

The effect of mean platelet volume-to-lymphocyte ratio on symptom onset in patients with carotid artery stenosis

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ABSTRACT

Objectives: In this study, we aimed to investigate the effect of mean platelet volume-to-lymphocyte ratio (MPVLR) on symptom onset in patients with moderate carotid artery stenosis (CAS).

Patients and methods: Between January 2016 and January 2018, a total of 294 patients (178 males, 116 females, mean age 57.9±9.1 years; range, 44 to 81 years) diagnosed with moderate CAS were retrospectively analyzed. The patients were divided into two groups according to their symptomatology as Group 1 (n=238) including asymptomatic patients and Group 2 (n=56) including symptomatic patients. The diagnosis of CAS was made using carotid angiography. The degree of stenosis was determined. The MPVLR was evaluated.

Results: The mean age was 53.6±8.5 years in Group 1 and 64.9±9.7 years in Group 2 (p<0.001). In the multivariate analysis, advanced age (odds ratio [OR]: 1.235, 95% confidence interval [CI]: 1.204-1.738, p=0.012), hypertension (OR: 1.030, 95% CI: 1.007-1.552, p=0.037), and MPVLR (OR: 2.156, 95% CI: 1.932-3.116, p=0.005) were found to be independent predictors of the symptom onset. The receiver operating characteristics analysis revealed that the cut-off value for MPVLR was 5.48 (area under the curve [AUC]=0.694, 95% CI: 0.563-0.806, p=0.008) with 69.7% sensitivity and 51.2% specificity.

Conclusion: Our study results show that the high MPVLR value, which is a cheap parameter that can be calculated easily, can be used as a promising parameter of CAS symptoms for clinicians.

Keywords: Carotid artery stenosis, cerebrovascular event, lymphocyte, mean platelet volume.

Atherosclerosis is a systemic disease which can affect all systems, particularly coronary, peripheral, and carotid arteries.^[1] The most catastrophic result of carotid artery stenosis (CAS) is stroke.^[2] In addition to being one of the leading causes of death today, stroke is also closely associated with morbidity. Approximately 30% of strokes are caused by CAS.^[2] Therefore, it is of utmost importance to determine the diagnosis and treatment strategies in a timely manner in patients with CAS. In such cases, symptom onset is critical to decide the most appropriate treatment modality.

Platelets play a key role in the pathogenesis of many cardiovascular diseases.^[3] The mean platelet

volume (MPV) is a marker showing platelet sizes and platelet activation.^[4] Platelets with a greater MPV value are known to be more enzymatically and metabolically active.^[4] In the literature, many studies have been conducted investigating the effect of increased MPV values on the pathogenesis and progression of cardiovascular diseases.^[5,6]

Lymphocytes also play an important role in inflammatory diseases, and low lymphocyte counts have been shown to be associated with poor clinical outcomes.^[7] Therefore, MPV-to-lymphocyte ratio (MPVLR) is used as a prognostic marker and is associated with early poor results in patients undergoing coronary intervention.^[8]

Received: June 09, 2020 Accepted: July 04, 2020 Published online: September 04, 2020

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Citation:

Erdolu B, Engin M. The effect of mean platelet volume-to-lymphocyte ratio on symptom onset in patients with carotid artery stenosis. Turk J Vasc Surg 2021;30(1):7-12

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In the present study, we aimed to investigate the effect of MPVLR, which is a simple and cheap parameter to obtain, on symptom onset in patients with moderate CAS.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital between January 2016 and January 2018. Patients diagnosed with moderate CAS were included in the study. The data of the patients were accessed from the hospital registry system and patient files. Demographic features such as age and sex, accompanying systemic disease states such as hypertension and diabetes mellitus were recorded. Those with a known systemic inflammatory disease, a previous history of endovascular or surgical intervention into the carotid artery, those with atrial fibrillation, stroke patients with permanent sequelae, and patients with hematological disease were excluded from the study. Finally, a total of 294 consecutive patients (178 males, 116 females, mean age 57.9±9.1 years; range, 44 to 81 years) were included. The patients were divided into two groups according to their symptomatology as Group 1 (n=238) including asymptomatic patients and Group 2 (n=56) including symptomatic patients. A written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee for Clinical Research of Bursa Yüksek İhtisas Training and Research Hospital (2011-KAEK-25 2019/10-11). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The most common symptoms in CAS patients are amaurosis fugax, transient ischemic attack (TIA), stroke, syncope, and vertigo. Stroke development which leaves permanent sequelae is one of the most catastrophic results. Other symptoms may occur due to microparticle embolism arising from the atherosclerotic structure in the carotid artery. In our study, stroke patients with permanent sequelae were excluded and the patients with other symptoms were assigned to Group 2.

All patients underwent Doppler ultrasound, and carotid angiography (digital subtraction angiography) was performed in patients who had at least 50% stenosis of the carotid artery. Using angiographic images, the degree of stenosis was determined according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) classification.^[1,2] According to this classification, patients with 50 to 79% stenosis were included in the study.

Routine laboratory analyses were performed using blood samples taken from the peripheral veins before angiography. Complete blood count and biochemical evaluations of the blood were done using automatic analyzers (Coulter LH 780 Analyzer, CA, USA and Beckman-Coulter AU5800, CA, USA, respectively).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or median (interquartile range [IQR]) or number and frequency. The Student's t-test was used for numerical values with normal distribution, while the Mann-Whitney U test was used for numerical data without normal distribution.

Table 1. Demographic and clinical characteristics of patients

	Group 1 (n= 238)			Group 2 (n= 56)			p
	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			53.6±8.5			64.9±9.7	<0.001†
Male sex	140	58.8		38	67.8		0.512*
Hyperlipidemia	47	19.7		23	41		0.029*
Hypertension	147	61.7		49	87.5		0.014*
Diabetes mellitus	424	18.4		13	23.2		0.613*
Tobacco use	58	24.3		21	37.5		0.296*
Chronic obstructive pulmonary disease	39	16.3		14	25		0.485*
Coronary artery disease	88	36.9		31	55.3		0.041*
Peripheral arterial disease	43	18		19	33.9		0.146*
Body mass index (kg/m ²)			26.9 ±5.1			28.2±4.6	0.207†

† Student's t-test; * Chi-square test.

Table 2. Laboratory data of patients

	Group 1 (n=238)		Group 2 (n=56)		p*
	Median	IQR	Median	IQR	
White blood cell (10 ³ /μL)	7.9	4.2-14.9	8.2	4.4-14.2	0.294
Hematocrit (%)	39.8	32.5-55	40.6	32.3-52	0.357
Platelet (10 ³ /μL)	239.8	134-479	249	130-490	0.196
Neutrophil (10 ³ /μL)	4.3	1.6-10	4.5	2.3-11.3	0.212
Lymphocyte (10 ³ /μL)	2	0.7-4.1	1.6	0.7-3.6	0.022
Mean platelet volume (fl)	8.6	6.5-10.7	9.2	7-12.1	0.019
Urea (mg/dL)	13	10-36	14	10-40	0.294
Creatinine (mg/dL)	1.1	0.5-1.78	0.94	0.6-1.87	0.276
C-reactive protein (mg/dL)	7.9	0.6-44.4	9.3	1-61.9	0.012
MPVLR	3.58	3.22-6.34	5.42	3.94-7.96	<0.001

IQR: Interquartile range; * Mann-Whitney U test; MPVLR: Mean platelet volume-to-lymphocyte ratio.

The chi-square test was carried out to compare categorical variables. A multivariate logistic regression analysis was utilized to evaluate significant parameters in the univariate analysis for predicting symptomatic patients. The receiver operating characteristic (ROC) curve was used to evaluate the predictive value MPVLR for symptoms and the area under the curve (AUC) was calculated. A *p* value of <0.05 was considered statistically significant.

RESULTS

The mean age was 53.6±8.5 years in Group 1 and 64.9±9.7 years in Group 2 (*p*<0.001). There was no statistically significant difference between the groups in terms of sex, diabetes mellitus, tobacco use, chronic obstructive pulmonary disease, peripheral arterial disease, and body mass index. However, the rates of hypertension, hyperlipidemia, and coronary artery disease were significantly higher in Group 2 (*p*=0.014, *p*=0.029, and *p*=0.041, respectively) (Table 1).

Table 3. Multivariate logistic regression analysis results

Variables	Exp(B)	95% CI	p
	Odds ratio	Lower-upper	
Age	1.235	1.204- 1.738	0.012
Coronary artery disease	0.834	0.614- 1.156	0.228
C-reactive protein	1.056	0.794- 1.379	0.195
Hyperlipidemia	1.434	0.816- 1.634	0.114
Hypertension	1.030	1.007- 1.552	0.037
MPVLR	2.156	1.932- 3.116	0.005

CI: Confidence interval; MPVLR: Mean platelet volume-to-lymphocyte ratio.

Laboratory data of the patients are presented in Table 2. There was no significant difference between the groups in terms of hematocrit, white blood cell count, platelet, urea, and creatinine values. However, the MPV, C-reactive protein (CRP), and MPVLR values were significantly higher in Group 2 (*p*=0.019, *p*=0.012, and *p*<0.001, respectively). The lymphocyte count was higher in Group 1 (*p*=0.022).

Multivariate logistic regression analysis was performed to identify the predictors of symptom onset

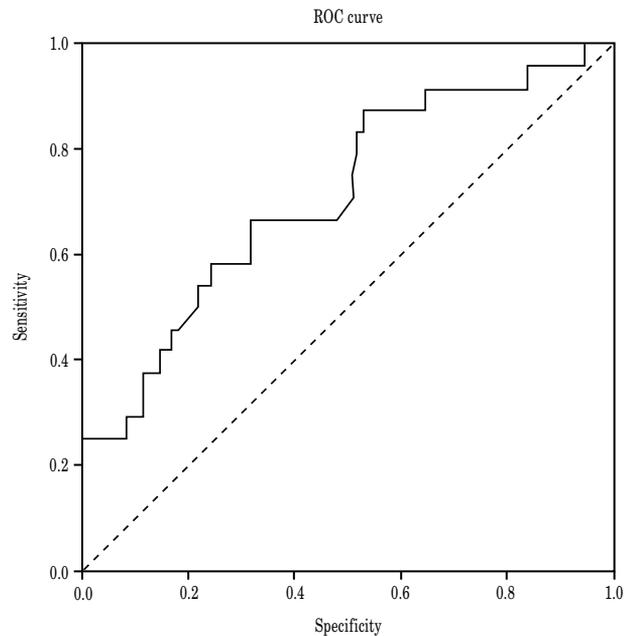


Figure 1. The ROC curve and AUC for mean platelet volume-to-lymphocyte ratio (cut-off= 5.48, AUC: 0.694, 95% CI: 0.563-0.806, *p*=0.008, 69.7% sensitivity, 51.2% specificity).

ROC: Receiver operating characteristic; AUC: Area under the curve; CI: Confidence interval.

in patients with moderate CAS (Table 3). Advanced age (odds ratio [OR]: 1.235, 95% confidence interval [CI]: 1.204-1.738, $p=0.012$), hypertension (OR: 1.030, 95% CI: 1.007-1.552, $p=0.037$), and MPVLR (OR: 2.156, 95% CI: 1.932-3.116, $p=0.005$) were found to be independent predictors of symptom onset. The ROC analysis revealed that the cut-off value for MPVLR was 5.48 (AUC=0.694, 95% CI: 0.563-0.806, $p=0.008$) with 69.7% sensitivity and 51.2% specificity (Figure 1).

DISCUSSION

Carotid artery stenosis is one of the most important atherosclerotic cardiovascular diseases. Symptoms of CAS appear due to hypoperfusion and usually embolization.^[9] Stroke and mortality are catastrophic results. In addition, symptoms such as amaurosis fugax, syncope, and TIA can predict a permanent stroke. Asymptomatic CAS patients who have up to 70 to 80% stenosis can be followed medically.^[10] In contrast, symptomatic patients who had >50% stenosis should be treated with invasive methods.^[10] In the current study, we investigated the possible factors which could affect the development of symptoms in patients with moderate CAS. Our study results showed that advanced age, hypertension, and MPVLR were independent predictors of the development of symptoms in these patients.

Platelets are blood cells which have important functions in cardiovascular diseases. In addition to their known coagulation roles, they also play an important role in maintaining endothelial integrity.^[11] The MPV is known to be an indicator of platelet activation.^[11,12] In a study including 3,134 patients with known cerebrovascular disease, MPV values were found to be higher in patients who had stroke.^[13] In another study, the MPV was associated with ischemic stroke severity and had a high value for discriminating severe from mild ischemic stroke.^[14] In addition, in a study involving 2,215 patients, the relationship between silent brain infarcts and MPV was investigated.^[15] The patients who underwent brain magnetic resonance imaging for routine health screening were included in the study. According to these imaging results, the MPV values were higher in patients with infarct areas. In another study investigating the relationship between cardiovascular diseases and MPV, high MPV values were found to be associated with early mortality in patients with myocardial infarction.^[16] Similarly, Celik et al.^[17] measured higher MPV values at the time of admission among acute myocardial infarction

patients which were associated with in-hospital major adverse cardiovascular events. Consistent with these findings, we also found higher MPV values in the symptomatic patient group. Given the fact that one of the most important factors in the development of symptoms in carotid artery patients is microembolism, high MPV values may be the reason for this result.

Lymphocytes play an important role in cardiovascular diseases. Therefore, the neutrophil-to-lymphocyte ratio (NLR) has been extensively investigated.^[18] The NLR elevation due to increased neutrophil and decreased lymphocyte counts have prognostic values in many cardiovascular diseases.^[18] Atherosclerosis is an inflammatory pathway and neutrophils contribute to this process by secreting various inflammatory mediators.^[12] In particular, due to the release of myeloperoxidase and superoxide radicals, the atherosclerotic plaque structure becomes more vulnerable, thereby, increasing the risk for plaque rupture, thrombosis, and microembolism.^[12] Lymphocytes can prevent this undesirable progression caused by neutrophils through immunomodulatory effects.^[19] Therefore, elevated lymphocyte count has protective effects, while decreased levels reveal poor prognosis in cardiovascular diseases. In our study, lymphocyte counts were lower in symptomatic patients. This may be the reason for the occurrence of the symptoms by causing instability of the atherosclerotic structure. In addition, the NLR values were significantly higher in Group 2.

Altogether, these findings indicate that MPVLR is an important parameter. In a study conducted by Ornek and Kurtul,^[20] the effect of MPVLR on coronary collateral circulation was investigated in 332 patients with stable angina as assessed by coronary angiography. At the end of the study, the authors found that increased MPVLR values were associated with decreased coronary collateral circulation. In another study including diabetic acute myocardial infarction patients, the MPVLR values were associated with early and late mortality.^[21] The authors also reported that MPVLR was more efficient than platelet-to-lymphocyte ratio in predicting late mortality. In a prospective study conducted by Chen et al.,^[22] the potent of MPVLR was investigated in predicting prognosis after thrombolytic therapy in patients with ischemic stroke. In this study, 241 patients were included and elevated MPVLR values were found to be associated with poor results. In our study, similarly, we found the MPVLR to be an independent predictor of symptom onset in patients with moderate CAS. Besides MPVLR, advanced age

and hypertension were also independent predictors of the onset of symptoms. Advanced age has been shown to be prognostic in many diseases. In a study investigating the relationship between platelet count and silent brain infarcts, advanced age was found to be associated with those infarcts.^[14] On the other hand, hypertension increases the stress on the vascular bed and increased endothelial stress can lead to thrombogenic events and microembolizations as a result of ruptures in the atherosclerotic plaque structures.^[1] This condition can develop in the cerebral, coronary or peripheral arterial systems.^[1]

Diagnosis and treatment of CAS patients before development of ischemic stroke is crucial. Although endovascular methods have become more popular in recent years, surgery can be performed as the gold-standard method with various techniques.^[23,24] Detailed imaging methods which can visualize plaque structures are also effective in the timing of treatment.^[25] However, these methods have not become widespread yet.

The main limitations of the present study are its single-center and retrospective design. Although our sample size seems to be sufficient, further large-scale, multi-center, prospective studies are needed to confirm these findings.

In conclusion, CAS is a disease with significant clinical consequences. In addition to the degree of stenosis, the presence of symptoms is also important to decide the treatment modality in patients with CAS. Based on our study results, we can speculate that the high MPVLR value, which is a cheap parameter that can be easily obtained, can be used as a promising parameter of CAS symptoms for clinicians.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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