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ORIGINAL ARTICLE

The Relationship Between Mean Platelet Volume/Platelet Count (MPV/PLT) Ratio and Peripheral Artery Disease

Ortalama Trombosit Hacmi/Trombosit Sayısı (MPV/PLT Oranı ile Periferik Arter Hastalığı Arasındaki İlişki

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ABSTRACT

Background/Aim: In our study, we aimed to evaluate the effect of mean platelet volume/platelet count ratio on the development of peripheral artery disease (PAD) by comparing it with the control group.
Material and Methods: A total of 115 patients with peripheral artery disease as a result of lower extremity color Doppler ultrasonography examination in our hospital were included in the study as the patient group and 100 individuals without peripheral artery disease as the control group.
Results: History of coronary artery disease (p<0.001), diabetes mellitus (p=0.009), hypertension (p<0.001) and smoking history (p<0.001) were significantly higher in the PAD group than in the control group. Serum glucose (121.27±25.66 vs. 104.81±34.77; p<0.001), MPV levels (9.99±0.79 vs. 9.04±0.7; p<0.001) and MPV/PLT ratio (0.041±0.07 vs. 0.037±0.006, p< 0.001) were found to significantly higher in the PAD group than in the control group. Serum HDL levels (45.03±11.5 vs. 48.67±12.52 p=0.026) were significantly lower in the PAD group than in the control group. In multivariate analysis, age, MPV and MPV/PLT ratio were determined as independent predictors for peripheral arterial disease.
Conclusion: In our study, we found that age, MPV and MPV/PLT ratio were independent predictors of peripheral artery disease.

Keywords: Mean Platelet Volume, Mean Platelet Volume/Platelet Count Ratio, Platelet activation, Peripheral arterial disease

ÖZ

Amaç: Çalışmamızda ortalama trombosit hacmi/trombosit sayısı oranının periferik arter hastalığı (PAH) gelişimine etkisini kontrol grubu ile karşılaştırarak değerlendirmeyi amaçladık.
Yöntem: Hastanemizde alt ekstremite renkli Doppler ultrasonografi incelemesi sonucu periferik arter hastalığı saptanan toplam 115 hasta ile periferik arter hastalığı olmayan 100 kişi kontrol olarak çalışmaya alınmıştır.
Bulgular: Periferik arter hastalığı (PAH) olan grupta ortalama yaş kontrol grubuna göre anlamlı olarak yüksek bulunmuştur (69.12±10.58 vs. 52.83±13.05, p<0.001). Grupların cinsiyet oranlarında istatistiksel olarak anlamlı fark yoktur (p=0.218). Koroner arter hastalığı öyküsü (p<0.001), diabetes mellitus (p=0.009), hipertansiyon (p<0.001) ve sigara öyküsü (p<0.001) PAH grubunda kontrol grubuna göre anlamlı olarak yüksek bulunmuştur. Serum glukozu (121,27±25,66 - 104,81±34,77; p<0,001), MPV seviyeleri (9,99±0,79 - 9,04±0,7; p<0,001) ve MPV/PLT oranı (0,041±0,07 - 0,037±0,006, p< 0.001) PAH grubunda kontrol grubuna göre anlamlı olarak yüksek bulunmuştur. Serum HDL düzeyleri (45,03±11,5'e karşı 48,67±12,52 p=0,026) PAH grubunda kontrol grubuna göre anlamlı olarak düşüktür. Çok değişkenli analizde yaş, MPV ve MPV/PLT oranı periferik arter hastalığı için bağımsız belirteçler olarak belirlenmiştir.
Sonuç: Çalışmamızda yaş, MPV ve MPV/PLT oranı periferik arter hastalığının bağımsız öngördürücüleri olarak bulunmuştur.

Anahtar Kelimeler: Ortalama Trombosit Hacmi, Ortalama Trombosit Hacmi/Platelet Sayısı Oranı, Periferik arter hastalığı, Trombosit aktivasyonu

Introduction

Peripheral arterial disease is a chronic and slowly developing disease on the basis of atherosclerosis, and its incidence is increasing with a long-life expectancy (1). It is estimated to affect more than 200 million people worldwide (2). Its association with other atherosclerotic diseases is common and the morbidity and mortality it causes constitutes a significant burden for the health system (3).

Peripheral arterial disease has been associated with typical atherosclerotic risk factors such as advanced age, smoking, diabetes mellitus (DM), hypertension (HT), hyperlipidemia (HL) (4). Although the most common symptom of peripheral arterial disease is intermittent claudication, most patients can be asymptomatic (5,6). The prognosis is adversely affected due to the increase in complications after the delay in the diagnosis of asymptomatic patients (7).

Platelets play a major role in the pathogenesis of atherosclerosis and development of thrombus (8). Mean platelet volume (MPV) can be easily detected in the complete blood count, which is one of the routine tests we frequently use in our daily practice. Previous studies have shown that MPV is correlated with platelet activation. As platelet volume increases, platelets contain enzymatically denser granules such as thromboxane A2, serotonin, beta-thromboglobin,

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and also express more adhesion receptors such as glycoprotein (GP) Ib and GPIIB/IIIa (9,10). As a result, an increase in mean platelet volume has been associated with conditions such as acute coronary syndrome, ischemic stroke, and pulmonary embolism (11,12). The MPV/PLT ratio was found superior to the individual MPV and PLT values in predicting mortality in patients with acute coronary syndrome (13).

Early diagnosis and treatment are very important in reducing the morbidity and mortality associated with peripheral arterial disease. Therefore, there is a need for inexpensive and practical new biomarkers that can be quickly interpreted by routine examinations in outpatient settings in the evaluation of individuals at the risk of peripheral arterial disease. In our study, it was aimed to examine the changes in platelet parameters between the group with peripheral artery disease and the control group.

Material and Methods

Patient population

This study included 115 patients who presented to the cardiology and cardiovascular surgery outpatient clinics of our hospital with the complaint of leg pain, and who were found to have peripheral artery disease as a result of physical examination findings and arterial Doppler ultrasonography and 110 individuals who did not have peripheral artery disease in the examinations.

This study was approved by the Ethics Committee of Sadi Konuk Training and Research Hospital (Protocol number: 2021/331). Demographic information and laboratory tests of the patients were obtained retrospectively from the hospital information system. Patients under 18 years old at the time of diagnosis, those with malignancy and hematological disease, patients with chronic kidney failure and chronic liver disease, pregnant women, and patients with active infection or chronic inflammatory disease were excluded from the study.

Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in clinical measurements or the use of antihypertensive medication (14). Diabetes mellitus was considered as fasting blood glucose ≥126 mg/dL or use of antidiabetic medication (15). Hyperlipidemia was considered as a total cholesterol level ≥200 mg/dl or antihyperlipidemic drug use. Patients with previous myocardial infarction or coronary revascularization procedures were considered to have coronary artery disease. Patients who smoked at the time of enrollment or up to 1 month ago were considered active smokers

Laboratory Analysis

Blood samples were taken from the antecubital superficial veins into ethylenediaminetetraacetic acid (EDTA) tubes and studied within 2 hours. Complete blood count parameters were measured using the XT-4000i Hematology Analyzer (Sysmex, Kobe, Japan). Other biochemical parameters were measured using the AU5800 Clinical Chemistry System (Beckman Coulter, Inc. California, USA) device.

Doppler Ultrasonography

Lower extremity arterial Doppler examinations of the patients were performed with the Toshiba Applio500 (TUS A500) ultrasonography device. The evaluation of the popliteal artery and proximal segments was performed in the prone position, while the evaluation of the other arterial segments was performed with the patients in the supine position. In the evaluation phase, the peak systolic velocity ratio was measured by dividing the maximum velocity at the narrowest part of any stenosis segment into the maximum velocity 1.5-2 cm proximal to the stenosis. A peak systolic rate ≥2 was considered as severe stenosis (over 50% stenosis). The absence of flow in the arterial lumen was accepted as occlusion (16).

Statistical Analysis

Statistical analyzes were performed with SPSS (Statistical Package for the Social Sciences) 24.0 program. The distribution of normality was analyzed by using Kolmogorov Smirnov test. The Independent Sample T-test was used to compare the normally distributed parameters, and the Mann-Whitney U test was used to compare the non-normally distributed parameters. The Chi-square test was employed in the evaluation of qualitative data. Continuous variables were expressed as (Mean ± Standard Deviation or median (25-75% percentile). Categorical variables were expressed as percent (%). Univariate and multivariate regression analyzes were performed to identify independent predictors of peripheral arterial disease. ROC (receive-operating characteristic) curve test was used to calculate the sensitivity and specificity values. $p<0.05$ values were considered statistically significant.

Results

Basic demographic characteristics and laboratory parameters of the study groups are given in Table 1. There was no difference between the groups in terms of gender (p=0.218). The mean age of the group with peripheral artery disease was significantly higher than the control group (69.12±10.58 vs. 52.83±13.05, $p<0.001$). History of diabetes mellitus (31.3% vs. 19%; p=0.009), hypertension (49.6% vs. 26%; $p<0.001$), coronary artery disease (44% vs. 12%; $p<0.001$), and smoking history (31.3% vs. 17%; $p<0.001$) were significantly higher in the peripheral arterial disease group than in the control group. No significant difference was observed between the groups in terms of hyperlipidemia (%29.6 vs. %23; p=0.562).

When laboratory data were compared, serum glucose levels were significantly higher in the PAD group than in the control group. (121.27±25.66 vs 104.81±34.77 $p<0.001$). Serum HDL levels were significantly lower in the peripheral arterial disease group than in the control group (45.03±11.5 vs. 48,67±12,52 p=0.026). When examined in terms of hematological parameters, MPV value (9.99±0.79 vs 9.04±0.7, $p<0.001$) and MPV/

Table 1. Laboratory data and demographic characteristics of the patients included in the study

		All patients (n=215)	Control group (n=100)	Peripheral Artery Disease group (n=115)	P value
Age;		61.5±14.3	52.83±13.05	69.12±10.58	[a]***0.001****
Gender; n (%)	***Male***	128 (59.5)	50 (50)	78 (67.8)	[b]***0.218***
	Female	87 (40.5)	50 (50)	37 (32.2)	
Diabetes; n (%)		55 (256)	19 (19.0)	36 (31.3)	[b]***0.009****
Hypertension; n (%)		83 (38.6)	26 (26.0)	57 (49.6)	[b]***0.001****
Hyperlipidemia; n (%)		57 (26.5)	23 (23.0)	34 (29.6)	[b]***0.562***
Coronary Artery Disease; n (%)		56 (26)	12 (12.0)	44 (38.3)	[b]***0.001****
Smoking; n (%)		53 (24.7)	17 (17.0)	36 (31.3)	[b]***0.001****
Glucose (mg/dL);		113.76±30.85	104.81±34.77	121.27±25.66	[a]***0.001****
Creatinine (mg/dL);		0.90±0.18	0.88±0.15	0.91±0.2	[a]***0.450***
AST (IU/L);		20.20±7.71	20.17±6.25	19.96±8.39	[a]***0.487***
ALT (IU/L);		19.65±7.87	19.94±7.06	18.88±8.41	[a]***0.220***
Total Cholesterol; **(mg/dl)**		204.85±42.46	208.83±38.06	202.01±46.21	[a]***0.656***
HDL; **(mg/dl)**		46.51±11.96	48.67±12.52	45.03±11.5	[a]***0.026****
LDL; **(mg/dl)**		122.44±35.86	126.6±33.41	119.13±37.34	[a]***0.335***
WBC; **($10^3/mm^3$)**		7.91±1.85	7.75±1.91	8.07±1.86	[a]***0.261***
HG; **(g/dL)**		13.46±1.69	13.57±1.47	13.27±1.83	[a]***0.065***
PLT; **($10^3/mm^3$)**		249.36±34.91	257.84±28.01	246.88±30.97	[a]***0.658***
MPV; **(fL)**		9.57±0.88	9.04±0.7	9.99±0.79	[a]***0.001****
MPV/PLT oranı ;		0.039±0.007	0.037±0.006	0.041±0.007	[a]***0.001****
Triglycerides; **(mg/dl) *25-75 (Median)***		101-208 (140)	100-197 (125)	106-210 (146)	[c]***0.255***

*aIndependent Sample T Testi bPearson Chi-Square cMann Whitney U Testi *p<0.05*
AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-density cholesterol, LDL: Low-density cholesterol, WBC: White blood cells, Hg: Hemoglobin, PLT: Platelet count, MPV: Mean platelet volume.

Table 2. Results of univariate and multivariate logistic regression analysis for peripheral arterial disease

Variables	Univariate			Multivariate		
	OR	***95% CI***	***p***	***OR***	***95% CI***	***p***
Age;	0.904	0.868-0.988	***0.001****	1.147	1.093-1.204	***0.001****
Gender	1.145	0.988-2.240	*0.091*	-	-	-
Diabetes	0.426	0.227-0.796	***0.001****	0.944	0.315-2.829	0.918
Hypertension	0.358	0.207-0.765	***0.001****	0.844	0.313-2.460	0.803
Hyperlipidemia	0.589	0.321-1.105	*0.121*	-	-	-
Coronary Artery Disease	0.255	0.101-0.354	***0.001****	2.468	0.786-7.752	0.122
Smoking	0.432	0.228-0.817	***0.001****	0.896	0.281-2.853	0.850
Glucose	0.978	0.697-0.990	***0.001****	1.012	0.997-1.027	0.120
Creatinine	0.596	0.138-2.574	*0.389*	-	-	-
AST	1.001	0.981-1.027	*0.286*	-	-	-
ALT	1.004	0.991-1.050	*0.128*	-	-	-
Total Cholesterol	1.001	0.97-1.010	*0.335*	-	-	-
HDL	1.018	1.001-1.056	***0.025****	0.966	0.926-1.009	0.116
LDL	1.002	0.997-1.015	*0.220*	-	-	-
WBC	0.908	0.788-1.046	*0.187*	-	-	-
HG	1.156	0.989-1.351	*0.075*	-	-	-
PLT	1.006	0.995-1.019	*0.487*	-	-	-
MPV	0.219	0.140-0.341	***0.001****	1.047	1.041-2.887	***0.001****
MPV/PLT	1.010	1.814-5.556	***0.001****	1.201	1.649-8.752	***0.001****
Triglycerides	0.980	0.996-1.001	*0.161*	-	-	-

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-density cholesterol, LDL: Low-density cholesterol, WBC: White blood cells, Hg: Hemoglobin, PLT: Platelet count, MPV: Mean platelet volume.

Table 3. ROC Analysis Results of MPV/PLT and MPV Measurements by Groups

					95% CI	
	Cut off Value	Area	Sensitivity	Specificity	Lower	Upper
MPV/PLT	≥0.038	0.784	0.617	0.760	0.725	0.844
MPV	≥9.55	0.821	0.670	0.780	0.766	0.877

PLT ratio (0.041±0.007 vs 0.037±0.006, p<0.001) were significantly higher in the PAD group compared to the control group. No statistically significant difference was found between the groups in terms of other data (Table 1).

Table 2 shows univariate and multivariate regression analysis to evaluate the factors predicting peripheral arterial disease. In the multiple regression analysis, age (OR: 1.147; 95% CI 1.093-1.204; p<0.001), MPV (OR: 1.047; 95% CI 1.041-2.887; p<0.001), and MPV/PLT ratio (OR: 1.201; 95% CI 1.649-8.752; p<0.001) were found as independent predictors of peripheral artery disease.

In the ROC curve analysis, an MPV value ≥9.55 (AUC: 0.821; 95% CI: 0.766-0.877; p<0.001) predicted the presence of peripheral arterial disease with a sensitivity of 67% and specificity of 78%, and MPV/PLT ratio ≥ 0.038 (AUC: 0.784; 95%; CI: 0.725-0.844; p<0.001) with a 61.7% sensitivity and 76% specificity (Table 3) (Figure 1).

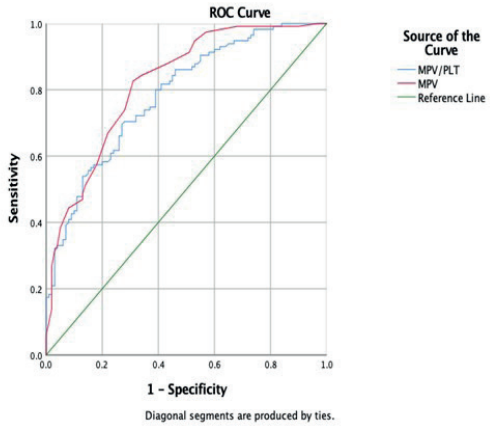

Figure 1. Sensitivity and specificity of MPV and MPV/PLT ratio in predicting the presence of peripheral artery disease.

Discussion

In our study, MPV value and MPV/PLT ratio were significantly higher in patients with peripheral artery disease compared to the control group. In addition, in the multivariate regression analysis, it was thought that MPV and MPV/PLT ratios could be independent predictors for peripheral arterial disease by maintaining their significance.

In the literature, advanced age, smoking, diabetes mellitus, and hypertension, which are atherosclerotic risk factors, have been associated with PAD (17). As the average life expectancy increases, the incidence of cardiovascular diseases such as PAD, which develops on the basis of atherosclerosis, increases. The prevalence of PAD reaches 29% in patients over 70 years of age (18). Hypertension plays a role in the development of atherosclerosis by causing endothelial dysfunction. In the Framingham Heart Study, it was shown that the frequency of PAD increased with an increase in blood pressure values (19). Similarly, diabetes mellitus causes a 2- to 4-fold increase in the frequency of PAD as a result of endothelial dysfunction. Duration of diabetes and hemoglobin A1c levels are associated with the severity of PAD and progression to amputation (20,21). Many studies have shown that the frequency of PAD increases 2-5 times in proportion to smoking and the amount consumed (22). There is a decrease in mortality and amputation rates with smoking cessation (23). In our study, in accordance with the literature, diabetes mellitus, hypertension, smoking, and age were significantly higher in the PAD group than in the control group.

Platelets, which play an important role in hemostasis and inflammatory response, are small cells that are composed of megakaryocytes in the bone marrow and do not contain nuclei (24). Platelets that adhere to damaged endothelial cells for any reason activate endothelial cells through the cytokines and pro-inflammatory mediators they secrete, giving them procoagulant properties. They also interact with circulating leukocytes and aggravate their role in inflammation (25). It has been shown that platelet-monocyte cell aggregations formed as a result of platelet-monocyte interaction are increased in individuals with coronary artery disease (26,27), and it has been claimed that inhibiting this aggregation may be a treatment for the development of atherosclerosis (28).

Increased activity of platelets plays a key role in the pathogenesis of atherosclerosis and developing thrombogenic complications. MPV has been associated with platelet function. MPV can be easily calculated with blood count devices in our daily practice (29). Large-volume circulating platelets are metabolically and enzymatically more active than small-volume platelets. As the platelet volume increases, their granule content, which plays a role in coagulation, increases, and they also express more intense glycoprotein Ib and glycoprotein IIb/IIIa receptors (9,10).

There are many studies in the literature on atherosclerotic diseases and their thrombotic complications. In a study evaluating the response of 133 patients with ST-segment elevation myocardial infarction to thrombolytic therapy, it was shown that patients with high MPV values had less response to thrombolytic therapy (30). In another study, MPV value was reported to have been correlated with mortality and recurrent myocardial infarction in the 2-year follow-up of 1716 male patients after myocardial infarction (31). In a study of 108 patients in which myocardial infarction patients with ST-segment elevation were compared with patients who had myocardial infarction without ST-segment elevation, MPV value was found higher in patients with ST-segment elevation (32). High MPV values have also been associated with pulmonary embolism, and the severity of pulmonary embolism and early mortality rates were higher in patients with pulmonary embolism who had high MPV values (33,34). On the other hand, according to the research by Taşoğlu et al., patients with mechanical

valve thrombosis have higher MPV values than control participants, and this was suggested as a potential follow-up marker of thrombosis in these group of patients (35).

In a study by Li et al., showing the relationship between MPV and peripheral arterial disease, patients were divided into 3 groups and the MPV value was found to be higher in the diabetic arm with impaired glucose tolerance than in the arm with normal glucose regulation. In addition, in this study, it was stated that a high MPV value is a risk factor for peripheral arterial disease (36). In previous research, the association between simple, routine tests such as the hemogram and the ratios produced from it and the PAD has also been investigated (37). In the 5-year follow-up data of 6354 patients, a high MPV value was determined as an independent risk factor for peripheral artery disease (38). It has been shown in patients with acute coronary syndrome that the use of the MPV/PLT ratio is superior to the use of MPV or PLT alone. (13). In a study involving 200 patients, the MPV/PLT ratio was higher in the group with the slow coronary flow than in the control group (39). In the 4-year follow-up of 619 patients with myocardial infarction without ST-segment elevation, the MPV/PLT ratio was associated with mortality. In another study comparing ST segment elevation patients who underwent primary percutaneous intervention (PCI) with the control group, the MPV/PLT ratio was higher in the PCI group, and MPV/PLT ratio was demonstrated to be correlated with the SYNTAX score. In our study, the ratio of MPV and MPV/PLT was higher in the peripheral arterial disease group, consistent with the literature (40).

In conclusion, in our study, we determined that the ratio of MPV and MPV/PLT was higher in patients with peripheral artery disease than in the control group. We also found that MPV and MPV/PLT ratios were independent predictors of the development of PAD. We believe that early diagnosis of patients at risk for PAD by routine blood examination in the outpatient setting will be beneficial in reducing the morbidity and mortality that may develop due to PAD.

Limitations

The most important limitation of our study is its retrospective design and an insufficient number of patients. In addition, it is known that platelet volumes change depending on the analysis time of blood samples taken into EDTA tubes. In our study, the blood samples taken were evaluated in the laboratory within 2 hours in order to minimize this problem. As we know, the gold standard diagnostic method for peripheral arterial disease is conventional angiography or contrast-enhanced tomography. Using Doppler USG in diagnosis in our study may be considered as a limitation.

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Conflict of Interest: The authors declare no conflict of interest to disclose.

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Data Availability: Data used in this study can be provided on reasonable request.

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