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Original Article NEUROLOGY

The importance of inflammatory biomarkers in ischemic stroke patients with carotid artery stenosis

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ABSTRACT

OBJECTIVE: This study aims to investigate inflammatory markers and their relationship with the degree of stenosis in ischemic stroke patients with carotid artery stenosis.

METHODS: This retrospective case–control study was conducted with 70 newly diagnosed ischemic stroke patients and 70 age- and gender-matched healthy controls. Laboratory analyses were carried out including serum hemogram, biochemistry profiles, erythrocyte sedimentation rate, and C-reactive protein (CRP). Mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-high-density lipoprotein cholesterol ratio (MHR) values were calculated, and compared between the patients and healthy controls. Patients were divided into two groups according to the degree of arterial carotid stenosis. The degree of carotid stenosis was <50% in Group 1 and it was 50% and above in Group 2.

RESULTS: In the patient group, neutrophil, monocyte, MPV, CRP, sedimentation, MHR, PLR, and NLR levels were significantly higher than the control group. There was no significant correlation between the level of carotid stenosis and inflammatory biomarkers. There was a significant correlation between the presentation NIHSS value and CRP, PLR, and NLR values.

CONCLUSION: Inflammatory biomarker values were higher in stroke patients with carotid artery stenosis than in healthy individuals. However, they should neither be used to predict the degree of carotid artery stenosis.

Keywords: Carotid artery stenosis; inflammatory markers; ischemic stroke; laboratories.

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The cerebrovascular attack is the most common, life-threatening neurological disorder. It ranks 3rd as a cause of death after heart disease and cancer, and 1st in terms of morbidity [1]. Inflammation is very significant in the pathogenesis of both hemorrhagic and ischemic stroke. Endothelial activation, disruption of the blood-brain barrier, leukocyte infiltration, and large amount of accumulation of oxidant and inflammatory mediators occur rapidly within hours and lead to secondary brain damage [2–5].

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most commonly used inflammatory markers in recent studies [6, 7]. Decreased high-density lipoprotein cholesterol (HDL-C) levels and increased monocyte counts are other markers of inflammation. Monocyte-to-HDL-C ratio (MHR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been proposed as new inflammatory biomarkers [4, 5, 8, 9]. Hence, the aim is to investigate ESR, CRP, MHR, NLR, PLR, and

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Mean platelet volume (MPV) levels and their relationship with the degree of stenosis in ischemic stroke patients with carotid artery stenosis.

MATERIALS AND METHODS

Our study which is a retrospective case-control study consists of 70 newly diagnosed ischemic stroke patients with carotid artery stenosis and 70 age- and gender-matched healthy controls. We screened the medical results of the patients who were diagnosed with acute ischemic stroke retrospectively. The patients who consulted our emergency department within the first 24 h following the onset of symptoms were investigated, and only the patients with available routine venous blood samples were included in the study. Myocardial infarction, congestive heart failure, heart valve disease, infections, autoimmune diseases, malignancies, atrial fibrillation, and pregnancy/puerperium were the exclusion criteria. Doppler carotid ultrasonography monitoring was performed in all patients. Patients were divided into two groups according to the degree of carotid artery stenosis. The degree of carotid stenosis was <50% in Stenosis I group and it was 50% and above in Stenosis II group.

With the usage of the National Institutes of Health Stroke Scale (NIHSS), clinical severity was evaluated. A control group among healthy people was selected. Laboratory analyses include serum hemogram and full biochemistry profiles including study parameters, which were measured with automated standard laboratory methods. Hematological test samples were collected in tubes with EDTA and biochemical tests into dry tubes. An automated hematology analyzer XE-1200 (Sysmex, Kobe, Japan) was used for each blood count measurement. A computerized database was used to receive laboratory data. The results of the groups were compared. The MHR, NLR, and PLR values were calculated to make a comparison between the patients and the healthy groups.

Ethical approval for this study was obtained from the Istanbul Training and Research Hospital Clinical Research Ethics Committee with the date August 03, 2018, and number 1377. The study was performed by the principles of the Declaration of Helsinki.

Statistical Analysis

Mean, standard deviation, median, lowest-highest values, frequencies, and ratio values were used in the descriptive analysis of the data. The distribution of variables was measured using the Kolmogorov–Smirnov test. Independent samples t-test and Mann–Whitney U test were used in the analysis of independent quantitative data. The Chi-square test was used to analyze qualitative independent data, and the Fischer's exact test was used when Chi-square test conditions were not seen. In the correlation analysis, Spearman's correlation analysis was used. The effect level and cutoff value were investigated using the ROC curve. The effect level was investigated by univariate and multivariate logistic regression. SPSS 22.0 program was used in the analysis (Version 22, Chicago, IL, USA).

Highlight key points

- Stroke is the second leading cause of death in the world.
- Various inflammatory parameters from routine blood tests can give information about cerebrovascular diseases.
- The inflammatory biomarkers were significantly higher in patients with ischemic stroke.

RESULTS

There was no difference between patients and group controls in terms of age and gender distribution ($p>0.05$). In the patient group, white blood cell (WBC), neutrophil, monocyte, MPV, CRP, sedimentation, MHR, PLR, and NLR values were significantly higher than the control group ($p<0.05$). In the patient group, PLT, lymphocyte, and HDL values were significantly lower than in the control group ($p<0.05$).

The demographic properties, laboratory findings of the patients, and controls are presented in Table 1.

There was no significant difference between the age and gender distribution of patients in the Stenosis I and Stenosis II groups ($p>0.05$).

In the Stenosis I and Stenosis II groups, PLT, monocyte, HDL, WBC, neutrophil, MPV, CRP, sedimentation, MHR, PLR, and NLR values were not different significantly ($p>0.05$) (Table 2).

There was no significant correlation between the presentation NIHSS value and WBC, PLT, neutrophil, lymphocyte, monocyte, MPV, HDL, and sedimentation values ($p>0.05$). There was a significant correlation between the presentation NIHSS value and CRP, PLR, and NLR values ($p<0.05$) (Table 3).

Table 1. Comparison of demographic and laboratory findings of the patient and control groups

	Control group			Patient group			p
	AVG±SD	n–%	Median	AVG±SD	n–%	Median	
Age	66.1±9.2		65.5	67.7±10.9		66.5	0.442
Gender							0.160
Female		30–42.9			22–31.4		
Male		40–57.1			48–68.6		
WBC	6.9±1.8		6.8	8.8±2.9		8.0	**0.000**
PLT ($\times 10^4$)	24.6±4.5		24.5	24.1±10.0		21.6	**0.033**
Neutrophil	4.0±1.0		4.1	5.7±2.6		4.9	**0.000**
Lymphocyte	2.6±0.6		2.4	2.1±1.2		1.9	**0.000**
Monocyte	0.5±0.2		0.5	0.7±0.2		0.7	**0.000**
MPV	9.7±0.7		9.5	10.7±0.8		10.7	**0.000**
HDL	52.5±14.2		49.5	38.0±9.4		38.0	**0.000**
CRP	0.34±0.12		0.35	1.46±1.84		0.66	**0.000**
MHR	1.07±0.50		1.01	1.91±0.95		1.74	**0.000**
PLR	1.00±0.30		1.00	1.46±0.97		1.22	**0.010**
NLR	1.64±0.55		1.44	3.86±4.02		2.50	**0.000**
Sedimentation	19.8±8.2		20.0	31.8±20.5		29.0	**0.000**

[t] t test/[m]Mann–Whitney u test/[X²] Chisq Chi-square; AVG: Average; SD: Standard deviation; WBC: White blood cell; MPV: Mean platelet volume; HDL: High-density lipoprotein; CRP: High sensitivity C-reactive protein; MHR: Monocyte-to-high-density lipoprotein ratio; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio.

DISCUSSION

Lymphocytes-mononuclear cells are the major inflammatory units in the body and they have a role in the formation of carotid atherosclerotic plaque and carotid artery stenosis. The prolonged inflammatory process causes the development and formation of carotid artery stenosis [7]. There is a severe and negative correlation between high-density lipoprotein (HDL) cholesterol and atherosclerosis. HDL leads to the inhibition of cytokine-induced expression of inflammatory adhesion molecules in endothelial cells, inhibiting monocyte and endothelium connection [10, 11]. Besides its antiatherosclerotic effects, it is stated that HDL avoids monocyte activation. It has been shown that activated monocytes can be inhibited by HDL and HDL declines CD11b expression dose-dependency and leads to the activation of primary human monocytes [12]. The monocyte-to-HDL ratio which is a marker obtained by dividing the serum level of monocyte count to HDL cholesterol level is an inflammatory marker that was recently recognized. Some studies on the MHR have shown the role of this ratio in anticipating inflammation [13, 14]. The MHR is a poor prognosis for cardiovascular mortality and it is an independent predictor of cardiovascular diseases in chronic renal failure [9]. In a study, it was determined that the MHR level was significantly higher in patients with symptomatic carotid stenosis of 50% or more [15]. However, in our study, no significant correlation was found between carotid stenosis level and MHR.

Although there are many studies on the effectiveness of inflammation in atherosclerosis and ischemia, there are few studies to state that there is a significant relationship between NLR and acute stroke notably [4, 16, 17]. In a study by Tokgoz et al. [4], NLR is found to be associated with short-term mortality in acute stroke patients. In their study, they found that short-term mortality sensitivity and specificity were 83.1% and 62%, respectively, when NLR was higher than five, and there was a positive relation between NLR and NIHSS scores. NLR increase has been declared to be significant in patients who died [16]. In another study, it was determined, higher NLR is associated with embolic stroke in non-valvular AF patients [17]. In our study, it was found that there was an important relationship between the presentation NIHSS value and CRP, PLR, and NLR values.

Table 2. Evaluation of the relationship between the degree of stenosis and laboratory parameters in the patient group

	Stenosis I			Stenosis II			p
	AVG±SD	n–%	Median	AVG±SD	n–%	Median	
Age	65.5±11.2		61.0	68.1±10.9		68.0	0.419
Gender							0.701
Female		4–36.4			18–30.5		
Male		7–63.6			41–69.5		
WBC	9.6±2.8		9.4	8.6±3.0		7.9	0.255
PLT (x10^4)	23.8±7.8		21.9	24.2±10.4		21.5	0.936
Neutrophil	5.6±2.0		5.0	5.7±2.7		4.9	0.747
Lymphocyte	2.5±0.8		2.4	2.0±1.3		1.8	**0.029**
Monocyte	0.8±0.2		0.7	0.7±0.2		0.6	0.074
MPV	11.0±1.3		11.0	10.7±0.7		10.6	0.336
HDL	37.6±10.9		38.0	38.1±9.2		38.0	0.916
CRP	1.3±1.3		0.5	1.5±1.9		0.7	0.529
Sedimentation	31.1±13.9		36.0	32.0±21.6		28.0	0.716
Monocyte/HDL x100	2.3±1.3		1.7	1.8±0.9		1.8	0.223
PLR	1.1±0.9		0.9	1.5±1.0		1.3	0.112
NLR	2.7±2.2		2.0	4.1±4.3		2.8	0.112

[m]Mann–Whitney u test/X^2 Chi-square test; AVG: Average; SD: Standard deviation; WBC: White blood cell; MPV: Mean platelet volume; HDL: High-density lipoprotein; CRP: High sensitivity; C-reactive protein; ESR: Erythrocyte sedimentation rate; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio.

Table 3. Evaluation of the relationship between presentation NIHSS scores and laboratory parameters

	WBC	PLT (×10^4)	Neutrophil	Lymphocyte	Monocyte
Presentation NIHSS					
r	0.128	0.184	0.228	-0.202	-0.049
p	0.291	0.127	0.057	0.093	0.690
	MPV	Cholesterol	Triglyceride	HDL	LDL
Presentation NIHSS					
r	-0.020	-0.094	-0.138	-0.193	-0.086
p	0.867	0.438	0.253	0.109	0.479
	CRP	PLR	NLR	Sedimentation	MHR
Presentation NIHSS					
r	0.277	0.247	0.275	0.161	0.089
p	0.020	0.039	0.021	0.183	0.464

Spearman Correlation. NIHSS: National Institutes of Health Stroke Scale; WBC: White blood cell; PLT: Platelet; MPV: Mean platelet volume; HDL: High-density lipoprotein; LDL; Low-density lipoprotein; CRP: High sensitivity C-reactive protein; MHR: Monocyte-to-high-density lipoprotein ratio; PLR: Platelet-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio.

The platelets play significant roles in atherosclerosis, and the relationship between MPV, which is a platelet activation marker, and the rate of stenosis in the carotid artery was displayed [18]. Some studies investigate the severity of carotid artery disease and the development of symptoms, and predict the development of stroke using the PLR value [19, 20]. As et al. [20] found that high PLR and NLR values revealed in asymptomatic patients with stenosis of 50% or more in the carotid arteries are independent predictors of symptom development.

The previous studies relating CRP level to carotid stenosis have demonstrated conflicting findings. Huang et al. [21] suggested that CRP was associated with asymptomatic carotid artery stenosis, especially in older patients. However, the Framingham heart Study showed that CRP was positively associated with internal carotid artery intima-media thickness, but not with carotid stenosis [22]. Puz et al. [23] found a relation between the activity of inflammatory markers and atherosclerotic unstable internal carotid artery stenosis. However, they claimed that there is no relationship between the serum concentration of inflammatory markers and the degree of carotid artery stenosis which is consistent with our results.

Our study had some limitations as it was a retrospective and non-randomized study with a relatively small number of participants. Differences in the frequency of comorbid chronic diseases (such as hypertension, which is a risk factor for stroke) between groups may affect the results. Patients with stenosis below 50% could not be categorized separately because of the small number of participants.

Conclusion

We have shown that the inflammatory biomarkers were significantly higher in patients with ischemic stroke when compared to the control group. However, there was no significant correlation between the degree of carotid stenosis and inflammatory markers. Hence, they should neither be used to predict the degree of carotid artery stenosis.

Ethics Committee Approval: The Istanbul Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 03.08.2018, number: 1377).

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Authorship Contributions: Concept – AT; Design – AY; Supervision – ABD; Fundings – ABD; Materials – ABD; Data collection and/or processing – AT; Analysis and/or interpretation – AY; Literature review – AY; Writing – AT; Critical review – AY.

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