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The relationship between monocyte HDL-C ratio and reduced left ventricular systolic function in patients among acute myocarditis

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Abstract

Myocarditis contributes to the global burden of cardiovascular disease mainly through sudden death and chronic cardiomyopathy in young age groups. Monocyte/high-density lipoprotein cholesterol (HDL-C) ratio (MHR) has developed as a new inflammation biomarker. In this study has investigated that relationship between admission MHR levels and the reduced left ventricular systolic functions after acute myocarditis. The study included a total of 156 consecutive cases wanted by their doctors to undergo cardiovascular magnetic resonance imaging for “acute myocarditis” as the clinical diagnosis between 2009 and 2017 at our hospital. Study participants were split into two groups; group I patients (patients with LVEF <40%), group II patients (patients with LVEF ≥40%) at last follow-up visit. 13 case had reduced left ventricle systolic function (LVEF <40%) at their last follow-up visit. MHR was significantly higher in the group-I ($P < 0.05$). A level of 14.6 for MHR showed an association with reduced in left ventricular systolic function with 84% sensitivity and 76% specificity. Multivariate logistic regression analyses showed that high MHR were significantly associated with reduced left ventricle systolic functions (for all; $p < 0.05$). MHR had a significantly positive correlation with CRP level in the correlation tests ($r = 0.356$; $p < 0.001$). We presented admissions MHR levels of the with cases after acute myocarditis with reduced left ventricle systolic functions were significantly higher than cases with normal left ventricle systolic functions. This parameter may be utilized to estimate worse clinical endpoints in patients with acute myocarditis.

Keywords: Inflammation, monocyte HDL ratio, myocarditis

Introduction

Myocarditis is an inflammatory pathology of the heart muscle [1]. It contributes to the global burden of cardiovascular disease mainly through sudden death and chronic cardiomyopathy in young age groups [2]. The clinical symptoms are markedly heterogeneous, most patients diagnosed with myocarditis recover without clinically related persistent damage [3]. Nevertheless, myocarditis might result in acute or chronic heart failure, arrhythmias or death [4]. According to previous studies, it is known that 6-30% of patients may develop dilated cardiomyopathy (DCM) after myocarditis [5]. Besides, the previous studies have reported that 10-50% of DCM patients have deposition of inflammation in the myocardial tissue [6].

The question as to whether or not they recover completely over time or whether their morbidity is still compromised after years has not yet been explained. For this reason, it is very important to predict prognosis, risk stratification, prevention of complications, and improving clinical conclusion in patients diagnosed with myocarditis.

Monocytes and macrophages are significant cell kinds for excretion of prooxidant and proinflammatory substances at the location of inflammation [7]. On the other hand, It is demonstrated that serum high-density lipoprotein cholesterol (HDL-C) inhibits expression of inflammatory adhesion molecules in endothelial cells induced by cytokines [8]. A short time ago, monocyte/high-density lipoprotein cholesterol (HDL-C) ratio (MHR) has developed as a novel inflammation biomarker [9]. Until now, it has not been investigated that association between clinical endpoints and MHR levels after acute myocarditis. Therefore, we aimed to evaluate association between admission MHR levels and clinical endpoints after acute myocarditis

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Materials and Methods

The study included a total of 172 consecutive cases wanted by their doctors to undergo cardiovascular magnetic resonance (CMR) imaging for “acute myocarditis” as the clinical diagnosis between 2009 and 2017 at our hospital.

Acute myocarditis was considered in patients who supplied the certain criteria: a novel or permanent finding suspected for myocarditis (effort intolerance, difficult or laboured breathing, palpitations, tiredness or angina), new or continuing evidence of myocardium damage (electrocardiographic disorders, left ventricular dysfunction, or high troponin), previous history of known viral illness; and exception of coronary artery disease (CAD) on computed tomography coronary angiography (CT-A) or coronary angiography (CAG). All study patients were at least 18 years of age.

Patients with previously known cardiomyopathy or genetically known cardiomyopathy were excluded. Exclusion criteria were chronic antiviral, immunomodulatory, immunosuppressive or antihyperlipidemic treatment within the last 6 months, active infection, chronic inflammatory disorder, acute or chronic renal insufficiency, active cancer, and deficiency to the consent form. All patients underwent coronary angiography or coronary CT-A for the evaluation of their coronary status. Patients underwent CMR imaging on 3.0-T or on 1.5-T within 36 h of admission.

Of these 172 patients, 2 patients were not included owing to incomplete data, 5 patients were excluded due to discharge against medical recommendation, and 9 patients were excluded because CAG demonstrated important CAD. Therefore, 156 patients after acute myocarditis were examined. The clinical, laboratory and follow-up data of patients were obtained from the hospital registry system. Patients were followed for at least 12 months after the diagnosis of acute myocarditis.

The assessment included physical examination, C-reactive protein (CRP) levels, troponin T levels, proB-type natriuretic peptide (proBNP) levels, and transthoracic echocardiography at each visit. However, we used the MHR value measured at the admission of hospitalization when acute myocarditis was diagnosed.

All echocardiographic images and conventional doppler flow velocities were obtained with commercially available ultrasound equipment. (GE Healthcare, Chalfont St Giles, UK) using a 2.5–3.5 MHz probe. Conventional, transthoracic echocardiography parameter were recorded in all patients at each visit.

Left ventricular ejection fraction (LVEF) was evaluated by utilization of Modified Simpson criteria. Reduced left ventricular (LV) systolic function was accepted as an LVEF of less than <40% at last visit. 156 patients were split into two groups; group I patients (LVEF <40%), group II patients (LVEF ≥40%).

The samples of venous blood were obtained from all patients at baseline and collected in tubes with EDTA for the hematological test. White blood cell measurement was done by hematology assay device XE-1200 (Sysmex, Kobe, Japan). The HDL-C measurement was performed by solubility technique.

MHR was measured by parting the number of the monocytes by the number of the HDL-C [10].

Diabetes mellitus (DM) was determined as current usage of the antidiabetic drugs or insulin. Hypertension (HT) was determined as an average blood pressure of ≥ 140/90 mmHg or current usage of antihypertensive therapy. Smoking was determined as current smoking.

The study received approval from our local ethics committee.

Statistical analysis

All data evaluated utilizing the SPSS 22.0 Statistical Package Program for Windows (IBM, SPSS). Numerical values acceptable for normal distribution were shown as mean ± standard deviation. Categorical parameters were shown as number and percent (%). Spearman rank test was applied to explain the correlation of CRP and MHR. Student t-test was used for normally distributed continuous variables, and the Mann-Whitney U test was performed for without normal distribution continuous variables.

Categorical variables were compared using Chi-Square or Fisher's Exact test. A univariate logistic regression analysis was employed to predict reduced LV systolic function.

Parameters demonstrating $p < 0.05$ in univariable logistic analysis were evaluated in multivariable logistic regression analysis. The receiver operating characteristic (ROC) was utilized to determine level of MHR in predictiveness reduced LV systolic function. A p value of < 0.05 was accepted statistically significant.

Results

156 cases were evaluated after acute myocarditis. Baseline characteristics are presented in Table 1. A total of 132 patients (84.6%) were male and mean age of study population were 25.4 ± 8.8 years old. Patients were followed for at least 12 months after the diagnosis of acute myocarditis. 13 patients (8.3%) had reduced LV systolic function (LVEF <40%) at their last follow-up. There were six deaths due to major adverse cardiovascular events during the follow-up time (four from progressive heart failure and two from sudden death). Six patients had diabetes mellitus, sixteen patients had hypertension.

In group-I patients were higher smoking rate than group-II patients ($p < 0.05$). In group I patients, Monocyte count, CRP levels, serum creatinine values and MHR were higher ($P < 0.05$), glucose values and HDL-C level were lower than group-II patients ($p < 0.05$; Table 1).

In ROC analysis, area under the curve was 0.862 (95% Confidence Interval [CI]:0.780-0.944; $p < 0.001$). Prediction the reduction of left ventricular systolic function was used a cut-off level of 14.6 for MHR with a sensitivity of 84% and specificity of 76% (Figure1). Multivariate logistic regression analyses showed that high MHR were significantly related the reduced LV systolic functions (for all; $p < 0.05$) (Table 2).

MHR was positively correlated with the CRP level ($r = .356$; $p < 0.001$) (Figure 2).

Table 1. Baseline clinical, demographical, laboratory and echocardiographic characteristics of the study population

	Group-I (LV EF <40%) n = 13	Group-II (LV EF ≥40%) n = 143	p-value
Age (year)	29.9 ± 13.7	25.0 ± 8.2	0.481
Male/Female, n (%)	11/2 (84.6%-14.4%)	121/22 (84.6%- 15.4%)	0.627
Current Smoking	3 (23.0%)	7 (4.8%)	0.003
Baseline LVEF, %	26.5 ± 6.7	60.5 ± 10.6	<0.001
Diabetes mellitus, n (%)	2 (15.3 %)	4 (2.7 %)	0.080
Hypertension, n (%)	5 (38.4 %)	11 (7.6 %)	0.005
Urea, (mg/dl)	30.5 ± 6.0	28.1 ± 5.5	0.067
Creatinine (mg/dl)	1.0 ± 0.4	0.7 ± 0.2	0.044
LDL-C (mg/dL)	92.5 ± 19.0	64.4 ± 8.36	0.139
HDL-C (mg/dl)	38.16 ± 3.6	47.6 ± 12.1	<0.001
WBC (x10³/ μL)	9.4 ± 1.0	10.6 ± 6.5	0.057
Monocyte (x10³/ μL)	0.7 ± 0.1	0.5 ± 0.01	<0.001
Hemoglobin (mg/dl)	13.4 ± 1.3	13.9 ± 0.9	0.135
CRP	43.6 ± 9.8	7.6 ± 1.0	0.010
Fasting plasma glucose (mg/dl)	105.0 ± 5.4	114.4 ± 8.3	0.039
Monocyte/HDL ratio	20.1 ± 5.9	12.2 ± 7.9	<0.001
MHR>14.6, n (%)	11 (84.6%)	33 (23.0%)	<0.001
Cardiovascular Death	6 (46%)	0	<0.001

Data are presented as mean ± standard deviation or n (%).

LVEF: Left ventricular ejection fraction; LDL: Low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; WBC: White blood cell; CRP: C-reactive protein

Table 2. Univariate and multivariate logistic regression analyses for prediction of reduced left ventricular systolic function.

	Univariate		Multivariate	
	Odds ratio (95% confidence interval)	P value	Odds ratio (95% confidence interval)	P value
Monocyte	0.996 (0.994- 0.999)	0.006	1.004 (0.999- 1.009)	0.124
HDL-C	1.170 (1.077- 1.271)	<0.001	1.162 (1.035- 1.304)	0.011
CRP	0.932 (0.901- 0.964)	<0.001	0.938 (0.899- 0.978)	0.003
Creatinine	0.380 (0.123- 1.172)	<0.001		
Glucose	1.002 (0.987- 1.018)	0.772		
Monocyte/HDL ratio ≥14.6	0.055 (0.012- 0.259)	<0.001	0.075 (0.007- 0.848)	0.036

HDL-C: High-density lipoprotein cholesterol; CRP: C-reactive protein.

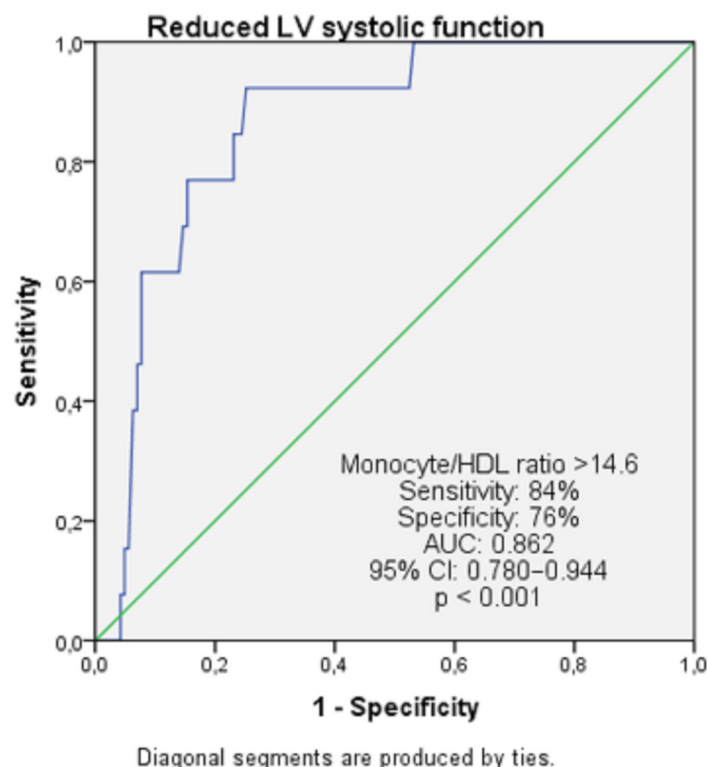


Figure 1. Receiver operating characteristic curve analysis of MHR to predict reduced left ventricular systolic function in patients with acute myocarditis

AUC: Area under curve

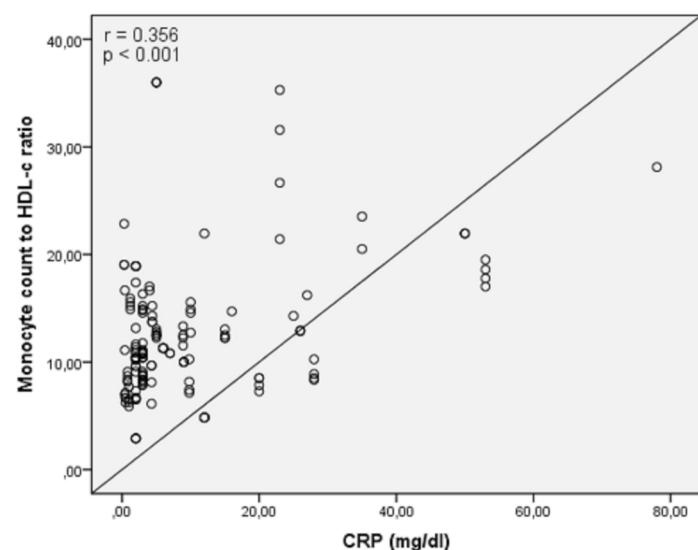


Figure 2. The monocyte count to HDL-cholesterol ratio was positively correlated with C-reactive protein (CRP).

Discussion

This research showed that MHR was related to reduced LV systolic functions during follow up time after acute myocarditis. Higher CRP levels and lower HDL-C together with higher MHR were significant predictors of reduced LV systolic function. This study is the first that exhibition the relationship between MHR and reduced left ventricular systolic function after acute myocarditis.

Myocarditis is a disease characterized by an inflammatory

process of the myocardium. [1, 11]. Inflammation, together with immune reaction are acknowledged to be an important factor in acute myocarditis [12]. There is no known predictor of whether myocardial systolic dysfunction will occur in the follow-up of the disease. Previous studies have showed a correlation between reduced LVEF and adverse cardiovascular events in acute myocarditis patients [13-15]. It has been shown that patients presenting with low LV systolic function have a poor prognosis than those presenting with normal LV systolic function [16, 17]. Myocarditis is an inflammatory state in the myocardium, and increased inflammation has been defined in manner of development of a disease of progression of acute myocarditis to an inflammatory cardiomyopathy [18, 19]. It was assumed that a mononuclear infiltration of the myocardium with injury to cardiomyocytes is related to the pathophysiological mechanism of acute myocarditis [20]. In recent decades, a significant relationship between inflammatory markers and acute myocarditis has been demonstrated. Ammirati et al. shown that the CRP were high in myocarditis that cases with requiring inotropes treatment or mechanical support [15]. Berg et al. presented that the high CRP with myocarditis is a risk factor for prognosis of patients [21]. Additionally, it was postulated that oxidative stress, nuclear factor (NF), NF erythroid 2-related factor 2/Keap1, neurohumoral factors are connected to the pathophysiological mechanism of myocarditis [22]. Inflammation can be evaluated using a diversity of biochemical and hematological markers. All these inflammatory parameters such as NF- κ B and Nrf2/Keap1 are also not widely available in current daily practice. So, a clinically simple and cost-effective method to assess inflammation and resulting fibrosis is required. Recently, MHR has been appearing a simply reachable new marker indicating inflammation.

In this study, the importance of MHR has investigated in predicting LV systolic functions. Monocytes have a critical effect on the pathogenesis of cardiovascular diseases related to inflammation and remodelling [23-25]. Monocytes can activate an inflammatory pathway involving the phagocytosis, antigen presentation, and production of cytokines [26, 27]. Accordingly, infiltration of the heart muscle results in myocardial remodelling and heart failure [28]. Levels of circulating monocytes have related to worse prognosis and adverse cardiac events in patients with heart failure [24, 28].

Contrarily, HDL-C prevent these pro-oxidant and proinflammatory impacts of monocytes through restraining the differentiation-proliferation of the progenitor cells that cause monocyte production [29, 30]. Additionally, recent studies have shown the role of HDL in managing the grow up of progenitor cells that lead to monocytes and in managing of monocyte adhesiveness and activation [29, 31]. Thus, monocytes exhibit an inflammatory effect, while HDL exhibit a reverse effect on inflammation pathway. Considering all these, MHR has developed a novel and common prognostic marker. Nonetheless, the role of MHR was not completely understood contribution to the progression of reduced LV systolic function after acute myocarditis. Recent studies showed, MHR was high in patients with peripartum cardiomyopathy that LV systolic dysfunction [24], existence and severity of isolated coronary artery ectasia [32], slow coronary flow [33], the severity of rheumatic mitral valve stenosis [34], bare metal stent restenosis [35] and stent thrombosis for ST-segment elevation myocardial infarction [9].

All these results indicate the cruciality of MHR in inflammation status that a significant factor in cardiovascular diseases.

According to the results our study, MHR has a significant correlation with CRP. Myocarditis is a disease that occurs with inflammation of the myocardium. therefore we suggested that markers that may reflect inflammation may be considered to be an important factor in the prognosis of acute myocarditis. We recognized, MHR levels were significantly high in patients with reduced LV systolic functions after acute myocarditis.

This parameter may be utilized to estimate worse clinical endpoints after acute myocarditis.

This study was performed retrospectively and we utilized a one MHR value for this study instead of time-related values. Second, an endomyocardial biopsy could not be performed for all patients. This study has small number of patients that may have impacted the statistical power of the study. Different physicians performed the echocardiographic examination. There was no control group. HDL is synthesized in the liver. It is typical for heart failure or shock independently of aetiology that liver functions are disturbed as well as other organs. As a result, diverse laboratory markers are involved showing a decrease curve. In this respect the possibility that HDL may be a part of inflammation of myocardial cells is not clearly.

Conflict of interests

The authors declare that they have no competing interests.

Financial Disclosure

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Ethical approval

Ankara City Hospital Ethics Committee was approved by 08.07.2020 and number 30433.

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