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ORIGINAL RESEARCH

Neutrophil Percentage to Albumin Ratio as a Predictor for Coronary Slow Flow Phenomenon in Patients with Myocardial Ischemia with No Obstructive Coronary Arteries

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Background: Accumulating evidences suggest that low-grade inflammatory response plays a key role in the pathophysiology of coronary slow flow phenomenon (CSFP). As a new hematological inflammatory indicator, the neutrophil percentage to albumin ratio (NPAR) and its role in the occurrence and development of CSFP remains unclear. In this study, we aimed to investigate the predictive value of NPAR in the presence of CSFP in patients with myocardial ischemia and no obstructive coronary arteries (INOCA).

Methods: In total, 1323 individuals with INOCA were included in this study. 85 patients developed CSFP were included in the CSFP group. 1:2 age-and sex-matched patients were selected from the absence of CSFP, with normal blood flow, as the control group. Clinical characteristics, laboratory parameters, and angiographic findings were compared between groups. NPAR was also calculated to explore its relationship with CSFP.

Results: NPAR was significantly higher in the CSFP patients than in the controls (19.3±2.5 vs 16.7±1.8, p<0.001). The NPAR increased with the number of coronary arteries involved in CSFP. Multivariate logistic regression analysis showed that an elevated NPAR level was an independent predictor of CSFP (OR 1.915, 95% CI 1.612–2.275, P < 0.001). The ROC curve showed that when NPAR was > 17.39, the sensitivity and specificity were 90.6% and 78.8%, respectively, and the area under the ROC curve (AUC) was 0.860 (95% CI: 0.811–0.909, P < 0.001). The AUC of neutrophil percentage was 0.845 (95% CI: 0.794–0.897, p < 0.001), and that of albumin was 0.808 (95% CI: 0.753–0.864, p < 0.001).

Conclusion: Elevated NPAR levels are an independent predictor of CSFP in patients with INOCA. NPAR could improve the predictive value of CSFP compared with neutrophil percentage or albumin ratio alone.

Keywords: neutrophil percentage-to-albumin ratio, coronary slow flow phenomenon, myocardial ischemia with no obstructive coronary arteries, predictors

Introduction

Myocardial ischemia with no obstructive coronary arteries (INOCA) was suggested by Prof. Berry in 2017 and is characterized by symptoms and signs of myocardial ischemia without obvious coronary stenosis (≥50%).[1] INOCA includes various clinical conditions such as microvascular angina, vasospastic angina, and myocardial diseases.[1] As a quite common angiographical finding, coronary slow flow phenomenon (CSFP) is defined as slow blood flow in the three main coronary arteries without obvious coronary stenosis (≥50%).[2] According to the diagnostic criteria for microvascular angina by the International Study Group of Coronary Vasomotor Disorders (COVADIS), CSFP is considered evidence of impaired coronary microvascular circulation. However, the risk factors, predictors, and pathophysiology of CSFP remain unclear. Nevertheless, accumulating evidence suggests that low-grade inflammatory response plays a key role in the pathophysiology of CSFP.[3–6]

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As the classic and most commonly used indicator of acute and chronic inflammation, neutrophils have been shown to be associated with the development of atherosclerosis.[7] A higher neutrophil percentage has also been demonstrated to be an independent predictor of late cardiogenic shock.[8] Plasma albumin plays a key role in systemic and local inflammatory responses. Albumin levels decrease when inflammation developed.[5] Moreover, plasma albumin effectively scavenges free oxygen radicals, which may damage the coronary vascular endothelium.[9] A previous study suggested that lower plasma albumin levels are related to the occurrence of CSFP.[5] Recently, the neutrophil percentage to albumin ratio (NPAR) was suggested as a new indicator for the assessment of systemic and local inflammation.[10] Combined with the plasma albumin and neutrophil percentages, NPAR provides a better reflection of the inflammatory response.[11] Accumulating studies have shown that an increased level of NPAR is related with a higher risk of all cause of mortality in atrial fibrillation,[12] chronic heart failure,[13] acute myocardial infarction (AMI)[14] as well as cardiogenic shock.[15] Elevated levels of NPAR are also independent predictors of free wall rupture in AMI.[16] However, to date, no study has focused on the relationship between the NPAR and CSFP. Therefore, we aimed to investigate the potential role of NPAR in predicting the occurrence of CSFP to improve the identification of high-risk individuals and management of patients with CSFP.

Methods

Study Population

The flowchart of the study is shown in Figure 1. From January 2022 to December 2023, a total of 1323 individuals with INOCA were included in this study. Among them, 85 patients developed CSFP and were divided into the CSFP group. Age-and sex matched 170 controls with normal blood flow were included in the control group. The exclusion criteria are displayed in Figure 1. This study was approved by the Ethics Committee of Luohu People's Hospital, and informed consent was obtained from all patients.

Coronary Angiography

All included patients underwent coronary angiography via the right radial artery using the standard Judkins technique. TIMI frame count (TFC) was used to assess coronary blood flow, which was calculated as the last frame count minus the first frame count.[2] The TFC was assessed and determined by two interventional cardiologists. The first frame count was defined as the contrast agent filling at least 70% of the ostium of the left main or right coronary artery (RCA). The last

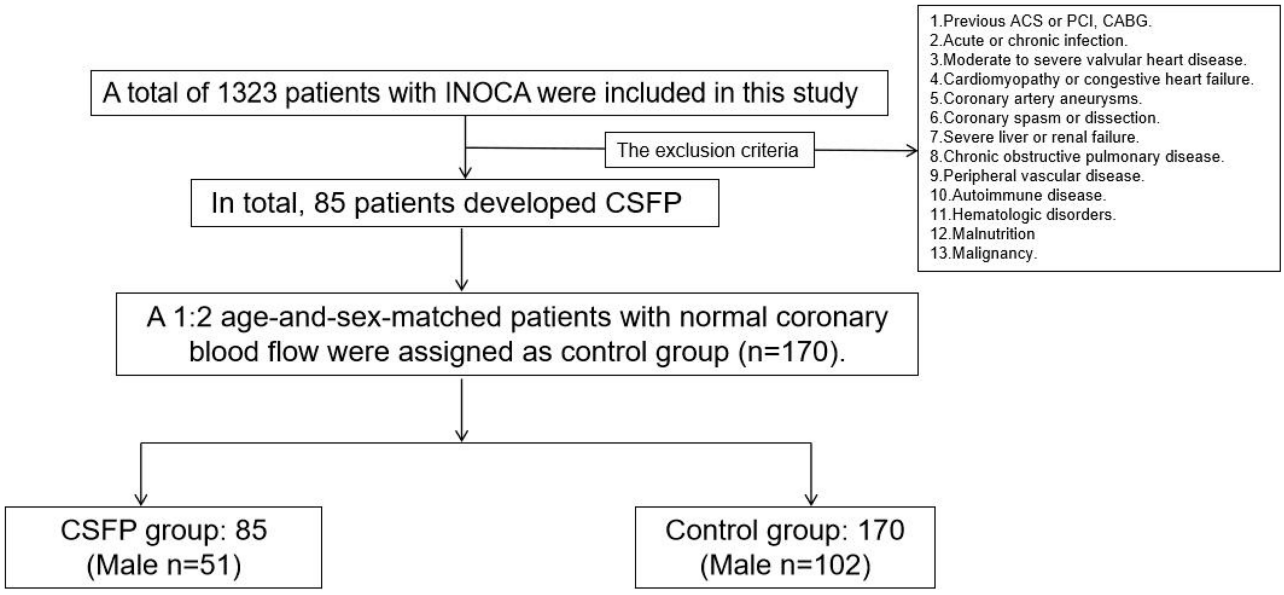

Figure 1 The study flow chart.

frame count was when the contrast agent reached the distal "landmark", which was defined as the distal bifurcation of 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). Since the LAD is longer than the LCX or RCA, the corrected TFC (cTFC) was used to assess coronary blood flow, which was calculated as the TFC divided by 1.7.[17] The TFC was 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.[17] SCFP develops when the TFC was more than 2 standard deviations (SDs) above the threshold values.[18] The mean TFC (mTFC) was determined as the sum of the TFC for the LAD, LCX, and RCA and then divided by 3.[18]

Laboratory Measurements

Blood samples were collected from the median cubital vein after an overnight fast. The samples were tested at the core laboratory of our hospital. All laboratory indicators were obtained from the hospital. The NPAR was calculated and collected to investigate its role in the development of CSFP.

Statistical Analysis

Data analysis was performed using the SPSS 20.0. Categorical variables were displayed as rates or percentages, which were analyzed using the chi-square or Fisher's exact test, as applicable. Continuous variables are shown as mean ±standard deviation, median and 25th-75th percentile values, which were analyzed using an unpaired *t*-test or 1-way analysis of variance (ANOVA), as applicable. Logistic regression analysis was used to assess the predictors of CSFP. Multivariate logistic regression analysis was performed to explore independent predictors of CSFP. The receiver operating characteristic (ROC) curve was used to identify the sensitivity and specificity of the independent predictors of CSFP.A 2-sided at P<0.05 was considered statistically significant.

Results

Baseline and Clinical Characteristics

This study included 255 patients (85 in the CSFP group and 170 in the control group) with chest pain and angiographically confirmed normal coronary arteries. In total, 85 patients had CSFP in at least one coronary artery, representing an incidence of 6.4% in patients with chest pain and angiographically proven normal coronary arteries. The patient demographics, comorbidities, and medications used at admission are shown in Table 1. There were no differences between the CSFP and control groups with regard to age, sex, smoking status, dyslipidemia, hypertension, or diabetes mellitus (p>0.05). There were no medication differences during hospitalization regarding angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), angiotensin receptor enkephalinase inhibitors (ARNI), β-antagonists, calcium channel antagonists, antiplatelet agents, or statins (p>0.05) (Table 1). However, patients in the CSFP group had higher BMI and increased nitrate usage (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 CSFP tended to have a significantly higher neutrophil percentage, albumin level, and NPAR level (p < 0.05) (Table 2). Moreover, the NPAR increased as the number of coronary arteries involved in CSFP increased (Figure 2). No differences were noted in the other indicators, including glycemia, creatinine, uric acid, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) (Table 2).

Angiographic Characteristics of the Two Groups

The angiographic findings of this study are summarized in Table 3. The CSFP patients had a higher TFC than that of the controls (p<0.001). In the CSFP group, 51.8% (44/75) of the patients developed CSFP in the LAD artery, 55.3% (47/75) in the LCX, and 81.2% (69/75) in the RCA. In addition, 36.5% (31/75) of the patients developed one-vessel CSFP, 38.8% (33/75) developed two-vessel CSFP, and 24.7% (21/75) developed three-vessel CSFP (Table 3).

Table 1 Baseline Characteristics and Medication of the Two Groups

	CSFP group (n=85)	Control group (n=170)	P value
Demographics			
Age, years	55.5±11.9	55.5±11.9	1
Male sex, n (%)	51(60.0)	102(60.0)	1
Comorbidities			
BMI, Kg/m^2	25.2±2.9	24.1±3.6	0.015
Current smoking, n (%)	28(32.9)	46(27.1)	0.380
Dyslipidemia, n (%)	22(25.9)	39(22.9)	0.642
Hypertension, n (%)	32(37.6)	59(34.7)	0.679
SBP, mmHg	123.5±16.2	123.9±14.9	0.854
DBP, mmHg	75.8±9.3	74.7±9.3	0.395
Heart Rate, beats/min	72.7±10.6	72.5±11.4	0.889
Diabetes mellitus, n (%)	38(44.7)	62(36.5)	0.222
Medication usage			
ACEI/ARB/ARNI, n (%)	27(31.8)	50(29.4)	0.773
Beta-blocker, n (%)	18(21.2)	39(22.9)	0.873
Calcium canal blocker, n (%)	21(24.7)	44(25.9)	0.880
Aspirin, n (%)	46(54.1)	92(54.1)	1.000
Clopidogrel, n (%)	15(17.6)	34(20.0)	0.737
Statin, n (%)	62(72.9)	120(70.6)	0.770
Nitrates, n (%)	26(30.6)	31(18.2)	0.026

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor enkephalinase inhibitor.

Table 2 Laboratory Parameters of the Two Groups

	CSFP group (n=85)	Control group (n=170)	P value
Fasting blood glucose, mmol/L	5.9±0.9	5.9±1.0	0.805
Creatinine, mmol/L	72.2±17.0	71.4±17.1	0.734
Uric acid, mmol/L	330.4±83.7	326.6±93.9	0.752
Neutrophil percentage	70.9±3.2	66.2±3.2	<0.001
Albumin, g/L	36.7±2.2	39.8±2.9	<0.001
TC, mmol/L	4.2±0.8	4.1±0.8	0.366
TG, mmol/L	2.0±1.5	1.7±0.8	0.011
HDL-C, mmol/L	0.9±0.2	1.0±0.2	0.249
LDL-C, mmol/L	2.7±0.8	2.7±0.8	0.499
NPAR	19.3±2.5	16.7±1.8	<0.001

Abbreviations: TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NPAR, neutrophil percentage to albumin ratio.

Predictors of CSFP

Univariate analysis revealed that BMI, TG, and NPAR were associated with the presence of CSFP. Multivariate analysis revealed that BMI (OR 1.114, 95% CI 1.012–1.323, P=0.048) and NPAR (OR 1.915, 95% CI 1.612–2.275, P < 0.001) were independent predictor of CSFP (Table 4). The ROC curve showed that when NPAR was > 17.39, the sensitivity and specificity were 90.6% and 78.8%, respectively, and the area under the ROC curve (AUC) was 0.860 (95% CI: 0.811–0.909, P < 0.001). The AUC of neutrophil percentage was 0.845 (95% CI: 0.794–0.897, p < 0.001), and that of albumin was 0.808 (95% CI:

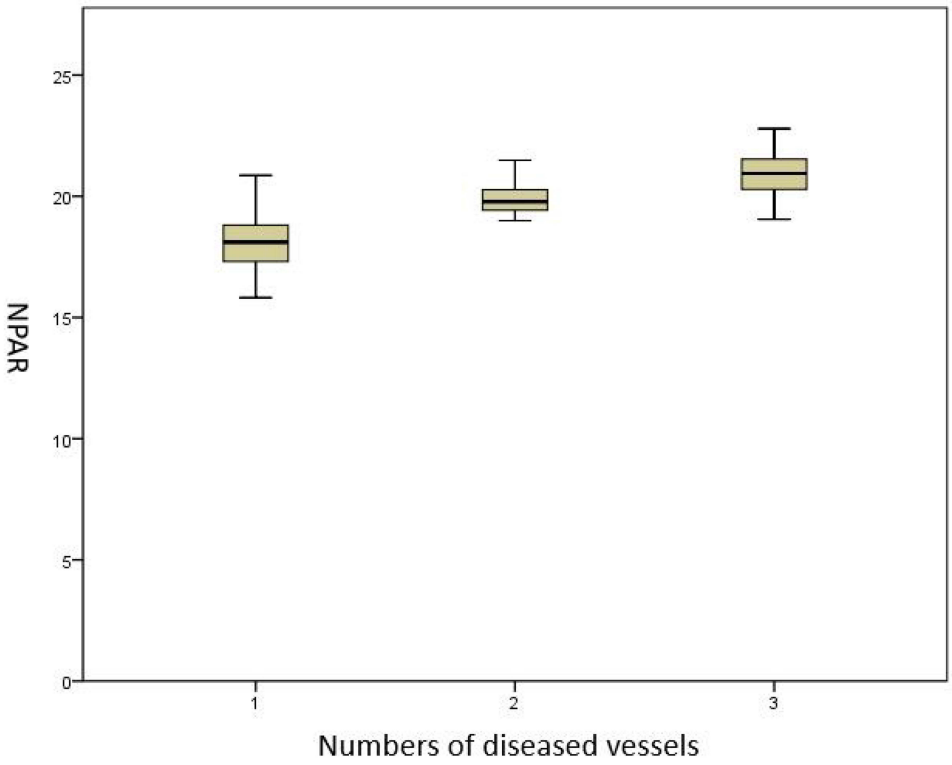

Figure 2 Correlation between the number of vessels involved in CSFP and NPAR.

0.753–0.864, $p < 0.001$) (Figure 3). NPAR had a higher predictive value in the presence of CSFP than neutrophil percentage or albumin level alone. (Figure 3).

Discussion

In this study, we investigated the potential role of NPAR in CSFP in patients with INOCA. We found that NPAR was significantly higher in the CSFP group than in the control group. Moreover, NPAR increased as the number of

Table 3 Angiographic Characteristics of the Two Groups

	CSFP group (n=85)	Control group (n=170)	P value
TIMI frame count			<0.001
LAD	32.5 ±15.9	19.4 ± 9.5	
LCX	28.9 ± 10.3	17.6 ± 8.9	
RCA	28.1 ± 9.2	18.1 ± 7.9	
Mean TFC	29.8 ± 11.8	18.4 ± 9.2	
Distribution of CSFP			
LAD, n (%)	44 (51.8)		
LCX, n (%)	47 (55.3)		
RCA, n (%)	69 (81.2)		
Numbers of vessels involved in CSFP	31 (36.5)		
1, n (%)	33 (38.8)		
2, n (%)	21 (24.7)		
3, n (%)			

Abbreviations: TIMI, thrombolysis in myocardial infarction; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TFC, TIMI frame count; CSFP, coronary slow flow phenomenon.

Table 4 Univariate and Multivariate Logistic Regression Analysis for Presence of SCFP

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
BMI	1.101	1.017–1.191	0.017	1.114	1.012–1.323	0.048
Current smoking	1.125	0.803–1.284	0.262			
Hypertension	1.372	0.876–1.998	0.105			
Diabetes mellitus	1.258	0.689–1.150	0.118			
Uric acid	1.000	0.998–1.003	0.751			
TC	1.157	0.844–1.586	0.364			
TG	1.363	1.054–1.763	0.018	1.258	0.924–1.711	0.144
HDL-C	0.488	0.144–1.652	0.249			
LDL-C	1.107	0.726–1.269	0.497			
NPAR	1.929	1.629–2.285	<0.001	1.915	1.612–2.275	<0.001

Abbreviations: BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NPAR, neutrophil percentage to albumin ratio.

vessels involved in CSFP increased. Multivariate logistic regression analysis revealed that NPAR was an independent predictor of CSFP. To the best of our knowledge, this is the first study to explore the relationship between NPAR and CSFP.

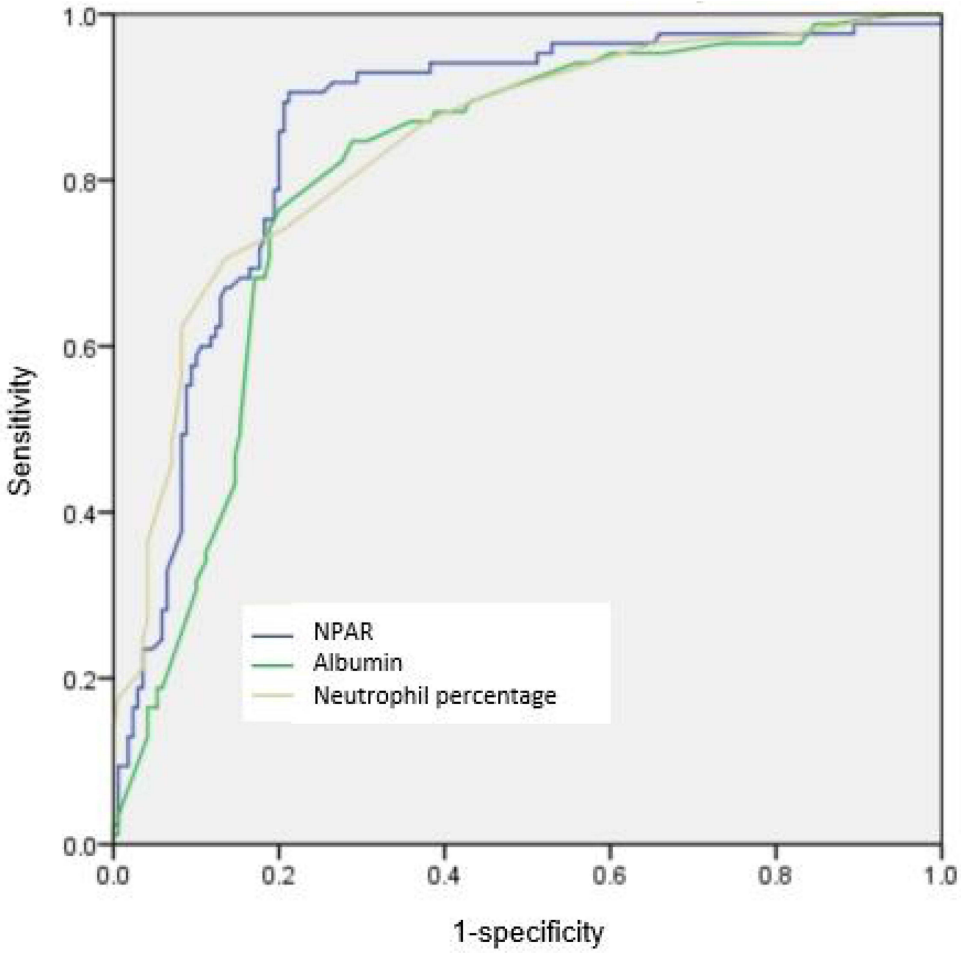

Figure 3 ROC curve showing the predictive value of risk factors for CSFP.

CSFP is not only a simple angiographic finding but also a distinct entity with a specific pathophysiology, clinical presentation, and long-term prognosis.[19] A previous study suggested that CSFP usually affects young men with higher BMI and smoking history.[5,19] The potential role of traditional cardiovascular risk factors such as hypertension, diabetes mellitus, and dyslipidemia in the occurrence and development of CSFP remains controversial. Some studies have suggested that hypertension, diabetes mellitus, and dyslipidemia are risk factors for CSFP,[20,21] whereas other studies have found no correlation.[5] In this study, we found no correlation between CSFP and these risk factors. We suggest that traditional cardiovascular risk factors cannot directly predict the pathophysiology of CSFP. Moreover, patients with CSFP tend to suffer from recurrent angina pectoris, which leads to a serious reduction in their quality of life. Some patients suffer from serious or life-threatening conditions such as myocardial infarction,[22] ventricular fibrillation,[23] and sudden cardiac death.[23] Therefore, exploring the risk factors and predictors of CSFP is clinically significant.

Although the exact pathophysiology of CSFP remains unclear, accumulating evidence suggests that chronic inflammation,[3,24,25] oxidative stress[3,24] and subclinical atherosclerosis[26] played important roles in its occurrence and development. As the most commonly used inflammatory indicator, neutrophils have been suggested to be associated with the development of atherosclerosis.[6] A higher level of neutrophil percentage has also been demonstrated as a independent predictor for the late cardiogenic shock[7] as well as acute kidney injury and poor short-term prognosis in elderly patients with acute myocardial infarction.[27] In this study, we found that patients with CSFP had a higher neutrophil percentage. As an easily acquired inflammatory indicator, neutrophil percentage may participate in the physiology of CSFP.

Plasma albumin is the most abundant protein in the human body, and has anti-inflammatory and antioxidant.[28] Plasma albumin concentration decreases when an inflammatory reaction occurs.[7,29] In addition, the plasma albumin concentration can adversely affect coronary blood flow velocity, resulting in endothelial dysfunction.[30] Additionally, plasma albumin has high antioxidant capacity, which may reduce the damage caused by free radicals in endothelial cells.[30] Accumulating evidence has shown that lower albumin levels are related to a variety of diseases, which may result from malnutrition and inflammatory reactions.[31] Cetin et al discovered that patients with CSFP had lower plasma albumin levels, which could serve as a predictor of CSFP.[32] Similar to a previous study, we also demonstrated that plasma albumin levels decreased in patients with CSFP, which could be used as a risk factor for the presence of CSFP.

Recently, NPAR has been suggested as a new indicator of systemic and local inflammation.[10] As a combination of two inflammation-related indicators, NPAR could provide a more comprehensive evaluation of inflammation, as well as additional information. The degree of inflammatory reaction varies in different situations. When inflammation occurs, plasma albumin and neutrophils show a reverse response, which Results in an elevated neutrophil-to-albumin ratio. Therefore, as a combination of the two inflammatory biomarkers, NPAR may provide a more reliable and sensitive indicator for predicting CSFP. A recent study from China suggested that NPAR is associated with all-cause mortality in patients with chronic heart failure.[13] Moreover, NPAR provides a better predictive value than albumin or neutrophil percentage alone.[13] Sun et al suggested that NPAR is an independent predictor of all-cause mortality in critically ill patients with coronary artery disease.[31] Although both neutrophil percentage and albumin level had an effect on prognosis, NPAR had a better predictive value based on statistical analysis.[31] An elevated level of NPAR was also associated with an increased risk of all cause of mortality in atrial fibrillation,[12] acute myocardial infarction (AMI)[14] as well as cardiogenic shock.[15] NPAR, which is composed of neutrophil percentage and albumin, represents two different mechanisms that lead to CSFP, and there may be a synergistic effect between them. Neutrophil counts varied among individuals. Therefore, neutrophil count itself cannot properly reflect the degree of inflammation. The neutrophil percentage can eliminate individual differences, thereby providing a better reflection of inflammation. Therefore, in this study, we used the neutrophil percentage-to-albumin ratio, instead of the neutrophil-to-albumin ratio, to determine the degree of inflammation. We found that NPAR levels were higher in patients with CSFP. Moreover, the NPAR level increased when the number of vessels involved in CSFP increased. The NPAR is an independent predictor of CSFP occurrence. In addition, NPAR provided a better predictive value than the neutrophil percentage or albumin level alone. To the best of our knowledge, this study is the first to explore the potential role of NPAR in CSFP. As a novel inflammation-related biomarker, NPAR was easily acquired and calculated, and could be used as a promising predictor as well as risk stratification for CSFP in INOCA.

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, although multivariate analyses were conducted, residual covariates may still exist, which may have affected the predictive value of the NPAR. Third, we did not include inflammatory indicators, such as C-reactive protein. Finally, the patients included in this study represented a specific population. Large-sample, multicenter studies are needed to validate our conclusions.

Conclusion

Elevated NPAR levels are an independent predictor of CSFP in patients with INOCA. NPAR could improve the predictive value of CSFP compared with neutrophil percentage or albumin ratio alone. In the clinical practice, the value of NPAR is easily calculated and readily available, which could serve as a parameter for risk stratification for CSFP in patients with INOCA. Moreover, anti-inflammatory therapy could exert therapeutic effect in the management of CSFP patients.

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 Shenzhen Luohu People's Hospital, and all subjects provided written informed consent before participation in the study, which was performed in accordance with the relevant guidelines and regulations. Also this study complies with the Declaration of Helsinki.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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