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The association between symptomatic carotid stenosis and hematological parameters

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Abstract

Background & Objectives: Symptomatic carotid artery stenosis (SCAS) is one of the most important causes of ischemic stroke. We aimed to investigate the relationship between hematological and inflammatory parameters in patients with SCAS and controls. *Method:* Patients who underwent digital subtraction angiography for SCAS were evaluated retrospectively. Patients with carotid stenosis greater than 50% who had a stroke in the last six months were included in the study. Clinical and sociodemographic characteristics, stent characteristics, filter use, balloon dilatation status, arch type, presence of contralateral occlusion, and complication status were recorded. Hemogram was evaluated using fluorescence flow cytometry. Data were analyzed among patients with SCAS, ischemic stroke patients without stenosis and healthy control group. *Results:* SCAS was higher in patients with advanced age, male, hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, and a history of stroke as compared to healthy individuals ($p<0.001$). Smoking and atrial fibrillation were higher in group without carotid stenosis and who had ischemic stroke ($p<0.001$). Hemoglobin and hematocrit values were higher in healthy control group ($p=0.001$). Red blood cell distribution width (RDW) and platelet/lymphocyte ratio (PLR) were higher in SCAS patients ($p<0.001$); Neutrophil and neutrophil/lymphocyte ratio (NLR) was higher in the group with stroke and without stenosis ($p <0.001$). There was no relationship between blood parameters and procedure technical features and complications ($p> 0.05$).
Conclusion: Hematologic parameters like PLR, NLR and RDW level are correlated with SCAS. PLR, NLR and RDW value can be an inexpensive and useful biomarker for predicting SCAS.

Keywords: Carotid stenosis, ischemic stroke, hematological parameters

INTRODUCTION

Cerebrovascular diseases (CVD) are the second leading cause of death in the world and the first cause of disability in adulthood.[1] About 75% of ischemic strokes is located at the anterior system, one third of these are caused by carotid artery stenosis (CAS). Strokes due to CAS have a higher risk of recurrence within the first seven days. The risk of recurrence in the first two years of stroke due to symptomatic carotid artery stenosis (SCAS) is up to 26% in those treated with medication after the first event.[2] As the degree of CAS increases, the risk of stroke increases. While the risk of stroke is 1% in stenoses below 60%, this risk increases to 3-5% over 80%.[3] While the probability of having a stroke again in the first two days in a patient with symptomatic CAS is 5.5%, this risk reaches 20% within 90 days.[4]

Carotid color doppler, computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) can be used noninvasively in the diagnosis of CAS. Each method has its own advantages and disadvantages. The definitive diagnosis is made by digital subtraction angiography (DSA).[4,5]

The most important cause affecting the internal carotid artery (ICA) is atherosclerosis. Inflammation plays an important role in both ischemic stroke and atherosclerosis.[5,6] Many of the studies with blood parameters as an indicator

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of ischemia and inflammation were significant. Neutrophil/Lymphocyte ratio (NLR) has been evaluated as a marker of systemic inflammation. There are studies showing that NLR levels and mean platelet volume (MPV) levels also increase in stroke patients.[7] It was found that the rate of CAS was higher in patients with a high Platelet/Lymphocyte ratio (PLR).[8] There are publications showing that the sensitivity of the red cell distribution width (RDW) or mean erythrocyte volume for ischemic stroke is 57%, the specificity is 86%, and the accuracy rate is 65%.[9]

It has been shown that blood parameters can predict disease progression and mortality in diseases such as stroke, coronary artery disease, and diabetes mellitus. However, different results were observed between studies. In this study, we aimed to examine the relationship between various easily accessible hematological parameters in stroke patients due to CAS.

METHODS

Ethical procedure and patient population

Approval was obtained from the Local Ethics Committee for Clinical Researches at Selcuk University before the study (Approval number:2019/36). In this study patients who applied to Selcuk University Faculty of Medicine Neurology Clinic between 1 November 2017 and 31 December 2018 due to CAS and underwent DSA were evaluated retrospectively. The files of the patients were reviewed. Hemogram parameters of the patients at the time of first admission were evaluated within 24 hours. Patients with comorbidities that were thought to affect the study data and results were excluded from the study (Table 1).

A total of 122 patients were included in our study. Carotid stent was placed in 100 patients. Anemia in 12 patients, neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease in 4 patients, infection in 8 patients, chronic renal failure in 3 patients and various malignant diseases in 3 patients, totaled 30 patients were excluded from the study. As a result, 92 patients were included. Carotid artery stenting was performed in 70, and carotid endarterectomy in 22. A control group was formed with 130 patients with cerebrovascular disease and 135 healthy volunteers.

Data collection and analysis

The files of the patients were scanned for age, gender, diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease and previous cerebrovascular disease, smoking, atrial fibrillation, hemogram (leukocyte, hemoglobin, hematocrit, mean platelet volume (MPV), neutrophil count, RDW), platelet count, platelet distribution width (PDW), lymphocyte count, monocyte count, NLR and PLR parameters were recorded.

CAS leading to minor infarction or transient ischemic attack in the last six months, it was evaluated as SCAS. These patients consisted of patients who were symptomatic due to carotid artery stenosis and had more than 50% stenosis according to the NASCET method. CAS degree values were based on DSA.

Blood parameters were analyzed between symptomatic carotid stenosis patients who underwent stenting, and healthy volunteers and symptomatic patients. In addition, risk factors,

Table 1: Study inclusion and exclusion criteria

Inclusion Criteria
– Symptomatic due to carotid artery disease and 50% according to NASCET method those with stenosis.
– Routine laboratory values were examined in the first 24 hours after acute ischemic stroke and those whose electrocardiogram was examined.
– Absence of permanent sequelae.
– The degree of carotid artery stenosis was determined by DSA.
– Having undergone neuroimaging (computerized tomography (CT) or MRI) to the patients
Exclusion Criteria
– Intracranial hemorrhage, systemic inflammatory patient cancer, acute coronary syndrome. Cases with severe heart valve disease, renal and hepatic malaise, hematological disease, body temperature of 37°C and above, presenting with active infection, plasma leukocyte level of 12.000/μL and above, using anti-inflammatory drugs or antibiotics, and anemia.
– Those with neurodegenerative disease

age, symptomatic side, and percentage of stenosis were examined in patients with CAS by forming a different group, including patients who underwent carotid endarterectomy (CEA) due to CAS. Hemogram parameters were performed by flow cytometry method on Beckman Coulter DXH 800 (USA). In addition, the determination of leukocyte sub-parameters was carried out by laser method.

Statistical analysis

The obtained data were analyzed with SPSS 21.0 (SPSS Inc., Chicago, Illinois, USA) package program. The conformity of the variables used in the study to the normal distribution, Kolmogorov-Examined with the Smirnov test. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as numbers and percentages. Categorical variables were compared with Chi-square and Fisher's Exact tests, and continuous variables were compared with Student-t and Mann-Whitney U tests. Comparisons of more than two groups were made with the Kruskal Wallis test and one-way analysis of variance (One-way ANOVA). Tukey HSD, Bonferroni and Tamhane's T2 tests were used to determine the group causing significance. Statistical analysis of the data obtained in this study was performed with a confidence interval of 95% and a $p<0.05$ was considered significant.

RESULTS

Cases included in the study were examined in 3 different groups: Group-1 (healthy individuals), Group-2 (those who had CVD but did not have CAS), and Group-3 (those who had CVD and had CAS). All demographic parameters of groups were demonstrated in Table 2.

Table 2: Comparison of healthy volunteers, patients with CVD and patients with CAS in terms of blood parameters, age, gender, history

Variable	Group-1 (n=135)	Group-2 (n=130)	Group-3 (n=92)	P value
Age	59.8±4.5	65.6±12.6	69.4±8.8	p<0.001
Gender				p<0.001
Male	65 (%48.1)	72 (55.4%)	74 (80.4%)	
Female	70 (%51.9)	58 (44.6%)	18 (19.6%)	
Hypertension	-	102 (78.5%)	77 (83.7%)	p<0.001
Hyperlipidemia	-	26 (20%)	44 (47.8%)	p<0.001
Diabetes mellitus	-	49 (37.7%)	36 (39.1%)	p<0.001
Coronary artery disease	-	53 (40.8%)	44 (47.8%)	p<0.001
Smoking	22 (16.3%)	56 (43.1%)	35 (38%)	p<0.001
Stroke history in family	-	7 (5.4%)	4 (4.3%)	0.02
Stroke history for patient	-	48 (36.9%)	82 (89.1%)	p<0.001
Atrial fibrillation	-	24 (18.5%)	15 (16.3%)	p<0.001
Hemoglobin	14.4±1.4	13.6±1.5	13.8±1.1	p<0.001
Hematocrit	42.9±3.8	41.1±4.3	41.4±3.2	0.001
Platelet	250.6±52.4	244.9±87	252.4±65.9	0.09
WBC	7.2±1.6	8.3±1.9	8±1.7	p<0.001
Neutrophil	4.1±1.2	5.6±2	5.2±1.6	p<0.001
Lymphocyte	2.3±0.6	2±0.8	2.1±0.8	p<0.001
Monocyte	0.6±0.4	0.6±0.2	0.6±0.2	0.001
RDW	13.7±1.1	14.4±1.6	14.3±1.3	p<0.001
MPV	8.5±0.9	8.4±1	8.4±0.9	0.49
NLR	2±1.2	3.4±2.4	3±1.9	p<0.001
PLR	119.1±46	135.5±57.8	141.6±71.6	0.03

WBC: white blood cells, RDW: Red cell distribution width, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/Lymphocyte ratio, CVD: Cerebrovascular disease, MPV: Mean platelet volume

When these three groups were compared with each other in terms of various variables, there was a statistically significant difference between all three groups in terms of age, gender, hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, smoking, family history, previous CVD, and atrial fibrillation (p<0.001, respectively). p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p=0.02, p<0.001 and p<0.001) (Table 2). Compared to the other groups, the patients in Group-3 were older (69.4+8.8 years), male gender was more (80.4%), hypertension (83.7%), hyperlipidemia (47.8%). diabetes mellitus (39.1%), coronary artery disease (47.8%) and previous CVD (89.1%) were more common. On the other hand, smoking (43.1%) and atrial fibrillation (18.5%) were statistically more common in Group-2 compared to other groups.

When the hematological parameters were examined, the hemoglobin value of the patients in Group-1 was statistically higher when compared to the other groups. (Group-1: 14.4±1.4, Group-2: 13.6±1.5, Group-3: 13.8±1.1, p<0.001; Table 2). When comparing the subgroups, there was a significant difference between Group-1 and Group-2 (p<0.001) and between Group-1 and Group-3 (p=0.001), while there was a significant difference between Group-2 and Group-3 (p=0.84), no statistical difference was detected. (Table 3).

The hematocrit values of the patients in Group-1 were statistically higher than the other

Table 3: Comparison of hemogram parameters of healthy volunteers, patients with CVD and patients with CAS in pairs

			P value
Hemoglobin	Group-1	Group-2	p<0.001
	Group-1	Group-3	0.001
	Group-2	Group-3	0.84
Hematocrit	Group-1	Group-2	0.001
	Group-1	Group-3	0.004
	Group-2	Group-3	0.92
WBC	Group-1	Group-2	p<0.001
	Group-1	Group-3	0.001
	Group-2	Group-3	0.19
Neutrophil	Group-1	Group-2	p<0.001
	Group-1	Group-3	p<0.001
	Group-2	Group-3	0.28
Lymphocyte	Group-1	Group-2	0.003
	Group-1	Group-3	0.03
	Group-2	Group-3	0.59
Monocyte	Group-1	Group-2	0.45
	Group-1	Group-3	0.29
	Group-2	Group-3	0.71
RDW	Group-1	Group-2	p<0.001
	Group-1	Group-3	0.001
	Group-2	Group-3	0.99
NLR	Group-1	Group-2	p<0.001
	Group-1	Group-3	p<0.001
	Group-2	Group-3	0.51
PLR	Group-1	Group-2	0.03
	Group-1	Group-3	0.02
	Group-2	Group-3	0.87

WBC: white blood cells, RDW: Red blood cell distribution width, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/Lymphocyte ratio, Group-1 (healthy individuals), Group-2 (those with CVD but not CAS), Group-3 (those with ischemic stroke and CAS)

groups (Group-1: 42.9±3.8, Group-2: 41.1±4.3, Group-3: 41.4±3.2, p=0.001; Table-3.1). When comparing the subgroups, there was a significant difference between Group-1 and Group-2 (p=0.001) and between Group-1 and Group-3 (p=0.004), while there was a significant difference between Group-2 and Group-3 (p=0.92). no statistical difference was detected (Table 3).

When the platelet value was compared between all groups, no statistically significant difference was found. (Group-1: 250.6±52.4, Group-2: 244.9±87, Group-3: 252.4±65.9, p=0.09; Table 2).

The WBC values of the patients in Group-2 were statistically higher than the other groups (Group-1: 7.2±1.6, Group-2: 8.3±1.9, Group-3: 8±1.7, p<0.001; Table 2). When comparing the subgroups, there was a significant difference between Group-1 and Group-2 (p<0.001) and between Group-1 and Group-3 (p=0.001), while there was a significant difference between Group-2 and Group-3 (p=0.19) no statistical difference was detected (Table 3)

Neutrophil values of the patients in Group-2 were statistically higher than the other groups (Group-1: 4.1±1.2, Group-2: 5.6±2, Group-3: 5.2+1.6, p<0.001; Table 2). When comparing the subgroups, there was a significant difference between Group-1 and Group-2 (p<0.001) and between Group-1 and Group-3 (p<0.001), while there was a significant difference between Group-2 and Group-3 (p=0.28) no statistical difference was found (Table 3).

Lymphocyte value of the patients in Group-1 was statistically higher than the other groups (Group-1: 2.3±0.6, Group-2: 2+0.8, Group-3: 2.1±0.8, p<0.001; Table 2). When comparing the subgroups, there was a significant difference between Group-1 and Group-2 (p=0.003) and between Group-1 and Group-3 (p=0.03), while there was a significant difference between Group-2 and Group-3 (p=0.59) no statistical difference was found (Table 3).

Lymphocyte value of the patients in Group-1 was statistically higher than the other groups (Group-1: 2.3±0.6, Group-2: 2+0.8, Group-3: 2.1±0.8, p<0.001; Table 2). When comparing the subgroups, there was a significant difference between Group-1 and Group-2 (p=0.003) and between Group-1 and Group-3 (p=0.03), while there was a significant difference between Group-2 and Group-3 (p=0.59) no statistical difference was found (Table 3).

When all three groups were compared, there was a statistical difference between the groups in terms of monocyte values (Group-1: 0.6+0.4, Group-2: 0.6±0.2, Group-3: 0.6±0.2, p=0.001; Table 2). However, when the subgroup comparisons are examined, there is a statistical difference between Group-1 and Group-2 (p=0.45), Group-1 and Group-3 (p=0.29), and Group-2 and Group-3 (p=0.71). (Table 3).

The RDW value of the patients in Group-3 was statistically higher than the other groups (Group-1: 13.7±1.1, Group-2: 14.4±1.6, Group-3: 14.3±1.3, p<0.001; Table 2). When comparing the subgroups, there was a significant difference between Group-1 and Group-2 (p<0.001) and between Group-1 and Group-3 (p=0.001), while there was a significant difference between Group-2 and Group-3 (p=0.99). no statistical difference was detected (Table 3)

The NLR values of the patients in Group-2 were statistically higher than the other groups (Group-1: 2+1.2, Group-2: 3.4±2.4, Group-3: 3+1.9, p<0.001; Table 2). When comparing the subgroups, there was a significant difference between Group-1 and Group-2 (p<0.001) and between Group-1 and Group-3 (p<0.001), while there was a significant difference between Group-2 and Group-3 (p=0.51) no statistical difference was determined (Table 3).

The PLR value of the patients in Group-3 was statistically higher than the other groups (Group-1: 119.1+46, Group-2: 135.5±57.8, Group-3: 141.6±71.6, p=0.03; Table 2). When comparing the subgroups, there was a significant difference between Group-1 and Group-2 (p=0.03), and between Group-1 and Group-3 (p=0.02), while Group-2 and Group-3 (p=0.02). =0.87) no statistical difference was found (Table 3).

The RDW value of the patients in Group-C was statistically higher than the other groups (Group-A: 13.4±0.5, Group-B: 13.7±0.4, Group-C: 15.3±1.5, p<0.001; Table 4). While there was a significant difference between the subgroups between Group-A and Group-C (p<0.001) and between Group-B and Group-C (p<0.001), there was a statistically significant difference between Group-A and Group-B (p=0.24). no difference was detected (Table 5).

No statistically significant difference was found when MPV value was compared between all groups. (Group-A: 8.6±1, Group-2: 8.1±0.8, Group-3: 8.4±0.8, p=0.16; Table 4).

NLR values of the patients with Group-C were statistically higher than the other groups (Group-A: 1.9±0.6, Group-B: 2.3±1.1, Group-C: 4.2±+2.2, p<0.001; Table-3.4). While there was a significant difference between the subgroups

Table 4: Comparison of RDW, MPV, NLR, PLR values according to carotid artery stenosis rates

	<50-69% (n=21)	70-89% (n=33)	≥90% (n=38)	P value
RDW	13.4±0.5	13.7±0.4	15.3±1.5	p<0.001
MPV	8.6±1	8.1±0.8	8.4±0.8	0.16
NLR	1.9±0.6	2.3±1.1	4.2±2.2	p<0.001
PLR	89.8±23.2	107.4±26.9	201.7±79.9	p<0.001

RDW: Red blood cell distribution width, MPV: Mean platelet volume, NLR: Neutrophil/lymphocyte ratio, PLR Platelet/Lymphocyte ratio

between Group-A and Group-C (p<0.001) and between Group-B and Group-C (p<0.001), there was no statistical difference between Group-A and Group-B (p=0.68). no difference was detected (Table 5).

Group-C patients had a statistically higher PLR value than the other groups (Group-A: 89.8+23.2, Group-B: 107.4-26.9, Group-C: 4201.7+79.9, p<0.001; Table 4). While there was a significant difference between the subgroups between Group-A and Group-C (p<0.001) and between Group-B and Group-C (p<0.001), there was no statistically significant difference between Group-A and Group-B (p-0.12). no difference was detected (Table 5).

DISCUSSION

Stroke is an important cause of mortality and morbidity. CAS has an important place in the etiology of stroke and is usually caused by atherosclerosis. Inflammation plays an important role in the initiation and progression of carotid atherosclerosis, such as coronary atherosclerosis.[10]

In Cerşit *et al*. 2018, 27 patients were included in the study and 70.3% (19) of them were male. The mean age was 71.6 years. 59.3% of the patients had HT, 37% had DM, 18.5% had hyperlipidemia, 29.5% had cigarette smoking, and 29.6% had coronary artery disease.[11] In Özdemir *et al*. 2018, 220 patients were included in the study, of which 76.8% (169) were men. The mean age was 66. Of the patients, 85% had HT, 32.7% had DM, 55% had hyperlipidemia, 29.5% had cigarette smoking, and 71.4% had coronary artery disease.[12] In our study, 92 patients were included. Consistent with the literature, male gender was higher than females with a rate of 80.4% (74). The mean age was found to be 69.4 years. 83.7% of the patients had hypertension, 39.1% DM, 47.8% hyperlipidemia, 38% smoking, 47.8% coronary artery disease.

Different results have been reported for the relationship between MPV and stroke in the literature. In a study, it was shown that the MPV value is higher in patients with ischemia compared to the normal population.[13] Mayer *et al*. in 2014; published a study examining atherosclerotic plaque progression and clinical outcomes in asymptomatic CAS patients. They showed that MPV was an independent risk factor for predicting adverse cardiovascular outcomes in patients with asymptomatic carotid artery stenosis, but there

Table 5: Comparison of blood parameters in pairs according to carotid artery stenosis rates

			P value
RDW	50-69%	70-89%	0.24
		≥90%	p<0.001
	70-89%	≥90%	p<0.001
NLR	50-69%	70-89%	0.68
		≥90%	p<0.001
	70-89%	≥90%	p<0.001
PLR	50-69%	70-89%	0.12
		≥90%	p<0.001
	70-89%	≥90%	p<0.001

RDW: Mean erythrocyte volume, NLR: Neutrophil/lymphocyte ratio, PLR Platelet/Lymphocyte ratio

was no statistically significant association between MPV and the severity of CAS.[14] In our study, when the MPV values of healthy individuals, patients with stroke and patients with carotid artery stenosis were compared, no statistical difference was found. Similarly, MPV was not significant in the analysis performed according to the degree of stenosis of patients with CAS.

There are studies showing that RDW is a strong predictor of mortality in older adults with and without age-related diseases.[15] Many studies have demonstrated the association between RDW and coronary artery disease. High RDW has been associated with an increased incidence of cerebral infarction in the general population, according to a study published in 2015 that included 26879 patients. RDW was also associated with carotid intima-media thickness, but not with the carotid plaque.[15,16] Many studies have demonstrated the relationship between RDW and coronary artery disease. Soderholm *et al*. in 2015 included 26,879 patients. High RDW was associated with an increased incidence of total stroke and cerebral infarction from the general population in this study. RDW was also associated with carotid intima-media thickness, but not with the carotid plaque.[16] Wonnerth *et al*. in 2016 investigating the relationship between RDW and patients with carotid atherosclerosis found that RDW was significantly and independently associated with all-cause and cardiovascular deaths.[17] Massiot *et al*. in 2019 reported a positive correlation between high RDW and death due to ischemia. It was thought that inflammation and oxidative stress developed after stroke, increasing RDW by affecting the bone marrow.[13] In our study, the RDW values of healthy subjects, patients with stroke and patients with carotid artery stenosis were lower in healthy subjects and this rate was statistically significant. There was no significant difference in RDW between stroke patients and patients with CAS. However, RDW; was significantly higher especially in those with a CAS of 70% or more.

Neutrophil/lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have been identified as predictive factors in various cardiovascular diseases. However, studies on patients with CAS are insufficient. In a study published in 2019 that included 270 patients who underwent CEA, it was shown that preoperative high NLR and PLR levels were significantly associated with symptomatic ICA stenosis.[18] In a 2017 study of 150 patients, PLR was evaluated as an independent predictor for carotid artery disease and stroke. In a study of 146 patients with CAS evaluated according to NASCET criteria and followed for an average of 16 months, high PLR was found to associated with an increase in all-cause mortality.[11] Evaluated according to NASCET criteria and detected CAS; Tek *et al*. in a study of 146 patients followed for an average of 16 months, high PLR was found to be associated with an increased rate of all-cause mortality.[10]

In conclusion, our study demonstrated that a significant correlation was detected between high PLR, NLR, RDW values and the severity of CAS. PLR, NLR, RDW value can be an economical, easily accessible and useful biomarker in predicting the degree of severe carotid artery stenosis.

DISCLOSURE

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