Association of Monocyte-to-HDL Cholesterol Ratio with Cardiac Syndrome X is Linked to Systemic Inflammation

Elnur Alizade, Anıl Avcı, Ahmet Güner, Mehmet Mustafa Tabakcı, Regayip Zehir, Ahmet Güler, Servet İzci, Selçuk Pala

Kartal Koşuyolu High Specialty Training and Research Hospital, Department of Cardiology, İstanbul, Turkey

ABSTRACT

Introduction: The aim of this study was to investigate an easily available inflammatory marker and monocyte-to-high-density lipoprotein cholesterol ratio (MHR) in patients with cardiac syndrome X (CSX).

Patients and Methods: The study population included 100 patients of which 50 had CSX (CSX group) and 50 had normal coronary angiograms (control group).

Results: Total white blood cell (WBC) count, monocyte count, neutrophil count, NLR, high-sensitivity C-reactive protein (hs-CRP), C-reactive protein (CRP) and MHR were higher in the CSX group ($p< 0.05$), whereas high-density lipoprotein cholesterol (HDL-C) level was significantly lower in the CSX group as compared with that in the control group ($p< 0.05$). In the correlation analysis, MHR revealed a significantly positive correlation with hs-CRP ($r= 0.375$, $p< 0.001$) and CRP ($r= 0.403$, $p< 0.001$). In the multivariate logistic regression analysis, MHR was independently associated with the presence of CSX (odds ratio: 1.250, 95% confidence interval [CI]: 1.240-1.461, $p< 0.001$). Using a cut-off level of 90.6, pre-procedural MHR predicted the presence of slow coronary flow (SCF) with a sensitivity of 78% and specificity of 70%.

Conclusion: In conclusion, our findings revealed that higher MHR levels were significantly and independently associated with the presence of CSX.

Key Words: Cardiac syndrome X; monocyte-to-HDL cholesterol ratio; inflammatory markers

Monositin HDL Kolesterole Oranının Kardiyak Sendrom X ve Sistemik İnflamasyon ile İlişkisi

ÖZET

Giriş: Bu çalışmanın amacı, kardiyak sendrom X (KSX) hastalarında monositin HDL kolesterole oranı (MHO)'nı ve kolay kullanılabilir inflamatuvar göstericileri araştırmaktır.

Hastalar ve Yöntem: Çalışmaya 50'si KSX ve 50'si normal koroner arterlere sahip toplam 100 hasta dahil edilmiştir.

Bulgular: Total beyaz küre sayısı, nötrofil sayısı, monosit sayısı, lenfosit sayısı, nötrofil/lenfosit oranı, C-reaktif protein, hsCRP ve MHO KSX grubunda artmıştır ($p< 0.05$), ancak HDL kolesterol CSX hastalarında kontrol grubuna göre azalmıştır ($p< 0.05$). Korelasyon analizinde MHO'nun hsCRP ($r= 0.375$, $p< 0.001$) ve CRP ($r= 0.403$, $p< 0.001$) ile pozitif yönde korelasyon olduğu gösterilmiştir. Multivariate logistic regresyon analizinde MHO'nun KSX hastalığını göstermede bağımsız bir gösterge olduğu bulundu [odds ratio: 1.250, 95% confidence interval (CI): 1.240-1.461, $p< 0.001$]. Sınır değeri 90.6 alırsak, MHO bu oran ile KSX hastalığının varlığını %78 duyarlılık ve %70 özgüllükle göstermektedir.

Sonuç: Çalışmamızda MHO KSX hastalarını göstermede ciddi ve bağımsız bir gösterge olduğu gösterilmiştir.

Anahtar Kelimeler: Kardiyak sendrom X; monositin HDL kolesterole oranı; inflamatuvar göstergeler

INTRODUCTION

Cardiac syndrome X (CSX) is a syndrome of typical angina pectoris or angina-like chest pain during a positive stress test with a normal coronary angiogram in the absence of any other recognised causes of chest pain. Approximately 3-10% of patients undergoing coronary arteriography because of typical chest pain have normal coronary arteries and qualify for the definition of CSX[1-3]. A wide range of pathophysiological mechanisms involving inflammation, changes in micro-vascular tonus, impaired coronary flow reserve, insulin resistance, altered sodium-hydrogen exchange activity and increased sensitivity of cardiac pain have been described in several studies[4-6]. Among these mechanisms, endothelial dysfunction and

Correspondence

Elnur Alizade

E-mail: elnur17@yahoo.com
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micro-vascular ischemia mediated by inflammation have been proposed to be the main factor underlying CSX; however, the exact mechanism remains unknown[7].

Inflammation plays a key role in the initiation and progression of cardiovascular disease. Macrophages and monocytes are the most important cell types for the secretion of pro-inflammatory and pro-oxidant cytokines at the site of inflammation[8]. In addition, high-density lipoprotein cholesterol (HDL-C) has been shown to defend endothelial cells against the unfavourable effects of low-density lipoprotein (LDL) and to prohibit the oxidation of LDL molecules[9,10]. Therefore, it was thought that HDL-C exhibits both anti-inflammatory and anti-oxidant actions. Recently, monocyte-to-high-density lipoprotein cholesterol ratio (MHR) was identified as an independent predictor of atrial fibrillation (AF) recurrence after cryoballoon-based catheter ablation, and it was significantly and independently associated with the presence of slow coronary flow (SCF)[11-13]. Karataş et al. also investigated that higher admission pre-procedural MHR is an independent predictor of in-hospital mortality and MACE in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI)[14]. To the best of our knowledge, no study till date has evaluated the association of MHR with CSX patients.

PATIENTS and METHODS

Study Population

The protocol of this cross-sectional, observational and retrospective study was approved by the institutional review board of Kartal Kosuyolu Heart and Training Hospital and performed in accordance with the guidelines proposed in the Helsinki Declaration. Written informed consent was obtained from all the participants. The study population comprised 100 patients who underwent coronary angiography on an outpatient basis at the cardiology departments of Kartal Kosuyolu Heart and Training Hospital. Fifty consecutive patients (54.1 ± 7.8 years old, 49 females) diagnosed with CSX according to the presence of typical exercise-induced angina pectoris, transient ischemic ST-segment depression (> 1 mm) during the treadmill exercise test and angiographically normal coronary arteries constituted the study group. The control group comprised 50 consecutive age- and sex-matched patients with anginal chest pain whose coronary arteries were normal and had no inducible ischemia on the exercise stress test.

Patients with the following problems were excluded from the study: previous myocardial infarction, unstable chest pain, any coronary artery atherosclerotic lesions (including plaques and ectasia), coronary vasospasm, moderate-to-severe valvular heart disease, left ventricular systolic dysfunction by echocardiography (ejection fraction < 0.40), renal dysfunction (serum creatinine > 1.5 mg/dL for males and > 1.4 mg/dL for females), hepatic insufficiency (liver function tests greater than twice the upper limit of the laboratory reference range), malignancies, acute or chronic infectious or inflammatory diseases, haematological disorders or steroid therapy.

Hypertension (HT) was defined as the current use of anti-hypertensive drugs or systolic blood pressure of > 140 mmHg or diastolic blood pressure of > 90 mmHg measured at the outpatient clinic. Diabetes mellitus (DM) was defined as fasting blood glucose of ≥ 126 mg/dL or use of anti-diabetic medication. Smoking was described as the regular use of tobacco.

Treadmill Exercise Tests

Treadmill exercise tests were conducted in accordance with the modified Bruce protocol19. All the patients had refrained from ingesting food, alcohol or caffeine or smoking within 3 h of the test. Beta-blockers and non-dihydropyridine calcium channel blockers had been stopped for 72 h before the test. The target heart rate was at least 85% of the age-predicted heart rate (220-age in years). This protocol involved three stages, each lasting for 3 min. The first stage was performed at 1.7 mph with a 0% grade, and the second at 1.7 mph with a 5% grade. In the third stage, the gradient was increased to 10% while the speed was maintained. All the subjects continued walking for a 1-min cool-down period after reaching the target heart rate. The total exercise time was from 8 to 12 min. ST-segment depression was measured at 60 ms after the J-point in all 12 electrocardiographic leads. A horizontal or down-sloping ST-segment depression of ≥ 1 mm was accepted as significant.

Coronary Angiography

Coronary angiography was performed by a femoral approach using the standard Judkins technique without the use of nitroglycerin, adenosine or a calcium channel blocker. Coronary arteries in the left and right oblique planes and the cranial and caudal angles were demonstrated. Iopromide (Ultravist-370; Schering AG, Berlin, Germany) was used as the contrast agent and was injected manually (4-6 mL of contrast agent at each position) during coronary arteriography. All the angiograms were evaluated by two experienced physicians who were blinded to the group assignments and the laboratory and exercise treadmill or exercise MPI results of the study participants. The coronary arteries were classified as normal on the basis of a visual assessment in the absence of any luminal irregularities. During coronary angiography, to exclude the possibility of coronary artery vasospasm, the patients who had normal coronary anatomy underwent a hyperventilation test, which was applied by asking the patients to breathe rapidly and deeply for 5 min[6,15].

Laboratory Analysis

Blood samples were obtained from patients in the morning, after 12 h of fasting, for the measurement of biochemistry panel, including lipid parameters, before the index coronary angiography. Samples for complete blood count (CBC) analysis (with differential analysis) were collected in EDTA anti-coagulated Monovette tubes (Sarstedt, Leicester, United

Kingdom). Calibration was assessed daily with the commercial calibrant (Beckman Coulter; Fullerton, California), and monitored 3 times daily with an internal quality control material. Monocyte count was calculated using data obtained from the CBC differential analysis. The reference value for monocyte in our laboratory ranges from 2 to 10%. C-reactive protein (CRP) measurements were conducted on Cobas Integra analyzer (Roche Diagnostics, Istanbul, Turkey) using the turbidimetric method. High-sensitivity C-reactive protein (hs-CRP) was measured using an automatised analyzer (Beckman Coulter IMMAGE) using the nephelometric measurement before the index coronary angiography.

Statistical Analysis

The SPSS statistical software package was used for statistical analyses (PASW Statistics for Windows, Version 18.0; SPSS Inc., Chicago, IL, USA). The normality of distribution of the continuous variables was evaluated using the Kolmogorov-Smirnov test and histograms. Continuous variables are presented as mean ± standard deviation and were compared with Student's t-test. Categorical data are presented as numbers and percentages and were compared using the chi-squared test (and Fisher's exact test, if needed). Correlation analyses were performed using Pearson's test. Receiver-operating characteristic (ROC) analysis was performed for MHR to determine optimal cut-off values and to obtain the sensitivity and specificity of each variable for predicting the presence of CSX. A multivariate logistic regression model was used that included parameters that were significantly different between the groups and to identify the independent predictor of CSX patients.

RESULTS

A total of 100 patients were included in this study (50 in the CSX group and 50 in the control group). Baseline clinical, demographic features and laboratory findings of the two groups are shown in Table 1. There were no differences in the two groups for EF, smoker, family history of CAD, DM, HT, and hypercholesterolemia and for values of haemoglobin, total cholesterol, triglyceride, creatinine and LDL-C. Total white blood cell (WBC) count, monocyte count, neutrophil count, NLR, hs-CRP, CRP and MHR were higher in the CSX group ($p< 0.05$), whereas HDL-C level was significantly lower in the CSX group as compared with that in the control group ($p< 0.05$; Table 2).

In the correlation analysis, MHR revealed a significantly positive correlation with hs-CRP ($r= 0.375$, $p< 0.001$) and CRP ($r= 0.403$, $p< 0.001$). In the multivariate logistic regression analysis, MHR was found to be independently associated with the presence of CSX (odds ratio= 1.250, 95% confidence interval [CI]= 1.240-1.461, $p< 0.001$) (Table 3). Moreover, NLR, WBC

Table 1. Baseline clinical, demographic features and laboratory findings of the two groups

	CSX group (n= 50)	Control group (n= 50)	p
Age, years	56.3 ± 9.2	54.6 ± 8.7	NS
Gender (female, male)	18, 32	20, 30	NS
BMI, kg/m^2	27 ± 2	26 ± 3	NS
Family history of CAD n, (%)	10, (20)	12, (24)	NS
Hypertension n, (%)	32, (64)	30, (60)	NS
Diabetes mellitus n, (%)	7, (14)	6, (12)	NS
Smoking n, (%)	13, (26)	12, (24)	NS
Ejection Fraction, (%)	61.23 ± 5.61	61.04 ± 5.34	NS
Fasting blood sugar, mg/dL	98.61 ± 21.03	107.68 ± 28.64	NS
Total plasma cholesterol, mg/dL	201.23 ± 30.34	203.42 ± 25.89	NS
LDL-C, mg/dL	116.01 ± 26.31	112.74 ± 25.61	NS
HDL-C, mg/dL	44.71 ± 8.77	50.06 ± 8.08	0.003
Triglycerides, mg/dL	149.56 ± 61.62	147.71 ± 58.62	NS
Creatinine, mg/dL	1.14 ± 0.18	0.98 ± 0.14	NS
Urea, mg/dL	30.9 ± 6.1	31.8 ± 6.9	NS
Statins, %	12	18	NS
Calcium channel blockers, %	15	17	NS
Nitrates, %	9	4	NS
ACE inhibitors/ARB, %	29	32	NS
Beta-blockers, %	28	22	NS

CSX: Cardiac sydrome X, BMI: Body mass index, CAD: Coronary artery disease.

Table 2. Haematological measurements of the two groups

	CSX group (n= 50)	Control group (n= 27)	p
White blood cell count, /mm^3	6.9 ± 1.4	6.1 ± 1.1	< 0.01
Neutrophil count (10^3/mm^3)	4.6 ± 1.3	4.0 ± 1.2	< 0.01
Lymphocyte count (10^3/mm^3)	2.21 ± 0.8	2.05 ± 0.7	< 0.01
Monocyte count (10^3/mm^3)	0.44 + 0.14	0.40 + 0.12	0.02
Platelets count (10^3/mm^3)	249 ± 86	252 ± 78	NS
hs-CRP (mg/L)	3.1 ± 2.2	2.3 ± 1.8	< 0.01
CRP (mg/L)	1.9 ± 0.8	1.2 ± 0.7	< 0.01
NLR	2.8 ± 1.4	1.9 ± 1.2	< 0.01
MHR	100.61 ± 18.4	79.78 ± 22.4	< 0.01

CSX: Cardiac sydrome X, CRP: C-reactif protein, NLR: Neutrophil/lymphocyte ratio, MHR: Monocyte/HDL-C ratio.

Table 3. Multivariate logistic regression analysis showing independent predictors for the presence of CSX

Variables	Adjusted OR	95% CI	p
White blood cell count, /mm^3	1.314	1.069-1.642	0.07
hs-CRP (mg/L)	1.143	1.036-1.545	< 0.01
CRP (mg/L)	1.126	1.028-1.532	0.03
NLR	1.245	1.078-1.656	0.02
MHR	1.250	1.240-1.461	< 0.01

CSX: Cardiac Sydrome X, NLR: Neutrophil/lymphocyte ratio, MHR: Monocyte/HDL-C ratio.

count, CRP and hs-CRP were independently associated with CSX. The ROC curve explored the discriminatory capability of MHR for the presence of CSX (Table 3). The area under the curve was 0.755 (95% CI= 0.707-0.802; p< 0.001). Using a cut-off level of 90.6, the pre-procedural MHR predicted the presence of CSX with a sensitivity of 78% and specificity of 70% (Figure 1).

DISCUSSION

In the present study, we found that MHR was significantly higher in the CSX group than in the control group. Besides, there were positive correlations between hs-CRP and CRP with plasma level of MHR. In addition, our findings revealed that higher MHR levels were significantly and independently associated with the presence of CSX. These results indicate that elevated serum MHR may be associated with the ongoing inflammation in the pathophysiology of CSX.

The pathophysiology of CSX has not been clearly identified yet, although multiple abnormalities including abnormal coronary flow reserve, insulin resistance, abnormal autonomic control, enhanced sodium-hydrogen exchange activity, abnormal cardiac sensitivity, microvascular spasm, endothelial dysfunction, oxidative stress and silent atherosclerosis have been reported[4-7]. Previous studies have demonstrated that the elevated levels of inflammatory molecules are markers of an atherosclerotic disease activity and also indicate an increased risk of the progression of atherosclerosis. Inflammation has been shown to be associated with endothelial dysfunction and silent atherosclerosis in patients with CSX[7]. Increased concentrations of circulating CRP correlate with vascular abnormalities in patients with CSX[7]. Previous studies showed that hs-CRP, WBC count and NLR ratio were higher in the

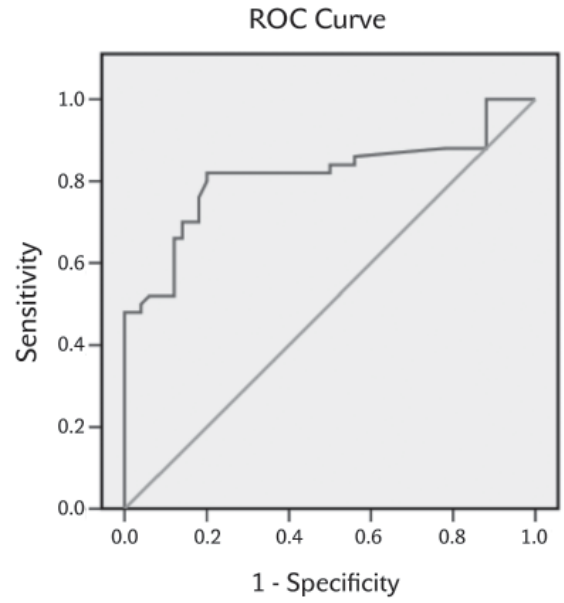

Figure 1. ROC curve: Using a cut-off level of 90.6, pre-procedural MHR predicted the presence of CSX with a sensitivity of 78% and specificity of 70%.

CSX group than in the control group[16]. The increased levels of hs-CRP, WBC count and NLR ratio may suggest that these markers may be used in clinical practice for the assessment of the inflammatory status of CSX. The results of this study conform to those of previous studies.

As shown in various pathologic conditions, inflammation is a well-known mechanism during the development and progression of atherosclerosis. Monocyte activation is a very important step in the beginning of the atherosclerotic process. Activated monocytes interact with the damaged or activated endothelium, which result in the overexpression of pro-inflammatory cytokines/adhesion molecules including monocyte chemotactic protein-1 ligand and vascular cell adhesion molecule-1 and intercellular adhesion molecule-1[17]. The count of circulating monocytes, as the source of tissue macrophages and foam cells, was found to be a predictor for new plaque development[18]. It has been known that monocyte activation plays an important role in chronic inflammation and cardiovascular disease, in which monocytes and differentiated macrophages can modulate inflammatory cytokines[12]. HDL-C molecules counteract macrophage migration and remove cholesterol from those cells. HDL-C exerts anti-inflammatory, anti-oxidant and anti-thrombotic effects[17,19,20]. Classically known as the anti-atherogenic lipoprotein, HDL promotes reverse cholesterol transport from the arterial wall, specifically from lipid-laden macrophages[19,20]. HDL is highly effective in inhibiting the endothelial expression of adhesion molecules and preventing monocyte recruitment to the artery wall[21]. HDL can prevent inflammatory responses by acting directly on monocytes[22,23]. Therefore, monocytes exert a pro-inflammatory effect, but HDL-C functions as a reversal factor during this process. However, the role of both monocytes and HDL-C remains unknown during the development of CSX. Inflammation associated with endothelial dysfunction is also a pathophysiologic mechanism underlying CSX development[7]. In our study, we also found that both monocyte and WBC counts were higher and that HDL-C level was lower in the CSX group.

MHR was defined as a novel potential marker to determine inflammation, and it has been used to predict clinical outcome in a few trials. One may hypothesise that increased MHR is a predictor for atherosclerosis development and progression and, hence, cardiovascular events[24]. MHR is a newly introduced inflammatory marker. Kanbay et al. reported that an increased MHR was an independent predictor of major cardiovascular events during a follow-up in the patients with chronic kidney disease[11]. Canpolat et al. investigated that MHR is an independent predictor of AF recurrence after cryoballoon-based catheter ablation and significantly related to SCF[12,13]. To the best of our knowledge, no study till date has investigated the association of MHR with CSX. On the basis of these findings and the pathophysiological role of inflammation in CSX, we hypothesised that MHR is associated with CSX. Our findings indicated that MHR > 90.6 was significantly and independently related with CSX. Besides its close relation with the severity of CSX, MHR also has a strong positive correlation with serum hs-CRP level and CRP, which supports its role in systemic inflammation in our study. Moreover, our findings revealed that higher MHR levels were significantly and independently associated with the presence of CSX. From a clinical viewpoint, as a new inflammatory marker, MHR may gain a role in the prediction of isolated CSX during daily clinical practice.

Study Limitation

Our study should be interpreted with some limitations. First, owing to its retrospective design, it lacks a prognostic value of MHR on adverse cardiovascular outcomes. Second, we used a single MHR value for our analysis rather than a temporal trend. We relied on visual assessments for the detection of coronary lesions. We did not perform specifically intravascular studies or TIMI frame counting to confirm or exclude the presence of endothelial or microvascular dysfunction in our cases. This study was not designed for long-term follow-up data either. We did not study any other inflammatory markers. Therefore, additional studies are certainly required to replicate and extend our findings in a larger population. Last, the number of patients was relatively small, and further extensive studies are required to detect a causal relationship between MHR and CSX.

CONCLUSION

In conclusion, our findings revealed that higher MHR levels were significantly and independently associated with the presence of CSX. In addition, MHR was positively correlated with serum CRP and hs-CRP levels as an evidenced marker of systemic inflammation. These results suggest that a higher MHR level has a pro-inflammatory effect on CSX. As widely available and inexpensive parameters of the CBC and lipid panel, MHR can be simply calculated in clinical practice for the prediction of CSX. However, our findings should be confirmed in large-scale prospective studies to explain the exact mechanistic role of MHR in CSX.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: EA
Analysis/Interpretation: EA
Data Acquisition: AG, AA
Writing: EA, RZ
Critical Revision: AG, SP
Final Approval: All of authors

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