European Review for Medical and Pharmacological Sciences 2022; 26: 4303-4308

Predictive value of lymphocyte to monocyte ratio for cardiac syndrome X

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Abstract. – OBJECTIVE: Cardiac syndrome X (CSX) is typically described with ischemia in stress tests in addition to angina-like chest pain and without stenosis in coronary angiography. We aimed at determining the relationship between LMR and CSX.

PATIENTS AND METHODS: We retrospectively collected patients with CSX between January 2016 and December 2019. Patients with typical angina-like chest pain, normal 12-lead electrocardiography at rest, a positive response to the exercise test (> 0.1 mV ST-segment depression at 80 ms after the J point in two or more contiguous leads) or ischemia on myocardial perfusion scintigraphy and normal coronary angiography were included in the study as CSX patients.

RESULTS: This study consisted of 116 patients with CSX and 153 control groups. The mean age of the patients with CSX was 52.7±9.7 years, and the mean age of the control group was 53.7±10.6 years (*p*= 0.416). The patients with CSX were more likely to have higher monocyte counts and LMR. According to the Pearson correlation test, the CRP value negatively correlated with the LMR. In multivariate logistic regression analysis, LMR remained a significant predictor of CSX. In ROC analysis, LMR < 4.1 had 64% sensitivity and 50% specificity (ROC area under curve: 0.587, 95% CI: 0.519-0.655, *p*=0.015) in accurately predicting a CSX diagnosis.

CONCLUSIONS: We showed that lower LMR levels were associated with the presence of CSX.

Key Words:
Lymphocyte to monocyte ratio, Cardiac syndrome X, Inflammation markers.

Introduction

Combining typical (anginal) chest pain, angiographically normal coronary arteries, and myocardial ischemia by noninvasive testing is known as cardiac syndrome X (CSX), which is a consequence of coronary microvascular dysfunction[1]. Approximately 3-10% of patients, who had typical anginal chest pain and underwent coronary angiography have normal coronary arteries and are diagnosed with CSX[2]. The term 'syndrome X' was first described by Kemp in 1973[3]. Chest pain elicited by exertion, an exercise test demonstrating ST-segment depression or pathologic thallium scan, and angiographically normal coronary arteries (no inducible or spontaneous spasm of the coronary arteries by acetylcholine or ergonovine provocation) are the three characteristic features of CSX[4]. Although the pathophysiological mechanism of CSX is not clear, studies[5] show that coronary microcirculatory dysfunction, endothelial dysfunction, and chronic inflammation play a significant role in the etiology of CSX.

The relation between high monocyte counts or low lymphocyte counts with adverse cardiovascular events in patients with atherosclerosis has been shown in several studies[6]. Activated monocytes differentiate into macrophages, and both modulate and activate inflammatory cytokines, thus plays a crucial role in the chronic inflammatory response in cardiovascular disease[7].

The lymphocyte-to-monocyte ratio (LMR) is a new systemic inflammatory marker. The LMR has been extensively studied in cardiovascular disease, infectious disease, cancer, and autoimmune disease[8-11]. In this study, we aimed to investigate the relationship between the LMR and the presence of CSX.

Patients and Methods

Study Population

We designed this study as a single center observational study. Patients who had diagnosed CSX were retrospectively enrolled between January 2016 and December 2019. The CSX group consisted of 116 patients, and the control group

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consisted of 153 patients. The inclusion criteria for the CSX group were:

1. Patients who had angina;
2. Normal findings on 12-lead electrocardiography, ischemia was shown by myocardial perfusion scintigraphy or positive exercise test (> 0.1 mV ST-segment depression at 80 ms after the J point at least in two contiguous leads);
3. Normal coronary angiography.

The control group consisted of patients whose sex and age demographics matched those of the CSX group, who had normal echocardiographic findings, in whom treadmill exercise test or myocardial perfusion scintigraphy showed no evidence of ischemia, and patients without abnormal coronary angiography.

The exclusion criteria of the study were (1) a history of surgical or mechanical revascularization and (2) angiographically proven coronary artery disease. In addition, following clinical conditions and diseases were excluded: left ventricular hypertrophy (interventricular septum >11 mm), congenital heart disease, left ventricular dysfunction (ejection fraction <50%), valvular disease (any valve stenosis or moderate-severe valve regurgitation), coronary slow flow phenomenon, positive hyperventilation test, peripheral artery disease, bridge of coronary artery, chronic obstructive pulmonary disease, dilated cardiomyopathy, restrictive cardiomyopathy, dysphagia, hepatic or renal insufficiency, hyperthyroidism, autoimmune diseases, hypothyroidism, bowel motility disorders, malignant diseases, use of nonsteroidal anti-inflammatory drugs or corticosteroids, acute or chronic infectious diseases. In addition, patients' baseline parameters, such as sex, age, smoking, dyslipidemia, diabetes mellitus, hypertension, urea, glucose, and creatinine, were recorded.

We conducted the study in accordance with the guidelines of the Helsinki Declaration. All patients gave written informed consent for participation in this study. The Ethics Committee of the Dicle University approved this study (Dicle University Medical Faculty Ethics Committee for Noninterventional Studies, No. 2020-107).

Hematological and Biochemical Parameters

Venous blood samples were drawn from the antecubital vein and collected in a tube containing K3 EDTA to measure hematologic indices in all patients. Automated hematology analyzer was used to measure total and differential leukocyte counts (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, IL, USA). For analyzes, absolute cell counts were used. Standard methods were used for measurement of glucose, urea, creatinine, lipid profile, and other routine biochemical tests. We divided the lymphocyte count to monocyte count to calculate LMR.

Coronary Angiographic Analysis

In all cases, the standard Judkins technique for coronary angiography was used (Siemens Medical Solutions, Erlangen, Germany) without using nitroglycerin. Two experienced physicians who were blind participated in the analysis of the angiograms. Coronary arteries with visually smooth contours without wall irregularities were accepted as normal. In these patients, a hyperventilation test was performed to exclude coronary artery vasospasm. For the hyperventilation test, patients were taking deep and rapid breaths for 5 minutes.

Statistical Analysis

SPSS software version 18.0 was used to analyze data (SPSS Inc., Chicago, IL, USA). Continuous variables were defined as means ± standard deviation or median values (interquartile range). The chi-square test was used for categorical variables and the independent-samples *t*-test or Mann-Whitney U test for continuous variables. We used the Kolmogorov-Smirnov test to check the normality of the distribution of continuous variables. For correlation analysis we used the Pearson test. Statistical significance was defined as p-value <0.05. We performed the multivariate logistic regression analysis to evaluate the independent predictors of CSX. All variables found to be significant in the univariate analysis and clinically dependent were included in the logistic regression model. Results were presented as odds ratios (OR) with 95% confidence intervals (CIs). We performed the receiver operating characteristic curve analysis (ROC) to determine the optimal cutoff values for LMR associated with CSX.

Results

This study included 116 patients with CSX and 153 control subjects. The mean age of CSX group and the control group were 52.7 ± 9.7 years, and 53.7 ± 10.6 years respectively (p=0.416). Table I lists the baseline hematologic, demographic, echocardiographic, and biochemical data. Patients in the CSX group had higher monocyte

Table I. Demographic hematologic, and clinical characteristics of cardiac syndrome X group.

Variables	Control (n=153)	CSX (n=116)	p
Age, years	53.7 ± 10.6	52.7 ± 9.7	0.416
Female gender, n (%)	97 (63.4)	67 (57.8)	0.348
Hypertension, n (%)	44 (28.8)	34 (29.3)	0.921
Diabetes mellitus, n (%)	31 (20.3)	23 (19.8)	0.930
Smoking, n (%)	38 (24.8)	35 (30.2)	0.330
Hemoglobin, g/dL	13.9 ± 1.6	14.1 ± 1.6	0.200
White blood cell count, 10^3/µL	8.2 (7.0-9.5)	8.3 (7.1-9.4)	0.971
Neutrophil count, 10^3/µL	4.9 (4.0-6.0)	4.8 (3.9-6.0)	0.804
Lymphocyte count, 10^3/µL	2.6 ± 0.8	2.5 ± 0.7	0.696
Monocyte count, 10^3/µL	0.56 ± 0.18	0.62 ± 0.19	**0.009**
Platelet count, 10^3/µL	266.0 ± 72.0	259.6 ± 61.3	0.438
Creatinine, mg/dL	0.74 (0.67-0.85)	0.74 (0.67-0.8)	0.745
Glucose, mg/dL	102.0 (92.0-121.5)	101.0 (92.0-120.0)	0.826
Total cholesterol, mg/dl	200.1 ± 40.7	198.0 ± 43.3	0.682
Triglycerides, mg/dl	149.0 (102.0-214.0)	134.5 (100.5-220.8)	0.545
Left ventricular EF, %	60.0 ± 5.1	60.2 ± 4.9	0.887
CRP, mg/dL	0.18 (0.05-0.38)	0.20 (0.08-0.52)	0.091
LMR	4.9 ± 1.7	4.3 ± 1.3	**0.002**

Data are presented as number (percentage) and mean±standard deviation or median (interquartile range) values. CRP – C-reactive protein; EF – ejection fraction; LMR – lymphocyte-to-monocyte ratio.

counts and LMR compared to the control group.

We analyzed the correlation between CRP and LMR using the Pearson test. According to the Pearson test, CRP level correlated negatively with LMR (r: -0.150, p=0.014).

LMR, age, diabetes mellitus, hypertension, and male gender were analyzed by multivariate logistic regression analysis. LMR remained a significant predictor of CSX. (OR: 0.758, 95% CI: 0.627-0.915, p=0.004; Table II). LMR < 4.1 had a sensitivity of 64% and a specificity of 50% in the ROC analysis (ROC area under curve: 0.587, 95% CI: 0.519-0.655, p=0.015) (Figure 1).

Discussion

This study was designed to investigate the relationship between LMR and CSX. Our results showed that LMR values were lower in the CSX group compared to the control group. To the best of our knowledge, this study is the first to demon-

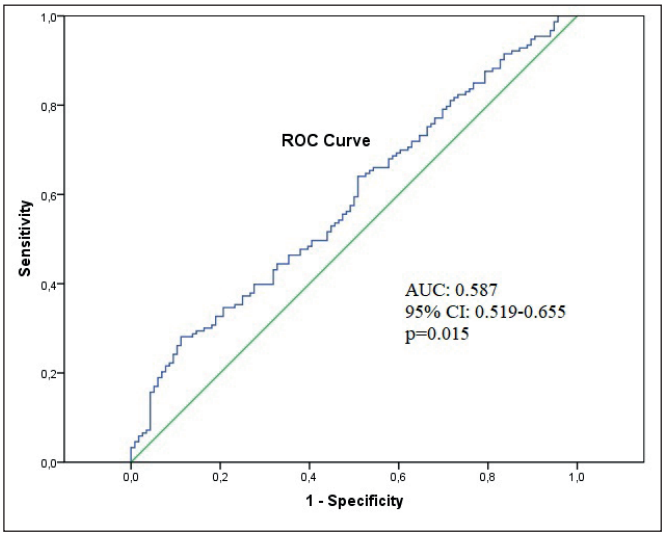

Figure 1. Receiver operating characteristics curve of LMR to predict cardiac syndrome X.

Table II. Significant predictors of CSX in multiple logistic regression analysis.

	Multiple logistic regression analysis		
	OR	(95% CI)	p
Age	0.987	(0.962-1.012)	0.307
Male gender	0.961	(0.572-1.616)	0.882
Diabetes mellitus	0.942	(0.502-1.765)	0.851
Hypertension	0.958	(0.547-1.676)	0.880
LMR	0.758	(0.627-0.915)	**0.004**

CI: confidence intervals, LMR: lymphocyte-to-monocyteratio, OR: odds ratio.

strate this association. Moreover, this study shows that chronic inflammation may be one of the causes of the unclear pathogenesis of CSX.

Although several abnormalities, such as oxidative stress, endothelial dysfunction, abnormal pain perception, microvascular spasm, abnormal, autonomic control, abnormal coronary flow reserve, and silent atherosclerosis, have been implicated, the exact pathophysiology of CSX remains to be elucidated[12]. CSX is considered a benign disease compared with obstructive coronary artery disease[13]. However, stable angina patients with normal coronary arteries or nonobstructive CAD had an increased risk for serious all-cause mortality, and adverse cardiac events compared to control group[14].

The association between inflammation, endothelial dysfunction, and silent atherosclerosis has been established in CSX patients[15]. In CSX patients, elevated C-reactive protein (CRP) levels has been shown to be correlated with vascular abnormalities[16]. Neutrophil-lymphocyte ratio (NLR) and leukocyte subtype are also indicators of systemic inflammation and have prognostic significance in cardiovascular disease[17]. The association between atherosclerotic progression in vessels and NLR has been demonstrated in a previous study[18]. In a study by Demirkol et al[19], the patients with CSX and CAD had higher NLR compared with the control group. The association between CSX and higher NLR values suggests that, in addition to endothelial dysfunction, silent atherosclerosis may be involved in the etiopathogenesis of CSX, similar to CAD.

Elevated inflammatory markers have been previously reported[20] as indicators of activity of atherosclerotic disease and risk of progression. In CSX, inflammation has been found to be one of the causes of endothelial dysfunction[21]. In one imaging study[22], cardiovascular magnetic resonance imaging showed abnormal subendocardial perfusion in patients with CSX. Atheromatous plaques and intimal thickening have been observed in the coronary arteries of CSX patients by using the intravascular ultrasonography (IVUS)[23]. These findings all support silent atherosclerosis as the cause of CSX.

The relationship between hematologic markers and CSX has been extensively investigated in recent studies. RDW and plateletcrit (PCT) were independently associated with the presence of CSX. RDW and CRP levels were also positively correlated[24,25]. In other studies[26,27], researchers found that MPV levels were significantly higher in both the CAD and CSX groups compared with the normal coronary artery group. Dogan et al[28] showed that CSX patients tended to have higher MHR levels monocyte counts, PCT, and platelet counts.

Both monocytes and lymphocytes are an important part of the immune system associated with the atherosclerotic process in the vessels. High monocyte count and low lymphocyte count have a prognostic and predictive value in cardiac diseases, such as myocardial infarction, stable CAD, and heart failure[29,30]. Monocytes secrete pro-inflammatory cytokines in the peripheral circulation. Monocytes accumulate in the arterial wall, transform into macrophages, and release pro-inflammatory cytokines that cause local damage[31]. A low lymphocyte count has been shown to be associated with inflammation, atherosclerosis, and plaque development[32]. Thus, combining elevated monocyte and low lymphocyte levels into a single integrated inflammatory marker may provide more additional information than either parameter alone. Fan et al[33] investigated the association between plaque vulnerability assessed by IVUS and LMR in patients with stable angina. Their study found that LMR can be used to determine vulnerable plaques in the stable angina. In a study[34] that examined the association between CAD severity and LMR in patients with stable

CAD, LMR was associated with high SYNTAX scores and the presence of CAD.

Consequently, LMR can be used in the evaluation of CSX patients in clinical practice as a cheap and simple method to detect inflammation. Nevertheless, by larger studies this study should be supported.

Limitations

The small sample size was the main limitation of our study. The ergonovine test is the ideal method to diagnose exclude the coronary spasm, but we used the hyperventilation test. Also, measurement of coronary flow reserve by Doppler wire and IVUS are two invasive methods that could be used to diagnose microvascular dysfunction and exclude of atheromatous plaques. For measuring the coronary flow reserve positron emission, tomography can be used. None of these evaluations were found in our retrospective study.

Conclusions

Low LMR, indicating increased inflammation, is independently and significantly associated with the presence of CSX. The LMR value appears to be complementary to the traditional expensive methods commonly used to predict CSX.

Conflicts of Interest
The authors declare no conflicts of interest.

Funding
None.

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