Assessment of Monocyte Count to HDL Cholesterol Ratio in Patients With Ascending Aortic Dilatation

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Abstract: Objective. Ascending aortic dilatation (AAD) is a frequent but potentially fatal condition that is usually incidentally diagnosed. The association of AAD with inflammation and oxidative stress is well documented. Monocyte count to high-density lipoprotein cholesterol ratio (MHR), a novel inflammatory and oxidative stress marker, has been used to predict adverse cardiovascular outcomes. In this study, we aimed to investigate the relationship between MHR and AAD and the utility of MHR in patients with AAD. **Methods.** A total of 220 patients were investigated in this observational and cross-sectional study. MHR was calculated according to admission blood tests. The study population was divided into 2 groups according to the presence of AAD (131 patients with AAD, 89 healthy controls). Multivariate logistic regression analysis was used to determine the independent predictors of AAD. **Results.** MHR was significantly higher in the AAD group than the control group (13.7 ± 5.8 vs 9.2 ± 3.5; $P<.001$). There was a statistically significant positive correlation between the ascending aortic diameter and MHR ($r = .541$; $P<.001$). Age, MHR, and high-sensitivity C-reactive protein were determined as independent predictors of AAD according to multivariate logistic regression analysis. Receiver-operating characteristics curve analysis showed that MHR >9.3 predicted AAD with a sensitivity of 62.9% and a specificity of 81.7%; positive predictive value; 70%; and negative predictive value, 76.4% (area under the curve: 0.723; 95% confidence interval, 0.652-0.794; $P<.001$). **Conclusions.** Our study showed that MHR is independently associated with dilatation of the ascending aorta. Furthermore, MHR may be useful to identify patients with AAD.

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Key Words: ascending aortic dilatation, inflammation, monocyte count to HDL cholesterol ratio

Introduction

Ascending aortic dilatation (AAD) is mostly silent and incidentally diagnosed in a large proportion of patients.[1] It can be fatal if unnoticed at an early stage and presents with a complication of dissection or rupture. Patients who require emergency surgery have a relatively high incidence of morbidity and mortality compared with elective ascending aortic replacement.[2] Thus, early identification of patients with AAD is crucial to reduce the risk of rupture, dissection, and mortality.

Oxidative stress and inflammation play important roles in the process of atherosclerosis[3] and are well-known predictors of adverse cardiovascular events. Also, previous studies have shown the association of oxidative stress and inflammation with the pathogenesis of both thoracic[4,5] and abdominal aortic aneurysms.[6]

Monocytes and macrophages were documented as primary elements of inflammation via release of proinflammatory cytokines to the inflammation site.[7] Additionally, high-density lipoprotein cholesterol (HDL-C) is a molecule that inhibits both oxidative stress and inflammation.[8] Therefore, monocyte count to HDL-C ratio (MHR) has recently been defined and used as a prognostic and diagnostic inflammatory biomarker.

MHR provides prognostic information and predicts adverse cardiovascular events in patients with chronic kidney disease.[9] The importance of MHR in ectasia of coronary arteries, slow coronary flow, stent thrombosis, and disrupted elastic properties of the aorta in patients with hypertension has been demonstrated in most reports.[10-13] However, the relationship between MHR and AAD remains controversial. Therefore, this study aimed to investigate the association of MHR with AAD and its usefulness in this group of patients.

Methods

A total of 184 consecutive patients who were diagnosed with AAD between April 2020 and October 2020 were enrolled to our observational and cross-sectional study. AAD was defined as a maximum ascending aortic diameter of 37 mm or greater measured by transthoracic echocardiography. Ninety patients were incidentally diagnosed with AAD at routine hospital visits; 41 patients were previously diagnosed and referred to our hospital. The healthy control group (n = 89) was composed of patients who were admitted to our outpatient clinic during that enrollment period and approved to participate in the study.

Our study complied with the edicts of the 1975 Declaration of Helsinki and was approved by the local medical ethical committee. Written informed consent was obtained from all patients.

Exclusion criteria were defined as patients in need of emergency operation for AAD and patients with ischemic heart disease, recent infection, malignancy, connective tissue disease, and severe renal or hepatic failure. Of these, 3 patients were excluded due to the need for an emergency operation; 24 due to ischemic heart disease; 3 due to having recent infections; 4 due to malignancies; 3 due to connective tissue disorder; and 16 due to severe renal or hepatic failure. This resulted in 131 patients for the analysis.

The data regarding the baseline and clinical characteristics and laboratory measurements of the study group were recorded from the electronic hospital database. The demographic and clinical data included age, gender, presence of hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (HL), smoking status, and previous family history of ascending aortic aneurysm.

All venous blood samples were obtained from the study population the day after hospital admission following 12 hours of fasting and included a complete blood count (CBC) and detailed biochemical parameters such as glucose, total serum cholesterol, HDL-C, low-density lipoprotein cholesterol, triglycerides, and high-sensitive C-reactive protein (hs-CRP). Monocyte count was calculated from CBC and MHR and was determined for each patient. The study population was divided into 2 groups according to the presence of AAD, which was defined as the patients with AAD group (n = 131) and the healthy control group (n = 89).

Statistical Analysis

Continuous variables were given as mean ± standard deviation, while categorical variables were recorded as percentages. The Kolmogorov–Smirnov test was used for testing the normality of distributions. Student-T test or Mann–Whitney U test were used for continuous variables, and the chi-square test was used for categorical variables for comparison between the study groups. Independent predictors of AAD were determined by the multivariate logistic regression analysis. Pearson's correlation analysis was used to test the relation between MHR, monocyte count, HDL-C, and AAD. The predictive accuracy and performance of the MHR was calculated with receiver operating characteristic (ROC) analysis curve for AAD. Values of $P<.05$ were considered statistically significant. SPSS 22 software was used for statistical analysis.

Results

The clinical, demographic characteristics, and laboratory parameters of the study population are shown in **Table 1**. Patients with AAD were older with a more frequent history of HTN. In addition, prevalence of DM, HL, male gender, smoking, and family history of AAD were similar between the groups. Levels of uric acid, monocyte, hs-CRP, and MHR were significantly higher, whereas HDL-C levels were lower in the AAD group. Also, diameter of ascending aorta and angiotensin

Table 1. Baseline characteristics and laboratory parameters of the study population.

	AAD group (n = 131)	Control group (n = 89)	*P* value
Age, years	58 ± 8.8	53 ± 10	***<.001***
Gender (male), n (%)	71 (54.2%)	37 (41.6%)	.066
BMI, kg/m^2	28.5 ± 5.1	28 ± 3.7	.984
Smoker, n (%)	27 (20.6%)	18 (20.2%)	.989
Alcohol, n (%)	1 (0.8%)	1 (1.1%)	1.000
Hypertension, n (%)	86 (65.6%)	38 (42.7%)	***<.001***
Diabetes mellitus, n (%)	30 (22.9%)	24 (27.0%)	.533
Hyperlipidemia, n (%)	27 (20.6%)	24 (27.0%)	.279
Family history of AAA, n (%)	23 (17.6%)	19 (21.3%)	.491
Glucose, mg/dL	101.0 ± 18.8%	98.8 ± 17.8	.276
Creatinine, mg/dL	0.83 ± 1.6	0.80 ± 0.15	.083
TSH, mU/L	1.4 ± 0.8	1.4 ± 0.9	.729
Uric acid, mg/dL	5.7 ± 1.6	4.4 ± 1.3	***<.001***
AST, U/L	22 ± 7.8	19.3 ± 6.2	.078
ALT, U/L	21.1 ± 9.6	19.8 ± 9.1	.317
GGT, U/L	23.1 ± 6.7	21.4 ± 6.9	.084
Hs C-reactive protein, mg/L	1.01 (0.20-2.95)	0.20 (0.18-0.91)	***<.001***
Total cholesterol, mg/dL	197.0 ± 41.1	214.6 ± 44.6	***.030***
LDL-C, mg/dL	121.6 ± 33.8	134.3 ± 39.4	***.010***
HDL-C, mg/dL	43.2 ± 9.5	51,6 ± 12.6	***<.001***
Triglycerides, mg/dL	150.7 ± 71.0	138. ± 61.3	.164
White blood cell x 10^3/µl	7.4 ± 2.1	7.3 ± 1.9	.539
Hemoglobin, g/dL	13.5 ± 1.4	13.7 ± 3.0	.516
Monocyte count x 10^3/µl	0.53 ± 0.14	0.45 ± 0.13	***<.001***
Lymphocyte x 10^3/µl	2.3 ± 0.7	2.4 ± 0.9	.530
Neutrophil x 10^3/µl	4.8 ± 1.8	4.3 ± 2.2	.052
Platelet x 10^3/µl	247 ± 55.8	251 ± 63.5	.685
Neutrophil–lymphocyte ratio	2.4 ± 1.4	2.0 ± 1.1	.092
Monocyte/HDL-cholesterol	13.7 ± 5.8	9.2 ± 3.5	***<.001***
Ascending aortic diameter (mm)	45.2 ± 2.2	29.6 ± 3.7	**<.001**
ACEI, n (%)	27 (20.6%)	20 (22.4%)	.741
ARB, n (%)	39 (29.8%)	13 (4.6%)	***.009***
CCB, n (%)	33 (25.2%)	14 (15.7%)	093
Beta-blocker, n (%)	74 (56.5%)	30 (33.7%)	***.001***
ASA, n (%)	27 (20.6%)	15 (16.9%)	.487
Statin, n (%)	22 (16.8%)	12 (13.5%)	.505
Oral antidiabetic, n (%)	18 (13.7%)	19 (21.3%)	.139

AAA = ascending aortic aneurysm; AAD = ascending aortic dilatation; ACEI = angiotensin-converting enzyme inhibitor; ALT = alanine aminotransferase; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; AST = aspartate aminotransferase; BMI = body mass index; CCB = calcium channel blocker; GGT = gamma-glutamyl transferase; HDL-C = high-density lipoprotein cholesterol; hs = high sensitive; LDL-C = low-density lipoprotein cholesterol; TSH = thyroid-stimulating hormone.

Table 2. Predictors of AAD in univariate and multivariate logistic regression analysis.

	Univariate Model			Multivariate Model		
	OR	% 95 CI	*P* value	OR	% 95 CI	*P* value
Age, years	1.06	1.03-1.09	**.001**	1.07	1.03-1.11	**.001**
Hypertension	2.68	1.54-4.69	**.001**			
Uric acid	1.77	1.41-2.21	**.001**			
C-reactive protein, mg/L	1.46	1.15-1.86	**.002**	1.34	1.10-1.69	**.016**
Monocyte to HDL cholesterol ratio	1.29	1.18	**.001**	1.22	1.11-1.34	**<.001**

AAD = ascending aortic dilatation; CI = confidence interval; HDL = high-density lipoprotein; OR = odds ratio.

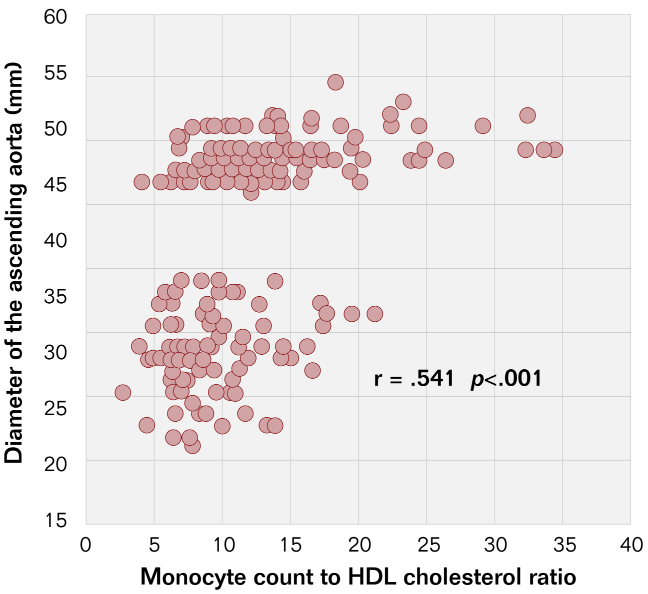

Figure 1. Correlation analysis of monocyte count to high-density lipoprotein cholesterol ratio and diameter of the ascending aorta.

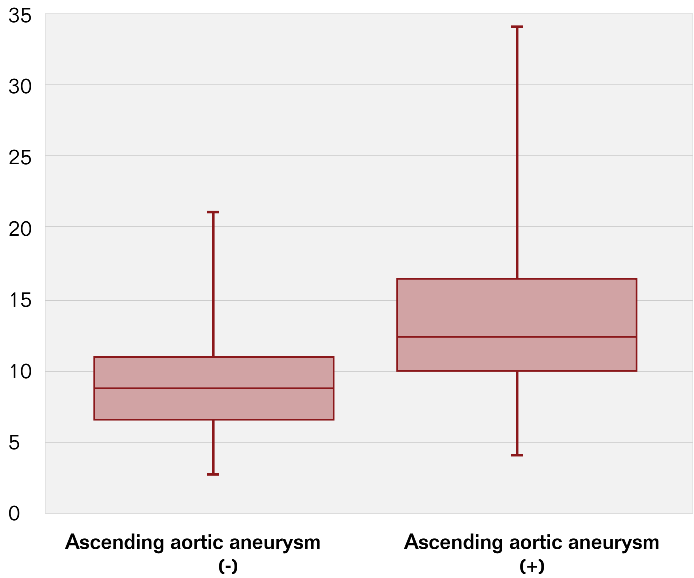

Figure 2. Monocyte count to high-density lipoprotein cholesterol ratio in study groups.

receptor blocker (ARB) and/or beta-blocker usage were significantly higher in the AAD group. The results of univariate and multivariate logistic regression analysis according to AAD are shown in **Table 2**. This analysis was based on the following variables: age, HTN, uric acid, hs-CRP, and MHR. Among these variables; age (odds ratio [OR], 1.07; 95% confidence interval [CI], 1.03-1.11; *P*=.001); hs-CRP (OR, 1.34; 95% CI, 1.10-1.69; *P*=.016); and MHR (OR, 1.22; 95% CI, 1.11-1.34; *P* <.001) were identified as independent predictors for AAD.

MHR was significantly higher in the patients with AAD group than the healthy control group. (13.7 ± 5.8 vs 9.2 ± 3.5; *P* <.001) **(Figure 1)**. There was a statistically significant positive correlation between ascending aortic diameter and MHR (r= 0.541; *P*<.001) **(Figure 2)**. ROC curve analysis showed that MHR >9.3 predicted AAD with a sensitivity of 62.9% and a specificity of 81.7%; positive predictive value, 70%; and negative predictive value, 76.4% (area under the curve, 0.723; 95% CI, 0.652-0.794; *P*<.001). ROC curve analysis demonstrating the predictive accuracy of MHR in AAD is shown in **Figure 3**.

Discussion

In the present study, we demonstrated that MHR was significantly associated with AAD. In addition, age, MHR, and hs-CRP were determined as independent predictors of AAD.

AAD is defined as an increase in the diameter of the ascending aorta indexed by age, sex, and body surface area.[14] Most AAD is

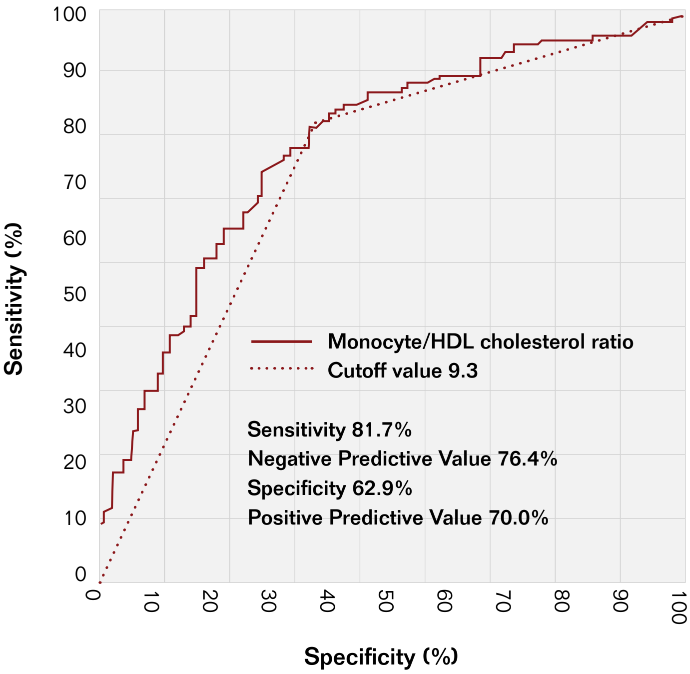

Figure 3. Receiver operating characteristic curve analysis of monocyte count to high-density cholesterol ratio for predicting ascending aortic dilatation.

asymptomatic and incidentally noticed on echocardiography or chest X-ray examinations.[15] AAD is a progressive disease with an increased risk of aortic rupture or dissection. If any of these complications occur, high morbidity and mortality rates are seen even after emergency operations.[16] The risk of morbidity and mortality is closely associated with the size of the aorta and aortic wall strength. Age-related changes in media layer, such as fragmentation and loss of elastin tissue, can cause weakening of the aortic wall.[17] This explains why AAD is more common among older adults. Consistent with the literature, our results showed that patients in the AAD group were older than in the healthy control group.

Monocytes are the cornerstone of the inflammation process. Proinflammatory cytokines and adhesion molecules are overexpressed due to the interaction of activated monocytes with the damaged endothelium. Macrophages, which are generated by differentiated monocytes, then ingest the oxidized LDL cholesterol to form the foam cells. HDL-C inhibits the macrophage migration and promotes the outflow of oxidized cholesterol from these cells. Apart from its antioxidative and anti-inflammatory effects, HDL-C increases endothelial nitric oxide synthase expression and vasorelaxation. Monocytes show pro-oxidant and pro-inflammatory effects, whereas HDL-C appears as a factor that reverses this process.[18]

Antoniadis et al previously reported that media layers of the ectatic coronary segments were infiltrated with inflammatory cells.[19] Besides degenerative process involving all layers of the vessel wall, inflammation is considered an important component of the pathogenesis of aortic dilatation. In our study, we observed that patients with AAD had increased levels of hs-CRP compared with the control group. Moreover, hs-CRP, a well-known inflammatory index, was identified as an independent predictor of AAD. These findings suppose that inflammation may play a role in the pathogenesis of AAD.

Increased levels of local or systemic inflammatory biomarkers are the main diagnostic and prognostic indicators of inflammatory diseases. Because inflammation plays a role in the pathogenesis of different clinical conditions, clinicians search for new and easily calculable inflammatory biomarkers. MHR, as a readily available and inexpensive inflammatory marker, had been recently identified. The significance of MHR was evidenced in high SYNTAX score prediction in patients with stable coronary artery disease,[20] AAD identification in patients with bicuspid aortic valve,[21] and contrast-induced nephropathy prediction in acute ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention.[22]

Because inflammation has a pathophysiological role in coronary ectasia and MHR has been defined as a novel inflammatory marker, we hypothesized that MHR may be associated with AAD. The relationship between MHR and AAD suggests that patients with low levels of HDL-C and high concentrations of circulating monocytes may have a more dilated ascending aorta. Because MHR provided information regarding the presence of aortic dilatation, it may be a useful tool to identify patients with AAD. Wider usage of MHR in daily clinical practice may enable earlier initiation of preventive therapy for progression of AAD and closer follow-up of these patients.

Our study had several limitations. First, it was as a single-center study with a limited number of patients. Second, long-term follow-up data cannot be provided. Third, only admission MHR was used rather than several measurements taken at different times of hospitalization, and inflammatory parameters other than complete blood count and hs-CRP were not assessed. Although the association of MHR and AAD was documented, validation of our findings in further larger prospective studies are needed.

In conclusion, our results showed that MHR is independently associated with AAD. Thus, the widespread clinical use of MHR may be beneficial in identification of AAD patients before development of catastrophic complications. ■

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