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CAN MEAN PLATELET VOLUME/PLATELET COUNT RATİO BE USED TO PREDİCT THE MORTALİTY İN ACUTE İSCHEMİC STROKE PATİENTS?

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ABSTRACT

Objective: It is revealed that, increased mean platelet volume/platelet count ratio (MPV/PC), obtained by dividing mean platelet volume (MPV), which indicates platelet function and activity, by platelet count, is associated with the increase of the thromboembolic disease risk. Our aim was to determine the effects of MPV and MPV / PC on the development of acute ischemic stroke (AIS) and 60- day mortality. **Materials and Methods:** Our study retrospectively included 512 patients with AIS between January 2010 and 2016, along with 408 age- and sex-matched controls. During their 60 day-hospitalization, 87 of these 512 patients died. Blood samples were taken to measure MPV and MPV/PC ratio within 24 hours. Patients and controls were compared in terms of MPV and MPV/PC values; these were also compared between non-surviving and surviving patients. **Results:** Patients had significantly higher MPV and MPV/PC values than controls; these results were similar between non-surviving and surviving patients. The univariate and multivariate logistic regression analyses indicated that MPV and MPV/PC were independent predictors of 60- day mortality in AIS. ROC analysis showed that cut-off values of 9.65 for MPV (AUC: 0.68, 95% CI: 0.54- 0.78, sensitivity: 54.1%, specificity:65%) and 0.047 for MPV/PC may be used to determine 60-day mortality due to AIS (AUC: 0.73, 95% CI: 0.65- 0.82, sensitivity: 71.1%, specificity: 68.3%). **Conclusion:** It could be suggested that MPV and MPV/PC values are increased in AIS patients, and that the elevations of MPV and especially MPV /PC values can be used to predict 60-day mortality in AIS patients.

KEYWORDS: Mean platelet volume, platelet count, mean platelet volume/platelet count, mortality, acute ischemic stroke.

INTRODUCTION

Acute ischemic stroke (AIS) with high mortality and morbidity rates is defined as infarction due to occlusion of the cerebral arteries and is the most common neurological cause of Emergency department admission. It accounts for 80% to 85% of all cerebrovascular disease.[1]

Thrombosis, platelet activation and inflammation are essential in the pathophysiology of AIS.[2] Platelets play an important role in the atherosclerotic plaque development, destabilization and rupture and development of platelet-fibrin heading in complicated atherosclerotic plaque.[2,3] In addition, the recent studies have shown that platelet count is associated with the occurrence and prognosis of AIS and acute myocardial infarction (AMI).[2,3]

Platelet size measured by mean platelet volume (MPV) is a significant indicator of platelet function.[4] Increased platelet volume is associated with elevated platelet reactivity, decreased bleeding time, increased platelet aggregation, and high thrombotic potential. Increased MPV levels were determined in previous studies performed in AIS patients compared to healthy controls.[4,5]

Recently, MPV /PC ratio obtained by dividing MPV value by platelet count has been considered as a prognostic indicator for diseases such as AMI, anemia, hepatocellular carcinoma, lung cancer, pulmonary embolism.[5,6] However, there is only limited information about its possible effect on development and prognosis of AIS.

For these reasons, our aim in this study was to determine the effects of the MPV value, platelet count and MPV / PC ratio on AIS development and 60-day mortality by comparing these values of the patients admitted to our clinic with the diagnosis of AIS with healthy controls.

MATERIALS AND METHODS

Study Population

We retrospectively reviewed 2761 patients who admitted to our clinic between January 2010 and 2016. Our study included 512 patients who met our criteria and did not

have any missing information, along with 408 age- and sex-matched controls. The anamnesis, neurological examination, detection of newly occured cerebral ischemic area by computerized brain tomography (CT) or cranial magnetic resonance imaging (MRI), and exclusion of the diagnosis leading to similar clinical and imaging findings (intracranial mass, intracerebral hemorrhage, cerebral sinus venous thrombosis...) were used in order to identificate the diagnosis of AIS. There were no restrictions regarding gender and age among the patients. The patients, who were younger than 18 years or had any systematic acute/ chronic inflammatory/ autoimmune diseases, history of infection, acute coronary syndrome, major surgery or trauma within one month before admission, cancer, severe liver, kidney or heart failure, or who used immunosuppressants, antiinflammatories or steroids were not included in this study. Then the patient group was divided into two subgroups according to the 60-day patient mortality. While the patients in the first group were alive, the patients in the second group died within 60 days after AIS.

While the Glaskow coma scale (GCS) was used to assess the consciousness status of the patients at admission, the National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS) were utilized to determine the severity of AIS.

All patients included in the study were evaluated in terms of age, gender, presence of diabetes mellitus / hypertension, statin and / or tobacco use, body mass index (BMI), GCS, NIHSS, MRS, duration of hospital stay, platelet count, MPV and CRP levels, MPV / PC ratio and 60-day mortality.

The control group consisted of 408 patients who gave blood samples for reasons other than AIS (dizziness, headache, numbness…) at the same time interval and did not suffer from any uncontrolled systemic diseases (diabetes mellitus, hypertension, cardiovascular diseases, cancer or liver, kidney or heart failure) or did not have history of major surgery or trauma within one month before admission.

The missing information in this retrospective study was obtained by phone call with the patients or their relatives. Our study was approved by the ethics committee.

Laboratory Analyses

Blood samples of the patients included in the study were taken from antecubital vein to tubes containing ethylenediaminetetraacetic acid (EDTA) within the first 24 hours following AIS. Complete blood counts were analyzed with Diagon kits on a Mindray BC-6800 device and the platelet counts and MPV values of the patients were obtained from this device. The MPV / PC ratios were determined by dividing the MPV values by the number of platelets.

Statistical Analyses

Data obtained from this study was evaluated by using the SPSS 22.0 program. The descriptive statistics of the data were presented as mean (±) standard deviation and percentage (%). Data were evaluated with the Kolmogorov– Smirnov test in terms of normal distribution. The Mann-Whitney U test was used in the analysis of quantitative data, the Chi-square test was used in the analysis of qualitative data, and the Fischer's exact test was used when the Chi-square test conditions were not met. The effects of MPV value, platelet count and MPV / PC ratio as a prognostic indicator in patients with AIS were investigated by the univariate and multivariate logistic regression analyzes. Receiver operating characteristic curve (ROC) analysis was utilized for determining the optimum cut-off values of MPV ve MPV/PC for predicting the 60-day mortality of AIS. The maximum Youden Index was used to determine the optimum cut-off values. The statistical significance level was accepted as $p < 0.05$.

RESULTS

The comparison of the patient and control groups in terms of baseline demographic characteristics revealed that there was no significant difference between the two groups in terms of age, gender, the presence of diabetes mellitus, statin or tobacco use, and BMI values. Besides, hypertension was found more frequently in the patient group (p=0.01) (Table 1).

Table 1: The demographic and laboratory characteristics of the patient and control groups.

	Patient Group (n=512)	Control Group (n=408)	X^2	p
Male, n (%)	275(53.71%)	209 (51.22%)	0.01	0.82
Hypertension, n (%)	**394(76.94%)**	**248 (60.78%)**	**4.26**	**0.01**
Diabetes mellitus, n(%)	143(27.99%)	89 (21.81%)	1.21	0.36
Statin use, n(%)	210 (41.01%)	118 (28.92%)	0.54	0.11
Tobacco use, n(%)	199 (38.87%)	184 (45.09%)	3.35	0.43
Age(mean ± SD)	77.2±0.43	75.5±1.14		0.11
BMİ(kg/m^2) (mean ± SD)	25.8±0.1	25.0±0.5		0.10
Glucose* (mg/dL)(median)(min-max)	125 (66- 248)	128 (67- 212)		0.46
Creatinine*(mg/dL)(median)(min-max)	0.95 (0.56- 1.2)	1.01(0.50- 1.3)		0.35
Total cholestrol(mg/dL)(mean ± SD)	172.2±2.7	179.7±5.3		0.43
LDL(mg/dL) (mean ± SD)	**119.3±1.9**	**102.5±4.0**		**0.002**
HDL(mg/dL)(mean ± SD)	**38.8±0.5**	**44.0±1.9**		**0.02**
MPV(fL)(mean ± SD)	**9.55±0.10**	**8.00±0.10**		**<0.001**
MPV/PC(mean ± SD)	**0.046±0.003**	**0.038±0.001**		**<0.001**
Platelet*($\times10^4/\mu l$)(median)(min-max)	21(15.2- 37.8)	20.5(15.6- 35.4)		0.62
CRP(mg/l)(mean ± SD)	8.70±0.40	6.80±0.50		0.77

Abbreviations: BMI: body mass index; CRP: C-reactive protein; HDL: high-density cholestrol; LDL: low-density cholestrol; MPV: mean platelet volume; MPV / PC: mean platelet volume / platelet count.
* Since there were nonparametric variables, median values were used.

When the patient and control groups were compared in terms of platelet count and MPV and MPV/ PC values, the platelet counts were not significantly different between the two groups (p=0.62), and the MPV and MPV/ PC values were higher in the patient group (p<0.001). The comparison of the patient and control groups in terms of the other laboratory parameters showed that, while the mean low-density lipoprotein level (LDL) was higher (p = 0.002) in the patient group; the mean high-density lipoprotein (HDL) value was lower (p=0.02). In addition, there was no statistically significant difference in levels of glucose, creatinine, total cholesterol and C-reactive protein (CRP) (Table 1).

Then the patient group was classified into two subgroups according to the 60-day mortality. The first group patients died within 30 days after AIS (n=87), while patients in the second group were alive (n=425). The comparison of the these two groups in terms of baseline demographic characteristics demonstrated that while there was no significant difference between two groups in terms of gender, hypertension or diabetes mellitus presence and statin or tobacco use (p=0.37, p=0.08, p=0.92, p=0.054, p=0.32), the mean age of the first group were statistically higher. Moreover, when the non-surviving and surviving groups were compared in terms of platelet count and MPV and MPV/ PC values, the MPV and MPV / PC values were higher in non-surviving group (p = 0.02, p = 0.04) and there was no significantly difference between the two groups in terms of platelet count (p = 0.18) (Table 2).

Table 2: The demographic and laboratory characteristics of the non-surviving and surviving groups.

	Non-surviving Group (n=87)	Surviving Group (n=425)	X^2	p
Male, n(%)	44(50.51%)	234(55.05%)	0.11	0.37
Hypertension, n(%)	69(79.31%)	315(74.12%)	2.26	0.08
Diabetes mellitus, n (%)	24(27.58%)	115(27.05%)	1.45	0.92
Statin use, n(%)	31(35.63%)	187(44.00%)	0.54	0.054
Tobacco use, n(%)	37(42.52%)	157(36.94%)	3.35	0.32
Age(mean±SD)	**79.9±0.61**	**75.2±0.57**		**<0.001**
BMİ(kg/m^2)(mean±SD)	**26.91±0.20**	**24.50±0.30**		**<0.001**
GCS (admission)(mean±SD)	**7.79±0.21**	**13.58±0.10**		**<0.001**
NİHSS (admission)(mean±SD)	**5.25±0.17**	**16.83±0.36**		**<0.001**
MRS (admission)(mean±SD)	**4.31±0.05**	**2.36±0.06**		**<0.001**
Duration of hospital stay (day)(mean±SD)	**26.24±1.25**	**11.45±0.62**		**<0.001**
Glucose * (mg/dL)(median)(min-max)	142(66- 256)	135(89- 248)		0.21
Creatinine*(mg/dL) (median)(min-max)	1,2 (0.78- 1.5)	0,9 (0.56- 1.2)		0.13
Total cholesterol(mg/dL)(mean ± SD)	**156.41±3.32**	**184.90±2.81**		**<0.001**
LDL(mg/dL) (mean ± SD)	**111.01±2.92**	**125.90±2.53**		**<0.001**
HDL(mg/dL) (mean ± SD)	38.51±0.83	38.90±0.62		0.39
MPV(fL)(mean ± SD)	**9.81±0.33**	**9.12±0.11**		**0.02**
Platelet*(10^4/mL)(median)(min-max)	21 (16.6- 35.6)	20 (15.2- 34.0)		0.18
MPV/PC(mean ± SD)	**0.049±0.002**	**0.045±0.001**		**0.04**
CRP(mg/l)(mean ± SD)	9.21±0.82	8.30±0.41		0.28

Abbreviations: BMI: body mass index; CRP: C-reactive protein; GCS: Glasgow coma scale; HDL: high-density cholestrol; LDL: low-density cholestrol; MRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke scale MPV: mean platelet volume; MPV / PC: mean platelet volume / platelet count.
* Since there were nonparametric variables, median values were used.

Additionally, the comparison of the non-surviving and surviving groups in terms of the other laboratory parameters showed that while the levels of glucose, creatinine, HDL and CRP were not significantly different between two groups (p = 0.21, p = 0.13, p = 0.39, p = 0.28), the total cholesterol and LDL values were higher in non-surviving patients (p<0.001). In terms of clinical parameters, while the GCS score was lower in non-surviving patients; the NIHSS and MRS scores and the mean duration of hospital stay were significantly higher (p < 0.01) (Table 2).

The determination of risk factors related to the 60-day mortality of AIS patients included platelet count, MPV and MPV/ PC values, presence of hypertension, the GCS, NIHSS and MRS scores at admission, which were used as independent variables (p<0.005) (Table 3). Application of multivariate analyses on these parameters showed that MPV and MPV/PC values, the GCS, NIHSS and MRS scores at admission were statistically significant independent variables for the prediction of 60-day mortality in AIS patients (p=0.028, p=0.012, p<0.001, p=0.002, p=0.001) (Table 3).

Table 3: The univariate and multivariate logistic regression analyzes to predict 60-day mortality.

	Univariate Analysis					Multivariate Analysis				
	OR	**95% CI**			**p**	**OR**	**95% CI**			**p**
Age	1,019	1,00	-	1,04	0,075					
Gender	1,329	0,83	-	2,12	0,231					
Diabetes mellitus	1,189	0,71	-	1,98	0,506					
Hypertension	0,134	0,05	-	0,34	***0,000***					
GCS(admission)	0,549	0,48	-	0,62	***0,000***	0,534	0,45	-	0,63	***0,000***
NIHSS(admission)	1,082	1,06	-	1,10	***0,000***	3,901	1,63	-	9,35	***0,002***
MRS(admission)	10,564	6,12	-	18,23	***0,000***	1,248	1,17	-	1,33	***0,001***
MPV	5,056	2,76	-	9,26	***0,000***	1,155	1,03	-	1,29	***0,012***
MPV/PC	1,045	1,02	-	1,07	***0,001***	1,039	1,00	-	1,08	***0,028***
Platelet Count	1,001	1,00	-	1,00	0,507					
Logistic Regression Analysis (Univariate / Multivariate)										

Abbreviations: CI: confidence interval; GCS: Glasgow coma scale; MRS: modified Rankin scale; NIHSS: National Institutes of Health Stroke scale; OD: odds ratio; MPV: mean platelet volume; MPV / PC: mean platelet volume / platelet count.

In addition, receiver operating characteristic curve (ROC) analysis was used for determining the optimum cut-off MPV and MPV/PC values for predicting 60-day mortality in AIS patients. While the optimum cut-off MPV value was observed as 9.65 with a sensitivity of 54.1%, and a specificity of 65% (the area under the curve (AUC): 0.68, 95% Confidence interval (CI): 0.54- 0.78) the optimum cut-off value for MPV / PC was 0.047 with a sensitivity of 71.1% and a specificity of 68.3% (AUC: 0.73, 95% CI: 0.65 - 0.82)(Fig. 1).

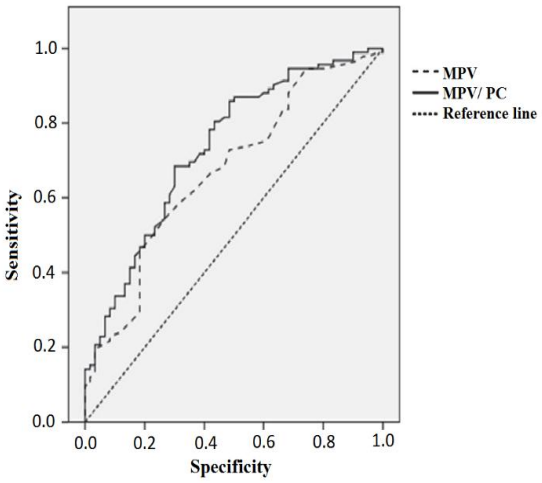

Figure 1: Receiver operating characteristic curve of MPV and MPV/PC values and 60-day mortality in acute ischemic stroke patients.

The optimum cut-off value for MPV was 9.65 (the area under the curve (AUC): 0.68, 95% Confidence interval (CI): 0.54- 0.78, sensitivity: 54.1%, specificity: 65%), the optimum cut-off value for MPV / PC was 0.047 (AUC: 0.73, 95% CI: 0.65- 0.82, sensitivity: 71.1%, specificity: 68.3%).

DISCUSSION

Inflammation, platelet activation and aggregation take a major part both in the pathogenesis of AIS and in the development of adverse events after AIS.[5,6] The platelets have a number of roles in pathophysiological processes, including hemostasis, thrombosis, vessel constriction, and the development of inflammation, which also plays an essential role in the progression of atherosclerosis.[7] Mean platelet volume (MPV) is one of the most commonly used laboratory parameters to elucidate platelet functions. Platelets, which are large due to the dense content found in their granules, are more active both metabolically and enzymatically than small ones.[8] Large platelets produce more prothrombotic factor and secrete more thromboxane A2. Besides large platelets also show more aggregation with adenosine diphosphate. Thus, the increase in MPV values leads to an increase in the secretion of prothrombotic agents.[8] Gary et al. demonstrated that high platelet volume could increase inflammation by altering blood viscosity.[9] In addition, it was revealed that the platelet volume increased in diseases such as diabetes mellitus, hypercholesterolemia, metabolic syndrome, and renal artery stenosis.[5] Recent studies have supported the respect that high MPV levels may be a risk factor for development of AMI or AIS.[4,6] The PROGRESS trial, which included 3134 patients, demonstrated an 11% increase in annual relative stroke risk in patients with high MPV levels during a mean follow-up of 3.9 years.[10] However, there are also opposite results in this respect. While Cho et al., Güldiken et al. and Ntaios et al. showed that there was no statistically significant difference between the patients with AIS and the controls in terms of MPV values.[11,13]; Arıkanoğlu et al. and O'Malley et al. determined higher MPV values in patients with AIS than control group.[9] Besides, it was revealed by Arıkanoğlu et al. that the MPV values were also effective in detecting 10-day mortality.[4,14] In our study, the MPV value, which was higher in the patient group than the control group; was even statistically significant higher especially in patients who died within 60 days as in the study of Arıkanoğlu et al. In addition, the ROC analysis revealed that MPV values above 9.65 were useful in detecting 60-day mortality in ischemic stroke patients.

It is known that, increased platelet count is associated with inflammation and elevated level of soluble CD40 ligand. Decreased platelet count in the blood circulation may be due to platelet accumulation in the inflamed area. Furthermore, the surface expression and plasma concentration of glycoprotein VI were found higher in individuals with low platelet counts.[15,17] The results of the studies about platelet count of AIS patients are contradictory. While Butterworth et al. detected lower platelet counts in the stroke group[6]; higher platelet counts were showed in patients with AIS in some other studies.[18,19] In our study, no statistically significant difference was found both between patient and control groups and non-surviving and surviving groups in terms of the number of platelets.

The MPV/PC ratio obtained by dividing the value of MPV by the number of platelets is a recently used indicator for predicting thrombotic diseases. Recent studies have indicated that MPV / PC ratio is superior to individual use of MPV and platelet count in predicting prognosis of acute coronary syndrome.[20] While the study of Azab et al. revealed the association between the MPV/PC ratio at admission and all-cause mortality for four years in patients with AMI, there was no relationship between MPV value and platelet count and mortality in these patients.[21] Elsayed et al. found that MPV and MPV/PC values were higher in patients with AIS compared to controls.[5] Furthermore, in this study, the patients with higher MPV and MPV/PC values within the first 24 hours after AIS were found to have higher MRS and NIHSS scores associated with neurological sequela, suggesting that high MPV and MPV/PC values may be associated with poor prognosis after AIS. However, the association of MPV/PC ratio with mortality in AIS patients is yet unknown. In our study, MPV and MPV/PC values were found higher in patients with AIS compatible with this study. Besides in our study the significant independent effects of both MPV and MPV/PC values were determined on the 60-day mortality of AIS. Logically, it is thought that MPV value and platelet count are generally inversely related[22]; it can be assumed that the MPV/PC ratio has more diagnostic value than MPV value alone. In our study, the AUC value of MPV/PC ratio was calculated higher than the AUC value of MPV value to determine the 60-day mortality in patients with AIS. Based on this result, it can be claimed that MPV/PC value is a more valuable predictor in determining 60-day mortality in AIS patients. In conclusion, the MPV value, which are obtained easily from the complete blood count, and so does not require additional expense and the MPV/PC value obtained by dividing the value of MPV by the platelet count were higher in the patients with AIS and these two values may be used as a predictor in determining the 60-day mortality of AIS.

There are several limitations of our study. Firstly, the design of our study was retrospective. Otherwise, the only MPV and MPV/PC values at the admission were used for the study and serial measurements were not performed in the following days. In addition, the number of patients was small, because it was a single-centered study and the medical information of all patients was not available. So this small study group may be not enough to make a generalization for population. The single end point of this study was only 60-day mortality. Furthermore, the etiologic causes of AIS and the causes of mortality were not evaluated in detail. For these reasons, there is a need for more detailed prospective randomized studies with a larger study population in the future.

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