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The relationship between neutrophil percentage-to-albumin ratio and slow and normal coronary flow phenomenon

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Abstract

Background The relationship between several inflammatory biomarkers and slow coronary flow phenomenon(SCFP) has been reported. However, the correlation between neutrophil percentage-to-albumin ratio (NPAR) and SCFP is lacking. In this study, we aimed to assess the relationship between NPAR and SCFP.

Methods A total of 228 patients were enrolled in this study according to the diagnostic and exclusion criteria. 76 patients were included in the SCFP group, and 152 age-matched patients were included in the normal coronary flow (NCF) group. The baseline data, laboratory parameters and coronary angiography were recorded and compared.

Results The values of NPAR were significantly higher in the SCFP group than those in the NCF group (1.78[1.58,1.88] vs. 1.42[1.24,1.66], $P<0.001$). NPAR elevated as the number of vessels involved SCFP increased. In the multiple logistic regression tests, NPAR was an independent predictor of SCFP (OR: 1.239, 95%CI: 1.124–1.367, $p<0.001$). The receiver operating characteristic curve analysis showed that the cutoff value of NPAR for predicting SCFP was > 1.57 with a 76.3% sensitivity and 67.1% specificity [the area under the curve (AUC) = 0.727, 95%CI: 0.659–0.795, $p<0.001$]. NPAR had a better predictive value of SCFP than neutrophil percentage, but not albumin.

Conclusion Elevated NPAR may be an independent and valuable predictor of SCFP.

Keywords Slow coronary flow phenomenon, Neutrophil percentage-to-albumin ratio, Predictors

The slow coronary flow phenomenon(SCFP) is a slowing of opacification in the main vessels without obstruction in the distant bed [1]. This occurrence of coronary angiography is known as the primary SCFP. It has been regarded as a specific disease entity [2]. The pathophysiology of SCFP is still not well understood. The proposed causes for the SCFP include systemic/local inflammatory response [3], endothelial dysfunction [3, 4], microvascular [5], elevated resting coronary vasomotor tone [6], platelet function abnormality [7], and diffuse atherosclerosis [8]. SCFP occurs in 1–7% of patients who undergo coronary angiography. Owing to SCFP has been linked to life-threatening adverse cardiovascular events such as acute coronary syndrome, ventricular fibrillation, and sudden cardiac death

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[2], It has increasingly acquired more clinical attention, in combination with ongoing progress in cardiovascular research.

As inflammatory response was proved to play an important role in the process of SCFP, Neutrophil, as a classic inflammatory mediator producer, play a significant role in mediating inflammatory reactions [9]. Besides, lower serum albumin concentration has been identified as an underestimated predictor of cardiovascular disease mainly due to increased inflammation, oxidative stress and malnutrition [10]. Neutrophil percentage-to-albumin ratio (NPAR), as a combination of two inflammatory biomarkers, can amplify the changes of these two indicators and is thought to reflect inflammatory levels precisely. Recently, several studies have demonstrated that NPAR was a novel and robust predictors for assessing coronary artery disease severity and extension [11], free-wall rupture of acute myocardial infarction [12] and prognosis in patients with ST-segment elevation myocardial infarction [13]. Since SCFP was closely associated with atherosclerotic cardiovascular disease and impaired its prognosis [14], to our knowledge, no research evaluating the value of NPAR in the prediction of SCFP has been reported. In this study, we aim to investigate the relationship between NPAR and SCFP.

Methods

Study population

In this single-center study, data of patients with chest pain or coronary heart disease based on the diagnostic and exclusion criteria were retrospectively recorded and analyzed. We conducted a 1:2 age-matched case-control research using unaffected comparators. Ultimately, a total of 76 individuals were identified with SCFP and angiographically normal coronary arteries which named SCFP group, along with 152 patients with normal coronary flow (NCF) and angiographically normal coronary arteries which named NCF group. The patients with cerebrovascular disease, decompensated heart failure, cardiomyopathy, severe or moderate valvular heart disease, history of revascularization such as coronary artery bypass grafting, percutaneous coronary intervention(PCI) or thrombolysis, coronary aneurysmal dilation or coronary artery spasm, chronic obstructive pulmonary disease, acute infectious disease, severe liver or renal failure, systemic autoimmune or inflammatory diseases, malignancy and hematological diseases were excluded from the study. This study was approved by the Ethics Committee of Suzhou Ninth Hospital affiliated to Soochow University (Decision no: KYLW2024-008-01), and informed consent was obtained from all participants.

Clinical data

After hospitalization, the general data of patients were obtained and assessed, including age, sex, family history of coronary artery disease, medical history of hypertension, diabetes and dyslipidemia as defined in the previous guideline [15], history of smoking and previous medication. The vital signs such as blood pressure and heart rate were also collected. Transthoracic echocardiography was performed on all patients, and left ventricular ejection fraction (LVEF) was evaluated using the biplane Simpson technique. Blood samples were taken from patients following admission prior to coronary angiography. The Sysmex XN9000 auto hematology analyzer (Sysmex) was used to performed hematological tests such as white blood cell (WBC) count, neutrophil percentage, hemoglobin and platelet count. The ADVIA2400 auto biochemical analyzer (Siemens) was used to measure several biochemical indices such as albumin, uric acid (UA), low density lipoprotein cholesterol (LDL-C).

Coronary angiography

Coronary angiography was performed with Judkins technique via the radial or femoral artery.

Two experienced interventional cardiologists were evaluated the angiographic images including thrombolysis in myocardial infarction (TIMI) flow grade of the main coronary vessels. SCFP was defined as TIMI1–2 flow. NCF was defined as TIMI 3 flow.

Statistical analysis

Statistical analyses were performed using SPSS version 24.0 (SPSS Inc.) for Windows. Continuous variables between two groups expressed as mean ± standard (SD) or median [Interquartile rang (IQR)] were compared by Student's t-test or Man-Whitney U test. The normality distribution of continuous variables was tested by Shapiro–Wilk test. Categorical variables between two groups presented as percentage were compared by Chi-square or Fisher exact test. Spearman's correlation analysis was used to analyze the correlation of neutrophil percentage and NPAR as well as albumin and NPAR. Collinearity diagnosis was used to analyze whether the values entering the multivariate logistic analysis were highly correlated. Multivariate logistic regression analysis by forward method was performed to identify the independent predictors of SCFP. Receiver-operating characteristic (ROC) curve was plotted and used to evaluate the best cutoff value, sensitivity and specificity of NPAR, neutrophil percentage and albumin in distinguishing SCFP. The areas under the ROC curve (AUC) of NPAR, neutrophil percentage and albumin were compared by the De Delong test in MedCalc statistical software version 22.0.17 (MedCalc Software Ltd). All tests were two-sided, and

p value of less than 0.05 were considered as statistically significant.

Results

A total of 228 individuals with angiographically normal coronary arteries (76 in the SCFP group and 152 in the comparators) were enrolled in this study. The mean age of the study population was 57.29 ± 13.1 years. Table 1 showed the baseline characteristics and medications of the study groups. There were significant differences in terms of sex between SCFP group and NCF group (female rate, 42.1% vs. 28.3%, $P = 0.036$). There was no significant difference between two groups in terms of family history of coronary artery diseases, hypertension, diabetes, dyslipidemia, smoking history, heart rate, systolic blood pressure, diastolic blood pressure, LVEF ($P > 0.05$). There was also no previous medication difference with regard to antiplatelet, statin, Beta-blocker, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, angiotensin receptor enkephalinase inhibitors and calcium canal blocker ($p > 0.05$) (Table 1).

Table 1 The baseline characteristics and medications of two study groups

	SCFP group ($n = 76$)	NCF group ($n = 152$)	t/X^2	*P* value
Age (years)	57.29 ± 13.11	57.29 ± 13.07	0.000	1.000
female gender (n, %)	32(42.1)	43(28.3)	4.381	0.036
Family history of CAD (n, %)	16(21.1)	35(23.0)	0.114	0.736
Hypertension (n, %)	37(48.7)	80(52.6)	0.316	0.574
Diabetes mellitus (n, %)	24(31.6)	34(22.4)	2.266	0.132
Dyslipidemia (n, %)	40(52.6)	76(50.0)	0.140	0.708
History of smoking (n, %)	41(53.9)	70(46.1)	1.264	0.261
Heart rate (bpm)	72.59 ± 13.57	75.46 ± 15.23	-1.389	0.166
SBP (mmHg)	129.83 ± 21.80	131.14 ± 20.89	-0.440	0.661
DBP (mmHg)	72.79 ± 12.70	74.80 ± 12.16	-1.161	0.247
LVEF	61.80 ± 4.97	62.24 ± 4.86	-0.631	0.529
Medication use (n, %)				
Antiplatelet	16 (21.1)	38 (25.0)	0.437	0.509
Statin	22 (28.9)	50 (32.9)	0.365	0.546
Beta-blocker	13 (17.1)	20 (13.2)	0.638	0.425
ACEI/ARB/ARNI	32 (42.1)	77 (50.7)	1.485	0.223
Calcium canal blocker	24 (31.6)	46 (30.3)	0.041	0.839

The data are expressed as n (%) or mean ± SD

SCFP: slow coronary flow phenomenon; NCF: normal coronary flow; CAD: coronary artery diseases; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; ACEI: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNI: angiotensin receptor enkephalinase inhibitors

Table 2 listed the laboratory parameters. WBC count (8.40[6.06,10.60] vs. 7.28[5.52,9.09], $P = 0.020$),hemoglobin (133.05 ± 14.71 vs. 137.63 ± 16.47, $P = 0.042$),neutrophil percentage (68.10[58.88,73.55] vs. 58.35 [50.98,67.25], $P < 0.001$), NPAR (1.78[1.58,1.88] vs. 1.42[1.24,1.66], $P < 0.001$),LDL-C (2.42[2.00,3.12] vs. 2.17[1.70,2.67], $P = 0.017$), UA (386.00[326.75-503.25] vs. 359.50[284.00-437.50], $P = 0.032$) were found to be higher in the SCFP group than in the comparators. Meanwhile, Serum albumin was significant lower in the SCFP group than that of NCF group (38.45[36.43, 40.40] vs. 40. 30[38.00, 43.30], $P < 0.001$) (Table 2).

According to coronary angiography, 47 of 76 SCFP group patients revealed SCFP in the left anterior descending artery,32 of 76 SCFP group patients in the left circumflex artery,40 of 76 SCFP group patients in the right coronary artery. Moreover, 34 of 76 SCFP group patients revealed single vessel SCFP, 27 of 76 SCFP group patients revealed two vessels SCFP, and 15 of 76 SCFP group patients revealed three vessels SCFP. Figure 1 showed that NPAR elevated as the number of vessels involved SCFP increased (Fig. 1).

To identify risk variables for SCFP, baseline clinical data with *p*-value < 0.05 (Tables 1 and 2) was analyzed using univariate logistic regression. The *p*-value of female gender, LDL-C, UA, hemoglobin, WBC count, neutrophil percentage, albumin and NPAR*10 remain statistically significant. There were significant linear correlations between neutrophil percentage and NPAR ($r = 0.902$, $p < 0.001$) and albumin and NPAR ($r = 0.516$, $p < 0.001$). After eliminating neutrophil percentage and albumin, collinearity diagnostics was used. Values of female gender, LDL-C, UA hemoglobin, WBC count and NPAR*10 showed a variance inflation factor < 10, a tolerance degree > 0.1 and the multivariate logistic regression model contained all of them. NPAR*10 was showed as an independent predictor of SCFP by multivariate logistic regression analysis (OR: 1.239, 95%CI: 1.124–1.367, $p < 0.001$) (Table 3).

The ROC curve showed that the cutoff value of NPAR for predicting SCFP was > 1.57 with a 76.3% sensitivity and 67.1% specificity (AUC = 0.727, 95%CI: 0.659–0.795, $p < 0.001$). The cutoff value of > 65.75 for neutrophil percentage indicated SCFP (AUC: 0.675,95% CI: 0.601–0.750, $p < 0.001$) with 61.8% sensitivity and 74.3% specificity. In addition, for albumin, a cutoff value > 40.98 indicated SCFP, with 80.3% sensitivity and 48.7% specificity (AUC = 0.667, 95%CI: 0.595–0.738, $p < 0.001$) (Fig. 2).

The ROC curves of NPAR, neutrophil percentage and albumin were compared in the SCFP prediction. The AUC for NPAR was significantly greater than that for neutrophil percentage (0.727 vs. 0.675, z = 3.287, $P = 0.001$). However. there was no significant difference of AUC between NPAR and albumin as well as neutrophil

Table 2 The laboratory parameters of two study groups

	SCFP group (*n* = 76)	NCF group (*n* = 152)	t/Z	*P* value
WBC count (×10^9/L)	8.40[6.06,10.60]	7.28[5.52,9.09]	-2.335	0.020
Platelet count (×10^9/L)	248.50[199.25,300.75]	243.00[189.00,288.00]	-1.118	0.263
Hemoglobin (g/L)	133.05 ± 14.71	137.63 ± 16.47	-2.049	0.042
Neutrophil percentage (%)	68.10[58.88,73.55]	58.35 [50.98,67.25]	-4.316	< 0.001
Monocyte count (×10^9/L)	0.55 ± 0.25	0.51 ± 0.24	1.135	0.257
Lymphocyte count (×10^9/L)	1.39[1.03,2.29]	1.49[1.22,1.97]	-0.416	0.677
Fasting blood glucose (mmol/L)	5.47[4.5840,6.71]	5.18[4.35,6.34]	-1.535	0.125
Albumin (g/L)	38.45[36.43, 40.40]	40. 30[38.00, 43.30]	-4.100	< 0.001
NPAR	1.78[1.58,1.88]	1.42[1.24,1.66]	-5.590	< 0.001
NPAR*10	17.82[15.77,18.84]	14.15[12.38,16.62]	-5.590	< 0.001
Creatinine (umol/L)	74.79 ± 16.96	71.20 ± 14.55	1.661	0.098
AST(U/L)	23.93 ± 7.71	23.15 ± 6.48	0.806	0.421
ALT(U/L)	21.68 ± 7.90	20.89 ± 6.75	0.793	0.429
TG (mmol/L)	1.35[0.87,1.91]	1.25[0.81,1.93]	-0.551	0.582
LDL-C (mmol/L)	2.42[2.00,3.12]	2.17[1.70,2.67]	-2.385	0.017
HDL-C (mmol/L)	1.11 ± 0.35	1.06 ± 0.34	0.886	0.377
RDW (%)	12.90[12.50,13.30]	12.80[12.30,13.30]	-1.097	0.273
UA (umol/L)	386.00[326.75-503.25]	359.50[284.00-437.50]	-2.142	0.032
MPV(fL)	10.86 ± 0.99	10.63 ± 0.95	1.694	0.092

The data are expressed as mean ± SD or median[Q1-Q3]

SCFP: slow coronary flow phenomenon; NCF: normal coronary flow; WBC: white blood cell; NPAR: neutrophil percentage-to-albumin ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; RDW: red cell distribution width; UA: uric acid; MPV: mean platelet volume

percentage and albumin (0.727 vs. 0.667, z = 1.390, *P* = 0.1646 and 0.675 vs. 0.667, z = 0.159, *P* = 0.8734).

Discussion

In this study, we demonstrated that higher NPAR was independently associated with SCFP and found to be a more effective independent predictor for SCFP than neutrophil percentage, but not albumin. Besides, The NPAR elevated as the number of vessels involved SCFP increased. To our knowledge, this is the first study to explore the relationship between PFAR and SCFP.

The pathophysiology of SCFP remains unknown. Several etiological insults have been postulated earlier. Possible causes of SCFP include microvascular damage and illness, endothelial dysfunction, atherosclerosis, inflammation and oxidative stress [5]. Various studies have yielded divergent results. In our investigation, we observed that the levels of female gender, WBC count, LDL-C, and UA were significantly higher in the SCFP group compared to the NCF group. Conversely, hemoglobin levels were significantly lower in the SCFP group. However, these indicators in the logistic regression analysis did not reveal statistical significance, which is inconsistent with some previous findings [16, 17]. This discrepancy may be attributed to differences in the study populations, including variations in ethnicity, inclusion criteria, and cardiac status.

Inflammation may be an important in the pathogenesis of SCFP. Wang et al. have proven that elevated inflammatory indicators, soluble interleukin – 2 receptor, tumor necrosis factor-α and high-sensitivity C-reactive protein, were independent risk factors for SCFP in non-ST segment elevation myocardial infarction patients [18]. In another study, it was also demonstrated that interleukin-6 was closely associated with SCFP [19]. Neutrophils are one of the most widely recognized cellular effectors, and as a component of WBC, they play an important role in mediating inflammatory reactions [9]. Earlier studies have suggested that high neutrophil-lymphocyte ratio was related to SCFP [20, 21]. Wang er al have reported that Neutrophil counts were independent clinical predictors of no-reflow following primary PCI in patients with ST segment elevation myocardial infarction patients [22]. In our study, we also found that high neutrophil percentage levels were related to SCFP. There are several reasons can be proposed. Firstly, neutrophils can produce serum ingredients and cytokines, such as matrix metalloproteinase-9, tumor necrosis factor-α, which can injury the coronary flow [23, 24]. Secondly, reactive oxygen species., which is release by neutrophils, is also the driver of SCFP [25], In addition, Tang et al. [26] found that neutrophil can trigger sporadic thrombosis in small myocardial vessels and was related with immune thrombotic dysregulation.

Albumin has long been viewed as a sign of the body's nutritional state. Albumin also has anti-inflammatory, anti-oxidant, anticoagulant, and antiplatelet aggregation properties [27], which is inversely correlated with

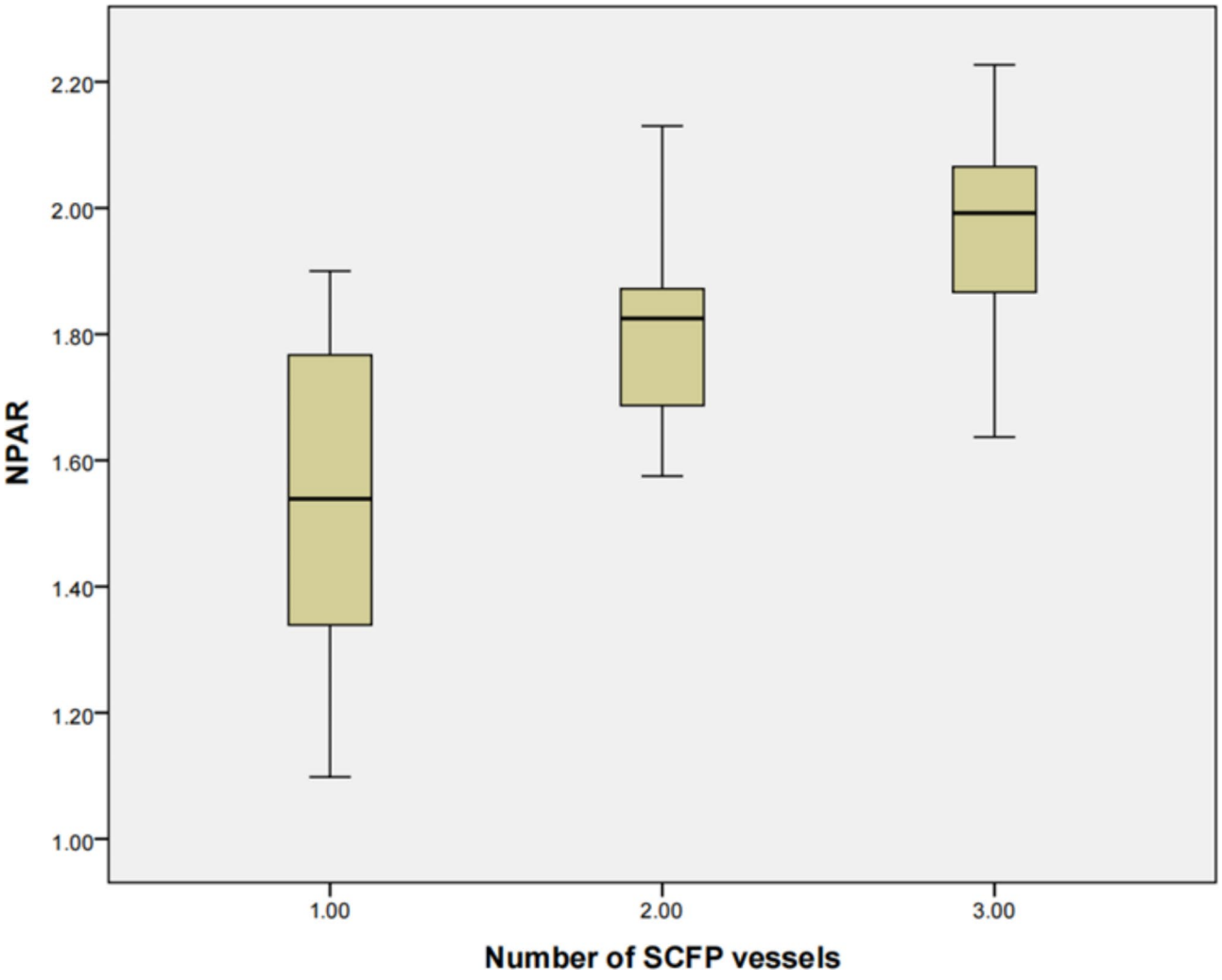

Fig. 1 Correlation between neutrophil percentage-to-albumin ratio (NPAR) and number of slow coronary flow phenomenon (SCFP) vessels

Table 3 Univariate and multivariate logistic regression analysis of factors for SCFP

Univariate analysis				**Multivariate analysis**		
variables	**Odds ratio**	**95%CI**	**P**	**Odds ratio**	**95%CI**	**P**
Female gender	1.844	1.036-3.280	0.037	1.304	0.600-2.833	0.502
LDL-C	1.377	1.014-1.871	0.040	1.356	0.969-1.896	0.075
UA	1.003	1.000-1.005	0.028	1.002	0.999-1.004	0.209
hemoglobin	0.982	0.965-0.999	0.043	0.984	0.961-1.007	0.161
WBC count	1.129	1.031-1.235	0.008	1.095	0.993–1.207	0.070
Neutrophil percentage	1.057	1.029-1.086	< 0.001			
Albumin	0.843	0.775-0.918	< 0.001			
NPAR*10	1.266	1.152-1.392	< 0.001	1.239	1.124–1.367	< 0.001

SCFP: slow coronary flow phenomenon; LDL-C: low density lipoprotein cholesterol; UA: uric acid; WBC: white blood cell; NPAR: neutrophil percentage-to-albumin ratio; CI: confidence interval

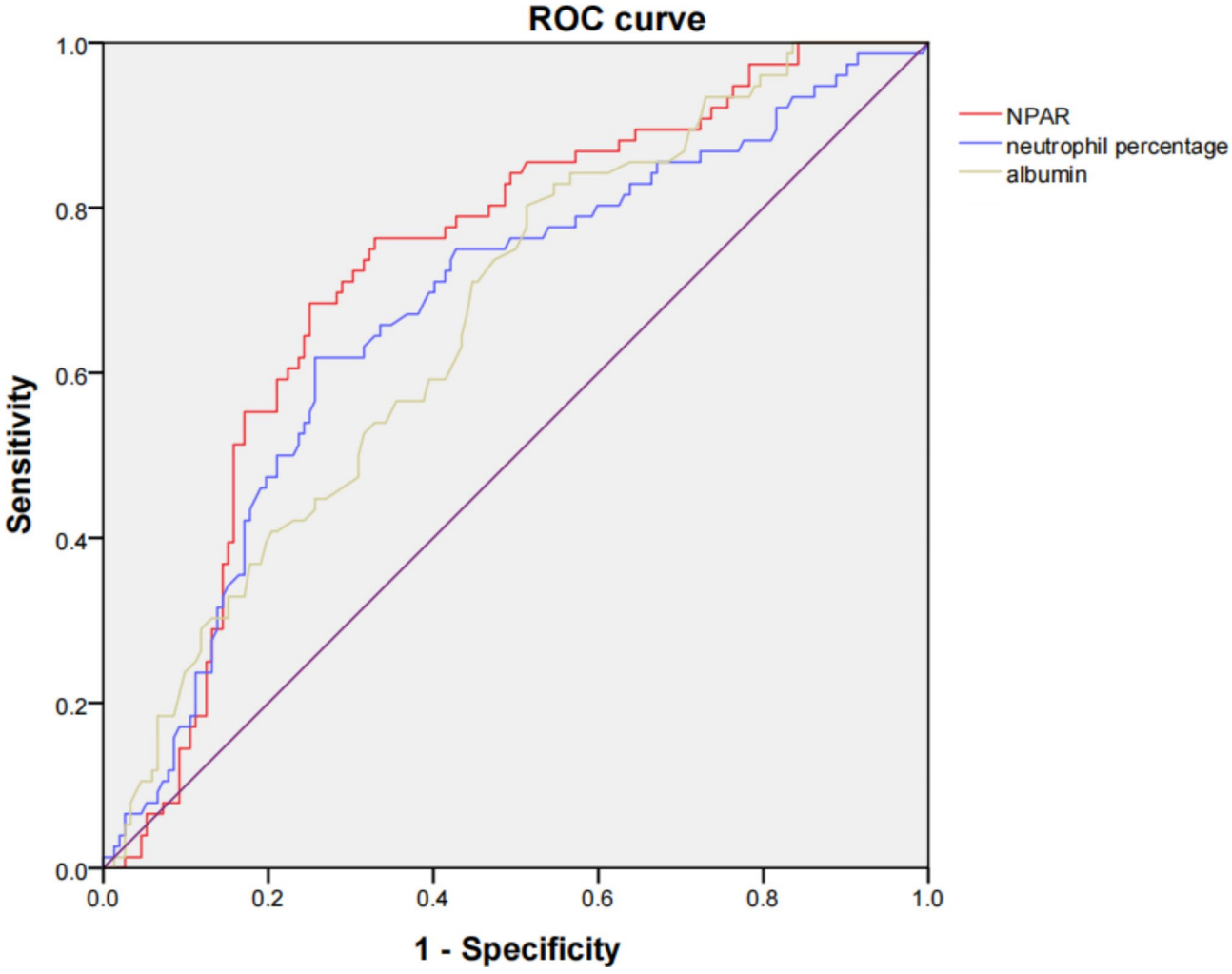

Fig. 2 Receiver operating characteristic (ROC) curves showing the predicting value of neutrophil percentage-to-albumin ratio(NPAR), neutrophil percentage and albumin for slow coronary flow phenomenon

a variety of cardiovascular diseases, including ischemic heart disease, atrial fibrillation, venous thromboembolism, and ischemic stroke [28–30]. In recent years, low albumin levels has been recognized as an underestimated predictor of cardiovascular disease. Yoshioka et al. have reported a one-year follow-up of 1,424 patients with myocardial infarction, revealing that serum albumin levels below 3.8 g/dL were significantly associated with the risk of cardiovascular events and all-cause mortality [31]. Several studies also observed that lower levels of plasma albumin were closely related with SCFP [32–34], Similar to those results, we also indicated that lower levels of albumin were detrimental to coronary flow. We proposed that reduced plasma albumin levels might play an essential role in the pathophysiology of SCFP by activating inflammatory responses, lowering antioxidative stress and stimulating platelet aggregation.

Because NPAR are a combination of two inflammatory markers, its calculation exacerbates changes in their values. Besides, as a composite inflammatory marker, NPAR can reflect inflammation more accurately. Karasu et al. [11] have suggested that NPAR was a novel biomarker for assessing coronary artery disease severity and extension in patients suffering from non-ST-segment elevation acute myocardial infarction. Dai et al. [12] have found NPAR was a predictor of free-wall rupture in patients with acute myocardial infarction. NPAR was closely associated with the atrial fibrillation severity and kidney injury [35, 36]. It has also been proposed to be a predictor of worse prognosis in patients with heart failure and atrial fibrillation [37–39]. Additionally, several composite indices have been identified as being associated with coronary slow flow. Zhang et al. have reported that the uric acid to albumin ratio was served as a novel predictor of coronary slow flow phenomenon in patients with chronic coronary syndrome and non-obstructive coronary arteries [34]. Toprak et al. have identified the Non-HDL-C/HDL-C Ratio as a novel predictor of

coronary slow flow [17]. In this study, we demonstrated that higher NPAR was independently associated with SCFP and was also related with the number of vessels involved SCFP. A one-unit increase in NPAR increases the likelihood of SCFP by 0.239. NPAR was a more effective independent predictor for SCFP than neutrophil percentage, but not albumin. The association between NPAR and SCFP might be due to a variety of aspects. Local or systemic inflammatory response as a possible initial and predominant cause [3, 5]. Oxidant-Antioxidant unbalance also promote the pathological process of SCFP. Endothelial dysfunction and coronary atherosclerosis which is caused including inflammatory and oxidative stress may play an important role in the pathogenesis of SCFP [3, 33]. What's more, microvascular abnormalities are another mechanism for SCFP [40]. The risk factors mentioned above are interrelated and involved in the development and progression of SCFP.

This study also had several limitations. Firstly, this was a single-center retrospective study, which can lead to selection bias and limit the sample size. Secondly, the changes of laboratory parameters during hospitalization were not collected. Thirdly. We were unable to include all biomarkers of inflammation, such as C-reactive protein. Finally, the follow-up data was not provided in this study.

Conclusion

In this study, we demonstrated that elevated NPAR was independently associated with SCFP and had better predictive value of SCFP than neutrophil percentage, but not albumin. Future investigations with larger sample sizes will be required to verify NPAR 's values of SCFP.

Author contributions

All authors have made a substantial intellectual contribution to this study. YRL, ZW, CWH conceived the study, collected the data, performed data analysis, and wrote the initial draft. SJ contributed to data collection and analysis. WYM collected the data and helped to draft the manuscript. WZM conceived the study, revised the manuscript and provided final approval. All authors read and approved the final manuscript.

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Data availability

The datasets generated and analyzed during the current study are not publicly available due to some relevant further studies but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Suzhou Ninth Hospital affiliated to Soochow University (Decision no: KYLW2024-008-01) and the study complied with the Declaration of Helsinki. Informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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