Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1409450

Anatolian Curr Med J. 2024;6(2):116-120

Relationship between coronary artery disease and high-density lipoprotein cholesterol-monocyte ratio

Eyüp Özkan, Aslan Erdoğan

Department of Cardiology, Başakşehir Çam and Sakura City Hospital, İstanbul, Turkiye

Cite this article as: Özkan E, Erdoğan A. Relationship between coronary artery disease and high-density lipoprotein cholesterol-monocyte ratio. *Anatolian Curr Med J.* 2024;6(2):116-120.

Received: 25.12.2023 ◆ **Accepted**: 23.01.2024 ◆ **Published**: 08.03.2024

ABSTRACT

Aims: To investigate the association between high-density lipoprotein cholesterol (HDL-C)-to- monocyte ratio(HMR) and coronary artery disease (CAD) proven by coronary angiography.

Methods: A total of 311 patients were enrolled in the retrospective study. The grouping was based on whether the stenosis of one coronary artery exceeds 50%. Gensini Score (GS) to evaluate the severity of coronary artery stenosis. Spearman correlation analysis, progressive logistic regression, and receiver operating characteristic (ROC) curve analysis were used.

Results: The HMR difference between the CAD and non-CAD groups was statistically significant (P<0.001). Spearman correlation analysis showed that the HMR was slightly and moderately correlated with other independent risk factors of CAD (r<0.5). HMR was a new independent risk factor by progressive logistic regression analysis (odds ratio=0.784. 95% CI, 0.682-0.901). HMR was related to the GS of CAD patients (r=-0.244, P<0.001). Moreover, the HMR was better than HDL-C and HDL-C-to-cholesterol by comparing AUC (AUC HDL-C-to-monocyte=0.642, AUC HDL-C=0.603, AUC HDL-C-to-cholesterol=0.584).

Conclusion: HMR was an independent factor of CAD and can be used as a biomarker to evaluate the severity of CAD.

Keywords: Coronary artery disease, HDL-C-to-monocyte ratio, coronary angiography

INTRODUCTION

Despite the rapid advancements in diagnosis and treatment, coronary artery disease (CAD) continues to be the primary cause of mortality in developed nations. The most prevalent etiology is atherosclerosis, which is classified as a systemic inflammatory immune disorder.[1] Inflammation, endothelial dysfunction and oxidative stress are essential mechanisms of the atherosclerotic process.[2]

Recently, high density lipoprotein cholesterol (HDL-C) and monocyte ratio (HMR) research has been gradually found and wildly applied to heart disease, diabetes, and other aspects. HMR is a recently emerged inflammation-based marker. The marker, circulating monocytes give rise to inflammatory and pro-thrombotic through releasing various molecules and cytokines to activate platelets and endothelial cells.[3] On the contrary, HDL-C hinders low-density lipoprotein (LDL) oxidation and macrophage migration and rapid cholesterol efflux from these cells leading to anti-inflammation and antioxidation.[4,5] Research on inflammatory markers associated with atherosclerosis has been a top topic in recent years, including HDL-C and monocytes. This study aimed to investigate the independence between HMR and multiple factors of coronary artery disease and the relevance of HMR in coronary artery severity.

METHODS

The Research Ethics Institute of the in our hospital of reviewed this study involving human subjects. It is approved by Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 13.12.2023, Decision No: KAEK/2023.12.714). This study was conducted per the guidelines outlined in the Declaration of Helsinki.

311 patients who were discharged from the Cardiology department after coronary angiography (CAG) in our hospital between January 1, 2020 and July 12, 2023 were included in the study. 165 patients with CAD were selected as the CAD group, 146 patients including coronary arteriosclerosis with 1%-50% stenosis and no coronary atherosclerosis as the non-CAD group.

Corresponding Author: Eyüp ÖZKAN, dreyupozkan@gmail.com

This work is licensed under a Creative Commons Attribution 4.0 International License.

Exclusion criteria record previous coronary artery bypass grafting, previous coronary artery stenting, incomplete or unobtainable documented monocyte count, HDL-C, or other essential data, continuous use of lipid-lowering drugs for more than three months, malignant tumors, severe liver and kidney dysfunction, blood system diseases, immune system diseases, undergoing immunosuppressive therapy, major surgery and severe trauma within three months.

Coronary Angiography Methods

The Judkins technique was utilized to perform CAG via the right or left femoral approach with a French (F) catheter of 6 or 7. As an opaque agent, either Iopromide (Ultravist-370®) or Iohexol (Omnipaque® 350 mg/ml) was utilized. Coronary artery imaging was performed in the left and right oblique planes, with cranial and caudal orientation, on all patients. CAG image evaluations of all patients were performed by two experienced cardiologists. The intra- and interobserver variability for assessing CCC was 2% and 3%, respectively.

Severe CAD was defined as >50% stenosis in a major coronary artery. The Gensini scoring (GS) system was used to determine the severity of CAD.[6] This method scores the prevalence and severity of coronary artery stenosis as well as its classification. Firstly, in this system, stenosis between 1% and 25% is scored as 1 point, between 26% and 50% as 2 points, between 51% and 75% as 4 points, between 76% and 90% as 8 points, between 91% and 99% as 16 points, and total occlusion as 32 points. This score is then multiplied by a factor indicating the importance of the localization of the lesion in the coronary artery system. Scores for localization are multiplied by 5 for the left main coronary, 2.5 for the proximal left anterior descending (LAD) and left circumflex (LCX), 1.5 for the mid-segment LAD and LCX, 1 for the distal segment of the LAD and LCX, 0.5 for the first diagonal branch, first broadside branch, right coronary artery, posterior descending artery and intermediate arteries, and second diagonal and second broadside branches. After obtaining GS in CAD patients, receiver operating characteristic (ROC) analysis was performed to define cut-off values. CAD patients were divided into two groups: below the cut-off value and above the cut-off value.

The first group was composed of patients with mild atherosclerosis (GS<25 points [mild CAD group]) and the second group was composed of patients with severe atherosclerosis (GS≥25 points [severe CAD group]), and this grouping was performed as follows: consistent with the literature.[7]

Laboratory Measurements

In all patients, blood samples were collected between 08 and 10 am following a 12-hour fasting period before CAG for laboratory analysis. Antecubital venous blood samples were collected in tripotassium EDTA-based anticoagulated tubes. Venous blood samples measuring basic blood variables (such as comprehensive metabolic panel and complete blood count) and thiol levels were obtained. All routine biochemical tests were performed on an autoanalyzer (Roche Diagnostic Modular Systems, Tokyo, Japan). Haematological parameters were stored at 4°C and evaluated with a Sysmex K-1000 autoanalyzer within 30 min after sampling. HMR was found by dividing the HDL-C level by the number of monocytes.

Transthoracic Echocardiography

Transthoracic echocardiography was conducted on every participant in both the patient and control groups. The measurements were conducted with a Vivid 5 machine, (GE Medical System in Horten, Norway), equipped with a 3.5 MHz transducer. We conducted 2D echocardiographic measures to evaluate the left ventricular ejection fraction (LVEF) and identify any valvular diseases. We employed Simpson's technique and color Doppler echocardiography to evaluate the ejection fraction and valvular diseases, respectively, in the apical 4-chamber view.

Statistical Analysis

Statistical analyses were performed using SPSS version 21.0 (SPSS Inc, Armonk, NY, USA). Baseline characteristics were divided into two groups according to coronary angiographic findings and were presented as mean (SD) or IQR for continuous data and frequency (percent) for categorical data. We compared two groups by the independent-sample t-test for continuous variables and the $\chi 2$ test for categorical ones. A two-tailed P value <0.05 was deemed statistically significant.

Spearman correlation coefficient was calculated to describe the correlation of HMR and other CAD risk factors included in the study, of HMR and GS. The forward, conditional progressive logistic regression analysis within a 95%confidence interval and at a two-ailed P value < 0.05 was performed to identify that HMR was an independent risk factor. Obtain AUC by drawing a ROC curve to compare the performance of HMR, HDL-C, and HDL-C-to-cholesterol models.

RESULTS

After excluding patients who met the exclusion criteria, 311 patients were included. In the light of the results of coronary angiography,165 patients entered the non-CAD group, and 146 patients entered the CAD group. Compared with the non-CAD group, the CAD group had higher levels of age, smoking, hypertension, diabetes mellitus, LVEF, Neutrophils count, and monocyte count

and had lower levels of HDL-C and higher involvement rate of the left main coronary artery, left anterior descending, left circumflex artery, right coronary artery, and their main branches (**Table 1**).

Table 1. Baseline clinical and angiographic characteristics of the study population

	Non-CAD group (n=165)	CAD group (n=146)	P value
Male, n(%)	75 (45.4)	98 (67.1)	<0.001
Age (years)	65.17±7.51	68.16±8.26	0.03
Smoking, n (%)	35 (21.2)	61 (41.7)	<0.001
HTN, n (%)	80 (48.4)	74 (50.6)	0.475
DM, n (%)	35 (21.2)	46 (31.5)	0.006
LVEF (%)	59.00 (54.00-67.00)	62.00 (56.00-68.00)	0.04
TC (mmol/L)	4.67±1.19	4.58±1.23	0.415
TG (mmol/L)	1.78±1.12	1.85±1.28	0.434
C-LDL (mmol/L)	2.97±1.01	2.96±1.13	0.921
HDL-C (mmol/L)	1.21±0.36	1.09±0.37	<0.001
NEUP (10^9/L)	4.74 (2.60-7.56)	5.63 (3.82-7.47)	<0.001
LYMPH (10^9/L)	1.92±0.58	2.03±0.47	0.934
MONO (10^9/L)	0.46±0.29	0.54±0.24	<0.001
Target coronary artery			
LMS, n (%)	2 (1)	12 (8.9)	<0.001
LAD, n (%)	42 (25.4)	120 (82.1)	<0.001
LCx, n (%)	11 (6.6)	130 (89.0)	<0.001
RCA, n (%)	52 (17.6)	91 (62.3)	<0.001
HDL-C/monocyte	2.91 (1.90-3.90)	2.07 (1.55-2.86)	<0.001

HTN, Hypertension; DM, Diabetes mellitus; TC, Cholesterol; TG, Triglycerides; C-LDL, low density lipoprotein cholesterol; HDL-C, High density liptein cholesterol; LVEF, Left Ventricular Ejection Fractions; NEUP, Neutrophils count; LYMPH, Lymphocyte count; MONO, monocyte count; LMS, left main coronary artery; LAD, left main coronary artery; LCx, Left circumflex artery; RCA, Right coronary artery

The CAD risk factors involved in the study were analyzed for correlation. Due to that the variables were Dichotomous and continuous variables, and Kolmogorov-Smirnov test at two-tailed for continuous variables showed that all variables did not conform to the normal distribution (P<0.001), Spearman correlation analysis was used. The results revealed that HMR was slightly and moderately correlated with other CAD risk factors (r<0.5) and LDL was strongly correlated with cholesterol (r=0.816).

To determine the independent risk factors of CAD. Multivariable logistic regression analysis was conducted for the variables included in the study, and the progressive logistic regression analysis at forwarding conditional was conducted. Age, Smoking, Neutrophils count, and HMR be used as independent risk factors for CAD (**Table 2**).

Table 2. Multivariable analysis of independent factors for coronary artery disease

Variables	OR	95% CI	P value
Age	1.028	1.019- 1.047	<0.001
Smoking	2.347	1.554- 3.367	<0.001
Neutrophils count (10^9/L)	1.204	1.072- 1.346	<0.001
HDL-C-to-monocyte ratio	0.781	0.678- 0.920	<0.001

HDL-C, High density liptein cholesterol

ROC curve analysis was exploited to verify further the potential value of HMR in the screening of CAD patients. As shown in Figure 1, the AUC of HMR was more remarkable than HDL-C and HDL-C-to-cholesterol models (0.642 vs. 0.603, 0.584) (**Figure 1**).

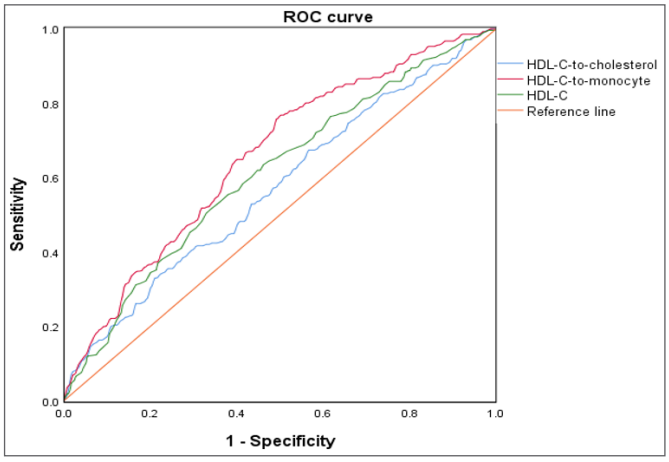

Figure 1. ROC curve for HDL-C-to-monocyte ratio and HDL-C and HDL-C-to-cholesterol

The scatter plot was based on the association between HMR's and the GS of CAD patients. The results showed that HMR was negative correlated with the GS of CAD r2=0.017). The correlation coefficient between the GS of CAD and HMR was -0.219 (P<0.001), which was better than that of monocyte count and HDL-C alone by Spearman correlation analysis (r monocyte count=-0.139, P monocyte count=0.021; r HDL-C=0.129, P HDL-C<0.001) (**Figure 2**).

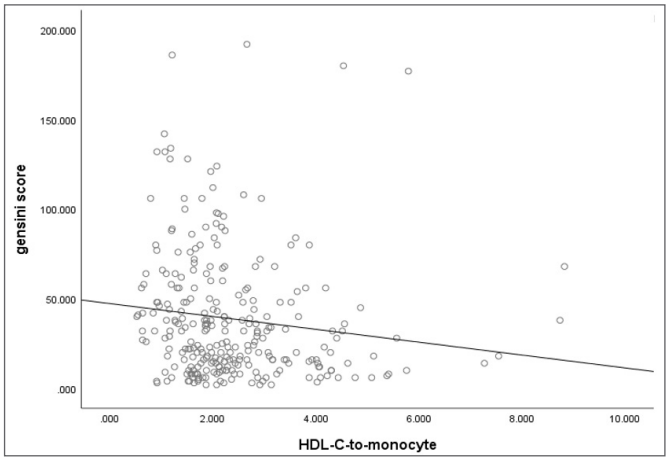

Figure 2. Distribution among of HDL-C-to-monocyte ratio and Gensini Score

DISCUSSION

In the light of the results of our study, it could be summarized as follows. First, the HMR was statistically different in patients with or without CAD, and this difference still existed after propensity score matching (PSM). Secondly, there is no strong correlation between HMR and other risk factors of coronary heart disease. Third, HMR could be used as an independent risk factor

of CAD. Forth, the HMR was superior to HDL-C and HDL-C-to-cholesterol in reflecting CAD and was related to the GS of CAD severity.

Inflammation plays significant role pathogenesis of atherosclerosis and cardiovascular disease.[2,8,9] Increasing concentration of mediators or markers of inflammation indicates that CAD might occur.[10] For example, C-reactive protein, neutrophil-to-lymphocyte ratio, IL-6, and platelet-to-lymphocyte ratio have been independent risk factors for atherosclerosis.[11-14] Monocytes are the source of macrophages and foam cells. Monocytes contribute significantly to the initiation and development of the atherosclerotic plaque by migrating to and attaching themselves to the location of the plaque. Within the subendothelial region, these cells undergo differentiation into macrophages and actively uptake oxidized LDL particles through scavenger receptors, resulting in the development of foam cells. Additionally, they are involved in the early inflammatory stage that follows the destabilization and rupture of the atherosclerotic plaque, as well as the development of an acute blood clot. Monocyte-platelet interactions induce the synthesis of enzymes that cause the degradation of the fibrous cap. During the healing process, particularly in the hypoxia phase, they have a role in both facilitating beneficial and detrimental inflammatory processes in the cardiac tissue. The resultant reactive oxygen species augment inflammation.[15-18] HDL-C primarily exerts its antiatherosclerotic action through its impact on reverse cholesterol transport. HDL-C induces vasodilation through the stimulation of nitric oxide synthesis in endothelial cells.[19] HDL-C resists monocyte macrophages by directly counteracting the migration of macrophages and removing cholesterol from macrophages, and ApoA1 inhibits monocyte activation by inhibiting the activation of CD11b.[19,20] Based on the characterization of monocytes and HDL-C in atherosclerosis, it is not unreasonable to speculate that HMR is closely associated with coronary artery severity in patients with CAD. Literature data also support this thesis.[21-25]

Our study has several advantages. We analyzed and verified our results by analyzing and adjusting potential confounding factors that might affect the relationship between HMR's and CAD incidence by PSM. We excluded the close relationship between HMR and other risk factors related to coronary heart disease included in this study.

Limitations

Our research still had some limitations. First, because we conducted a single-center retrospective study, our research had a potential bias. Further prospective research is needed to solve this problem. Secondly, many risk factors affect CAD, we did not cover all aspects in our research, which also affects the tightness of HMR and CAD. Third, our study indicated that HDL is an independent risk factor for CAD, but the predictive value of CAD patients and the prognostic value of CAD patients, especially those receiving the percutaneous coronary intervention, must be further verified. Fourth, the use of drugs affected the relationship between CAD and HMR's. Besides lipid-lowering drugs, there are antiplatelet drugs, antihypertensive drugs, B receptor blockers, which would cause significant bias in the results. In conclusion, further studies are needed to verify this result.

CONCLUSION

HMR is an independent risk factor for CAD. ROC analysis showed that the HMR is superior to monocyte and HDL-C alone in reflecting coronary artery disease. However, our results need to be verified by a large number of prospective studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Başakşehir Çam and Sakura City Hospital Clinical Researches Ethics Committee (Date: 13.12.2023, Decision No: KAEK/2023.12.714).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J.* 2013;34(10):719-728.
2. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol.* 2009;54(23):2129-2138.
3. Ancuta P, Wang J, Gabuzda D. CD16+ monocytes produce IL-6, CCL2, and matrix metalloproteinase-9 upon interaction with CX3CL1-expressing endothelial cells. *J Leukoc Biol.* 2006;80(5):1156-1164.

4. Parthasarathy S, Barnett J, Fong LG. High-density lipoprotein inhibits the oxidative modification of low-density lipoprotein. *Biochim Biophys Acta.* 1990;1044(2):275-283.
5. Executive summary of the third report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA*. 2001;285(19):2486-2497.
6. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol.* 1983;51:606
7. Oishi Y, Wakatsuki T, Nishikado A, Oki T, Ito S. Circulating adhesion molecules and severity of coronary atherosclerosis. *Coron Artery Dis.* 2000;11(1):77-81.
8. Montecucco F, Mach F. Atherosclerosis is an inflammatory disease. *Semin Immunopathol.* 2009;31(1):1-3.
9. Pedicino D, Giglio AF, Galiffa VA, et al. Infections, immunity and atherosclerosis: pathogenic mechanisms and unsolved questions. *Int J Cardiol.* 2013;166(3):572-583.
10. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med.* 2000;342(12):836-843.
11. Taniguchi H, Momiyama Y, Ohmori R, et al. Associations of plasma C-reactive protein levels with the presence and extent of coronary stenosis in patients with stable coronary artery disease. *Atherosclerosis.* 2005;178(1):173-177.
12. Kurtul A, Murat SN, Yarlioglues M, et al. Association of platelet-to-lymphocyte ratio with severity and complexity of coronary artery disease in patients with acute coronary syndromes. *Am J Cardiol.* 2014;114(7):972-978.
13. Kurtul S, Sarli B, Baktir AO, et al. Neutrophil to lymphocyte ratio predicts SYNTAX score in patients with non-ST segment elevation myocardial infarction. *Int Heart J.* 2015;56(1):18-21.
14. Danesh J, Kaptoge S, Mann AG, et al. Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. *PLoS Med.* 2008;5(4):e78.
15. Ghattas A, Griffiths HR, Devitt A, Lip GY, Shantsila E. Monocytes in coronary artery disease and atherosclerosis: where are we now? *J Am Coll Cardiol.* 2013;62(17):1541-1551.
16. Ley K, Miller YI, Hedrick CC. Monocyte and macrophage dynamics during atherogenesis. *Arterioscler Thromb Vasc Biol.* 2011;31(7):1506-1516.
17. Badimon L, Padró T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. *Eur Heart J Acute Cardiovasc Care.* 2012;1(1):60-74.
18. Mehu M, Narasimhulu CA, Singla DK. Inflammatory cells in atherosclerosis. *Antioxidants*. 2022;11(2):233.
19. Li XP, Zhao SP, Zhang XY, Liu L, Gao M, Zhou QC. Protective effect of high density lipoprotein on endothelium-dependent vasodilatation. *Int J Cardiol.* 2000;73(3):231-236.
20. Murphy AJ, Westerterp M, Yvan-Charvet L, Tall AR. Anti-atherogenic mechanisms of high density lipoprotein: effects on myeloid cells. *Biochim Biophys Acta.* 2012;1821(3):513-521.
21. Karataş MB, Çanga Y, Özcan KS, et al. Monocyte to high-density lipoprotein ratio as a new prognostic marker in patients with STEMI undergoing primary percutaneous coronary intervention. *Am J Emerg Med.* 2016;34(2):240-244.
22. Akboga MK, Balci KG, Maden O, et al. Usefulness of monocyte to HDL-cholesterol ratio to predict high SYNTAX score in patients with stable coronary artery disease. *Biomark Med.* 2016;10(4):375-383.
23. Canpolat U, Çetin EH, Çetin S, et al. Association of monocyte-to-HDL cholesterol ratio with slow coronary flow is linked to systemic inflammation. *Clin Appl Thromb Hemost.* 2016;22(5):476-482.
24. Çetin MS, Çetin EHO, Kalender E, et al. Monocyte to HDL cholesterol ratio predicts coronary artery disease severity and future major cardiovascular adverse events in acute coronary syndrome. *Heart Lung Circ.* 2016;25(11):1077-1086.
25. Li Y, Li S, Ma Y, Li J, Lin M, Wan J. Relationship between non-high-density lipoprotein cholesterol/apolipoprotein A-I and monocyte/high-density lipoprotein cholesterol ratio and coronary heart disease. *Coron Artery Dis.* 2020;31(7):623-627.