclamptic, 8 severe pre-eclamptic, and 43 control subjects. However, in that study sample size was small and NLR was not investigated[14].

The normally observed activation in maternal circulating neutrophils in pregnancy is more marked in patients with PE[15-17], probably due to elevated plasma levels of arachidonic acid in preeclamptic women[18,19]. In our study, neutrophil count was also higher among patients with PE than among controls. Similarly, Bartl et al. observed a decrease in total lymphocyte count with increasing severity of PE[20].

Several previous studies also suggested that NLR may be utilized as a marker of mortality in cancer patients[21,22]. Also in pre-eclamptic pregnancies, alterations in the function of neutrophils and lymphocyte are common. However, to our knowledge, no previous studies have examined the NLR in PE. The results of our study suggest that the increase in NLR

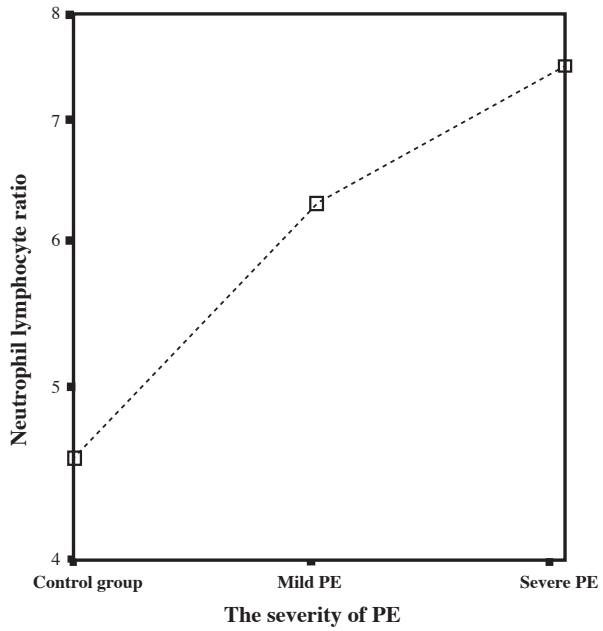

Figure 2. Association between the severity of PE and neutrophil lymphocyte ratio.

with increasing severity of HT may represent an independent predictor for the severity of HT (Figure 2).

The main limitations of the present study reside in its retrospective nature, as well as its single-center design and limited demographic data.

In conclusion, MPV and NLR are independent predictors of severity of hypertension in PE patients. Further prospective, multicenter studies are warranted to better define the association of the NLR and MPV with PE.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTORSHIP CONTRIBUTIONS

Concept/Design: MAA, MB, Yİ
Analysis/Interpretation: MAA, MA, HK, FE, SA
Data acquisition: HA, SYT, MA
Writing: MAA, HA, HK
Critical revision: MAA, FE, Yİ, MB, ST, MA, SA
Final approval: All of Authors

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