International Journal of General Medicine

Dovepress

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ORIGINAL RESEARCH

Association Between Systemic Inflammation Response Index and Slow Coronary Flow Phenomenon in Patients with Ischemia and No Obstructive Coronary Arteries

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Background: Inflammation plays a key role in the pathogenesis of slow coronary flow phenomenon (SCFP). SCFP is a condition that can complicate the management of ischemia and no obstructive coronary arteries (INOCA), making it essential to identify reliable predictors. Although the systemic inflammation response index (SIRI) has been proven to relate to various cardiovascular diseases. However, the predictive value of SIRI for SCFP in patients with INOCA remains unclear.

Methods: A total of 1422 patients with INOCA were consecutively included in this study. 89 individuals were diagnosed with SCFP (the SCFP group). A 1:2 age- and -sex-matched patients with INOCA and normal blood flow were selected as the control group (n=178). Plasma neutrophil, monocyte, and lymphocyte counts were collected so as to determine the value of SIRI.

Results: Patients with SCFP had an elevated level of body mass index (BMI) and an increased incidence of smoking and diabetes. The SIRI was significantly higher in the SCFP group than in the controls (2.3±1.3 vs 1.8±1.3, p=0.002). The SIRI increased as the number of coronary arteries involved in the SCFP increased. Univariate analyses showed that BMI, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and SIRI were associated with SCFP. Multivariate logistic regression analysis revealed that BMI and SIRI were independent predictors of SCFP occurrence. The ROC curve showed that when the SIRI was > 1.140, the sensitivity and specificity were 87.6% and 60.1%, respectively, and the area under the ROC curve (AUC) was 0.644 (95% CI: 0.578–0.710, P < 0.001).

Conclusion: The findings demonstrated that an increased SIRI may have a potential role in distinguishing SCFP in patients with INOCA. SIRI could improve the predictive value of SCFP compared to neutrophils, monocytes, and lymphocytes alone.

Keywords: systemic inflammation response index, slow coronary flow phenomenon, ischemia and no obstructive coronary arteries, predictors

Introduction

Coronary angiography (CAG) is the gold standard for diagnosing coronary artery disease and is widely performed in patients with chest pain and evidence of ischemia. Approximately 50% of patients with chest pain and objective evidence of myocardial ischemia have no obstructive coronary arteries (< 50% stenosis).[1,2] This chest pain syndrome, termed ischemia with no obstructive coronary arteries (INOCA), has been suggested to be associated with a poor prognosis during long-term follow-up.[1,2] Although there is considerable heterogeneity in the presentation of INOCA, accumulating evidences suggest that SCFP may play a key role in the occurrence of it.[3] SCFP was first reported by Tambe in 1972 and is characterized by delayed distal vessel opacification despite the absence of obstructive coronary artery disease.[4] Unlike cardiac X syndrome (CXS), are the most typical clinical manifestation of SCFP was recurrent episodes of angina at rest.[5] Moreover, 20% of patients had repeated emergency room visits or were readmitted to the CCU because of chest pain resembling acute coronary syndrome (ACS).[5,6] Although the pathogenesis and clinical predictors of SCFP have not been

Received: 5 June 2024
Accepted: 7 September 2024
Published: 13 September 2024

fully elucidated, accumulating evidence has demonstrated that local or systemic inflammation plays a key role in the development of SCFP.[6–8]

Recently, the systemic inflammation response index (SIRI) has emerged as a new biomarker based on neutrophil, monocyte, and lymphocyte count.[9] SIRI was first reported in 2016 by Chinese researchers, who suggested that it could be used as a predictor for the survival of patients with pancreatic adenocarcinomas who received chemotherapy.[9] In the subsequent decade, accumulating evidence demonstrated that SIRI are associated with various cardiovascular and cerebrovascular diseases. SIRI is associated with major adverse cardiovascular events (MACE) in patients with non-ST-segment elevation myocardial infarction (NSTEMI),[10] ACS undergoing PCI[11] and ischemic heart failure following PCI[12] Moreover, a recent study from China suggested that SIRI was associated with the presence of MACE in patients with myocardial infarction with no obstructive coronary arteries (MINOCA)[13] In addition, an elevated SIRI is associated with a higher risk of mortality and sepsis, as well as higher stroke severity[14] An increased SIRI was also associated with the risk of stroke and its subtypes in elderly patients with hypertension[15] However, few studies have evaluated the possible relationship between the SIRI and SCFP in patients with INOCA. Therefore, in this study, we aimed to investigate the association between SIRI and SCFP in INOCA to identify high-risk populations and formulate optimal management strategies.

Methods

Study Population

The angiographic records of 1422 individuals with INOCA who underwent CAG because of chest tightness or chest pain were retrospectively analyzed between June 2021 to March 2024. A total of 89 patients had SCFP and were divided into the SCFP group. Meanwhile, 1:2 age- and sex-matched patients (n=178) with normal blood flow were selected as the controls. We identified all the patients with SCFP one by one, and then selected the age-and-sex matched controls. If there are only two age-and-sex matched controls for a specific SCFP patients, then these two patients are chosen as controls for this SCFP patients. If there are more than 2 age-and-sex matched controls, these individuals were numbered. The random sampling method was used for the selection of the controls. The Thrombolysis in Myocardial Infarction frame count (TFC) was used to assess blood velocity,[14] which was recorded by two independent interventional cardiologists. The exclusion criteria were as follows: 1) previous ACS, PCI, or CABG; 2) local or systemic inflammatory diseases; 3) autoimmune diseases; 4) allergic diseases; 5) moderate to severe valvular heart disease; 6) cardiomyopathy or congestive heart failure; 7) coronary artery aneurysms; 8) coronary spasm or dissection; 9) severe liver or renal failure; 10) chronic obstructive pulmonary disease; 11) peripheral vascular disease; 12) autoimmune disease; 13) hematologic disorders; 14) malnutrition; and 15) malignancy.[6,8] This study was conducted in accordance with the ethical standards of the Helsinki Declaration. Informed consent was obtained from all the included patients.

Coronary Angiography

CAG was performed at the Luohu People's Hospital by experienced interventional cardiologists using the standard Judkins technique. The right radial artery was the preferred access for CAG. TFC was calculated as the last frame count minus the first frame count.[16] The first frame was considered to be an antegrade contrast agent that filled 70% of the proximal part of the vessel. The last frame was defined as the moment when the contrast reached the mustache area for the left anterior descending artery (LAD), bifurcation segment with the farthest distance for the left circumflex (LCX), and first branch of the posterolateral artery for the right coronary artery (RCA). Because the LAD is longer than the LCX and RCA, the TFC is divided by 1.7 to acquire a corrected TFC (cTFC).[14] The cut off value of TFC for the diagnosis of SCFP were 36.2±2.6 for the LAD (21.1±1.5 cTFC), 22.2±4.1 for the LCX, and 20.4±3.1 for the RCA.[16] SCFP was diagnosed when the TFC of any of the three main vessels exceeded the threshold.[6,8] The mean TFC (mTFC) was calculated by dividing the sum of the TFC of the three main vessels by three.[6,8]

Laboratory Measurements

Laboratory indicators, including routine blood tests, were tested in the core laboratory of Luohu People's Hospital using blood from the antecubital vein after 12 hours of fasting prior to CAG. Total blood count was measured in blood samples collected in di/tripotassium EDTA tubes using an automatic blood counter within two hours after venipuncture. The SIRI was calculated as (neutrophil count)×(monocyte count)/(lymphocyte count).[9–13]

Statistical Analysis

SPSS software (version 20.0) was used for data analysis. Categorical variables are presented as rates or percentages and compared using the chi-square or Fisher's exact test. Continuous variables are displayed as mean±standard deviation or median and 25th-75th percentile values, which were analyzed using unpaired *t*-test or 1-way analysis of variance (ANOVA), as applicable. The potential risk factors that may be associated with SCFP were shown in Table 1, which served as the variables in the univariate analysis. The indicators with P<0.10 in the univariate analysis were further added into the multivariate analysis to determine whether the independent predictors for SCFP. The receiver operating characteristic (ROC) curve was used to identify the sensitivity and specificity of the independent predictors of CSFP was 2-sided P<0.05 was considered statistically significant.

Results

Baseline and Clinical Characteristics

Age, sex, hypertension, and medication on admission were comparable between the two groups (p>0.05) (Table 1). The body mass index (BMI) and incidence of current smoking and diabetes were higher in the SCFP group than in the control group (p < 0.05) (Table 1).

Laboratory Parameters of the Two Groups

The laboratory parameters of the two groups are listed in Table 2. Patients with SCFP tended to have higher white blood cell, neutrophil, monocyte, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and SIRI values (p < 0.05) (Table 2). No statistical differences were observed in other indicators, including lymphocytes, hemoglobin, platelet, albumin, creatinine, uric acid, fasting blood glucose, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and hemoglobin A1c (p>0.05) (Table 2).

Table 1 Baseline Clinical Characteristics of the Two Groups

	SCFP Group (n=89)	Control Group (n=178)	*P* value
Demographics			
Age (years)	59.7±7.4	59.7±7.4	1
Males, n (%)	69(77.5)	138(77.5)	1
BMI, (kg/m^2)	25.1±3.1	24.3±2.4	0.02
Comorbidities			
Current smoker, n (%)	47(52.8)	66(37.1)	0.018
Hypertension, n (%)	49(55.1)	87(48.9)	0.365
Diabetes mellitus, n (%)	34(38.2)	43(24.2)	0.022
Medications			
ACEI/ARB/ARNI, n (%)	21(23.6)	45(25.3)	0.881
Beta-blocker, n (%)	22(24.7)	50(28.1)	0.661
Calcium canal blocker, n (%)	27(30.3)	50(28.1)	0.775
Aspirin, n (%)	28(31.8)	52(29.2)	0.672
Clopidogrel, n (%)	29(32.6)	55(30.9)	0.782
Statin, n (%)	27(30.3)	60(33.7)	0.678
Nitrates, n (%)	24(27.0)	35(19.7)	0.211

Abbreviations: BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor blocker and neprilysin inhibitor.

Table 2 Baseline Laboratory Characteristics of the Two Groups

	SCFP Group (n=89)	Control Group (n=178)	*P* value
White blood cell, (10^9/L)	7.7±1.4	7.0±1.7	0.002
Neutrophil, (10^9/L)	5.7±1.4	5.0±1.6	<0.001
Lymphocyte, (10^9/L)	1.4±0.5	1.5±0.6	0.095
Monocytes, (10^9/L)	0.5±0.2	0.4±0.2	0.030
Hemoglobin, g/L	139.6±6.0	139.2±5.4	0.541
Platelet, (10^9/L)	198.7±63.3	199.3±66.7	0.942
Albumin, g/L	36.9±5.6	37.7±3.2	0.110
Creatinine, mmol/L	99.1±80.0	84.3±57.9	0.085
Uric acid, mmol/L	344.4±114.1	367.9±232.0	0.367
Fasting blood glucose, mmol/L	6.2±2.4	5.9±2.0	0.311
TC, mmol/L	4.6±0.9	4.3±0.9	0.029
TG, mmol/L	1.4±0.9	1.4±0.7	0.782
HDL-C, mmol/L	1.2±0.8	1.1±0.6	0.329
LDL-C, mmol/L	3.0±0.7	2.8±0.7	0.041
HbA1c, %	6.0±1.2	6.1±1.4	0.694
SIRI	2.3±1.3	1.8±1.3	0.002

Abbreviations: TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c; SIRI, systemic inflammation response index.

Angiographic Characteristics of the Two Groups

The angiographic characteristics of patients are presented in Table 3. 89 patients had SCFP in at least one coronary artery (27.0% in one vessel, 39.3% in two vessels and 33.7% in three vessels). Among the coronaries involved, 70.8% were in the LAD, 53.9% in the LCX, and 82.0% in the RCA. Thus, we discovered that the two involved vessels were as common as the three vessels. Moreover, the RCA is mostly affected by SCFP. The TFC and mTFC were significantly higher in the SCFP group than in the control group ($p < 0.05$) (Table 3).

Predictors of SCFP

Univariate analyses were performed for BMI, smoking, diabetes mellitus, TC, LDL-C, and SIRI. As shown in Table 4, BMI, TC, LDL-C, and SIRI were associated with SCFP. Multivariate logistic analysis revealed that BMI and SIRI were independent predictors of SCFP (Table 4). Moreover, the SIRI increased as the number of vessels involved in SCFP increased (Figure 1). The ROC curve was used to determine the predictive value of the risk factors, which demonstrates

Table 3 Angiographical Characteristics of the Patients with SCFP

	SCFP Group (n=89)	Control Group (n=178)	*P* value
TFC(LAD)	37.1±3.8	27.6±3.2	<0.001
TFC(LCX)	22.1±4.3	16.9±2.1	<0.001
TFC(RCA)	24.7±3.9	15.7±2.0	<0.001
mTFC	28.0±2.9	20.0±2.0	<0.001
Vessels Involvement			
One (%)	24(27.0)		
Two (%)	35(39.3)		
Three (%)	30(33.7)		
Coronary Artery Involvement			
LAD(n, %)	63(70.8)		
LCX(n, %)	48(53.9)		
RCA(n, %)	73(82.0)		

Abbreviations: TFC, TIMI frame count; mTFC, mean TIMI frame count; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 4 Relationship Between the Mean TIMI Frame Count and Laboratory Parameters

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
BMI	1.119	1.016–1.233	0.022	1.158	1.046–1.282	0.005
Smoking	1.682	0.924–2.521	0.137			
Diabetes mellitus	1.785	0.872–3.581	0.185			
TC	1.365	1.029–1.811	0.031	1.598	0.919–2.780	0.097
LDL-C	1.451	1.013–2.078	0.042	0.993	0.499–1.974	0.983
SIRI	1.336	1.101–1.620	0.003	1.426	1.162–1.750	0.001

Abbreviations: BM, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; SIRI, systemic inflammation response index.

that SIRI has a moderate predictive value for SCFP, with the area under the ROC curve (AUC) of 0.644 (95% CI: 0.578–0.710, P < 0.001). Moreover, when the SIRI was > 1.140, the sensitivity and specificity were 87.6% and 60.1%, respectively (Table 5 and Figure 2). The AUC of BMI was 0.580 (95% CI: 0.501–0.658, p=0.031) (Table 5). The combined indicators of BMI and SIRI showed a better predictive value for the presence of SCFP than the indicators alone (Table 5 and Figure 2).

Discussion

This study is the first to discover that SIRI and BMI are independent predictors of SCFP in patients with INOCA. Moreover, the SIRI increased with the number of coronary arteries involved in SCFP. As a new inflammation-based indicator, the SIRI could serve as a promising parameter for the prediction of SCFP in patients with INOCA. To the best of our knowledge, this is the first study to explore the relationship between the SIRI and SCFP.

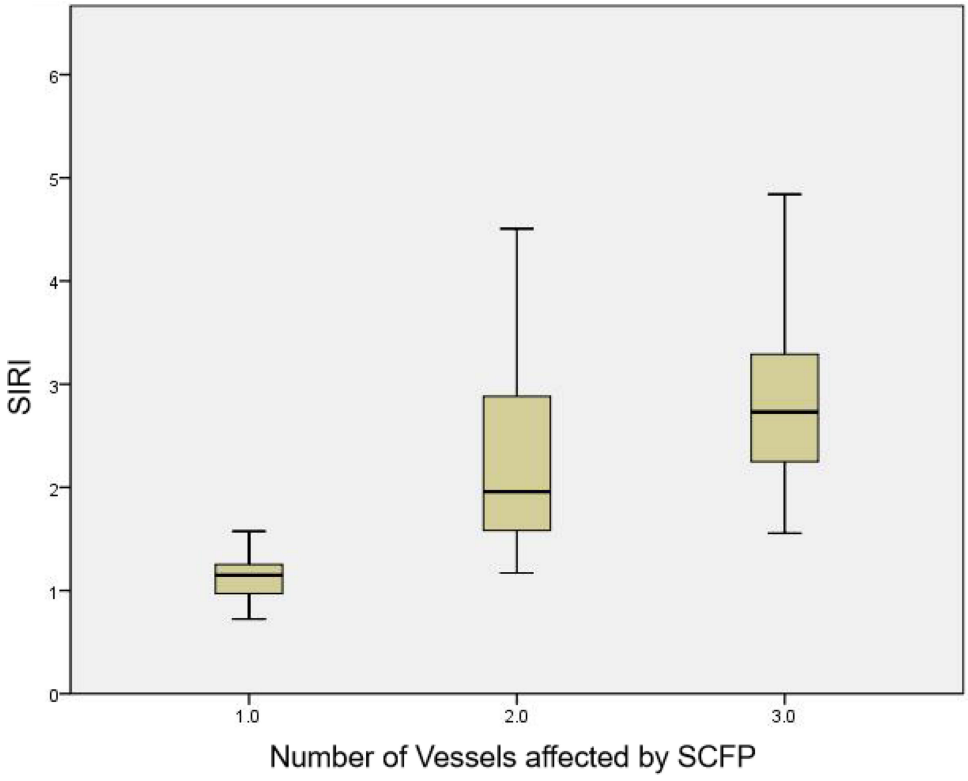

Figure 1 Correlation between the number of vessels affected by SCFP and SIRI.

Table 5 The Predictive Value of the Indicators

	AUC	95% CI	Sensitivity	Specificity	Diagnostic Threshold	p
BMI	0.580	0.501–0.658	0.502	0.831	25.960	0.031
SIRI	0.644	0.578–0.710	0.876	0.601	1.140	<0.001
SIRI+BMI	0.790	0.738–0.842	0.905	0.704	–	<0.001

Abbreviations: BMI, body mass index; SIRI, systemic inflammation response index.

SCFP is an angiographic finding first reported by Tambe et al in 1972.[4] In the earliest days, SCFP was considered as a "benign" angiographic finding. During the past fifty years, with the rapid development in the intra-coronary imaging and functional test, SCFP was considered as an "ominous" disease, which was predisposed to atherosclerosis and obstructive coronary artery disease.[17] Moreover, SCFP is associated with sudden cardiac death due to ventricular arrhythmias[18] and the presence of STEMI.[19] SCFP is quite different from CXS in the following ways: First, SCFP is a predilection among men[20] or is equally distributed between sexes.[21] Second, patients with SCFP tend to be obese[20,22] or more prone to developing metabolic syndrome.[20,22] Another clinical presentation is that patients with SCFP often experience angina attacks at rest or mixed-pattern angina rather than exertional angina on CXS.[23,24] As a result, both stable and unstable angina can be observed in SCFP patients. It was reported that nearly 20% of patients had repeated emergency room visits or were readmitted to the CCU because of chest pain resembling ACS.[5,6] Owing to its complex pathophysiology and varied clinical presentation, SCFP has been suggested as a clinical syndrome called cardiac Y syndrome (CYS,[25] rather than a simple angiographic finding.

Whether traditional cardiovascular risk factors such as hypertension, diabetes, or hyperlipidemia play a role in the development of SCFP remains uncertain. Evidence suggests that hypertension, diabetes, and hyperlipidemia are associated with the presence of SCFP.[26,27] However, no relationship was found in other studies.[6,8,24,25] In this study, we found that SCFP tended to have a higher incidence of diabetes; however, the multivariate logistic regression analysis showed no correlation between them. We suggest that SCFP has a unique pathogenesis, with a complex clinical presentation. Different clinical comorbidities, races, and interactions of various factors may result in different results. Therefore, it is clinically important to explore predictive factors for the presence of SCFP in patients with INOCA.

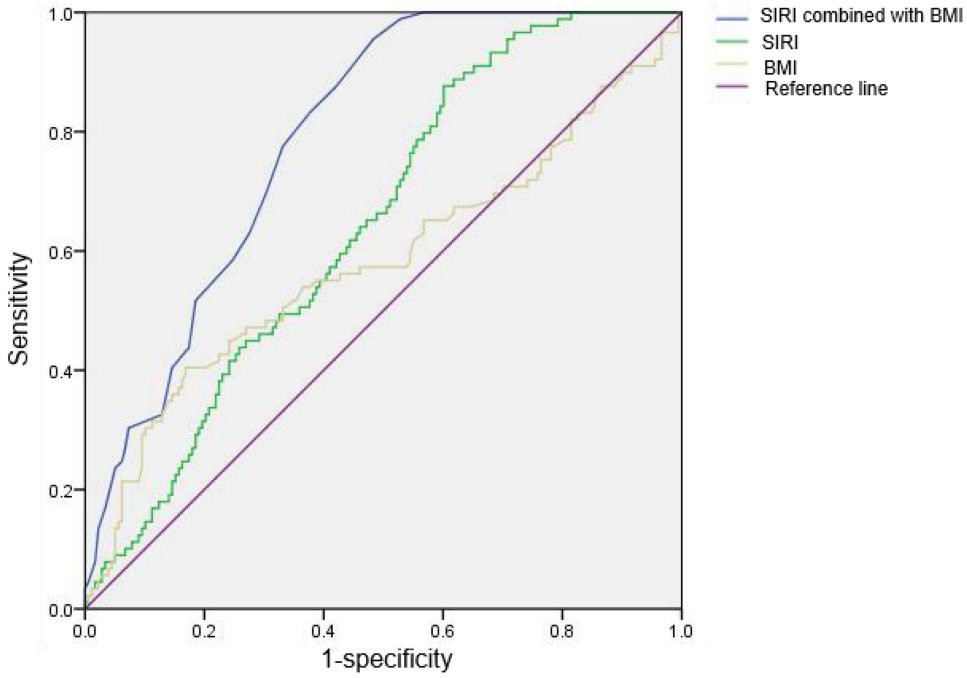

Figure 2 ROC curve showing the predicting value of risk factors for the presence of SCFP.

It is widely accepted that inflammation plays a key role in cardiovascular diseases including atherosclerosis.[28] Meanwhile, it is reported that neutrophils and monocytes are actively involved in the development of atherosclerosis and elevated frequently in atherosclerotic plaques.[29] The evidence was similar for the presence of SCFP. Important indicators of inflammation, such as interleukin-34[30] or serum soluble adhesion molecules, such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1),[31] have been suggested to be related to SCFP. As a novel parameter for inflammation, uric acid to albumin ratio was demonstrated to relate to SCFP and could provide a favourable predictive value for the occurrence of SCFP.[32] Moreover, inflammatory indicators derived from routine blood tests, including neutrophil-to-lymphocyte ratio (NLR),[33] platelet-to-lymphocyte ratio (PLR),[34] eosinophil-to-lymphocyte ratio (ELR),[35] lymphocyte-to-monocyte ratio (LMR),[36] pan-immune-inflammation,[37] and systemic immune-inflammation index (SII)[8] have also been demonstrated to be predictors of the presence of SCFP. The SIRI has been proven to be associated with various diseases as a newly reported indicator for the assessment of inflammation. SIRI is reportedly associated with MACE in patients with NSTEMI,[10] ACS undergoing PCI[11] and ischemic heart failure following PCI.[12] Moreover, a recent study from China suggested that SIRI was associated with MACE in patients with MINOCA.[13] In addition, SIRI has been proven to be related to the severity of coronary artery disease and the presence of ACS.[38] However, to date, no study has investigated the relationship between SIRI and SCFP in INOCA patients. In this study, we discovered that patients with SCFP had a higher SIRI. Multivariate logistic analysis showed that the SIRI was an independent predictor of SCFP in patients with INOCA. We suggest that the mechanism of SIRI results in SCFP is as follows: First, the SIRI combines three parameters: neutrophils, monocytes, and lymphocytes. All parameters showed a relationship with coronary artery disease. Neutrophils and monocytes are actively involved in the development of atherosclerosis and their levels are frequently elevated in atherosclerotic plaques.[29] In addition, lymphocytes hinder atherosclerosis.[39] A higher level of SIRI results from an elevated level of neutrophils and monocytes, or a decreased level of lymphocytes. Therefore, a higher SIRI level may cause SIRI in three ways. SCFP is associated with inflammation and atherosclerosis. SIRI combined with multiple indicators showed a better predictive value for SCFP than a single index alone. These indicators represent different mechanisms leading to SCFP, and there may be a synergistic effect between them. Blood cell counts vary greatly between individuals and races. Therefore, the blood cell count itself could not better reflect the inflammatory status. By using the combined indicators, the SIRI could eliminate individual differences to the maximum extent, thereby providing a better reflection of inflammation. In the clinical practice, SIRI was easily acquired and calculated, which could serve as an indicator for SCFP screening as well as risk stratification. However, the prognostic value of SIRI needs yet to be proved by large scale multicenter studies. Moreover, the influences of SIRI in the treatment of SCFP or INOCA still need further investigation.

Limitations

This study had some limitations. First, this was a single-center study with a small sample size, which could have led to a selection bias. Second, it was an retrospective study. We used multivariate regression analysis to adjust for known confounders and identify the independent predictors of SCFP. However, we could not include all potential factors associated with SCFP, which may have affected the predictive value of the SIRI. Third, we did not include inflammatory indicators, such as C-reactive protein (CRP) or IL-6. Finally, the patients were predominantly male and could not represent the general population. Therefore, our results cannot be extrapolated to the general population. Large-sample, multicenter studies are needed to validate our conclusions.

Conclusion

These findings demonstrate that an increased SIRI may have a potential role in distinguishing SCFP in patients with INOCA. SIRI could improve the predictive value of SCFP compared to neutrophils, monocytes, and lymphocytes alone. In the clinical practice, SIRI was easily acquired and calculated, which could serve as an indicator for SCFP screening as well as risk stratification. However, the prognostic value of SIRI needs yet to be proved by large scale multicenter studies.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available because of further study in this area but are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the ethics committee of Luohu People's Hospital, and all participants provided written informed consent before participation in the study, which was performed in accordance with relevant guidelines and regulations.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no conflict of interest.

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