

The usefulness of plateletcrit to predict cardiac syndrome X in patients with normal coronary angiogram

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Abstract

Introduction: Cardiac syndrome X (CSX) is a clinical entity defined as the triad of typical angina pectoris on exercise, electrocardiographic or metabolic findings of ischemia and normal epicardial coronary arteries. Platelets, whose amount in the blood is indicated with plateletcrit (PCT), play an important role in inflammatory and thrombotic processes and the physiopathology of cardiovascular events.

Aim: To investigate the association between cardiac syndrome X and PCT and platelet count.

Material and methods: A total of 113 patients with normal coronary angiogram were included in the study. Fifty patients with typical chest pain and evidence of myocardial ischemia in non-invasive tests formed the CSX patient group. The control group consisted of 63 age- and gender-matched patients with normal coronary arteries but without angina.

Results: The mean PCT value of the CSX group was significantly higher than that of the control group (0.22 ± 0.06 vs. 0.19 ± 0.04 ; respectively, $p = 0.03$). Higher PCT was found to be associated with the presence of CSX in patients with normal coronary arteries by multivariate logistic regression analysis.

Conclusions: We suggest that high PCT may predict the presence of cardiac syndrome X in patients with normal coronary arteries. The value of PCT appears additive to conventional expensive methods commonly used in CSX prediction.

Key words: cardiac syndrome X, plateletcrit, platelet count.

Introduction

Despite its typical angina and objective ischemic findings, cardiac syndrome X (CSX) is a clinical situation in which normal coronary arteries are detected in angiography [1, 2]. As CSX and angina pectoris caused by typical obstructive coronary heart disease share similar pain pattern, they should be distinguished from each other for effective treatment. In diagnosis of CSX, chest pain of non-cardiac origin such as esophageal disorders or psychiatric conditions should be considered and ruled out. Although there has not been a clear explanation of the exact pathophysiological mechanism underlying CSX, studies suggest that coronary micro-circular abnormalities and endothelial dysfunction play a role in the etiology of the disease [3–5].

Platelets, the amount of which in the blood is indicated with plateletcrit (PCT), are important for inflammation, thrombosis, and cardiovascular physiopathology. Plateletcrit actually shows the amount of circulating platelets in a unit volume of blood, and in this sense it is similar to the hematocrit for erythrocytes [6]. An increased number of platelets has been shown to be associated with worse cardiovascular outcome in patients with coronary artery disease and even in apparently healthy men [7]. However, there are limited data about the association between platelet count and CSX in the literature.

Aim

Therefore, in the current study, our objective is to investigate the relationship between CSX and PCT and platelet count.

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Material and methods

Study population

This study has a retrospective observational nature. It was based on a medical center called Dumlupinar University School of Medicine Evliya Celebi Education and Research Hospital, Department of Cardiology. In this study, 50 patients were included in the CSX group, and 63 patients formed the control group. The patients in the CSX group were selected based on our findings and their symptoms. Patients with typical angina-like chest pain, normal 12-lead electrocardiogram at rest, a positive exercise test response (> 0.1 mV ST-segment depression at 80 ms after the J point in two or more contiguous leads) and a normal coronary angiogram were included in the study of CSX. The control group consisted of age- and gender-matched patients who underwent coronary angiography due to suspicion of coronary artery disease (CAD), without any evidence of ischemia on ECG or myocardial metabolism during the treadmill exercise test or myocardial perfusion scintigraphy, respectively, whose coronary arteriogram revealed normal coronary arteries.

The exclusion criteria in the study were coronary artery disease at coronary angiography and surgical or mechanical revascularization. Also, patients with left ventricular dysfunction (ejection fraction $< 60\%$), a positive hyperventilation test in coronary angiography, coronary bridging, slow flow phenomenon, valvular heart disease (any valvular stenosis and moderate or severe valvular regurgitation), left ventricular hypertrophy (interventricular septum > 1.1 cm), acute or chronic hepatic and renal failure, chronic obstructive pulmonary disease, peripheral artery disease, congenital heart disease, restrictive cardiomyopathy, dilated cardiomyopathy, a history of dysphagia, swallowing as well as intestinal motility disorders, hypothyroidism, hyperthyroidism, malignancies, autoimmune diseases, acute or chronic infectious disease were also excluded from the study. Baseline characteristics including age, sex, diabetes mellitus, hypertension, dyslipidemia, smoking, family history of coronary artery disease, urea and creatinine of the patients were recorded.

Biochemical and hematological parameters

Antecubital venous blood was drawn from the patients in the morning after a night of 12-hour fast. A Beckman Coulter LH 780 automated hematology analyzer (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland) was used for the analyses. Standard techniques were employed for routine biochemical tests; these analyses showed the patients' total and differential leukocyte count measures.

Angiographic analysis

The standard Judkins technique without the use of nitroglycerin (Siemens Medical Solutions, Erlangen, Ger-

many) was used for the coronary angiography in all subjects. Two experienced physicians blinded to the study took part in the evaluation of angiograms. Angiograms with visually smooth contours with no wall irregularities were taken as normal. A hyperventilation test was applied to the patients who exhibited normal coronary anatomy during the coronary arteriography in order to avoid the risk of coronary artery vasospasm. In the procedure of the hyperventilation test, the patients were asked to breathe rapidly and deeply for 5 min.

Statistical analysis

In the data analyses procedure, the SPSS software version 18.0 for Windows (SPSS Inc, Chicago, Illinois) was used. The Kolmogorov-Smirnov test was conducted to test the normality of the distribution of continuous variables. Means \pm standard deviation and percentages were used to indicate continuous variables and categorical variables, respectively. In order to determine the differences in continuous variables of groups, the independent sample *t*-test and Mann-Whitney *U* test were used according to the distribution pattern; and the χ^2 test was used for categorical variables. The Pearson correlation test was used and significance was defined as $p < 0.05$. In order to evaluate the independent predictors of CSX, variables whose *p* value was < 0.05 in univariate analysis were assessed by multivariate logistic regression analysis. Therefore, after the univariate analysis, all significant variables were included in the logistic regression model. The results are shown as odds ratios (OR) with 95% confidence intervals (CIs). A receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off level for the PCT value that best predicted CSX.

Results

One hundred and thirteen patients with a mean age of 52.1 ± 10.7 years were included in the study. Patients were divided into two groups based on CSX. The baseline demographic, biochemical and hematological data of the patients according to the groups are presented in Table I. The patients with CSX were more likely to have higher platelet counts and PCT values. The mean PCT value of the CSX group was significantly higher than that of the control group (0.22 ± 0.06 vs. 0.19 ± 0.04 ; $p = 0.03$, respectively). No significant differences in age, gender, or other demographic biochemical and hematological parameters were observed between groups. Higher PCT values were found to be associated with the presence of CSX by multivariate logistic regression analysis (Table II). In ROC analysis, $PCT > 0.195$ had 62% sensitivity and 56% specificity (ROC area under curve: 0.643, 95% CI: 0.540–0.747, $p = 0.009$) in accurately predicting a CSX diagnosis (Figure 1).

Table I. Baseline characteristics of control and cardiac syndrome X groups

Variables	Cardiac syndrome X n = 50	Normal coronary artery n = 63	Value of p
Age [years]	50.8 ±10.9	53.1 ±10.5	0.253
Male gender, n (%)	21 (42)	26 (41)	0.938
Hypertension, n (%)	21 (42)	26 (41)	0.938
Diabetes mellitus, n (%)	13 (26)	24 (38)	0.174
Smoking, n (%)	15 (30)	19 (30)	0.985
Glucose [mg/dl]	112.7 ±41.9	122.7 ±47.6	0.242
Urea [mg/dl]	31.5 ±9.7	30.4 ±10.7	0.574
Creatinine [mg/dl]	0.8 ±0.2	0.8 ±0.2	0.369
Total cholesterol [mg/dl]	183.4 ±35.2	190.1 ±34.1	0.309
HDL cholesterol [mg/dl]	49.9 ±15.0	49.3 ±13.7	0.815
LDL cholesterol [mg/dl]	108.2 ±31.6	111.8 ±27.9	0.528
Triglyceride [mg/dl]	137.9 ±61.3	152.4 ±70.6	0.255
Hemoglobin [g/dl]	14.0 ±1.5	13.7 ±1.5	0.310
White blood cell count [10 ³ /μl]	8 ±1.9	7.5 ±1.8	0.136
Neutrophil count [10 ³ /μl]	4.9 ±1.6	4.6 ±1.4	0.226
Lymphocyte count [10 ³ /μl]	2.3 ±0.7	2.2 ±0.6	0.261
MPV [fl]	8.9 ±0.8	8.9 ±1.1	0.898
Platelet, count [10 ³ /μl]	257.0 ±69.0	227.0 ±51.8	0.013
Plateletcrit (%)	0.22 ±0.06	0.19 ±0.04	0.03

HDL – High-density lipoprotein, LDL – low-density lipoprotein, MPV – mean platelet volume, RDW – red cell distribution width.

Table II. Significant predictors of cardiac syndrome X in multiple logistic regression analyses

Parameter	Odds ratio	95% CI	Value of p
Plateletcrit	3.173	1.035–9.726	0.05
Platelet count	1.109	0.532–2.684	0.786
Male gender	1.849	0.753–4.538	0.180
Age	0.992	0.955–1.030	0.674

CI – Confidence interval.

Discussion

In the current study, we investigated the association between CSX and PCT and platelet count. Our results revealed that platelet counts and PCT levels of patients with CSX were higher than those of the control group consisting of patients with a normal coronary artery without angina.

Kemp *et al.* first mentioned the term CSX in 1973 to describe this condition in patients [8]. Angina-like chest pain, a positive response to noninvasive stress testing and angiographically normal coronary arteries are the

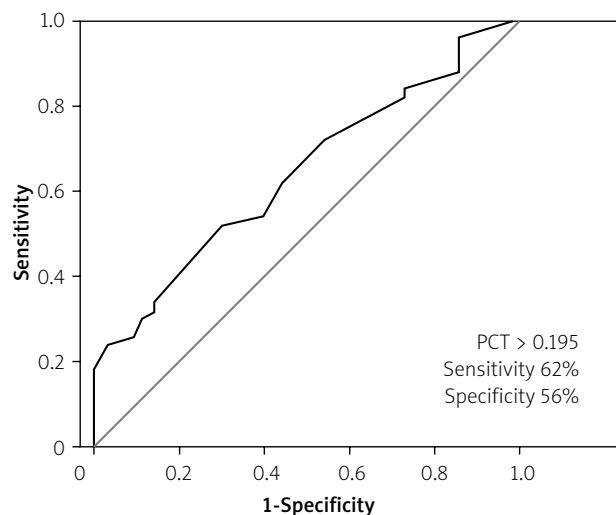


Figure 1. Receiver operating characteristics curve of plateletcrit for predicting cardiac syndrome X

criteria for CSX diagnosis. In a study, CSX was not reported to be associated with higher risk of death; however, the quality of life was found to be negatively affected by it [9]. However, in a more recent large-scale study, pa-

tients with stable angina and normal coronary arteries or diffuse non-obstructive coronary artery disease were found to have increased risks of major adverse cardiac events and all-cause mortality compared with a reference population without ischemic heart disease [10].

Patients with CSX have been stated to have multiple pathophysiological abnormalities. Generalized endothelial dysfunction and inflammation were reported as the most convincing evidence of CSX [11, 12]. Also, in patients with CSX, inflammation was thought to be related to endothelial dysfunction. Elevated levels of inflammatory molecules were previously reported as markers of atherosclerotic disease activity and as an indication of increased risk for the progression of atherosclerosis [13]. Moreover, in patients with either coronary artery disease or cardiac syndrome X, C-reactive protein was reported to be associated with impaired endothelial function. In a study in patients with cardiac syndrome X, CRP level was found to be correlated with the activity of the disease [14]. In a similar vein, elevated red cell distribution width (RDW) levels were found to be independently associated with presence of CSX, and in the same study RDW and CRP levels were reported to correlate positively [15]. In another study, the presence of endothelial dysfunction and sub-angiographic atheroma was revealed in patients with CSX [16]. Furthermore, some intravascular ultrasonographic studies with CSX patients discovered presence of abnormal coronary arteries with atheromatous plaques and intimal thickening [16, 17]. Additionally, magnetic resonance imaging revealed abnormal sub-endocardial perfusion in patients with CSX [18]. For all these reasons, it could be considered that the etiopathogeneses of coronary artery disease and CSX are similar.

Complete blood count allows clinical practitioners to easily gather data regarding platelet indices, such as platelet count, mean platelet volume (MPV), and PCT. Increased platelet activation and aggregation were reported to be closely associated with cardiovascular complications [19]. The average size of platelets is described as mean platelet volume. Larger platelets have been found to be biologically more active, and their prothrombotic properties are more powerful. Platelets were also reported to have a significant role in the pathogenesis, morbidity, and mortality of acute coronary syndromes [20]. In another study, the relationship between MPV and angiographic severity of coronary artery disease was investigated, and a positive correlation between them was found [19]. Cay *et al.* documented elevated MPV in patients with acute coronary syndrome and CSX [21]. In another study by Demirkol *et al.* [22] three groups of patients were studied, namely the CSX group, the coronary artery disease group and the normal coronary artery group, to compare the MVP values. The MVP values were significantly higher in the CSX and coronary artery disease groups than those of the control group.

Plateletcrit is a cardiovascular disease marker which is not commonly used; however, it has a great advantage of providing more comprehensive data about total platelet mass. Plateletcrit could be defined as the percentage of blood volume occupied by platelets, and it is the product of the platelet count and the mean platelet volume [23]. In this sense, plateletcrit gives similar data to the hematocrit [23]. In a study of patients with chronic inflammatory diseases, PCT was shown to correlate with CRP, an inflammatory marker [24]. Furthermore, PCT values in patients with coronary slow flow were shown to be an independent predictor [25]. There were also various studies revealing the relationship between MPV, which reflects platelet function and activity, and CSX [21, 22]. However, no research study in the field has investigated the relationship between PCT, which reflects total platelet mass, and CSX. Therefore, in the current study, we investigated the relationship between PCT and total platelet count, and CSX. In the CSX group, PCT and total platelet counts were significantly higher than those of the control group. The implications of our results could be stated in two parts; PCT might have a role in predicting the prognosis of cardiac syndrome X, and PCT has a relation to inflammation.

The fact that we found elevated PCT values in the current study might help better understand the pathogenesis of CSX. It should also be highlighted that PCT is a readily available marker, and therefore it may be valuable in predicting patients with CSX.

The main limitation of our study was the small sample size. Another limitation was the use of the hyperventilation test to exclude patients with the possibility of underlying coronary artery spasm in patients with CSX. However, the ergonovine test would have been the ideal method for this task. Also, coronary flow reserve measurement using Doppler wire and intravascular ultrasound are two invasive methods that could be used in the diagnosis of microvascular disease and exclusion of atheromatous plaques on the coronary vessel wall, respectively. Positron emission tomography might be used for detection of abnormalities in the coronary vasomotor functions caused by microvascular disease and to measure the coronary flow reserve. Moreover, perfusion abnormalities caused by coronary microvascular disease could be reliably detected by contrast stress echocardiography and cardiac magnetic resonance, which are non-invasive assessments. None of these tests were performed in our study subjects, who were assessed retrospectively in this study.

Conclusions

We suggest that high PCT is associated with presence of CSX in patients with normal coronary arteries. As we consider that PCT is a parameter of routine complete blood count which does not require any additional ex-

pense, it may be useful for encouragement of patients with high PCT and normal coronary arteries for stricter life style modifications and application of primary prevention recommendations. Further large-scale, multi-center, prospective studies are needed to clarify the association between PCT level and cardiac syndrome X.

Conflict of interest

The authors declare no conflicts of interest.

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