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Evaluation of serum levels of homocysteine and C-reactive protein in patients with ischemic stroke

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ABSTRACT

Stroke is the third most common cause of death in the world. Plasma homocysteine is an emerging risk factor for stroke. Also, previous studies have shown that serum levels of C-reactive protein (CRP) are significantly associated with mortality and function in patients with ischemic stroke. In the present study, we examined homocysteine and serum CRP levels in patients with ischemic stroke. This descriptive-analytical study was performed on 100 patients with ischemic stroke. Blood samples were taken in the first 24 hours of a stroke to measure homocysteine and CRP. The Axis homocysteine ELISA kit (IBL, Germany) measured plasma homocysteine. Doppler ultrasound of cerebral arteries was also performed in the first five days. Independent chi-square, ANOVA, and t-tests were used to analyze the data. It was observed that the NIHSS mean was not significantly different from the age of the patients (P = 0.876). Significant relationship was not observed between NIHSS level with HTN (p = 0.070), HLP (p = 0.103), DM (p = 0.999), history of CVA (p = 0.946), history of MI (p = 0.262), smoking (p = 0.109), and the number of CVA risk factors (p = 0.383). Data analysis showed that homocysteine level was significantly associated with hypertension (p = 0.021). There was also a significant relationship between serum CRP level and the location of internal carotid artery stenosis (p = 0.015) and middle cerebral artery (p = 0.006). In general, this study showed that increased homocysteine in the high range in patients with stroke has a high frequency. Also, stenosis of the internal carotid artery and middle cerebral artery is more common in patients with ischemic stroke whose serum CRP levels are high. This finding suggests that abnormal CRP may be more associated with stenosis of some cerebral arteries.

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Introduction

Ischemic strokes are the third most common cause of death and the number one cause of disability in all societies (1). The most important underlying cause of ischemic stroke is atherosclerosis, for which several risk factors such as blood pressure, diabetes, and hyperlipidemia have been suggested. In atherosclerosis, an increase in the thickness of the arterial wall is secondary to smooth muscle cell proliferation, lipid deposition, and fibrosis (2). Rupture or rupture of atherosclerotic plaques containing lipids cause thrombosis (atherothrombosis), leading to events such as stroke or heart attack (1).

Homocysteine is an amino acid whose serum level is disturbed by an increase in serum levels leading to thrombotic events, in which venous vascular events are more pronounced (3). In this case, the involvement was mainly in the veins inside the brain (4). The theory of homocysteine in the atherosclerosis phenomenon was first proposed in 1962. Since then, several studies have been conducted on the relationship between increased homocysteine and vascular events in the heart-brain and peripheral arteries (5). Very high levels of homocysteine are strongly known to be thrombogenic. However, there have been various discussions about its slight to moderate increase (for example, around 15-20μmol/L) (6). Elevated homocysteine levels can occur in the context of homocystinuria. This disorder is uncommon and has adverse clinical manifestations and vascular events, or it can occur to underlying problems such as smoking. In homocystinuria, patchy and lipid-free changes are seen in the arterial process, which is known to be the cause of atherosclerosis (as opposed to atherosclerosis) (4). The occurrence of vascular disease during homocystinuria is justified by cystathionine β-synthase (CBS) and methylenetetrahydrofolate reductase (MTHFR) deficiency or congenital disorders of cobalamin metabolism (7). This phenomenon is treatable because it has been proven that therapeutic doses of folate and vitamins B6 and B12 can reduce these levels and reduce the risk of vascular accidents (6).

On the other hand, many studies have shown that the level of some acute inflammatory reactants in people with ischemic stroke is higher than normal. One of the most important of these reactants is C-reactant protein (CRP), which has varied in various studies and has been reported to be up to 74% (8). Also, recent studies show that mortality rates in stroke patients with abnormal CRP levels are significantly higher. This finding also applies to

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the complications of a stroke. Currently, there is growing evidence about the role of inflammation in the development of vascular atherosclerosis, which suggests CRP as a potential marker for prognosis in patients with myocardial infarction in some articles (9). However, the exact nature of this relationship is unclear. So far, various studies have been published on which cerebral artery stenosis is associated with CRP levels. Some radiological and sonographic evidence suggests that carotid stenosis is higher in people with abnormal CRP levels (10). This finding has also been reported in asymptomatic cases (8). However, there is disagreement about the existence of such a strong association between CRP and intracranial stenosis. For example, some studies suggest a link between CRP and medial cerebral artery stenosis (11), and some deny such a link (12).

Due to the high prevalence of ischemic vascular events in the brain and various theories about the relationship between serum homocysteine levels and these events, the present study was performed to find the level of this thrombogene in patients. Also, due to the lack of a study that evaluated all intracranial and extracranial vessels simultaneously, in this study, we evaluated serum CRP levels in patients with thrombotic stroke.

Materials and Methods

Patients

In the present study, 100 patients referred to the hospital with a complaint of focal ischemic nerve injury were included in the study after imaging and diagnosing ischemic stroke. Then, patients' information was collected in a checklist, which included demographic data of patients, history of diabetes, hypertension, smoking, etc., and entered the list.

The patients had a stroke for the first time, and all were admitted in the first 24 hours after the onset of the disease. The diagnosis was confirmed by paraclinical methods (CT-Scan and MRI), and, if necessary, contrast material was used, and suspected cases were removed from the study. Then, cardiac examinations, including ECG, echocardiography, and cardiologist visit, were performed for all patients, and embolism cases were excluded from the study. If the patient has a history of surgery, a trauma in the last three months, a history of other illnesses (such as kidney failure, liver, heart, malignancy, vasculitis, infection), fever at the start of admission, or taking antibiotics in the last month The study was deleted. Drugs (except drugs that control ischemic heart disease, diabetes, hypertension, and hyperlipidemia) were also excluded.

Homocysteine measuring

Blood samples were provided from patients. Then they were taken in tubes containing EDTA anticoagulants, transferred to the laboratory for plasma homocysteine measurement, and stored at -20°C until testing. The Axis homocysteine ELISA kit (IBL, Germany) was used to measure plasma homocysteine. The basis of homocysteine measurement in this method was based on ELISA. First, the protein-bound homocysteine was converted to free homocysteine by dithiothritol and then to S-adenosyl-L-homocysteine by the enzyme S-adenosyl homocysteine hydrolase (SAH). In the following reaction, a competitive immunoassay, plasma homocysteine competed with ELISA-bound homocysteine to bind to homocysteine monoclonal antibody. In the next step, by adding substrate and labeled antibody to HRP, the peroxidase activity reaction was measured at 450 nm. In this reaction, the amount of light absorption is inversely related to homocysteine concentration.

Evaluating serum levels of C-reactive protein

For patients in the first 24 hours after the onset of clinical symptoms, blood samples were taken for measurement of CRP, and those who had more than 24 hours after the onset of symptoms were excluded from the study. ELISA measured serum CRP levels, and values more than 3μg/ml were considered abnormal (13). Also, for all patients, transcranial and extracranial Doppler cerebral arteries were performed in the first five days of hospitalization using a two-way CW / PW Doppler device connected to a software box (DWL) (Sipplingen, Germany). It uses two separate probes. A MHz4 probe is for Common Carotid Artery and Internal Carotid Artery and, a MHz2 probe is for Arterial Cerebral Artery, Middle Cerebral Artery, Posterior Cerebral Artery, Vertebral Artery, Ophthalmic Artery, and Basilar Artery.

Blood flow to each artery is examined at standard depth. For each vessel, Peak Systolic Velocity (PSV), Mean Flow Velocity (MFV), End Diastolic Velocity (EDV), Pulsatility Index (PI), and Resistance Index (RI) were considered. The device calculated it to remove the artifact and improve the accuracy, and the data were also calculated manually. In case of any discrepancy between the obtained data, manual items were determined as the study criterion. Strictness criteria of MFV> 80 cm/sec were considered for ACA and MCA arteries, the strictness criteria of MFV> 60 cm/sec for BA, and MFV> 50 cm/sec for PCA and VA. Also, for the ICA artery in the carotid siphon MFV> 70 cm/sec, and in the neck, ICA/CCA area PSV Ratio> 2 or PSV> 125 cm/sec was considered as the measure of stenosis (12).

A questionnaire containing demographic information (age and sex) was prepared for each patient. Patients were divided into two groups based on the normal and abnormal CRP, and the location of vascular stenosis was compared in the two groups. The area of the stenosis was also assessed based on the CRP mean. In this study, a person with high blood pressure was treated with medication or had systolic blood pressure above 160 or diastole above 90 mm Hg. He was also considered a person with diabetes who had more than 110 mg/ml of fasting blood sugar on medication or twice. Cases of hyperlipidemia were also cases that were treated with medication. Also, a person was considered a smoker who smoked five cigarettes a day, and cases of heart ischemia were also positive cases in which a cardiologist treated the person with medication (14).

Statistical analysis

Questionnaire information was statistically analyzed using SPSS software version 20. The Chi-square test and ANOVA were used to compare the frequencies, and the independent t-test was used to compare the means. In this study, a significant level of 0.05 was considered.

Results

After examining the age of the patients, it was obser-

ved that the mean age of the patients was 65.83 ± 15.32 years. The youngest patient in this study was 25 years old, and the oldest patient was 100 years old. To better assess the age of patients, patients were divided into ages less than 50 years and more than 50 years. The results showed that the majority of people were over 50 years old. The sex of the patients was also examined, and the results showed that 54 patients (54%) were male. Patients were asked about vascular risk factors. The results showed that most people with 45 patients (45%) had a single risk factor (Figure 1). About the risk factors, half of the patients had hypertension. The presence of diabetes mellitus is another risk factor for vascular disease among patients. The results showed that only 13 patients (13%) had such a history. Another risk factor for vascular factors is hyperlipidemia. The results showed that only 18 patients (18%) had such a history among patients. Among the studied patients, 31 patients had a history of smoking, of which four were female and 27 were male. Patients (or their companions) were asked about a history of similar brain damage in the past. The results showed that most people with 74 cases (74%) had such lesions for the first time.

Imaging methods examined involved cerebral arteries in patients. In this study, we evaluated the incidence of vascular lesions in two separate groups. Small vessels, large vessels, and embolic were divided into the first group. In the second group, Anterior arteries (Ant) and Posterior arteries (Post) were divided, and the results showed that 85 patients had anterior lesions (Figure 2).

Another history that was examined in patients was the occurrence of cardiovascular accidents. The results showed that 14 patients (14%) had a history of previous myocardial infarction. In 38 patients in this study, carotid stenosis was evaluated. The results showed that 17 patients (73.44%) had moderate stenosis (50-75% stenosis) and four patients (52.10%) had severe stenosis (less than 75% carotid stenosis), and the others had less than 50% stenosis. The National Institutes of Health Stroke Scale (NIHSS) was measured in patients, and the results showed that the mean score among patients was 6.59 ± 4.33. Also, after classifying this score, it was observed that most patients were in the minor range.

After measuring the homocysteine level among patients, it was observed that the mean of this substance in the serum of patients was 20.40 ± 12.24mmol/lit. The results also showed that 49 patients (49%) had normal homocysteine levels. In the present study, the lowest homocysteine level was five, and the highest was 52. After examining the level of homocysteine in male and female patients and analysis by T-test, it was observed that the mean of this

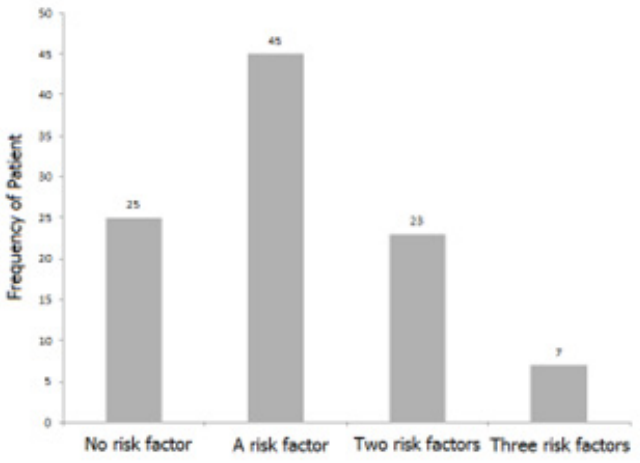

Figure 1. Frequency of patients by number of risk factors.

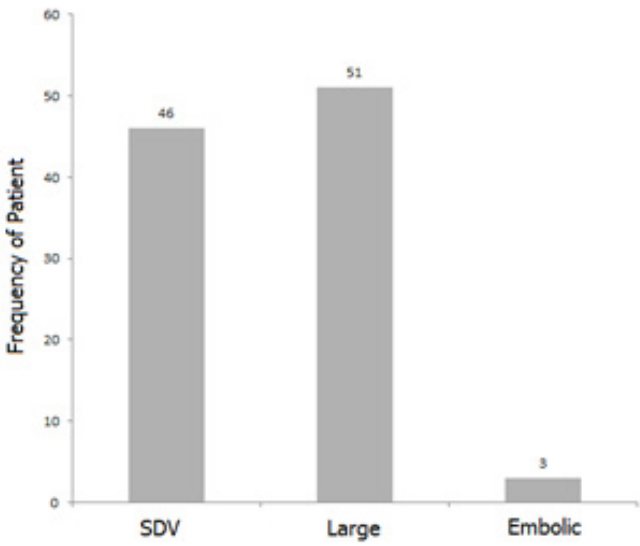

Figure 2. Frequency of patients by arterial involvement pattern.

substance in and in women was 19.78 ± 11.12mmol/lit in men, which was 21.13 ± 13.52mmol/lit, which was not significant. (p = 0.484). The Chi-Square test also analyzed homocysteine levels, and it was observed that there was no significant relationship (p = 0.558) (Table 1).

Also, homocysteine level in patients younger than 50 years and older than 50 years was analyzed by T-test, and it was observed that the mean of this substance in people more aged than 50 years is significantly higher than in people younger than 50 years (p = 0/004) (Table 2).

Homocysteine level was also analyzed by Chi-square test, and it was observed that there was a significant rela-

Table 1. Relationship between homocysteine levels and gender of patients.

Homocysteine Level	Male		Female		P-value	DF	Pearson Chi-Square
	Frequency	Percent	Frequency	Percent			
Normal	25	46.3	24	52.2	0.558	1	0.343
Abnormal	29	53.7	22	47.8			

Table 2. Relation between homocysteine level and patient age based on T-test.

Age	Mean of Homocysteine	Standard Deviation	P-Value	DF	T
<50	13.06	7.52	0.004	98	2.915
>50	22.01	12.51			

Table 3. Relation between homocysteine level and patient age based on Chi-Square test.

Homocysteine Level	Male		Female		P-value	DF	Chi-Square
	Frequency	Percent	Frequency	Percent			
Normal	15	83.3	34	41.5	0.001	1	10.354
Increased	3	16.7	48	58.5			

Table 5. Relation between NIHSS and homocysteine level of patients based on ANOVA.

NIHSS	Homocysteine Mean	Standard Deviation	P-value	DF	Mean Square
Minor	18	8.74	0.013	26	0.666
Moderate	21.77	14			
Mod to Severe	32	12.70			
Severe	10	0			

Table 6. Relation between NIHSS and homocysteine level of patients based on Chi-square.

NIHSS	Homocysteine	Frequency	Percent	P-Value	DF	Pearson Chi-Square
Minor	Normal	21	51.2	0.111	3	6.006
	Increased	20	48.8			
Moderate	Normal	26	49.1			
	Increased	27	50.9			
Mod to Severe	Normal	0	0			
	Increased	4	100			
Severe	Normal	2	100			
	Severe	0	0			

Table 7. Correlation between homocysteine levels and vascular risk factors.

Risk Factor		Mean	Standard Deviation	P-Value	T
Diabetes	Have	18.08	10.44	0.466	0.732
	Not Have	20.75	12.50		
Hypertension	Have	23.20	14.13	0.021	2.338
	Not Have	17.60	9.33		
Hyperlipidemia	Have	22.28	11.32	0.475	0.717
	Not Have	19.98	19.99		
Stroke History	Have	21.48	10.34	0.613	0.507
	Not Have	20.04	12.85		
MI History	Have	18.29	10.94	0.489	0.695
	Not Have	20.74	12.46		

tionship with patients' age (p = 0.001) (Table 3).

After examining the level of NIHSS in male and female patients and analyzing by T-test, it was observed that the rate of NIHSS in men was lower than in women, which was statistically close (p = 0.058) (Table 4).

The level of NIHSS in patients younger than 50 years and older than 50 years was also analyzed by T-test, and it was observed that the mean NIHSS was not significantly different from the age of patients (P = 0.876). No significant relationship between NIHSS level with HTN (p = 0.070), HLP (p = 0.103), DM (p = 0.999), history of CVA (p = 0.946), history of MI (p = 0.262), smoking (p = 0.109), and the number of CVA risk factors (p = 0.383) was not observed. NIHSS of patients with their homocysteine level was also analyzed by Chi-square and ANOVA tests (Tables 5 and 6).

Also, patients' NIHSS levels were analyzed separately by patients' homocysteine interval by T-test and it was observed that there was no significant relationship between patients homocysteine levels and patients' NIHSS levels (p = 0.745). In this study, homocysteine levels were assessed separately for vascular risk factors using a T-test. The results showed that in patients with hypertension, the level of homocysteine was significantly higher than in normotensive individuals (p = 0.021) (Table7).

Fifty-five percent of people with normal CRP and 60% of people with abnormal CRP were male. The mean serum CRP level in all patients was 92.5µg/ml with a standard deviation of 89.5. The mean serum CRP level was 33.1 58 58.7 in patients with stenosis and 75.1 ± 10.4 in those without stenosis. This difference was statistically significant (p = 0.004). 34% of people with normal CRP and 66% of those with abnormal CRP had stenosis. Cases of cerebrovascular stenosis were more common in people with abnormal serum CRP levels (p = 0.003). The most involved vessels in all patients were ICA, BA, ACA, MCA, and VA. MCA, ICA, BA, ACA, and VA were the most involved vessels in patients with abnormal CRP. MCA, ICA, ACA, and BA were the most involved vessels in patients with normal CRP. There was a significant relationship between serum CRP level (i.e., between normal and abnormal cases) and the site of vascular stenosis (ICA (p = 0.015)

Table 8. Frequency of normal and abnormal CRP cases according to risk factors for ischemic stroke.

Risk Factor	HTN		DM		HLP		IHD		Smoking	
	Have stenosis	Not have stenosis	Have stenosis	Not have stenosis	Have stenosis	Not have stenosis	Have stenosis	Not have stenosis	Have stenosis	Not have stenosis
Normal	51.2%	48.9%	46.7%	51.7%	50%	50%	66.7%	45.8%	52.2%	49.3%
Abnormal	48.8%	51.1%	53.3%	48.3%	50%	50%	33.3%	54.2%	47.8%	50.7%
P-Value	1.00		0.823		1.00		0.187		1.00	

and (p = 0.006) MCA, but there was no significant relationship between BA, ACA, and VA vessels. In the case of PCA and CCA vessels, no significance could be calculated due to lack of stenosis. There was no significant relationship between age and serum CRP level (p = 0.815). Also, no significant association was observed between stroke risk factors and serum CRP level (p> 0.05) (Table 8).

Discussion

In the present study, 100 patients were diagnosed with ischemic stroke with a mean age of 65.83 ± 15.32 years, 54% male and 46% female. In the study of Zongte et al. (15), it was observed that in the group with stroke, the mean age of the subjects was 19.62 years, 66.66% were male, and 34.33% were female. In the study of Li et al. (16), the mean age of the case group was 3.60 years, and 5.63% were male. In the study of Atanassova et al. (17), it was observed that in the case group, the mean age of patients was 4.46 years, 6.75% were male, and 4.24% were female. After examining the age and sex of the subjects in this study with similar studies, it was observed that the age and sex of the issues in the present study were similar to other studies. 25% had no vascular risk factor, and 45% had one risk factor. 50% had hypertension, 13% had diabetes, 18% had hyperlipidemia, 14% had a history of MI, and 31% had smoked. 74% of patients had no history of stroke. In the study of Li et al. (16), it was observed that 2.15% had a history of heart disease, 2.63% had a history of hypertension, and 4.12% had a history of diabetes. In the study of Atanassova et al. (17), it was observed that in the case group, 8.48% had a history of smoking. In Meiklejohn et al.'s study (18), 6.6% of patients with diabetes, 50% had a history of smoking, 55.41% had a history of hypertension, 2.13% had a history of hyperlipidemia, and 2.14% had no risk factor.

In the study of Zhang et al. (19), it was observed that 9.74% had hypertension, 6.17% had diabetes, and 4.41% had smoked. A review of other studies and the present study showed that hypertension is one of the most common risk factors for vascular disease, probably due to the high prevalence of this disease in elderly patients. In the study of Fischer et al. (20), the mean level of 14 was NIHSS (Between 3 to 38). The result showed that although risk factors could not predict digital obstruction in central obstruction (DSA) arteriography, several NIHSS scoring items, Such as level of consciousness, gaze neglect, and the motor leg, are significant predictors of this issue. No significant relationship was found between stroke risk factors and NIHSS level in the present study. It seems that stroke risk factors are involved in the development of atherosclerosis, which is one of the critical underlying causes of ischemic stroke in patients. However, they did not play a significant role in the severity of the stroke. The diversity of vascular risk factors in patients with stroke was not compatible with the severity of clinical symptoms and the extent and neurological severity according to NIHSS criteria. It suggests that even patients without vascular risk factors are more likely to develop CVA with a high NIHSS due to a lack of collateral arteries and cerebral dynamic response. Therefore, brain diseases such as CVA should be among the diagnostic and therapeutic priorities in patients without risk of vascular factors. However, further studies in this area are suggested. It was also observed that the homocysteine level in the studied patients had 24.12 ± 40.20nmol/lit, and 49% had an average homocysteine level. Finally, homocysteine level by sex (p = 0.584), age (p = 0.004), NIHSS (p = 0.745), and NIHSS level by sex (p = 0.058), age (p = 0 876) and homocysteine level (p = 0.013) were also examined. Data analysis showed that homocysteine level was significantly associated with hypertension (p = 0.021).

In the study of Zongte et al. (15), it was observed that the level of homocysteine in patients with stroke was 33.15 and in the control group was 52.12mmol/l (p = 0.030). In the present study, there was no relationship between homocysteine level and age, sex, history of diabetes, and hyperlipidemia in patients. In the study of Li et al. (16), it was observed that the level of homocysteine.

In the case group, it was 7.14. In the control group, it was 8.12. The case group was 9.41%, which had increased homocysteine level, and 7.25% in the control group. All of the mentioned cases were statistically significant. In the study of Atanassova et al. (17), the homocysteine level in patients was 4.13μmol/l and in the control group was 10.6μmol/l, which was statistically significant. In the study of Meiklejohn et al. (18), the homocysteine level in female patients in the case group was 1.8μmol/l and in the control group was 7.6μmol/l (P = 0.580). In the men in the case group, it was 2.9μmol/l and in the control group was 7.8μmol/l (p = 0.090). The results showed that the homocysteine level in the whole case group was not significantly different from the control group, and there was no relationship between gender and homocysteine level. In the study of Osunkalu et al. (21), in the case group, the level of homocysteine in the case group was 7.17μmol/l, and in the control group, it was 9.5μmol/l (p = 0.000).

Since this study was performed on one group and we could not do the present study as a case and control, we cannot show the homocysteine level in stroke disease as a risk factor. Still, after comparison with other studies, it was observed that the level of homocysteine in patients in the present study from other patients. Homocysteine levels were also significantly higher in patients with hypertension, so homocysteine may likely be involved in the pathogenesis of hypertension and play a key role in stroke.

The study results by Zhang et al. (19) showed a significant relationship between homocysteine levels above 16μmol and recurrent strokes. In our study in this field, no significant relationship was found, contrary to our expectations. Therefore, high homocysteine levels may not be a frequent risk factor for predicting CVA, and further studies are suggested. There was no significant relationship between homocysteine level and NIHSS level. There are two possibilities. The first is that the level of NIHSS and homocysteine are not significantly related to each other.

The frequency of abnormal cases of serum CRP levels in patients with stroke has been reported from 25 to 75%, and part of this statistical difference is due to the time of sampling and test method (22-24). It is not known why high serum CRP levels are associated with more stenosis in patients with stroke. CRP is essentially a blood protein whose function is not yet well understood and is associated with interleukins (25). Some studies have shown an adverse effect of CRP by impairing the coagulation process of fibrinogen or platelets (26, 27). Cytokines may also mediate the negative impact of CRP. LDL binding and vascular wall damage is other functions of CRP (28, 29). These findings suggest that high serum CRP levels may directly affect the course of atherosclerosis. Our study also had some limitations that need to be considered. First, CRP was measured only once, and serial measurements may increase accuracy. Second, in this study, the results were purely Doppler-based, and it is clear that duplex increases the value of the findings. Our findings show that ICA and MCA stenosis is higher in patients with ischemic stroke whose CRP is abnormal. This finding suggests that abnormal CRP may be more associated with narrowing some arteries.

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