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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

THE ROLE OF NEUTROPHIL/HIGH DENSITY LIPOPROTEIN, MONOCYTE/HIGH DENSITY LIPOPROTEIN AND LOW DENSITY LIPOPROTEIN/HIGH DENSITY LIPOPROTEIN RATIOS IN DETERMINING THE PRESENCE AND SEVERITY OF ASYMPTOMATIC CAROTID STENOSIS IN ELDERLY PERSONS

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ABSTRACT

INTRODUCTION: The importance of the lipid-related biomarkers, like neutrophil to high density lipoprotein cholesterol (HDL) ratio (NHR), monocyte to HDL ratio (MHR) and low density lipoprotein cholesterol (LDL) to HDL ratio (LHR), has been implicated in the pathological process of atherosclerosis. Our study was conducted to discuss and compare the predictive ability of the NHR, MHR and LHR in elderly patients with asymptomatic carotid stenosis(ACS).
METHODS: Our study included 124 patients, aged ≥ 65 years, complained with dizziness and applied to our clinic from January 2010 to September 2020 and 125 healthy controls of similar age and gender. When blood samples were taken for white blood cell count and biochemical analysis; carotid artery Doppler ultrasonography was performed to define carotid stenosis.
RESULTS: While NHR, MHR and LHR values were significantly higher in the patient group; a linear correlation was found between NHR, MHR and LHR values and the degree of carotid stenosis. In the ROC analysis performed to determine the cut-off values in detecting carotid stenosis, the area under the curve (AUC) for NHR was 0.68 and the cut-off point was 0.09; the AUC for MHR was 0.61, cut-off point was 0.01 and the AUC for LHR was 0.58 and the cut-off point was 1.61.
DISCUSSION AND CONCLUSION: As a result, we revealed that NHR, MHR, and LHR ratios can be used with a higher sensitivity than using these values individually in detecting asymptomatic carotid stenosis in elderly patients. In addition, NHR value was found to be a more valuable biomarker in defining the presence and degree of carotid stenosis compared to MHR and LHR values.
Keywords: Neutrophil to high density lipoprotein cholesterol ratio, monocyte to high density lipoprotein cholesterol ratio, low density lipoprotein cholesterol to high density lipoprotein cholesterol ratio, asymptomatic carotid stenosis, atherosclerosis.

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YAŞLI KİŞİLERDE ASEMPTOMATİK KAROTİS STENOZUNUN VARLIĞINI VE ŞİDDETİNİ BELİRLEMEDE NÖTROFİL/YÜKSEK YOĞUNLUKLU LİPOPROTEİN, MONOSİT/YÜKSEK YOĞUNLUKLU LİPOPROTEİN VE DÜŞÜK YOĞUNLUKLU LİPOPROTEİN/YÜKSEK YOĞUNLUKLU LİPOPROTEİN ORANLARININ ROLÜ

ÖZ

GİRİŞ ve AMAÇ: Aterosklerozun patolojik süreçlerinde nötrofil/yüksek yoğunluklu lipoprotein (NHO), monosit/yüksek yoğunluklu lipoprotein (MHO) ve düşük yoğunluklu lipoprotein/yüksek yoğunluklu lipoprotein (LHO) oranları gibi lipidle ilişkili biyobelirteçlerin önemi son zamanlarda anlaşılmıştır. Bu çalışmada NHO, MHO ve LHO'nun yaşlı hastalardaki asemptomatik karotis stenozunu ön görme yeteneğini tartışmayı ve karşılaştırmayı amaçladık.

YÖNTEM ve GEREÇLER: Çalışmamıza Ocak 2010- Eylül 2020 tarihleri arasında kliniğimize başvuran ve baş dönmesi şikayeti bulunan 65 yaş üzeri 124 hasta ile benzer yaş ve cinsiyete sahip 125 sağlıklı kontrol dahil edildi. Beyaz küre sayımı ve biyokimyasal analizler için tüm hastalardan kan örneği alınırken; karotis stenozunu saptamak amacıyla karotis arter doppler ultrasonografi uygulandı.

BULGULAR: NHO, MHO ve LHO değerleri hasta grubunda istatistiksel olarak anlamlı derecede yüksekken; NHO, MHO ve LHO değerleri ile karotis darlık derecesi arasında aynı yönlü bir ilişki bulundu. Karotis darlığını saptamada kesim değeri belirlemek amacıyla yapılan ROC analizinde NHO için eğri altındaki alan (EAA) 0.68, kesme noktası 0.09 olarak tespit edilirken; MHO için EAA 0.61, kesme noktası 0.01; LHO için ise EAA 0.58 ve kesme noktası 1.61'idi.

TARTIŞMA ve SONUÇ: Sonuç olarak yaşlı hastalardaki asemptomatik karotis stenozunu saptamada ek masraf gerektirmeyen ve kolay ulaşılabilir olan NHO, MHO ve LHO değerlerinin bu değerlerin tek başına olduklarından daha yüksek bir duyarlılıkla kullanılabileceğini ortaya koyduk. Ek olarak NHO değeri, MHO ve LHO değerleri ile kıyaslandığında karotis stenozunun varlığını ve derecesini tespit etmede daha değerli bir belirteç olarak saptandı..

Anahtar Sözcükler: Nötrofil/yüksek yoğunluklu lipoprotein oranı, monosit/yüksek yoğunluklu lipoprotein oranı, düşük yoğunluklu lipoprotein/yüksek yoğunluklu lipoprotein oranı, ateroskleroz, asemptomatik karotis stenozu..

INTRODUCTION

Cerebrovascular diseases, which are the most common reason for admission to the emergency department, are a significant cause of mortality and morbidity, particularly in the elderly population. Acute ischemic stroke (AIS) accounts for approximately 80-85% of all cerebrovascular events (1). Unfortunately, there is no effective treatment for AIS nowadays. Therefore, keeping risk factors under control is the best way to prevent AIS. Carotid atherosclerotic stenosis is one of the most significant risk factors for the development of AIS. It is known that as the degree of carotid stenosis increases, the risk of AIS also increases (2). It is showed that inflammation plays a role in the development, spread, and destabilization of carotid atherosclerosis, and therefore carotid atherosclerosis is closely related to inflammatory markers (3,4).

Recent studies have demonstrated that some white blood cell subtypes can also be used to indicate inflammation (5). Microglial cells are considered to be major cells that contribute to inflammation (6). It is known that macrophages and monocytes, which are accepted as the precursor cells of macrophages, take an essential part in all stages of atherosclerosis, from fatty streaking to plaque rupture and even the development of AIS (7). It is suggested that the increased number of circulating macrophages and monocytes, which represent the source of foam cells, is a predictor of new plaque development (8). Circulating neutrophils also play a fundamental role in the immunoinflammatory response that occurs in the pathogenesis of atherosclerosis (9). The increased neutrophil count is closely associated with the increased incidence of cardiac events (10). Recent studies have revealed that abnormal lipid metabolism also takes an essential part in the development and progression of atherosclerosis (11-14). It is known that HDL (high-density lipid) exerts antioxidant and anti-inflammatory effects by preventing the adhesion of monocytes to the endothelium, and therefore atherosclerosis decreases as the HDL value increases (15). Furthermore, recent studies have revealed that HDL can also regulate the functions of activated neutrophils (16). On the contrary, it has been suggested that activated

neutrophils may affect the structure and function of HDL (17). It is known that the serum LDL (low-density lipoprotein) value is very important for the development of atherosclerosis. Moreover, decreasing the serum LDL value is one of the main goals in both primary and secondary prevention from AIS and acute coronary syndrome (11,12). Recent studies have demonstrated that the ratios of these values to each other are more valuable in showing inflammation and atherosclerosis than they are alone (5-7,18). In line with these studies, an association between elevated neutrophil/HDL(NHR) and LDL/HDL ratios (LHR) and increased cardiovascular risk has been found (19,20). Besides, the monocyte/HDL (MHR) value obtained by dividing the monocyte count by HDL has been reported to be a suitable and efficient marker of cardiovascular disease such as ischemic cerebrovascular disease and acute myocardial infarction (7,8).

Therefore, our aim in this study is to determine whether NHR and LHR ratios, which are new potential lipid biomarkers, can be used as new inflammatory indicators in elderly individuals with asymptomatic carotid atherosclerotic stenosis determined by carotid Doppler ultrasonography (USG) and to reveal whether these ratios are superior to each other by comparing these ratios with the MHR ratio.

METHODS

Design of the Patient and Control Groups: One hundred twenty-four patients over the age of 65 who applied to the Neurology outpatient clinic of Sivas Cumhuriyet University Faculty of Medicine with dizziness between 01.01.2010-01.09.2020, in whom the diagnosis of cerebrovascular disease and causes of central vertigo were excluded by performing computed brain tomography (CCT) or cranial magnetic resonance imaging (c. MRI), who underwent bilateral carotid Doppler USG and in whom stenosis was detected were included in our retrospective study. No restrictions were made among the patients in terms of gender.

Patients with left ventricular hypertrophy, systolic dysfunction or moderate-severe diastolic dysfunction and severe valvular disease, arrhythmia, left bundle branch block, chronic heart, lung or renal failure, connective tissue disease, hematological disease, malignancy, acute / chronic inflammatory or autoimmune disease or thyroid disorder, with a history of infection in the last two weeks, using immunosuppressants, anti-inflammatory drugs or drinking alcohol and having a history of acute coronary syndrome, acute cerebrovascular disease or surgery in the last three months were not included in our study.

The baseline demographic and clinical information of the patients (information on risk factors such as age, sex, hypertension, the presence of diabetes mellitus and hyperlipidemia, or smoking) was obtained from the hospital's record system. The missing patient information was completed by calling the phone numbers of the patients registered in the hospital's system.

Our control group comprised healthy volunteers of similar age and gender to our patient group, who were examined in our outpatient clinic and gave blood samples for other reasons, who had no comorbidity (like hypertension, diabetes mellitus or hyperlipidemia) and did not use medications regularly. None of the participants in our patient and control groups were using statins.

The study was conducted in accordance with the Helsinki Declaration ethical standards. The written informed consent form was acquired from each patient and control, and only patients who gave consent were included in the study.

Ethics committee approval for our study was acquired from the Non-Interventional Ethics Committee of Sivas Cumhuriyet University (Number: 2020/10-12, Date: 21.10.2020).

Evaluation of Blood Parameters: The relevant measurements were made from blood samples taken from the antecubital vein into dry and EDTA tubes, following 12 h of fasting. Dry tubes were utilized for biochemical analysis, and EDTA tubes were used in hematological tests. While complete blood counts were performed using the Diagon kit on the Mindray BC-6800 device, neutrophil and monocyte counts were obtained from these measurements. Biochemical analyses (glucose, creatinine, uric acid, C-reactive protein, total cholesterol, LDL, HDL, triglyceride levels) were applied on the Beckman Coulter AU5800 device (Beckman Coulter Inc, Hialeah, Florida) using the kits of the same brand by a fully automated nephelometric method. NHR, MHR, and LHR values were obtained by dividing these values by each other.

Evaluation by Carotid Doppler USG: Before being evaluated by carotid Doppler USG, the patient was rested in the supine position for 15 minutes. Bilateral common carotid arteries (CCA), carotid bifurcation, internal carotid and external carotid arteries were examined using a3.5e10 MHz linear multi-frequency transducer (Toshiba -2900 or G device 320) on the longitudinal and transverse planes. The intima-media thickness (IMT) was calculated on the longitudinal planes, in a region free of atherosclerotic plaques of the common carotid artery far wall, at 0.5, 1, and 1.5 cm from the carotid bifurcation, taking for analysis the average of the three measurements. The stenosis caused by plaques as observed using carotid Doppler USG was assessed according to the criteria developed by the internal carotid artery stenosis criteria consensus committee. The significant atherosclerotic stenosis of the carotid artery was detected on the transverse plane and was defined as the focal structure exceeding ≥%50% of the surrounding IMT value.

Statistical Analysis: The data obtained from our study were assessed by utilizing the SPSS 23.0 program. Whether the data were normally distributed was revealed by the Kolmogorov-Smirnov test. While normally distributed continuous data were presented with mean ± standard deviation (SD), non-normally distributed continuous data were reported as median ± interquartile range. Categorical data were expressed as frequency and percentage. The chi-square test was conducted to evaluate the data obtained by counting. If the data met the parametric conditions, they were analyzed by the independent sample t-test for two independent groups. If they did not meet the parametric conditions, the Mann-Whitney U test was used. The Kruskal-Wallis H test was performed to compare the data of three independent groups. The relationship between the variables was determined by Pearson's correlation analysis. The analysis of receiver operating characteristic curves (ROC) was performed to find the optimum cut-off values of NHR, MHR, and LHR to predict carotid artery stenosis. The level of significance was taken as $p < 0.05$.

RESULTS

The demographic and clinical characteristics and laboratory findings of the patients and controls included in our study are presented in Table 1. While 64 of the individuals in our patient group were female (52%), 65 of the individuals in our control group were female (52%), and there was no difference between the two groups in terms of sex (p=0.94). Furthermore, the mean age of our patient group was 68.2 years, while the mean age of our control group was 67.8 years (p=0.45). Eighty-five of the patients in our patient group were diagnosed with hypertension (68%), 72 of them were diagnosed with diabetes mellitus (58%), 64 of them were diagnosed with hyperlipidemia (52%), and 75 of them (60%) were smoking, 2 were drinking 1-2 glasses of alcohol 1-2 times a week.

While the median HDL value in our patient group was 47 mg/dL, the mean LDL and total cholesterol values were 85.3±39.4 mg/dL and 186.9±39.3 mg/dL, respectively. When these values were compared with our control group, the HDL value was lower in our patient group, although it was not statistically significant (p=0.061), and the LDL and total cholesterol values were statistically significantly higher (p=0.021, p=0.045, respectively). When the cell counts were examined, the mean monocyte and neutrophil counts in the patient group were 0.58±0.093 10^9/ml and 4.93±1.26 10^9/ml, respectively. Likewise, these values were statistically significantly higher than the values in our control group (p=0.048, p=0.034). When the NHR, MHR, and LHR values obtained by dividing these values by each other were examined, these three values were statistically significantly higher in the patient group in comparison with the control group (p<0.01, p=0.028, p=0.034, respectively) (Table 1). Then our patient group were divided into two subgroups according to their degree of stenosis as a result of carotid artery Doppler USG. While the stenosis degrees of the patients in the first group were between 50% and 69% (n=84), the degree of stenosis of the patients in the second group was ≥70% (n=40). Afterward, the first group, second group, and control group were compared again in terms of neutrophil and monocyte count, HDL and LDL levels, and NHR, MHR and LHR values. NHR, MHR, and LHR values were statistically significantly higher in the second group compared to the other two groups (p=0.021, p=0.028, p=0.034, respectively). Moreover, NHR, MHR, and LHR values were significantly higher in the first group in comparison with the control group (Table 2).

Table 1. The comprassion of the baseline demographic/clinical characteristics and laboratory findings of patient and control groups.

	Patient Group (n=124)	Control Group (n=125)	X^2	p
Female, n(%)	64(52%)	65(52%)	0.01	0.94
Age (mean±SD)	68.2	67.8		0.45
Chronic diseases				
HT Presence, n(%)	85(68%)	-		
DM Presence, n(%)	72(58%)	-		
Hyperlipidemia Presence, n(%)	64(52%)	-		
Habits				
Tobacco use, n(%)	75(60%)	68(54%)	0.12	0.08
Alcohol use, n(%)	2(0.2%)	1(0.1%)	0.14	0.21
Biochemical analysis				
Glucose (mg/dL) (mean±SD)	145.9±72. 8	141.7±73.3		0.28
Creatine (mg/dL) (median)(IR)	0.9 (0. 5–1. 4)	0.8(0.5-1.3)		0.36
HDL (mg/dL) (median)(IR)	47(33-72)	56(44-81)		0.061
LDL (mg/dL) (mean±SD)	85.3±39.4	67.8±19.3		0.021
TotalChol (mg/dL) (mean±SD)	186.9±39. 3	134.7±21.1		0.045
Complete blood count values				
Hb (g/dL) (mean±SD)	14.6±1.3	14.1±1.4		0.21
WBC (10^9/ml) (median)(IR)	8.1 (4. 8–11. 1)	8.3 (4. 9–11. 4)		0.32
Monocyte(10^9/ml) (mean±SD)	0.58±0.093	0.51±0.087		0.048
Neutrophil (10^9/ml) (mean±SD)	4.93±1.26	3.92±1.11		0.034
Rates				
NHR	0.010±0.003	0.007±0.004		<0.01
MHR	0.012±0.002	0.009±0.001		0.028
LHR	1.81±0.35	1.35±0.25		0.034

All values are presented mean±standard deviation (SD), median value (IR) or number (%).
Abbreviations: HT: hypertension; DM: diabetes mellitus; HDL: high density lipoprotein; LDL: low density lipoprotein; TotalChol: total cholesterol; WBC: white blood cell; NHR: neutrophil to high density lipoprotein ratio; MHR: monocyte to high density lipoprotein ratio; LHR: low density lipoprotein to high density lipoprotein ratio.

Table 2. The comprassion of the neutrophil and monocyte counts and HDL, LDL and NHR, MHR and LHR values of the first, second and control groups.

	First Group (n=84)	Second Group (n=40)	Control Group (n=125)	p
HDL (mg/dL) (median)(IR)	49(33-69)	43(35-72)	56(44-81)	0.065
LDL (mg/dL) (mean±SD)	82.3±23.4	89.1±18.5	67.8±19.3	0.011
Monocyte(10^9/ml) (mean±SD)	0.56±0.083	0.63±0.086	0.51±0.087	0.048
Neutrophil (10^9/ml) (mean±SD)	4.88±1.16	4.95±0.98	3.92±1.11	0.034
NHR	0.099±0.002	0.115±0.003	0.007±0.004	0.021
MHR	0.011±0.002	0.014±0.003	0.009±0.001	0.028
LHR	1.679±0.25	2.069±0.34	1.35±0.25	0.034

All values are presented mean±standard deviation (SD), median value (IR) or number (%).
Abbreviations: HDL: high density lipoprotein; LDL: low density lipoprotein; NHR: neutrophil to high density lipoprotein ratio; MHR: monocyte to high density lipoprotein ratio; LHR: low density lipoprotein to high density lipoprotein ratio.

When the correlation between NHR, MHR and LHR values and the degree of carotid stenosis was evaluated, a correlation in the same direction was found between NHR, MHR, and LHR (r=0.16, r=0.11, r=0.08, respectively). However, the amount of this relationship was statistically insignificant and little (p>0.05).

ROC analysis was carried out to find the cut-off value for NHR, MHR, and LHR values in detecting carotid stenosis, and the results are presented in Figure. The area under the curve (AUC) for NHR was 0.68 (p<0.001, 95% confidence interval (CI) 0.62-0.75) and the cut-off point was 0.09 (sensitivity: 77.60%, specificity: 50.80%) (Figure a). The AUC for MHR was 0.61 (p=0.004, 95% CI: 0.54-0.68) and the cut-off point was 0.01 (sensitivity: 47.45%, specificity: 73.40%) (Figure b). The AUC for LHR was 0.58 (p=0.017, 95% CI: 0.51-0.65), and the cut-off point was 1.61 (sensitivity: 34.25%, specificity: 85.30%) (Figure c). As a result, the AUC for NHR was greater than for MHR and LHR and demonstrated a better predictive value in detecting asymptomatic carotid stenosis in elderly patients.

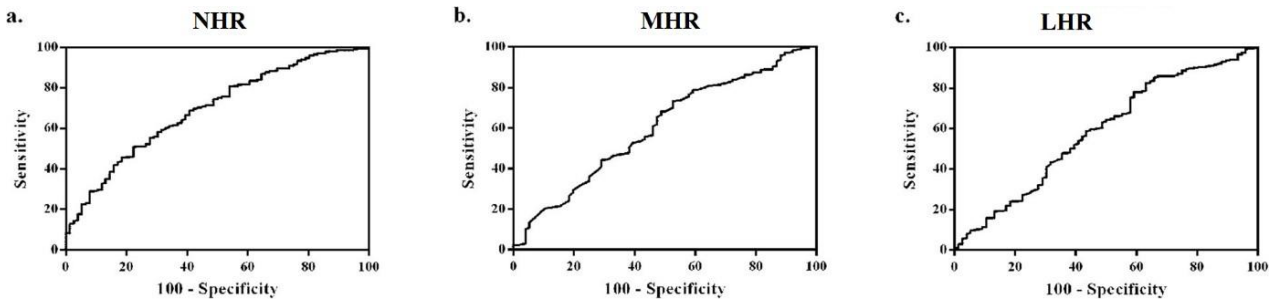

Figure. ROC curve analysis for NHR, MHR and LHR (a, b, c). a) The AUC for NHR was 0.68 (p<0.001) and the cutoff point was 0.09 (sensitivity: 77.60%, specificity: 50.80%). b) The AUC for MHR 0.61 (p= 0.004) and the cutoff point was 0.01 (sensitivity: 47.45%, specificity: 73.40%). c) The AUC for LHR 0.58 (p=0.017) and the cutoff point was 1.61 (sensitivity: 34.25%, specificity: 85.30%). Abbreviations: ROC: receiver operating characteristic; AUC: area under the curve; NHR: neutrophil to high-density lipoprotein cholesterol ratio; MHR: monocyte to high-density lipoprotein cholesterol ratio; LHR: low density lipoprotein to high density lipoprotein ratio.

DISCUSSION AND CONCLUSION

In the present study, we revealed that high NHR, MHR, and LHR ratios in elderly persons were associated with asymptomatic carotid stenosis. Furthermore, the NHR value was found to be a more valuable marker in detecting the presence and degree of carotid stenosis compared to MHR and LHR values. Additionally, a positive correlation was found between MHR and LHR levels and the degree of carotid stenosis.

Monocytes serve as an important source of pre-inflammatory cytokines in the atherosclerosis process. Monocytes transform into foam cells leading to the release of pro-inflammatory and pro-oxidant cytokines at the site of inflammation resulting in plaque formation and higher monocyte accumulation (18). Many studies have shown that increased monocyte count is a poor prognostic factor in atherosclerotic events such as ischemic stroke and cardiovascular diseases (18,21). HDL exerts an anti-inflammatory and antioxidant effect by preventing both the oxidation of LDL and the entry of monocytes through the vascular wall. Thus, the vascular endothelium is protected from inflammation and oxidative stress (18,21,22). As a result, while monocytes take an active part in the atherosclerosis process with their pro-oxidant and pro-inflammatory impacts, HDL acts as a neutralizer by suppressing inflammatory markers, e.g. monocytes. Therefore, the MHR value is considered to be a good indicator in evaluating atherosclerosis by investigating the relationship between inflammation and dyslipidemia. There are many studies indicating that the MHR value can be used both in determining the severity of the disease in the acute period and predicting its prognosis afterward in cardiovascular diseases, including ischemic stroke and acute myocardial infarction (AMI)(7,23-25). Furthermore, in their study, Yurtdaş et al. showed that the MHR value could be used as a marker to show clinically significant asymptomatic carotid stenosis (26). Similar to this study, in our study, the MHR value was found to be higher in elderly patients with asymptomatic carotid stenosis compared to healthy volunteers of similar age and sex. Additionally, as the severity of carotid stenosis increased, the MHR value also increased.

In another study, it was found that high LHR levels were associated with increased cardiovascular diseases (19,20). This result is not surprising when the complicated etiology of atherosclerosis, including altered lipid metabolism, inflammatory reaction, and oxidation damage, is taken into account (27,28). In the current study, we demonstrated that LHR ratios increased in atherosclerotic carotid stenosis compared to healthy controls, as in cardiovascular diseases. Furthermore, with the increase in the degree of carotid stenosis, the LHR value increased. Since there is no study in the literature conducted with this biomarker in atherosclerotic carotid stenosis, our study is the first one in this respect.

Moreover, it is known that neutrophils are an indispensable component of the immuno-inflammatory response in the development of atherosclerotic diseases, including AMI, and there are many neutrophils around the atherosclerotic lesion (29,30). Recent studies have demonstrated that the increased level of myeloperoxidase from the neutrophils can lead to coronary atherosclerosis (30). In their study, Yunoki et al. found that plasma myeloperoxidase levels were

inversely related to serum HDL level and activity (31). Furthermore, studies showed that HDL may also block inflammation and oxidation by preventing neutrophil activation, attachment, diffusion, and migration (9). Considering all these, it is not surprising that high NHR levels were detected in AMI patients depending on the increased neutrophil count and decreased HDL levels, as in the study performed by Huang et al. (20). In our study, similar to AMI patients, the NHR value was found to be high in patients with atherosclerotic carotid stenosis, and a positive correlation was detected between the NHR value and the degree of stenosis. Additionally, NHR values above 0.09 in our study were found to be a marker with a higher sensitivity in detecting atherosclerotic carotid stenosis in elderly patients compared to the other two ratios. Unfortunately, there is no other study in the literature showing the correlation between the NHR value and carotid stenosis, and our study is the first one in this respect, as in LHR.

Our study has various limitations. First of all, it is a retrospective and single-center study. Therefore, the number of our patients was comparatively low, and other inflammatory markers (such as CRP (C-reactive protein), fibrinogen, or myeloperoxidase) that are not routinely checked could not be included in the evaluation. Furthermore, patients were evaluated only by bilateral carotid Doppler USG, and digital subtraction angiography (DSA) or CT angiography was not performed to better evaluate the stenosis. Additionally, bilateral carotid Doppler USG was not performed in the control group to rule out carotid stenosis.

As a result, we revealed that NHR, MHR, and LHR ratios, which do not require additional costs and are easily accessible, can be used with a higher sensitivity than using these values individually in detecting asymptomatic carotid stenosis in elderly patients. There is a need for more comprehensive prospective randomized controlled studies on this subject in the future.

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Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Ethics Committee of Sivas Cumhuriyet University (Number: 2020/10-12, Date: 21.10.2020).
Informed Consent: The authors declared that informed consent was signed by the patients.
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