



## The role of platelet mass index in the prediction of preeclampsia full

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### Abstract

To assess the possible roles of platelet indices including platelet mass index (PMI), platelet count (PC), mean platelet volume (MPV) and PC/MPV in prediction of preeclampsia. 190 pregnant women diagnosed with preeclampsia and 100 healthy uncomplicated control patients were included in this retrospective study. Age, gestational week, fetal weight, alanine transaminase (ALT), aspartate transaminase (AST), creatinine, blood urea nitrogen (BUN), complete blood count parameters and platelet indices were compared. ROC curve was applied to analyze the cut-off values of the significantly differing parameters for prediction of preeclampsia. Preeclamptic patients gave birth significantly earlier than the controls. In preeclamptic patients, the mean values of PC, PC / MPV and PMI were significantly lower than the control group. Although mean MPV values were lower in preeclampsia patients, the difference was not significant. The cut-off values of PC, PC/MPV and PMI were found to be 207,500, 18448.16 and 2411.75 with a-sensitivity/specificity of 45.3%/ 44.3%, 42.2%/ 42.6% and 44.1%/ 44.3%, respectively. Indices such as PC, PC / MPV and PMI changed significantly in preeclampsia. Although they have low sensitivity and specificity, these indices can be combined with other parameters and used in the prediction of preeclampsia.

**Keywords:** mean platelet volume, platelet indices, platelet mass index, preeclampsia

### 1. Introduction

Preeclampsia is defined as the presence of systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure and proteinuria 300 mg or more per 24-hour urine collection (or this amount extrapolated from a timed collection) or protein/creatinine ratio of 0.3 mg/dL or more or dipstick reading of 2+ (used only if other quantitative methods not available) (1). In the absence of proteinuria, new-onset hypertension with the new onset of any of the following; Thrombocytopenia: Platelet count less than 100,000  $10^9/L$ ; Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal diseases; Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration; Pulmonary edema; New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms (2). Approximately 3% to 8% of pregnancies are complicated by preeclampsia and preeclampsia causes a significant increase in maternal and fetal complications in these pregnancies (between 14-53 % and 22-92 %, respectively) (3). Approximately 7% of patients who have preeclampsia in their current pregnancy also have preeclampsia in their later pregnancy (4). Although the exact pathophysiology of preeclampsia is not known, inadequate invasion of

trophoblasts into the maternal placental vascular bed and as a result the decreased placental blood flow have been accused (5). Inadequate placental invasion causes perfusion deficiency and increased maternal endothelial dysfunction and maternal endothelial dysfunction also causes intravascular coagulation resulting in platelet consumption. In these patients, the production of new platelets begins in the bone marrow to compensate for platelet consumption (6). As the severity of preeclampsia increases, it further increases platelet consumption (7). For this reason, some indices used to measure platelet numbers and functions are used in the estimation of preeclampsia severity. Platelet count (PC), mean platelet volume (MPV), platelet count/mean platelet volume (PC/MPV), and platelet count x mean platelet count/ $10^3$  (platelet mass index [PMI]) can be used for preeclampsia prediction (8). From these indices, PC and MPV have been investigated before for association with preeclampsia (9,10). In some studies, high MPV value was detected due to new platelets are produced in the bone marrow in bleeding-related platelet consumption and, instead of this, low MPV value was detected in diseases that progress with thrombocytopenia related increased destruction (11). The MPV value of young platelets arising from the bone marrow is high and these platelets form better hemostatic plugs (12). This study aimed to assess these platelet indices in preeclampsia including PMI which has not been assessed in this disease before and to

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investigate the possible roles in the prediction of preeclampsia.

## 2. Materials and Methods

The study was conducted retrospectively by reviewing the files of 190 pregnant women with preeclampsia and 100 control patients hospitalized between 2012 and 2020 in the Mersin University Faculty of Medicine Obstetrics and Gynecology Department. This retrospective case-control study was approved by the hospital ethics committee on 08/07/2020 with an approval number of 2020/491. Patients with proteinuria (>1 positive in spot urine or > 300 mg protein in 24-hour-urine) and systolic blood pressure  $\geq$  140 mm Hg or diastolic blood pressure  $\geq$  90 mm Hg measured every 6 hours after 20 weeks of pregnancy were accepted as “preeclamptic” and included in the study. Control patients were included from pregnant patients who were admitted to the service during the same period with similar age, body mass index (BMI), and gestational weeks without preeclampsia. Patients who have chronic hypertension, hyper/hypothyroidism, diabetes mellitus, chronic liver/renal/hematological disease, multiple pregnancies, or who suffered from PE during their previous pregnancies were excluded. Age, gestational week, fetal weight, alanine transaminase (ALT), aspartate transaminase (AST), creatinine, blood urea nitrogen (BUN), and complete blood count parameters and platelet indices of the patients were compared.

IBM SPSS version 22.0 statistics program was used to analyze the data. Before statistical analysis, all variables were checked for normality. Mean values were compared using Independent Samples T-Test and Mann-Whitney-U-Tests. ROC curve was applied to platelet indices that differed significantly. In the ROC curve, threshold values and specificity and sensitivity of these values were detected for preeclampsia prediction. P-values less than 0.05 ( $P < 0.05$ ) were accepted as significant.

## 3. Results

290 pregnant women were enrolled in the study; 190 preeclamptic patients and 100 age-gravida and BMI matched healthy pregnant control patients. Preeclamptic patients gave birth significantly earlier than the control patients (35 weeks vs 38 weeks,  $p=0.002$ ). WBC count, absolute neutrophil count, ALT, AST, BUN, and creatinine levels of preeclamptic patients were significantly higher than the control group. In preeclamptic patients, the mean values of PC, PC / MPV, and PMI were significantly lower than the control group. Although mean MPV values were lower in preeclampsia patients, the difference was not significant ( $10.99 \pm 2.34$  vs  $11.12 \pm 1.17$ , respectively,  $p=0.19$ ) (Table 1). ROC curve was applied to analyze the PC, PMI and PC / MPV levels that are significantly different in preeclampsia patients compared to the control group (Fig. 1).

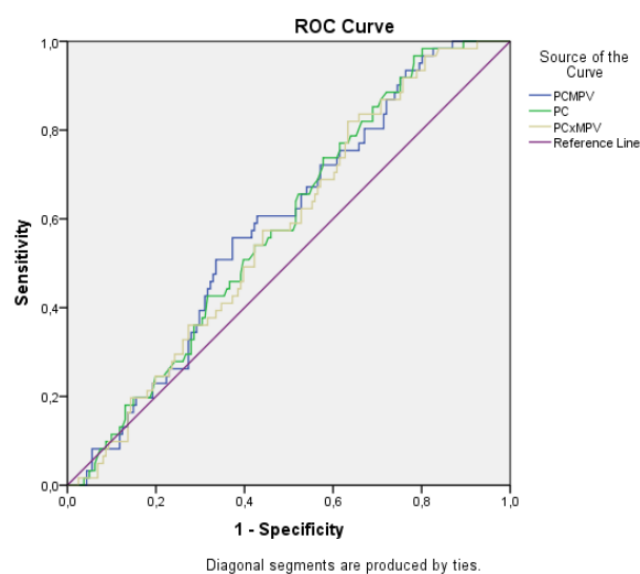


Fig 1. ROC curve of platelet indices in patients with preeclampsia

Table 1. Clinical and biochemical analyses of preeclampsia and control patients

	Preeclampsia patients (N=190)	Control Patients (N=100)	p
Age (year)	31.1 $\pm$ 6.1	29.9 $\pm$ 5.8	0.20
Gravida	3 (1-8)	2 (1-5)	0.119
Body Mass Index (BMI)	26.57 $\pm$ 2.91	27.86 $\pm$ 3.23	0.105
Birth week	35 $\pm$ 3	38 $\pm$ 1	<b>0.002*</b>
WBC ( $10^3/\mu\text{L}$ )	11.741 $\pm$ 3.655	9.971 $\pm$ 2.318	<b>0.001*</b>
Absolute neutrophil count ( $10^3/\mu\text{L}$ )	9.163 $\pm$ 6.106	7.210 $\pm$ 1.689	<b>0.001*</b>
Absolute monocyte count ( $10^3/\mu\text{L}$ )	705 $\pm$ 345	703 $\pm$ 163	0.39
Absolute lymphocyte count ( $10^3/\mu\text{L}$ )	2.044 $\pm$ 1.074	2.071 $\pm$ 538	0.17
Haematocrit (%)	34.9 $\pm$ 4.2	34.7 $\pm$ 3	0.81
Hemoglobin (g/dL)	11.8 $\pm$ 1.5	11.8 $\pm$ 1.2	0.83
ALT (U/L)	45 $\pm$ 80	13 $\pm$ 5.5	<b>0.001*</b>
AST (U/L)	70 $\pm$ 124	17.8 $\pm$ 5.3	<b>0.001*</b>
Blood urea nitrogen(BUN) (mg/dL)	25.3 $\pm$ 12	14.5 $\pm$ 3.8	<b>0.001*</b>
Creatinine (mg/dL)	0.68 $\pm$ 0.23	0.46 $\pm$ 0.08	<b>0.001*</b>
MPV (fL)	10.99 $\pm$ 2.34	11.12 $\pm$ 1.17	0.19
PC ( $10^3/\mu\text{L}$ )	206.500 $\pm$ 96.485	222.639 $\pm$ 60.992	<b>0.03*</b>
PMI	2248.4 $\pm$ 1.105.7	2449.6 $\pm$ 603.2	<b>0.04*</b>
PC/MPV	18894 $\pm$ 9.735	20.434 $\pm$ 6.740	<b>0.04*</b>

Independent Samples T Test and Mann-Whitney-U-Tests. \*  $p < 0.05$ . N-Number of Patients. m $\pm$ SD: mean  $\pm$  standard deviation. WBC: White Blood Cells. ALT: Alanine transaminase. AST: Aspartate transaminase. MVP: mean platelet volume. PC: Platelet count. PMI: Platelet Mass Index. PC/MPV: Platelet count / mean platelet volume

**Table 2.** Threshold values of platelet indices in the prediction of preeclampsia and sensitivity and specificity of these threshold values

	Threshold Value	Sensitivity	Specificity	AUC±SE	95% Confidence Interval		P
					Lower Bound	Upper Bound	
<b>PC (10<sup>3</sup>/μL)</b>	207,500	45.3%	44.3%	0.59±0.04	0.51	0.66	<b>0.038*</b>
<b>PMI</b>	2411.75	44.1%	44.3%	0.59±0.04	0.51	0.66	<b>0.045*</b>
<b>PC/MPV</b>	18448.16	42.2%	42.6%	0.59±0.04	0.51	0.67	<b>0.043*</b>

ROC test was applied\* p<0.05 AUC-Area Under the Curve. SE: Standard error. Platelet count-PC. platelet count x mean platelet volume-PMI. Platelet count/mean platelet volume-PC/MPV

The sensitivity and specificity of PC, PMI and PC / MPV to predict preeclampsia are shown in table 2 with ROC curve. Accordingly, it was determined that certain threshold values of these three parameters could predict preeclampsia with low sensitivity and specificity [(PC 45.3 % sensitivity, 44.3 % specificity (AUC: 0,59; 95%CI 0,51-0,66; p=0,038), PMI 44.1 % sensitivity, 44.3 % specificity (AUC: 0,59; 95 % CI 0,51-0,66; p=0,045), PC/MPV 42.2 % sensitivity, 42.6 % specificity (AUC: 0,59; 95 % CI 0,51-0,67; p=0,043)] (Table 2).

#### 4. Discussion

In preeclampsia the trophoblastic invasion of the myometrial arterioles is inadequate and as a result, maternal endothelial dysfunction occurs. Damaged endothelial cells stimulate clotting factors, which causes platelets to migrate to these regions. Migrating platelets also stimulate clotting factors. A vicious circle develops as this stimulus continues from the damaged endothelial cells. Disseminated intravascular coagulation develops for this reason (13). Platelet destruction in the intravascular environment causes a stimulus for the production of new and young platelets in the bone marrow. Studies are indicating that these young platelets will be larger and MPV values will be higher (13-16). In some other studies, it was found that consumption was higher than production (low PC), but the MPV value of the new platelets formed was normal (9,10,14,17). In the present study, although the PC was significantly lower, MPV was not found to be significantly different than the control group.

There may be some possible causes for the different results found in the literature regarding MPV values in preeclamptic patients (14). First, there are differences in the methods for collecting the blood specimen. As an example adding EDTA to the hemogram tube increases MPV. Secondly using different hematological cell counters may result in different results (18). Thirdly MPV values change throughout the gestational weeks and ignoring gestational weeks may result in different results. Finally, comorbid diseases accompanying preeclampsia such as diabetes mellitus which itself increases MPV should be considered. Therefore these results indicate that MPV values are not always significantly higher in preeclamptic patients and it cannot be a reliable predictor of preeclampsia (18).

In patients with preeclampsia, an increase in platelet consumption due to endothelial damage and a decrease in PC / MPV index with newly produced platelets are expected. In a study by Freitas et al. PC was found to be lower in patients with

preeclampsia than in the control group (19). In another study, Doğan et al found that not only PC but also PC / MPV values were lower in preeclampsia cases than in the control group (15). Yavuzcan et al did not find any difference between pregnant women with preeclampsia, pregnant women without preeclampsia, and non-pregnant women in their study. However, in another study by Yavuzcan et al., it was concluded that PC and PC / MVP may predict preeclampsia (18,20). Von Dadelszen et al suggested that the MVP / PC ratio reflects platelet consumption and can be used as a weak indicator of maternal progression in preeclamptic cases (21). In another study, Altınbaş et al did not find a significant relationship between preeclampsia and PC / MPV (9). In our study, PC and PC / MPV indices were found to be significantly lower in the patient group with preeclampsia than the control group.

Another index, PMI, is obtained by multiplying the platelet count by the mean platelet volume. As we mentioned before, in cases with preeclampsia, it is expected that PC would decrease due to consumption and MPV would increase with the production of new platelets. Therefore, PMI is expected to be different in preeclamptic patients compared to the controls. PMI has previously been studied in many different diseases, but there is no data regarding PMI in preeclampsia. Gerday et al. found that PMI is associated with prolonged PT time without increasing the risk of hemorrhage (12). Zisk et al found that the transfusion requirement would decrease by 11.5% if the PMI value was taken into consideration in platelet transfusion in a newborn study (22). However, despite the decrease in the need for transfusion in the group with high PMI, they did not indicate any difference in terms of bleeding episodes and mortality (23). In another study, it was found that in premature infants with low PMI which reflects decreased platelet activity, the incidence of intracranial hemorrhage increases, and this incidence decreases with increasing PMI (24). In addition, PMI was found to be more significant than the number of platelets used to evaluate the pathology in the second phase of premature retinopathy (25). In the review of the studies, it was concluded that PMI showed platelet activity better than PC (26). As far as we know, our study is the first study to evaluate PMI in preeclampsia. In the present study it was found that although MPV did not change in preeclamptic cases, it was found that PMI was significantly lower compared to control cases. Therefore, PMI appears as a parameter that can be used in the evaluation of platelet functions in preeclampsia patients.

In the literature, no threshold value has been defined for

platelet indices associated with preeclampsia. Dundar et al found the sensitivity for preeclampsia as 69% and the specificity as 71% when the PC threshold value was 221,000 (27). Howarth et al reported that the sensitivity of low PC high MPV was 90% and the specificity was 83% (28). In our study, since there was no significant relationship between preeclampsia and MPV, no threshold or sensitivity test was performed for MPV. The threshold values of the significant PC, PMI, and PC / MPV indices were determined in the ROC curve for the diagnosis of preeclampsia (207,500; 2411.75; 18488.16, respectively). According to these threshold values, the sensitivity and specificity of all three indices were found to be moderate. One reason why the previously studied PC sensitivities may differ from our study may be due to the calculated threshold value. The evaluation of different indices together in our study was an advantage of our study.

The positive aspect of the study is that a new parameter such as the PMI index is being evaluated in patients with preeclampsia. This study has several limitations. Limitations are that it is a single-center study and meaning our results may not be appropriate to the general population. In addition, low AUC value, sensitivity, and specificity values of PC, PC / MPV, and PMI parameters examined in the study are another weakness. Conducting a multi-center study can provide more precise results.

Evaluation of platelet functions is important because bleeding is a common complication in patients with preeclampsia. Many studies have been conducted on platelet indices in preeclampsia and the relationship between PC, MPV, and preeclampsia was mostly investigated in these studies. Although there is a consensus on the low PC in patients with preeclampsia, there is no complete consensus on MPV. In our study, we evaluated not only PC and MPV but also PC / MPV and PMI as platelet indices. The superiority of this study is the evaluation of all of these indices together (especially PMI was studied for the first time in preeclampsia). As a result, it was found that MPV value was not important in cases with preeclampsia, but indices such as PC, PC / MPV, and PMI changed significantly. Although they have low sensitivity and specificity, these indices can be combined with other parameters and used in the prediction of preeclampsia.

#### Conflict of interest

The author(s) declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article

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