

Assessment of the relationship between monocyte to high-density lipoprotein ratio and subclavian artery stenosis

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Abstract. – OBJECTIVE: Assessment of the monocyte-to-high-density lipoprotein ratio (MHR) is a new tool for predicting inflammation, which plays a major role in atherosclerosis. Subclavian artery stenosis (SAS) is usually asymptomatic, and atherosclerosis is the most common cause of chronic obstruction of the subclavian artery in adults. The aim of this study was to determine the relationship between the MHR and SAS.

PATIENTS AND METHODS: Between January 2015 and January 2020, 43 patients with SAS and 43 patients without SAS were enrolled in the study. The patients' angiographic, demographic and clinic characteristics were reviewed from their medical records. Monocytes and HDL (high-density lipoprotein) cholesterol were measured through a complete blood count. The MHR was calculated as the ratio of the absolute monocyte count to the HDL cholesterol value. The resulting MHR values were divided into the following three groups: low (7.16 ± 1.59), moderate (11.08 ± 1.53) and high (21.70 ± 5.62). A *p*-value of less than 0.05 was considered significant.

RESULTS: MHR was found to be significantly higher in the SAS group compared to the control group with normal subclavian arteries ($p < 0.001$). The frequency of SAS was found to increase with an increase in the MHR tertiles. Sensitivity and specificity values were 69.8% and 95.3%, respectively. The cut-off of the MHR value, taken as 13.39, was found to provide a significantly accurate prediction of the subclavian diagnosis (ROC area under the curve: 0.868, 95% CI: 0.789-0.947, $p < 0.001$). After adjusting for other hematological parameters in the multivariate analysis, MHR ($p = 0.061$) was found to be a predictor of the presence of SAS.

CONCLUSIONS: This study showed that MHR can be a convenient marker for predicting SAS because of the correlation between MHR and SAS.

Key Words:

Biomarkers, Atherosclerosis, Monocyte-to-high-density Lipoprotein ratio, Subclavian artery stenosis.

Introduction

Subclavian artery stenosis (SAS) accounts for approximately 2% of peripheral artery diseases, with left-sided SAS being more common than right-sided SAS^{1,2}. More than one-half of patients with peripheral artery disease suffer from left-sided SAS³. Furthermore, 50% of patients with subclavian artery disease also suffer from coronary artery disease (CAD) and 25% suffer from carotid and/or vertebral artery involvement⁴.

Although SAS has various causes, the most common cause is atherosclerosis². Previous studies² have shown that atherosclerotic SAS is associated with age, smoking, hypertension, and low levels of high-density lipoprotein cholesterol (HDL-C). HDL-C is an antioxidant and an anti-inflammatory molecule involved in the regulation of cholesterol flow between tissues and the modulation of oxidative stress and inflammation⁵. It has been shown in various studies^{6,7} that HDL-C protects the endothelium from the harmful effects of low-density lipoprotein cholesterol (LDL-C) and prevents the oxidation of LDL. Thus, HDL-C plays the role of an anti-inflammatory and antioxidant⁸. Two types of cells are essential for the synthesis and release of pro-inflammatory and prooxidant cytokines: monocytes and macrophages⁹. Previous studies¹⁰ have established that the monocyte to high-density lipoprotein ratio (MHR) is associated with numerous cardiovascular diseases, and it has been proposed as a marker of undesirable cardiac events and inflammation. However, to date, MHR has not been studied in patients with SAS. This study aims to investigate the relationship between SAS and MHR.

Patients and Methods

Of the patients admitted to our hospital between January 2015 and May 2020, 86 patients participated in this study. The study group comprised 43 patients with SAS, while the control group comprised 43 selected patients with similar characteristics, excluding SAS. Of the 86 participants, 43 were the patients who had undergone peripheral angiography, with results indicating $\geq 50\%$ SAS. Patients with the following medical conditions were excluded from this study: vasculitis, congenital malformation, malignancies, renal or liver dysfunction, acute or chronic inflammatory diseases, hematological diseases and chronic obstructive pulmonary diseases. However, in the control group, 43 patients had no known SAS diagnosis and no physical examination findings or symptoms that could suggest SAS. Both groups were similar in terms of demographic characteristics (such as age and gender), risk factors for atherosclerosis, incidence of CAD and drug use. Hypertension (HT) criteria were the use of anti-hypertensive drugs or a diagnosis of hypertension (with systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg). Diabetes mellitus (DM) criteria were the use of an anti-diabetic agent or the diagnosis of DM (fasting blood sugar ≥ 126 mg/dL). Hyperlipidemia (HL) criteria were the use of an antihyperlipidemic agent or the diagnosis of hyperlipidemia (total cholesterol ≥ 200 mg/dL, low-density cholesterol ≥ 160 mg/dL and triglycerides ≥ 200 mg/dL). The CAD criterion was the presence of coronary artery stenosis, as evident through angiography. Angiography images and blood test parameters of the patients were obtained from the patient records system.

Statistical Analysis

The data were entered into the IBM SPSS v. 23 program (IBM Corp., Armonk, NY, USA) and evaluated using statistical analysis. The normality assumptions of continuous variables were examined using the Kolmogorov-Smirnov test. Mean and standard deviation were used in the descriptive statistics of continuous variables, and frequency (n) and percentage (%) values were used to define categorical variables. The Mann-Whitney U test was used to compare continuous two-level variables with a non-normal distribution, and the t -test (independent samples) was used to compare continuous variables with a normal distribution. For three-fold comparisons, the following tests were performed: data with normal distribution were analyzed using the one-way analysis of variance (ANOVA), data with non-normal distribution were analyzed using

the Kruskal-Wallis test and significant differences were determined using the Bonferroni correction method. Relations between categorical variables were examined using Chi-square or Fisher exact analysis. Multivariate logistic regression analysis was performed to determine which variables were predictive of SAS diagnosis. Receiver operating characteristics (ROC) curve analysis was performed to determine the optimal cut-off of the MHR, and sensitivity and specificity values were calculated using the corresponding area under the curve (AUC). For all analyses, statistical significance was accepted at $p < 0.05$.

Results

A total of 86 participants were involved in the study, including 43 individuals with SAS (mean age: 65.65 ± 8.99 , sex: 69.8% male, 30.2% female) who were paired with 43 participants without SAS based on their age and gender (mean age: 65.91 ± 10.30 , sex: 69.8% male, 30.2% female).

Demographic information, along with the clinical and laboratory characteristics of both groups, are presented in Tables I and II. Table II shows that the values of total cholesterol, LDL, HDL, and hemoglobin were significantly higher in the control group than those in the SAS group ($p < 0.05$). However, white blood cell count, basophil count, neutrophil count, monocyte count and MHR values were found to be significantly higher in the SAS group than those in the control group ($p < 0.05$). Other variables between the two groups were not significantly different.

The MHR values were divided into the following three groups: low (7.16 ± 1.59), moderate (11.08 ± 1.53) and high (21.70 ± 5.62) (Table III). As shown in Table III, the values of total cholesterol and LDL in the second tertile were significantly higher than those in the third tertile ($p < 0.05$). While HDL values in the first tertile are significantly higher than those in the third tertile, the values of white blood cells and basophile are significantly lower ($p < 0.05$).

To predict an SAS diagnosis from the MHR, the ROC curve was obtained, and the sensitivity and specificity values were calculated from the corresponding AUC (Figure 1). The sensitivity and specificity values were 69.8% and 95.3%, respectively, when the MHR cut-off was 13.39. This MHR was found to make a significantly accurate prediction of SAS diagnosis (AUC of ROC curve: 0.868, 95%; CI: 0.789-0.947, $p < 0.001$).

Table I. Demographic and clinical characteristics of the study population.

Variables	Subclavian stenosis	Control	<i>p</i>
Age (years)	65.65 ± 8.99	65.91 ± 10.30	0.986
Male, n (%)	30 (69.8)	30 (69.8)	1.000
Hypertension, n (%)	30 (69.8)	29 (67.4)	0.816
Diabetes mellitus, n (%)	22 (51.2)	20 (46.5)	0.666
Coronary artery disease, n (%)	27 (62.8)	26 (60.5)	0.825
Stroke, n (%)	16 (37.2)	17 (39.5)	0.825
Peripheral artery disease, n (%)	17 (39.5)	19 (44.2)	0.662
Hyperlipidemia, n (%)	13 (30.2)	11 (25.6)	0.631
Smoking, n (%)	13 (30.2)	10 (23.3)	0.465
Carotid artery disease, n (%)	27 (62.8)	28 (65.1)	0.822

From the multivariate logistic regression analysis performed to determine independent variables that predict SAS diagnosis, none of the variables was found to make a significantly accurate prediction of SAS diagnosis, despite the near-significant predictions by neutrophil count and MHR value (Table IV).

Discussion

This study investigated the association between SAS and MHR. Patients with SAS were found to have a significantly higher MHR compared to patients in the control group. This study

is the first to demonstrate the relationship between SAS and MHR based on the premise that an increased MHR can serve as a predictor of SAS in patients with atherosclerotic subclavian artery disease.

SAS is usually asymptomatic, with stenosis often occurring within the initial 2 cm span of the subclavian artery, starting from the aortic origin. Atherosclerosis is the most common cause of chronic obstruction of the subclavian artery in adults. All the lesions in the study participants were caused by atherosclerosis².

Monocytes are essential cells with unique roles in the inflammatory processes occurring in peripheral blood during immune response^{11,12}. Mono-

Table II. Laboratory characteristics of the groups.

Variables	Subclavian stenosis	Control	<i>p</i>
Urea (mg/dL)	35.53 ± 9.00	33.74 ± 7.49	0.938
Creatinine (mg/dL)	0.92 ± 0.25	0.86 ± 0.11	0.554
Sodium (mEq/L)	138.88 ± 2.07	139.12 ± 2.11	0.831
Potassium (mEq/L)	4.34 ± 0.43	4.37 ± 0.39	0.695
Hemoglobin (g/dL)	13.11 ± 1.44	13.63 ± 1.05	0.015
White blood cell count (x 10 ³ /L)	8.33 ± 2.16	7.29 ± 1.42	0.010
Neutrophil count (x 10 ³ /L)	5.41 ± 1.59	4.48 ± 1.37	0.004
Lymphocyte count (x 10 ³ /L)	2.19 ± 0.89	2.11 ± 0.78	0.659
Monocyte count (x 10 ³ /L)	0.68 ± 0.21	0.40 ± 0.12	<0.001
Platelet count (x 10 ³ /L)	235.21 ± 56.15	241.23 ± 72.63	0.668
Basophil count	74.81 ± 32.58	60.93 ± 24.20	0.028
Eosinophil count	190.51 ± 188.36	234.84 ± 243.89	0.422
Total cholesterol (mg/dL)	189.65 ± 43.51	213.86 ± 40.34	0.009
LDL-C (mg/dl)	123.02 ± 30.37	138.70 ± 36.03	0.032
HDL-C (mg/dl)	40.94 ± 10.27	45.53 ± 7.24	0.019
Triglyceride (mg/dL)	157.00 ± 116.23	173.81 ± 80.10	0.179
MHR	17.86 ± 7.34	8.92 ± 2.59	<0.001

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; MHR: monocyte count/ HDL cholesterol ratio.

Table III. Demographic, clinic and laboratory characteristics of the MHR tertiles.

Variables	1 st tertile (n:28)	2 nd tertile (n:29)	3 rd tertile (n:29)	p
Age (years)	66.07 ± 8.94	66.48 ± 11.42	64.79 ± 8.46	0.901
Male, n (%)	16 (57.1)	20 (69.0)	24 (82.8)	0.108
Hypertension, n (%)	19 (67.9)	20 (69.0)	20 (69.0)	0.995
Diabetes mellitus, n (%)	16 (57.1)	13 (44.8)	13 (44.8)	0.564
Coronary artery disease, n (%)	17 (60.7)	17 (58.6)	19 (65.5)	0.858
Stroke, n (%)	11 (39.3)	11 (37.9)	11(37.9)	0.993
Peripheral artery disease, n (%)	10 (35.7)	13 (44.8)	13 (44.8)	0.725
Hyperlipidemia, n (%)	9 (32.1)	6 (20.7)	9 (31.0)	0.565
Smoking, n (%)	7 (25.0)	6 (20.7)	10 (34.5)	0.479
Carotid artery disease, n (%)	20 (71.4)	15 (51.7)	20 (69.0)	0.237
Urea (mg/dL)	35.25 ± 7.85	34.72 ± 7.80	33.97 ± 9.32	0.370
Creatinine (mg/dL)	0.87 ± 0.19	0.90 ± 0.16	0.90 ± 0.23	0.405
Sodium (mEq/L)	138.64 ± 1.93	139.45 ± 2.40	138.90 ± 1.86	0.416
Potassium (mEq/L)	4.37 ± 0.43	4.38 ± 0.41	4.32 ± 0.40	0.812
Hemoglobin (g/dL)	13.57 ± 1.25	13.41 ± 1.23	13.14 ± 1.37	0.382
White blood cell count (x10 ³ /L)	7.28 ± 1.38	7.54 ± 1.67	8.58 ± 2.30	0.021
Neutrophil count (x 10 ³ /L)	4.70 ± 1.56	4.61 ± 1.40	5.51 ± 1.56	0.039
Lymphocyte count (x 10 ³ /L)	1.97 ± 0.72	2.19 ± 0.76	2.28 ± 1.00	0.353
Monocyte count (x 10 ³ /L)	0.34 ± 0.10	0.50 ± 0.08	0.78 ± 0.17	<0.001
Platelet count (x 10 ³ /L)	235.36 ± 51.89	238.79 ± 79.93	240.41 ± 60.59	0.957
Basophil count	54.75 ± 24.48	70.21 ± 22.50	78.21 ± 35.30	0.008
Eosinophil count	211.82 ± 198.52	171.00 ± 138.40	255.17 ± 288.31	0.718
Total cholesterol (mg/dL)	210.82 ± 36.82	214.62 ± 44.94	180.14 ± 40.82	0.003
LDL-C (mg/dl)	134.54 ± 36.72	140.72 ± 33.25	117.45 ± 28.52	0.025
HDL-C (mg/dl)	47.50 ± 8.99	45.17 ± 6.49	37.19 ± 8.53	<0.001
Triglyceride (mg/dL)	161.43 ± 83.18	175.97 ± 71.75	158.69 ± 134.56	0.237
MHR	7.16 ± 1.59	11.08 ± 1.53	21.70 ± 5.62	<0.001

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; MHR: monocyte count/ HDL cholesterol ratio.

cytes play an important role in chronic inflammation and cardiovascular disease. During the early atherosclerotic process, most of the inflammatory cells that infiltrate the artery wall are monocytes. Circulating monocytes interact with pro-inflammatory cytokines, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and monocyte chemoattractant protein (MCP) secreted by damaged or activated endothelial cells and subsequently migrating into sub-endothelial spaces¹³. Monocytes that migrate into sub-endothelial spaces develop into mature macrophages and then transform into foam cells by engulfing oxidized LDL *via* scavenger SR-A and CD-36 receptors¹⁴. Foam cells secrete pro-inflammatory cytokines, matrix metalloproteinases, growth factors and tissue factor¹⁵. The role of monocytes in atherosclerosis is not limited to the arterial wall. They also play an active role in the circulatory system that is affected by activation

products created by growth factors, cytokines, oxidized lipids, and platelets, it is also impacted by soluble factors such as eicosanoid proteins which are associated with atherosclerosis. Therefore, circulating monocytes and macrophages contribute to the pathogenesis of cardiovascular disease and its complications through these inflammatory mediators¹⁶. In this study, the monocyte values were significantly higher in patients with SAS than in patients in the control group. The monocyte count is an important hematological parameter in the pathogenesis of atherosclerotic SAS.

Despite the pro-inflammatory effects of monocytes, HDL plays an anti-inflammatory role and contributes to the reversal of the inflammatory condition. Recent studies¹⁷⁻¹⁹ have shown that HDL-C plays an active role in monocyte activation, adhesion, and inflammation. It also plays an active role in controlling the proliferation of differentiated monocyte progenitor cells. HDL-C and apolipo-

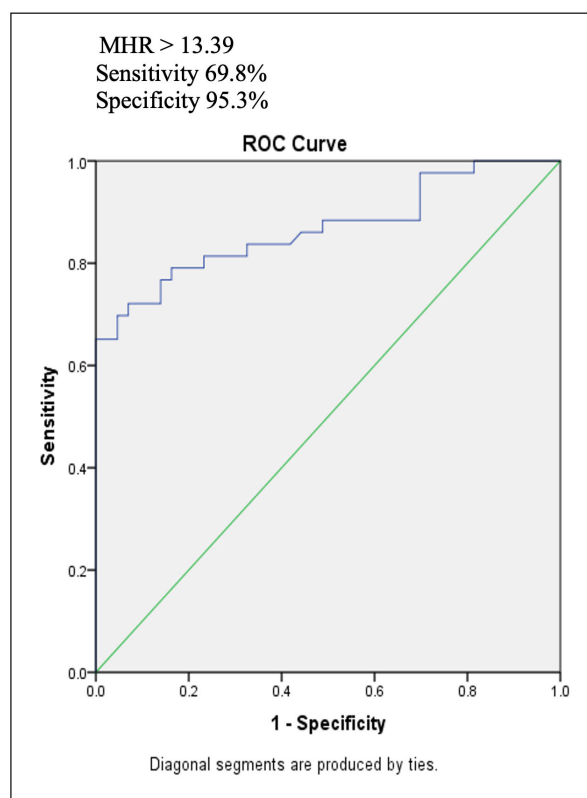


Figure 1. The receiver operative characteristic curve analysis of monocyte to high density lipoprotein cholesterol rate for predicting the presence of subclavian stenosis.

protein A-1 have been reported to have anti-inflammatory effects on monocytes *via* the inhibition of CD11b activation²⁰. HDL-C inhibits the expression of endothelial adhesion molecules, preventing the recruitment of monocytes into the artery wall²¹. HDL-C inhibits oxidation of LDL-C and promotes outflow of oxidized LDL-C from foam cells^{17,22}. Anti-atherosclerotic HDL-C has been shown to inhibit tissue factor expression in monocytes by preventing p38 activation and inhibiting phosphoinositide 3-ki-

nase²³. In addition to these anti-inflammatory properties, the HDL-C molecule increases nitric oxide production in the endothelium and thus causes vasorelaxation^{7,24}. Through these mechanisms and its anti-inflammatory, antioxidant and antithrombotic effects, HDL-C plays a vital role in preventing atherosclerosis. In this study, HDL-C levels were found to be lower in the study participants with SAS than those in the control group. Hence, low HDL-C values may play a significant role in subclavian artery atherosclerosis.

Recently, it has been considered that MHR may be a marker of inflammation and oxidative stress due to the pro-inflammatory effect of monocytes and the anti-inflammatory and antioxidant effects of HDL-C²⁵. First, an association between MHR and major cardiovascular events in patients with chronic kidney disease has previously been established²⁶. Furthermore, MHR has been found to be associated with asymptomatic organ damage in patients with hypertension²⁷. It has also been found to predict recurrence of atrial fibrillation after cryoablation²⁸ and the development of atrial fibrillation seven days postoperative²⁹. It has also been found to be associated with long-term in-hospital mortality for infective endocarditis³⁰. In addition, MHR was found to be high in patients with syndrome X compared to the control group³¹.

MHR has been shown to be an independent predictor of saphenous vein graft disease³². Furthermore, relationships have been established between the MHR and coronary slow flow³³, coronary ectasia³⁴, the prevalence of CAD¹², stent thrombosis after ST-elevation myocardial infarction (STEMI)³⁵, and bare stent restenosis in patients with angina pectoris³⁶. In-hospital and long-term major cardiac adverse events are also more common in STEMI patients with high MHR³⁷. It has also been shown that MHR can predict the development of contrast nephropathy after primary PCI³⁸.

Table IV. Multivariate analysis to detect independent variables for the diagnosis of subclavian stenosis.

Variables	Odds ratio	Confidence interval (95%)	p
Total cholesterol	0.983	0.948-1.019	0.355
LDL-C	1.021	0.977-1.068	0.351
HDL-C	1.290	0.962-1.730	0.089
White blood cell count	0.489	0.178-1.343	0.165
Basophil count	1.007	0.974-1.041	0.674
Hemoglobin	0.749	0.420-1.336	0.327
Neutrophil count	3.140	0.994-9.912	0.051
Monocyte count	0.000	0.000-49318.400	0.262
MHR	3.247	0.948-11.127	0.061

HDL: high density lipoprotein cholesterol; LDL: low density lipoprotein cholesterol; MHR: monocyte count/HDL cholesterol ratio.

Its association with the MHR in the circulatory system, excluding the coronary arteries, has been shown in several studies³⁹⁻⁴³. The MHR has also been found to be higher in patients with acute ischemic stroke, and it is an independent predictor of 30-day mortality³⁹. A study conducted by Yayla et al⁴⁰ found that the MHR is high in newly diagnosed and untreated hypertensive patients, which is associated with impaired aortic elasticity. The relationship between high MHR and the diameter of the abdominal aortic has been established by Cagli et al⁴¹. Chen et al⁴² have shown that MHR can be used in the diagnosis of subclinical atherosclerosis in patients with type-2 diabetes. Kirisci⁴³ demonstrated that a high MHR can be predictive of a diagnosis of carotid artery disease.

In this study, the MHR value was found to be significantly higher in patients with SAS compared to those in the patients of the control group. The main pathophysiological links between MHR and SAS may be due to endothelial dysfunction and chronic inflammation. In this study, in line with literature on cardiovascular disease, a high MHR value was found to be associated with the presence of SAS, in which pathophysiological inflammation plays a significant role. From a clinical perspective, as a new inflammatory marker, MHR may play a role in the prediction of SAS in daily clinical practice.

Limitations

There are various limitations to this study. First, this study has a retrospective, single-centered design with a small number of patients. Second, the MHR was not compared to any inflammatory markers, such as C-reactive protein, tumor necrosis factor- α , interleukin and cytokines. Furthermore, there was no long-term follow-up of discharged patients. Third, it was not taken into consideration that the MHR can be affected by many factors, including comorbid conditions (malignancy, infection, and rheumatic and inflammatory diseases), medications (non-steroid anti-inflammatory drugs, steroids and statins) and the nutrition and exercise habits of patients. Although individuals diagnosed with comorbid diseases were excluded from this study, some individuals with cases in the subclinical period who had undiagnosed silent inflammation may have been included.

Conclusions

This study investigates the relationship between MHR and SAS and shows that MHR val-

ues are significantly higher in patients with SAS than in patients in the control group. MHR was also found to be independently associated with the presence of SAS; hence, it can be used as an indicator to identify patients at high risk of inflammatory and atherosclerotic burden. In patients with a high MHR, more intensive and aggressive control of cardiovascular risk factors may be considered. MHR can also be used to monitor the inflammatory response and the effectiveness of treatment for high-risk populations, for which closer follow-ups can be recommended. However, given that the monocyte level can be affected by a wide range of factors, multi-centered, large-scale, randomized, and prospective studies are still required to corroborate these findings.

Ethical Approval

This study complies with the principles of the Declaration of Helsinki and was approved by the Ethics Review Committees of the Sakarya University.

Conflicts of Interest

The Authors declare that they have no conflict of interests.

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Informed Consent

The patients were informed, and consent was obtained.

Availability of Data

The data and materials generated/analyzed in the present study are available from the corresponding author upon request.

Authors' Contribution

Conception and design: Y. Can, İ. Kocayığıt and M. Aksoy; Acquisition of data: Y. Can, İ. Kocayığıt and M. Aksoy; Analysis and interpretation of data: Y. Can, M. Aksoy, İ. Kocayığıt and H. Kılıç; Drafting the article: Y. Can, H. Kılıç and R. Akdemir; Supervision: H. Kılıç and R. Akdemir; Validation and final approval: All authors.

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