Is Elevated Monocyte to High-Density Lipoprotein Ratio a Predictor of Symptomatic Plaque in Patients with Intermediate Carotid Artery Stenosis?

Monosit/Yüksek Yoğunluklu Lipoprotein Kolesterol Oranı Yüksekliği Orta Düzey Karotis Arter Darlığında Semptomatik Plak için Öngördürücü müdür?

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Abstract

Aim: Monocyte to high-density lipoprotein cholesterol (HDL-C) ratio (MHR) is a new and easily measurable marker positively associated with inflammation. In this study, we aimed to evaluate if there was a relationship between MHR and the risk of presence of symptomatic plaque in patients with intermediate carotid artery stenosis.

Materials and Methods: A total of 179 of patients who had 50%-70% stenosis in the carotid artery were included in this retrospective cohort study. Patients were assigned into two groups based on symptomatic (n=104) and asymptomatic (n=75) group. Groups were compared in terms of MHR. Predictive role of MHR for presence of symptomatic plaque was investigated.

Results: Monocyte to high-density lipoprotein cholesterol ratio was significantly higher in the symptomatic group (11.40±4.24 vs 18.33±9.06, p<0.001). Monocyte to high-density lipoprotein cholesterol ratio>13.48; had 70.19% sensitivity and 76.0% specificity for prediction of symptomatic plaque (AUC: 0.787, 95% CI: 0.720–0.840, p<0.001) in patients with intermediate carotid artery stenosis. In a univariate analysis age, gender, hemoglobin, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), smoking, total cholesterol and MHR were significantly associated with presence of symptomatic carotid plaques. Monocyte to high-density lipoprotein cholesterol ratio (OR:1.330, p<0.001) and hemoglobin (OR:1.441, p=0.013) were found to be significant independent predictors of symptomatic plaques in the carotid artery in a multivariate analysis, after adjusting for other risk factors.

Conclusion: MHR plays a moderate role for prediction of symptomatic plaques in the carotid artery.

Keywords: Monocyte/HDL-C ratio; carotid artery; symptomatic plaque

Öz

Amaç: Monosit/yüksek yoğunluklu lipoprotein kolesterol oranı (MHR), inflamasyon ile pozitif ilişkili yeni ve kolayca ölçülebilen bir belirteçtir. Bu çalışmada orta düzey karotis arter darlığı olan hastalarda MHR ile semptomatik plak varlığı arasında bir ilişki olup olmadığını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu retrospektif kohort çalışmaya karotis arterde %50-%70 stenozu olan toplam 179 hasta dahil edildi. Hastalar semptomatik (n=104) ve asemptomatik (n=75) olmasına göre iki gruba ayrıldı. Gruplar MHR açısından karşılaştırıldı. Semptomatik plak varlığı için MHR'nin prediktif rolü araştırıldı.

Bulgular: Semptomatik grupta MHR anlamlı olarak daha yüksekti (11,40±4,24'e karşı 18,33±9,06, p<0,001). MHR>13,48; orta düzey karotis arter darlığı olan hastalarda semptomatik plak (AUC: 0,787, %95 CI: 0,720-0,840, p<0,001) tahmini için %70.19 duyarlılığa ve %76,0 özgüllüğe sahipti. Tek değişkenli analizde; yaş, cinsiyet, hemoglobin, nötrofil sayısı, lenfosit sayısı, nötrofil-lenfosit oranı (NLR), sigara, total kolesterol ve MHR, semptomatik karotis plakların varlığı ile anlamlı derecede ilişkili bulundu. Çok değişkenli regresyon analizinde; diğer risk faktörleri ayarlandıktan sonra, MHR (OR: 1,330, p<0,001) ve hemoglobin (OR: 1,441, p=0,013) karotis arterdeki semptomatik plakların anlamlı bağımsız prediktörleri olarak bulundu.

Sonuç: MHR, karotis arterdeki semptomatik plakların öngörülmesinde orta derecede rol oynar.

Anahtar Sözcükler: Monosit/HDL-K oranı; karotis arter; semptomatik plak

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INTRODUCTION

Atherosclerosis is the leading cause of stroke. It is identified as a major cause up to 20-30% of all ischemic strokes in the world (1). The underlying pathology is inflammation. There is mounting evidence pointing that it plays a strong role for the onset, progression and rupture of atherosclerotic plaque (2,3).

Monocyte causes atherosclerosis via adhesion, infiltration to vascular endothelium and conversion to lipid-laden macrophages. Subsequently it becomes main cellular component of atherosclerotic plaque (3-5). It has been well documented that the number of monocyte and monocyte subsets are independent predictors of subclinical atherosclerosis and coronary artery disease (CAD) (6,7).

High-density lipoprotein cholesterol alleviates the deleterious effect of monocytes by blocking the expression of endothelial adhesion molecules. This alteration causes pronounced decrease in monocyte infiltration (3). In this process, monocytes have a proinflammatory effect, while HDL acts as a anti-inflammatory molecule that antagonizes this effect. Therefore, Monocyte/HDL-cholesterol ratio (MHR) is a simple parameter used to evaluate the inflammatory condition (8). It has also been reported as a new prognostic marker in cardiovascular diseases (8).

The degree of carotid artery stenosis (CAS) and symptoms are two main factors that determine the risk of stroke (9). According to current guidelines (10) two situations requiring intervention are as follows: 1) Symptomatic patients with at least 50% CAS, 2) Asymptomatic patients with at least 70% CAS. There is a gray zone including asymptomatic patients with intermediate (50-70%) CAS. Identification of high risk individuals with intermediate CAS for developing symptoms is of paramount importance. Hence we hypothesized that MHR may play an important role for prediction of symptomatic plaques in the carotid artery. We sought to compare symptomatic and asymptomatic patients with intermediate CAS in terms of MHR.

MATERIALS AND METHODS
Study Population

We retrospectively reviewed the medical records of 305 patients who admitted to cardiology outpatient clinic, with a previously reported 50%-70% stenosis in the carotid artery between 2013 and 2015. Patients with any of the followings were excluded: Acute coronary syndrome, previous cardiac surgery, known CAD, atrial fibrillation, concomitant severe valvular disease, heart failure, cardiomyopathy, congenital heart defects, renal or hepatic disease, hematological disorders, malignancy, and acute or chronic inflammatory disorders. Additionally 44 patients were not included in this analysis due to incomplete, poor data acquisition and lost to follow up. Finally 179 consecutive patients were enrolled in the study. Groups were divided in two groups as follows: 75 patients with asymptomatic intermediate CAS and 104 patients with symptomatic intermediate CAS. Symptoms were defined as a history of ischemic cerebrovascular event with or without sequelae, transient ischemic attack, and amaurosis fugax. Carotid stenosis was evaluated by computed tomography angiography (CTA) in all patients. All patients were evaluated by a committee consisting of a cardiologist, a neurologist, a radiologist and a cardiothoracic surgeon. Study was approved by the local ethics committee with the number 3842 on 06.03.2020 and the study was conducted in accordance with ethical principles described by the Declaration of Helsinki.

CTA assessments

A CT device with Philips Brilliance 64 detector (Netherlands) was used for CTA. After venous access was established through the antecubital vein and 80 mL non-ionic contrast agent was administered at a rate of 4.5 mL/sec, axial-plane CT images of the carotid and cerebral arteries were obtained using the tracking method. Acquired slices were transferred to the workstation (Philips Intellispace Portal) and multi-plane images, maximum intensity projection and volume rendering 3-dimensional images were developed by post-processing the original slices via appropriate software (AVA). These images were examined for vascular plaques and stenosis. The stenosis caused by plaques as detected using CDUS was assessed according to the criteria developed by the Internal CAS Criteria Consensus Committee. The severity of stenosis detected on CTA was evaluated according to the criteria of the North American Symptomatic Carotid Endarterectomy Trial.

Blood samples

Fasting blood samples were taken from a large antecubital vein of each patient to determine biochemical parameters and hemogram parameters. EDTA-tubes were used for automatic blood count. Blood counts were measured with a Beckman Coulter LH 780 Hematology Analyzer. Total cholesterol, triglyceride, low-density lipoprotein and high density lipoprotein levels were measured by colorimetric method (Abbott Laboratories, Abbott Park, IL,USA). The ratio of absolute monocyte count to HDL-cholesterol value was calculated as MHR.

Statistical analysis

All the statistical data were analyzed by the SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical data was expressed as percentages and continuous data was expressed as mean ± standard deviation. The Kolmogorov–Smirnov test was used to evaluate the distribution of continuous variables. Both groups were compared using the chi-square test for qualitative variables or the Fisher exact test when appropriate, and the independent t-test for normally distributed continuous variables. Continuous variables that were not normally distributed are presented as median and interquartile ranges. Pearson test was used in the correlation analysis between parametric variables. Receiver-operating characteristic (ROC) analysis was performed for MHR in order to determine optimal cut-off values and to obtain the sensitivity and specificity for each variable to predict the symptomatic carotid plaque. A multivariate logistic regression model was performed by including the parameters that differed significantly between the groups in order to identify the independent predictor of symptomatic carotid plaque. A p-value of <0.05 was considered significant.

RESULTS

Baseline demographical characteristics and clinical, laboratory data of 179 patients (104 symptomatic and 75 asymptomatic) were summarized in Table 1. Hypertension (p=0.016) and male gender (p=0.016) were higher in symptomatic group.

White blood cell count (p<0.001), neutrophil count (p<0.001), monocyte count (p=0.001), hemoglobin level (p=0.002), creatinine level (p=0.008), platelet distribution width (PDW) (p<0.001) were higher in the symptomatic group. However HDL (p<0.001), LDL (p=0.038), total cholesterol (p=0.008) and lymphocyte count (p=0.001) were found to be lower in the symptomatic group (Table 1).

MHR was found to be significantly higher in the symptomatic group (p<0.001). A receiver operating characteristic curve was generated for sensitivity and specificity, and the respective areas under the curve (AUCs) were used to investigate the predictive value of MHR for prediction of symptomatic plaque (Figure 1). MHR with a cut-off of 13.48; had 70.19% sensitivity and 76.0% specificity for prediction of symptomatic plaque (AUC: 0.787, 95% CI: 0.720–0.840, p<0.001) in patients with intermediate CAS. In a univariate analysis age, gender, hemoglobin, neutrophil count, lymphocyte count, NLR, smoking, total cholesterol and MHR were significantly associated with progression of symptomatic carotid plaques. MHR (OR:1.330, p<0.001) and hemoglobin (OR:1.441, p=0.013) was found to be a significant independent predictor of symptomatic plaques in the carotid artery in a multivariate analysis, after adjusting for other risk factors (Table 2).

DISCUSSION

The main findings of the present study were as follows: i) A raised MHR was found to be significantly higher in patients with moderate CAS who became symptomatic. ii) MHR had moderate sensitivity and specificity to predict symptomatic plaque in patients with intermediate CAS. iii) MHR was found to be a significant independent predictor for symptomatic plaque in patients with intermediate CAS, after adjusting for other risk factors in multivariate analysis.

Atherosclerosis is identified as a major cause of death worldwide (11). Inflammation and oxidative stress are two mechanisms known to be effective in the onset and progression of atherosclerosis (12). Monocytes play a key role in this process. Activated monocytes interact with the damaged endothelium, causing overexpression of proinflammatory cytokines and adhesion molecules. Monocyte chemotactic protein 1 ligand, vascular cell adhesion molecule 1, intercel-

Table 1. Demographic, clinic and laboratory characteristics of the groups studied

Variables	Asymptomatic group(n:75)	Symptomatic Group(n:104)	P value
Age, in years	70.55±10.08	70.59±9.72.	0.979
Male gender, n(%)	34 (45.3%)	66 (63.5%)	*0.016*
Hypertension, n(%)	37 (49.3%)	70 (67.3%)	*0.016*
Diabetes mellitus, n(%)	18 (24%)	33 (31.7%)	0.258
Smoking, n(%)	14 (18.7%)	32 (30.8%)	0.068
Glucose, mg/dl	113.52±59.29	115.94±41.19	0.747
Creatinine, mg/dl	0.84±0.19	0.93±0.22	*0.008*
Hemoglobin, gr/dl	12.93±1.46	13.66±1.64	*0.002*
White blood cell count, x 10³/L	7.52±1.81	8.67±2.46	*<0.001*
Neutrophil count, x 10³/L	4.22±1.35	5.72±2.15	*<0.001*
Lymphocyte count x 10³/L	2.50±0.72	2.12±0.80	*0.001*
Monocyte count x 10³/L	0.57±0.18	0.69±0.25	*0.001*
Rdw	14.29±1.64	14.25±2.08	0.874
Pdw	17.14±3.21	19.05±1.95	*<0.001*
Mpv	8.66±1.71	8.10±1.55	*0.023*
Platelet count x 10³/L	245.77±64.64	245.48±62.15	0.976
LDL cholesterol, mg/dl	125.14±27.75	115.41±32.73	*0.038*
HDL cholesterol, mg/dl	51.89±9.68	40.55±10.35	*<0.001*
Triglyceride (TG), mg/dl	150.78±89.49	144.86±65.42	0.609
Total cholesterol, mg/dl	206.23±39.65	189.48±42.15	*0.008*
Monocyte count/HDL cholesterol ratio (MHR)	11.40±4.24	18.33±9.06	*<0.001*

*RDW: Red cell distribution width, PDW: Platelet distribution width, MPW: Mean platelet volüme, HDL: High density lipoprotein, LDL: Low density lipoprotein

Table 2. Independent predictors of symptomatic carotid plaque in the multivariate logistic regression analysis

	Odds ratio	Confidence İnterval(%95)	P value
Age	1.019	0.973-1.067	0.420
Gender	0.610	0.364-1.025	0.062
Hemoglobin	1.441	1.079-1.926	*0.013*
Neutrophil count	1.162	0.439-3.081	0.762
Lymphocyte count	0.725	0.116-4.514	0.730
NLR	3.607	0.651-19.986	0.142
Smoking	1.275	0.741-2.196	0.381
Total cholesterol	1.002	0.992–1.013	0.700
MHR	1.330	1.186-14.930	*<0.001*

* NLR: Neutrophil tolymphocyte ratio; MHR: Monocyte to HDL-cholesterol ratio

lular adhesion molecule 1 and monocyte chemotactic protein 1 ligand are the most commonly encountered molecules in this process. Subsequently monocytes convert to macrophages that ingest oxidized LDL cholesterol and form foam cells (13).

HDL inhibits all aspects of atherosclerosis. The underlying pathophysiology of atherosclerosis is the interaction between monocytes and vascular endothelium. HDL breaks this vicious cycle by inhibiting activation, adhesion and infiltration of monocytes (14, 15). At cellular level HDL exerts its effect by block-

ing progenitor cells that form monocytes (16). On the other hand it induces vasodilatation and nitric oxide production (17-19). MHR emerges as a combination of these two parameters and reflects the underlying inflammatory process.

Previously, Açıkgöz et al. evaluated the endothelial function with the flow-mediated dilatation technique and reported that MHR was associated with endothelial dysfunction and systemic inflammation in Behçet's disease (20). Moreover Chen et al. showed that MHR was a useful parameter for detection and progres-
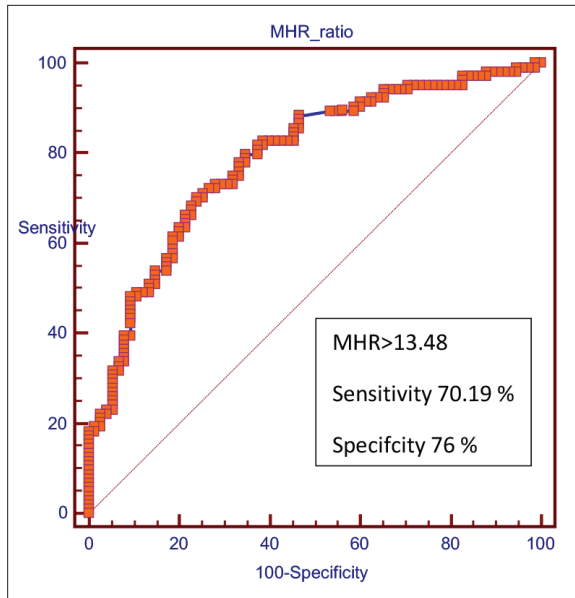
Figure 1. The receiver operating characteristic curve of the MHR for predicting symptomatic carotid plaque

sion of subclinical carotid atherosclerosis in diabetics (21). It has been previously postulated that MHR had a prognostic value in patients with CAD undergoing percutaneous coronary intervention (22) and was an independent factor for 30-day mortality in patients with acute ischemic stroke (23). Additionally MHR was found to be increased in myocardial bridge (24), coronary ectasia (25) and coronary slow flow (8).

The main pathophysiological connections between MHR and stroke can be endothelial dysfunction and inflammation. Inflammation not only causes monocyte activation and infiltration, but also reduces HDL. Previous studies showed that MHR was associated with systemic inflammation (8). In this study, we found that MHR was associated with symptomatic plaque progression in intermediate CAS. Although several parameters including neutrophil-to-lymphocyte ratio (NLR) were previously investigated for symptomatic plaque progression in the same patient group (26), there was no clinical study in the literature, which has evaluated the predictive value of MHR for this purpose. MHR had moderate sensitivity (70.19%) and specificity (76.0%) and was found to be a significant independent predictor of symptomatic plaque in our study.

Several uncertainties exist in asymptomatic intermediate CAS. MHR may provide additional benefit in

risk stratification and treatment algorithm. CTA could be performed frequently in high risk patients during follow up. Aggressive medical treatment including high dose statins and antiaggregants may be initiated earlier in patients with high MHR. Additionally early invasive strategy could be taken into account.

Some limitations of our study are as follows. It was a single center study and performed in the small population. Serial MHR changes were not evaluated because we only measured MHR at baseline. Due to the lack of registration, no comparison has been made between inflammatory marker levels such as C-reactive protein with MHR. Moreover, not all comorbidities and environmental factors that may affect inflammatory markers were taken into account.

CONCLUSION

MHR is a marker of inflammation and atherosclerosis. Increased MHR may be one of the factor associated with the development of symptoms in intermediate CAS.

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Conflict of Interest

There is no conflict of interest regarding this study.

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