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ORIGINAL RESEARCH

The Relationship Between the Neutrophil to Lymphocyte Ratio, The Platelet to Lymphocyte Ratio, and Cardiac Syndrome X

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Objective: This study aims to investigate the relationship between the neutrophil to lymphocyte ratio (NLR), the platelet to lymphocyte ratio (PLR), and cardiac syndrome X (CSX).

Methods: A total of 102 patients with CSX who were hospitalized in the Cardiology Department of our hospital from December 2018 to December 2020 were enrolled in the CSX group, and 102 subjects who underwent physical examinations during the same period were included in the control group. An automatic blood cell analyzer was adopted to detect the neutrophil count (NC), lymphocyte count (LC), and number of platelets (PLT) in the whole blood of the subjects in both groups, and the NLR and PLR were calculated. Electrocardiography was conducted on the subjects in both groups to detect whether any abnormality existed in the ST segment. The receiver operating curve (ROC) was used to evaluate the diagnostic value of each indicator of CSX, and multivariate logistic regression analysis was adopted for the analysis of the influencing factors.

Results: No significant differences existed in age, gender, smoking history, or family history of diabetes mellitus, hypertension, and tumors between the two groups ($p > 0.05$). When compared with the control group, the NC, PLT, NLR, PLR, and rate of abnormality of the ST segment on the electrocardiogram were significantly higher, and the LC was significantly lower in the CSX group ($p < 0.05$). Multivariate logistic regression analysis showed that the ST-segment abnormality (3.95 [2.10~7.41]; NLR > 2.21, 3.46 [1.87~6.39]; and PLR > 119.77, 3.66 [1.99~6.73]) was a correlated risk factor for the occurrence of CSX ($p < 0.05$).

Conclusion: Both the NLR and PLR in patients with CSX were significantly elevated, and both have a certain predictive value for the occurrence of CSX and are expected to be effective biomarkers for CSX.

Keywords: cardiac syndrome X, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, correlation analysis, inflammation

Introduction

Cardiac Syndrome X (CSX), also known as microvascular angina pectoris, is characterized by no typical exercise-induced angina, ST-segment changes during an exercise stress test, objective ischemia recorded on myocardial perfusion imaging, or epicardial coronary artery stenosis or vasospasm.[1] Currently, various pathophysiological mechanisms have been proposed for CSX, including endothelial dysfunction, altered autonomic status, and vascular inflammation, but the exact mechanism remains unclear.[2] Previously, CSX was considered a benign condition, but recent studies have shown that it is correlated with persistent chest pain, decreased quality of life, angiographic recurrence, and increased cardiovascular morbidity and mortality.[3] Although long-term survival is generally high in patients with CSX, mortality may increase in those with an ischemic response during exercise.[4]

Inflammation plays a key role in the development and progression of cardiovascular disease. The neutrophil to lymphocyte ratio (NLR) has been introduced as a marker of inflammation in various pathological conditions, including diabetes, thyroiditis, ulcerative colitis, functional bowel diseases, Covid-19 infection, thyroid conditions, and cancers,[5–11] and it has recently emerged as a potential marker in the identification of inflammation in cardiac and non-cardiac

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disease.[12] Platelets are also thought to play an important role in the pathogenesis of atherosclerosis.[13] The platelet to lymphocyte ratio (PLR) is also associated with many disorders, such as diabetes, malignant thyroid nodules, irritable bowel syndrome, Covid-19 infection, and thyroid conditions.[10,14–16] It is also correlated with morbidity in patients with acute myocardial infarction.[17] The NLR and PLR can be cost-effective predictors of inflammation and cardiovascular complications.[18] However, the changes in and clinical value of the NLR and PLR in CSX have not been reported.

In the present study, the NLR and PLR, which are correlated indicators for reflecting the degree of inflammation in an organism, were selected as observation indicators to explore their changes in and diagnostic value for CSX to provide a reference for the clinical prevention and treatment of CSX.

Materials and Methods

Study Subjects

A total of 102 patients with CSX including 58 males and 44 females aged 35–83 y (61.25 ± 12.17 y) who were hospitalized in our Cardiology Department from December 2018 to December 2020 were selected as the study subjects (CSX group). The coronary angiography of the CSX group showed no vascular stenosis. Another 102 subjects with no previous history of allergy including 61 males and 41 females aged 34–82 y (61.03 ± 11.92 y) who underwent healthy physical examinations were enrolled in the control group. There were no significant differences in age and gender between the two groups ($p > 0.05$), and the data were comparable. Informed consent was obtained from the patients and their families, and the study was approved by the Medical Ethics Committee of the Hebei Provincial People's Hospital.

Inclusion and Exclusion Criteria

(1) Inclusion criteria for patients with CSX: (a) met the diagnostic criteria for CSX,[19] which are typical symptoms of exertional angina pectoris with positive exercise plate test results and no cavity stenosis or irregular wall lesions on the coronary angiography together with the exclusion of a coronary spasm and (b) complete clinical data.

(2) Exclusion criteria: (a) other types of heart disease, such as angina pectoris; (b) severe cardiac, cerebral, pulmonary, renal, or other vital organ dysfunction; (c) malignant tumors; (d) other disorders that may affect NLR or PLR, such as diabetes, thyroiditis, ulcerative colitis, functional bowel diseases, Covid-19 infection, and thyroid conditions; and (e) lost during follow-up.

Electrocardiography Detection

Electrocardiography was performed when the patient complained of precordial discomfort. An electrocardiograph (Shenzhen Ribbon Precision Instruments Co., Ltd.) was used to detect abnormal changes in the ST segment of the study subjects before admission, including elevation, depression, extension, and shortening.

Liver and Kidney Function Index, Neutrophil and Lymphocyte Count, and Platelet Assay

Early on the day of hospitalization, 6 mL of fasting peripheral venous blood (3 mL in a non-anticoagulant tube and 3 mL in an ethylenediaminetetraacetic acid anticoagulant tube) was taken from the subjects. Serum creatinine, alanine aminotransferase, aspartate aminotransferase, triglyceride, whole blood neutrophil count (NC), lymphocyte count (LC) and platelet count (PLT) numbers in CSX group and control group were measured by an AU automatic biochemical analyzer (Bio-Rad Laboratories, Hercules, CA) and automatic blood cell analyzer (Bio-Rad Laboratories) The following equations were adopted to calculate the NLR and PLR: NLR = NC ÷ LC and PLR = PLT ÷ LC.

Statistical Analysis

The SPSS 23.0 software was adopted for the input and analysis of all data. The Shapiro–Wilk test was used to determine the normality of the data. The normally distributed continuous data were described as mean ± standard deviation ($\overline{x} \pm s$) and tested using the *t*-test. The non- normally distributed continuous data were expressed as median and interquartile range (M [Q1, Q3])

and compared using the Mann–Whitney *U*-test. The countable data were expressed as a number (%) and tested using the chi-squared test. The receiver operating curve (ROC) was used to assess the diagnostic value of each indicator of CSX, and logistic regression analysis was adopted for risk factor analysis. $P < 0.05$ was considered to be statistically significant.

Results

Comparison of the General Characteristics

A total of 204 study subjects were included in the present study, 102 in the CSX group and 102 in the control group. No significant differences existed between the CSX and the control groups in terms of age; gender; smoking history; or family history of diabetes mellitus, hypertension, and tumor ($p > 0.05$; see Table 1).

Comparison of the Electrocardiogram Results Between the Two Groups

When compared with the electrocardiogram (ECG) results of the control group, the rate of ST-segment abnormality in the ECG results of the CSX group was significantly higher ($p < 0.05$; see Table 2).

Table 1 Comparison of General Data Between the Two Groups[n (%)]

Items	CSX Group	Control Group	t/χ^2	*p*-value
Number of cases	102	102		
Age (Years, $\bar{x} \pm s$)	61.25±12.17	61.03±11.92	0.611	0.265
Gender [No.(%)]			0.182	0.670
Male	58(56.86%)	61(59.80%)		
Female	44(43.14%)	41(40.20%)		
Smoking [No.(%)]			0.314	0.575
Yes	52(50.98%)	48(47.06%)		
No	50(49.02%)	54(52.94%)		
Diabetes [No.(%)]			0.522	0.470
Yes	11(10.78%)	8(7.84%)		
No	91(89.22%)	94(92.16%)		
Hypertension [No.(%)]			1.700	0.192
Yes	15(14.71%)	9(8.82%)		
No	87(85.29%)	93(91.18%)		
Family history of cancer [No.(%)]			0.578	0.447
Yes	10(9.80%)	7(6.86%)		
No	92(90.20%)	95(93.14%)		
Serum creatinine (μmol/l, $\bar{x} \pm s$)	71.53±6.21	72.24±6.34	0.808	0.420
Alanine aminotransferase (U/L,$\bar{x} \pm s$)	21.51±1.92	21.93±1.87	1.583	0.115
Triglyceride (mmol/l, $\bar{x} \pm s$)	1.21±0.11	1.23±0.12	1.241	0.216

Abbreviation: CSX, cardiac syndrome X.

Table 2 Comparison of ECG Results Between the Two Groups[n (%)]

Group	Number of Cases (n)	ST-Segment Abnormality	ST Segment Normal
CSX Group	102	43 (42.16)	59 (57.84)
Control group	102	7 (6.86)	95 (93.14)
χ^2		34.336	
p-value		<0.001	

Abbreviations: ECG, electrocardiograph; CSX, cardiac syndrome X.

Table 3 Comparison of NC, LC, PLT, NLR and PLR in Peripheral Blood Between the Two Groups ($\bar{x} \pm s$)

Group	Number of Cases (n)	NC (10^9/L, $\bar{x}\pm s$)	LC (10^9/L, $\bar{x}\pm s$)	PLT (10^9/L, $\bar{x}\pm s$)	NLR [M (Q1, Q3)]	PLR [M (Q1, Q3)]
CSX Group	102	4.08±0.92	1.85±0.34	221.58±33.22	2.22 (1.74, 2.80)	117.19 (104.07, 145.01)
Control group	102	3.15±0.82	2.19±0.39	189.51±32.23	1.41 (1.07, 1.77)	86.76 (73.68, 101.82)
t/*z*		5.651	2.403	7.842	−8.177	−8.505
p-value		<0.001	0.029	<0.001	<0.001	<0.001

Abbreviations: NC, neutrophil count; LC, lymphocyte count; PLT, platelets; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio. CSX, cardiac syndrome X.

The Comparison of the NC, LC, PLT, NLR, and PLR in the Peripheral Blood Between the Two Groups

When compared with the control group, the NC, PLT, NLR, and PLR were significantly higher and the LC was significantly lower in the CSX group ($p < 0.05$; see Table 3).

Analysis of Diagnostic Value

The results of the ROC analysis showed that the area under the curve for the NLR and PLR was 0.727 and 0.887, respectively. The sensitivity of the NLR and PLR for the diagnosis of CSX was 75.1% and 88.7%, and the specificity was 72.5% and 85.2%, respectively (see Figure 1).

Multivariate Logistic Regression Analysis of the Influencing Factors of CSX

Multivariate logistic regression analysis was conducted using the occurrence of CSX as the dependent variable (no = 0 and yes = 1) and the variables that were significant in the univariate analysis as the independent variables. The results showed that ST-segment abnormalities, NLR > 2.21, and PLR > 119.77 were risk factors correlated with the occurrence of CSX ($p < 0.05$; see Table 4).

Discussion

The present study included a total of 204 study subjects (102 patients with CSX and 102 healthy subjects). The existing research data have shown that coronary heart disease, hypertension, and other diseases are closely correlated with the onset of

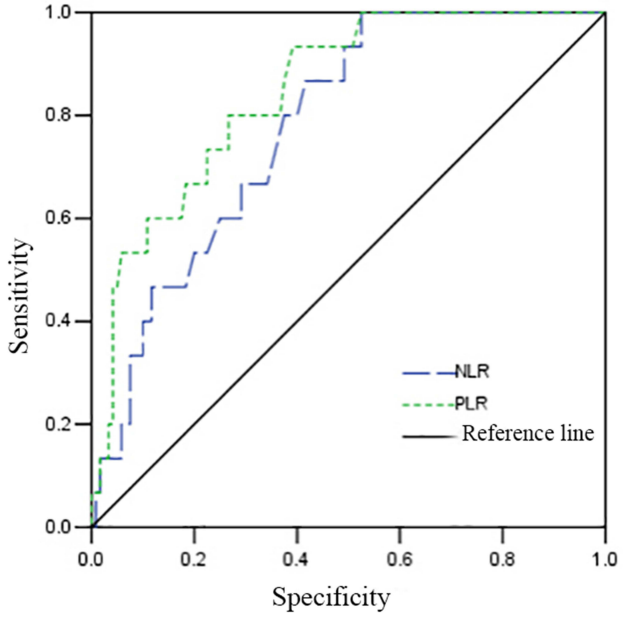

Figure 1 The receiver operating curve for the diagnosis of cardiac syndrome X by each indicator.

Table 4 Multivariate Logistic Regression Analysis of CSX Influencing Factors

Independent Variable	Regression Coefficient	Standard Error	Wald χ^2	*p*-value	OR (95% CI)
Electrocardiograph (Control group = NORMAL ST segment)	1.373	0.321	23.125	<0.001*	3.95 (2.10~7.41)
NLR (Reference group = below 2.21)	1.241	0.313	19.102	<0.001*	3.46 (1.87~6.39)
PLR (Control group = less than 119.77)	1.297	0.311	20.028	<0.001*	3.66 (1.99~6.73)

Note: *P<0.05.
Abbreviations: CSX, cardiac syndrome X; OR, odd ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

CSX and are risk factors for CSX. In this study, in order to ensure the reliability and comparability of the results, we performed initial tests on the two groups of subjects to identify differences in general demographic characteristics. No statistically significant differences were found in age, gender, smoking habits, the presence of diabetes or high blood pressure, family history of tumor, or liver and kidney function indexes.

The ECG is a routine examination that is performed when patients are admitted to hospital, and abnormal ECG results coupled with abnormalities in the related indicators in the body can reflect the cardiac health status of the patient. The 12-lead ECG is the most common cardiac test, and the results are of great importance for patients with cardiac symptoms, including chest pain, dyspnea, palpitations, and syncope.[20] In the present study, all the study subjects were examined using an electrocardiograph, and it was found that the rate of ST-segment abnormalities was significantly higher in the CSX group than in the control group, indicating that the occurrence of CSX may lead to both abnormalities in the ECG results and chest pain.

The NLR is an inexpensive indicator of systemic inflammation, is correlated with the prognosis of various diseases, eg, acute coronary syndrome and acute pancreatitis, and is useful in predicting subclinical atherosclerosis in patients with psoriasis.[21–23] The NLR can be used to predict survival after coronary intervention in non-ST-segment elevation and ST-segment elevation myocardial infarction.[24,25] Several reports have suggested the role of inflammation in the regulation of coronary microvascular responses in patients with CSX.[26] In addition, an elevated NLR may be correlated with persistent inflammation and asymptomatic atherosclerosis in the pathophysiology of CSX, which is strongly confirmed by the results of the present study.[27] The PLR has been considered as another indicator of systemic inflammation due to growing evidence that platelets play an early role in the process of inflammation and tissue repair,[28] although it has been studied less frequently than the NLR.[29] Platelets work closely with all types of leukocytes, and chemotactic substances secreted by the activated platelets, accelerating the binding of leukocytes to the endothelial surface and causing subsequent extravasation, and they may affect the inflammatory response of leukocytes in both a stimulatory and an inhibitory manner. Chronic low-grade inflammation may lead to an elevated PLR, and an increase in the PLR may be a sign of ongoing inflammation, which ultimately increases the risk of various diseases, including coronary artery disease, solid organ tumors, and autoimmune diseases.[30] Based on the above studies, we speculate that the NLR and PLR may have a certain application value in CSX diseases. In the present study, an automatic blood cell analyzer was used to detect the NC, LC, and PLT in all subjects, and the NLR and PLR were subsequently calculated. When compared with the control group, the NC, PLT, NLR, and PLR were significantly higher and the LC was significantly lower in the CSX group, suggesting that the incidence of inflammatory response was significantly higher in the CSX group than in the control group and that the occurrence of CSX may lead to an abnormal inflammatory response in the organism, which would result in a disturbance of the balance of the NC, PLT, and LC, thus causing an imbalance in the NLR and PLR. This also verifies that the development of CSX may be closely correlated with an inflammatory response in the organism. In the present study, the diagnostic value of each indicator was analyzed using an ROC, and the results of the ROC analysis showed that both the NLR and PLR have excellent diagnostic value for CSX. In addition, multivariate logistic regression analysis was used to analyze the influencing factors of CSX, and it was found that ST-segment abnormalities, NLR > 2.21, and PLR > 119.77 are risk factors correlated with the occurrence of CSX. Therefore, close attention should be paid to patients with these indicators to prevent the development of CSX. Although NLR and PLR are not included in the current diagnostic indicators for CSX, in the early stage of the disease, abnormal changes in blood indicators often

precede the appearance of clinical symptoms, so NLR and PLR have the potential to become auxiliary diagnostic indicators for CSX.

Some limitations existed in the present study. First, the limited sample size led to some discrepancies in the comparison of disease history and other information between patients in the present study and existing studies. Second, since the present study verified the existence of a relationship between the pathogenesis of CSX and inflammation, the pathogenesis of CSX could be explored in terms of immunity in patients.

Conclusion

NLR and PLR were abnormally elevated in the peripheral blood of patients with CSX. The abnormal elevation of these parameters may indicate dysregulated inflammatory responses in CSX. Therefore, inhibiting excessive inflammatory response may be a therapeutic strategy for the clinical treatment of CSX. Whether these parameters are related to the clinical prognosis of CSX patients will be analyzed in future studies.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Hebei General Hospital. A written informed consent was obtained from all participants.

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Disclosure

All authors declare that the work is original and has not been submitted or published elsewhere. None of the authors have any financial disclosure or conflicts of interest.

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