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ORIGINAL RESEARCH

Advanced Lung Cancer Inflammation Index as a Predictor of Coronary Slow Flow Phenomenon in Patients with Angina and Non-Obstructive Coronary Arteries

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Background: The advanced lung cancer inflammation index (ALI) is associated with the prognosis of cardiovascular diseases. However, the relationship between ALI and the occurrence of coronary slow flow phenomenon (CSFP) remains unclear.

Methods: We consecutively enrolled 1495 patients with angina and non-obstructive coronary arteries (ANOCA). In total, 93 patients were diagnosed with CSFP. A 1:2 age- and sex-matched patient with a normal coronary blood flow was selected as the control group. Demographic characteristics, laboratory parameters, and angiographic findings were compared between groups. Univariate and multivariate logistic regression analyses were performed to identify the independent predictors of CSFP in patients with ANOCA.

Results: A total of 93 individuals developed CSFP, accounting for 6.4% of the ANOCA patients. Compared with controls, patients with CSFP had a lower body mass index (BMI) and a higher incidence of nitrates before admission ($P<0.05$). The neutrophil count, neutrophil-to-lymphocyte ratio (NLR), and fasting blood glucose (FBG) level were significantly higher in patients with CSFP, whereas decreased lymphocyte count, albumin level, and ALI were found in patients with CSFP. Multivariable logistic regression analyses revealed that ALI was an independent predictor of CSFP. The receiver operating characteristic (ROC) curve showed that when ALI was ≤389.5, the specificity and sensitivity were 0.624 and 0.652, respectively (AUC, 0.694; 95% CI, 0.633–0.755, $P<0.001$). Moreover, ALI demonstrated a better predictive value than indicators alone, including albumin level, BMI, and NLR.

Conclusion: A lower ALI demonstrated a reliable predictive value for the occurrence of CSFP in patients with ANOCA. As an easily calculated and acquired parameter, ALI can be used for risk stratification and optimal management of patients with ANOCA.

Keywords: advanced lung cancer inflammation index, coronary slow flow phenomenon, predictor, angina and nonobstructive coronary arteries

Introduction

Angina with nonobstructive coronary arteries (ANOCA) is a common clinical entity in the rapidly developing era of interventional cardiology. ANOCA is challenging because of its heterogeneous pathogenesis and complex clinical manifestation.[1] Unlike traditional obstructive atherosclerotic cardiovascular diseases, ANOCA is a unique yet under-addressed clinical entity.[1] Although the pathogenesis of angina or chest pain is quite complex and varied, coronary causes remain a well-recognized cause despite nonobstructive coronary arteries. An example is cardiac syndrome X (CSX), which has a positive stress electrocardiograph yet normal coronary arteries. Another example is the coronary slow flow phenomenon (CSFP),which is characterized as slow coronary flow in nonobstructive coronary arteries.[2] In contrast to effort angina in CSX, patients with CSFP often suffer from resting angina pectoris, some resembling acute coronary syndrome, resulting in a high risk of readmission to the coronary care unit.[3,4] Therefore, the early identification of CSFP in ANOCA is important in clinical practice. CSFP has been suggested that CSFP is associated with increased

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inflammatory response, endothelial dysfunction, microvascular dysfunction, and diffuse atherosclerosis.[3–9] However, the exact pathogenesis of CSFP remains unclear.

The advanced lung cancer inflammation index (ALI) was first described by Jafri and his colleagues and has been suggested as a prognostic parameter for advanced non-small cell lung cancer.[10] ALI was calculated as body mass index (BMI) × albumin/neutrophil-to-lymphocyte ratio (NLR).[10] As a newly developed indicator, ALI combines inflammatory and nutritional components and has been demonstrated to be a reliable indicator of poor prognosis in cardiovascular diseases.[11–14] However, the association between ALI and CSFP remains unclear. Considering the close relationship between the components of ALI (BMI,[15] albumin,[6,9] NLR[16]) and CSFP, we speculated that ALI could help identify ANOCA patients at a high risk for CSFP. Therefore, in this study, we aimed to explore the relationship between ALI and CSFP in ANOCA patients.

Methods

Study Population

The flowchart of the study is presented in Figure 1. A total of 1495 patients with ANOCA were included in our study; 52 individuals were excluded from the present study, and 1443 ANOCA patients were consecutively enrolled. In total, 93 patients developed CSFP, accounting for 6.4% of patients with ANOCA. The exclusion criteria are shown in Figure 1. A 1:2 age- and sex-matched patient with a normal coronary blood flow was selected as the control group. Age- and sex-matched patients were numbered, and a simple random sampling method was used to select controls from ANOCA patients with normal coronary blood flow. All patients signed an informed consent form before the participation. This study was approved by the ethics committee of "General Hospital of Fushun Mining Bureau of Liaoning Health Industry" and conformed to the Declaration of Helsinki.

Clinical and Laboratory Data Assessments

Demographic characteristics including age, sex, and BMI were recorded. Comorbidities including current smoking, hypertension, and diabetes mellitus were also carefully recorded. Blood samples were collected before the procedure and tested in the central laboratory according to the relevant standards. ALI was calculated as BMI × albumin/NLR.[10] BMI is calculated as the height (m)/ weight (kg)^2.[10]

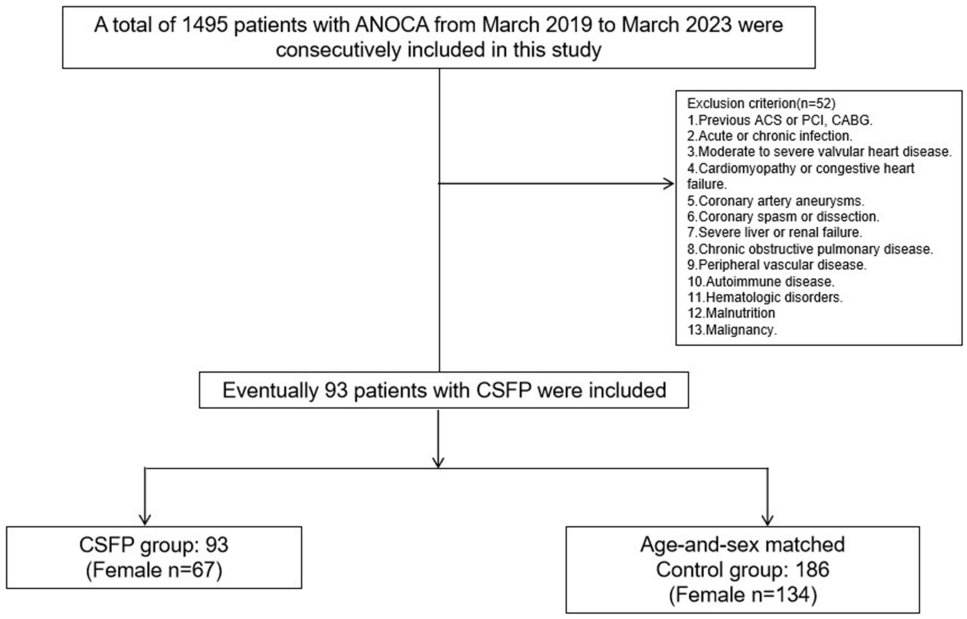

Figure 1 Study flowchart.

Coronary Angiography

Coronary angiography was performed by experienced cardiologists by using the standard Judkins technique. Thrombolysis in myocardial infarction (TIMI) frame count (TFC) was used as a quantitative method for evaluating coronary blood flow.[11] The projections for the determination of the TFCs of the left anterior descending (LAD) and left circumflex (LCX) arteries were cranial angulations and the right anterior oblique projection with caudal angulations, respectively. Left anterior oblique projection was used to assess the TFCs of right coronary artery (RCA). The initial frame was acquired when the contrast reached >70% of the proximal vessel lumen. The last frame was determined when the antegrade contrast reached the distal vessel landmark. The Mustache segment, distal bifurcation segment, and first branch of the posterolateral artery were used to evaluate the final TFCs of the LAD, LCX, and RCA, respectively.[11] The corrected TFC of the LAD was calculated as the TFC dividing by 1.7 so as to correct the longer distance of the LAD. When the sum of the three vessels divided by 3, the mean TFC was acquired. The cutt off value of TFCs were 36.2±2.6 for the LAD (cTFC 21.1±1.5), 22.2±4.1 for the LCX, and 20.4±3 for the RCA.[11] All patients received an intracoronary injection of 200μg of nitroglycerin during the procedure.

Statistical Analysis

Continuous data are shown as mean±standard deviation and were compared using the Student's *t*-test. Categorical variables are expressed as rates or percentages and compared using the chi-square test or Fisher's exact test. The baseline indicators with $p<0.1$ or the potential risk or protective factors for CSFP, were included in the univariate regression analysis. Factors with $p<0.05$, were then added to the multivariate logistic regression models to determine the independent predictors for the presence of CSFP in ANOCA patients. Receiver operating characteristic (ROC) curves were generated to determine the diagnostic cut-off value and predictive value of ALI for CSFP. Statistical significance was set at $P<0.05$.

Results

Baseline and Clinical Characteristics

The flowchart of the study is presented in Figure 1. A total of 1495 patients with ANOCA were included in our study, of which 93 patients developed CSFP, accounting for 6.4% of ANOCA patients. The exclusion criteria are shown in Figure 1. We found that patients with CSFP tended to have a lower BMI and a higher incidence of nitrates before admission ($P<0.05$) (Table 1). Age and female sex were comparable between the two groups ($p>0.05$) (Table 1). Comorbidities, including smoking, hypertension, and diabetes mellitus, were also comparable between the two groups ($p>0.05$) (Table 1). Medication history was also similar between the two groups except for nitrates ($p>0.05$) (Table 1).

Table 1 Baseline Characteristics and Medication of the Two Groups

	CSFP Group (n=93)	Control Group (n=186)	P value
Age, years	58.4±8.7	58.4±8.7	1
Female sex, n (%)	67(72.0)	134(72.0)	1
BMI, Kg/m^2	24.9±2.9	25.8±3.4	0.028
Current smoking, n (%)	35(37.6)	49(26.3)	0.071
Hypertension, n (%)	39(41.9)	65(34.9)	0.294
Diabetes mellitus, n (%)	21(22.6)	35(18.8)	0.526
ACEI/ARB/ARNI, n (%)	22(23.7)	40(21.5)	0.760
Beta-blocker, n (%)	29(31.2)	44(23.7)	0.178
Calcium canal blocker, n (%)	27(29.0)	52(28.0)	0.888
Antiplatelet, n (%)	29(31.2)	54(29.0)	0.781
Statin, n (%)	25(26.9)	54(29.0)	0.779
Nitrates, n (%)	38(40.9)	51(27.4)	0.029

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

Table 2 Laboratory Parameters of the Two Groups

	CSFP Group (n=93)	Control Group (n=186)	P value
WBC count, 10^9/L	7.2±2.4	6.8±1.6	0.134
Neutrophils count, 10^9/L	5.1±2.4	4.4±1.7	0.003
Lymphocytes count, 10^9/L	1.6±0.5	1.8±0.6	0.002
NLR	3.4±1.6	2.6±1.3	<0.001
Albumin, g/L	38.7±2.1	40.4±3.0	<0.001
FBG, mmol/l	5.7±0.5	5.5±0.6	0.049
Cr, mmol/l	69.4±14.0	68.2±16.3	0.546
Uric acid, umol/L	342.7±96.2	352.8±95.7	0.412
TC, mmol/l	4.3±0.9	4.4±0.9	0.307
TG, mmol/l	1.6±1.4	1.7±1.7	0.747
HDL-C, mmol/l	1.0±0.3	1.1±0.3	0.225
LDL-C, mmol/l	2.7±0.7	2.7±0.7	0.617
ALI	334.8±128.9	484.2±224.2	<0.001

Abbreviations: WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; FBG, fasting blood glucose; Cr, creatinine; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALI, advanced lung cancer inflammation index.

Laboratory Parameters of the Two Groups

The laboratory parameters are listed in Table 2. We found that patients with CSFP showed higher neutrophil counts, neutrophil-to-lymphocyte ratio (NLR), and fasting blood glucose (FBG) and decreased lymphocyte count, albumin, and ALI ($p<0.05$) (Table 2). Other indicators, including white blood cell count, creatinine, uric acid, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol showed no significant differences ($p>0.05$) (Table 2).

The Angiographic Findings of the Two Groups

The angiographic findings are shown in Table 3. The TFCs were significantly higher in patients with CSFP ($p<0.05$) (Table 3). From the aspect of the coronary arteries affected, the left anterior descending artery (LAD) comes first (80.6%), followed by right coronary artery (RCA) (76.3%) and the last was left circumflex artery (LCX) (54.8%). Moreover, from the number of vessels involved in CSFP, three vessels were the most common, accounting for 41.9% of the individuals (Table 3).

Table 3 Angiographic Findings of the Two Groups

	CSFP Group (n=93)	Control Group (n=186)	P value
TIMI frame count			<0.001
LAD	36.0±4.9	26.3±1.8	
LCX	23.0±4.8	18.9±2.5	
RCA	26.2±4.9	19.0±2.0	
Mean TFC	28.4±2.8	21.4±1.3	
Distribution of CSFP			
LAD, n (%)	75(80.6)		
LCX, n (%)	51(54.8)		
RCA, n (%)	71(76.3)		
Numbers of vessels involved in CSFP			
1, n (%)	28(30.1)		
2, n (%)	26(28.0)		
3, n (%)	39(41.9)		

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 CSFP

	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Current smoking	0.583	0.336–1.012	0.055			
Hypertension	0.744	0.446–1.239	0.256			
Diabetes mellitus	0.846	0.457–1.567	0.595			
FBG, mmol/l	1.576	1.000–2.486	0.050	1.599	0.973–2.625	0.064
LDL-C, mmol/l	0.910	0.630–1.314	0.615			
HDL-C, mmol/l	0.574	0.234–1.409	0.225			
ALI	0.996	0.994–0.997	<0.001	0.996	0.994–0.997	<0.001

Abbreviations: FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ALI, advanced lung cancer inflammation index.

Predictors for the Presence of CSFP

Univariate and multivariate logistic regression analyses were performed to identify the independent predictors of CSFP in patients with ANOCA. Univariate logistic regression analyses showed that FBG and ALI levels were significantly associated with CSFP ($p<0.05$) (Table 4). Multivariate logistic regression analysis revealed that ALI was an independent predictor of CSFP ($p<0.05$) (Table 4). The receiver operating characteristic (ROC) curve showed that when ALI was ≤389.5, the specificity was 0.624 and the sensitivity was 0.652 (AUC, 0.694; 95% CI, 0.633–0.755, P<0.001) (Figure 2). Moreover, ALI demonstrated a better predictive value than the indicators alone, including albumin level (AUC, 0.687; 95% CI, 0.625–0.749; P<0.001), BMI (AUC: 0.567; 95% CI, 0.498–0.637; p=0.066), and NLR (AUC, 0.673; 95% CI, 0.611–0.735; P<0.001) (Table 5, Figure 2).

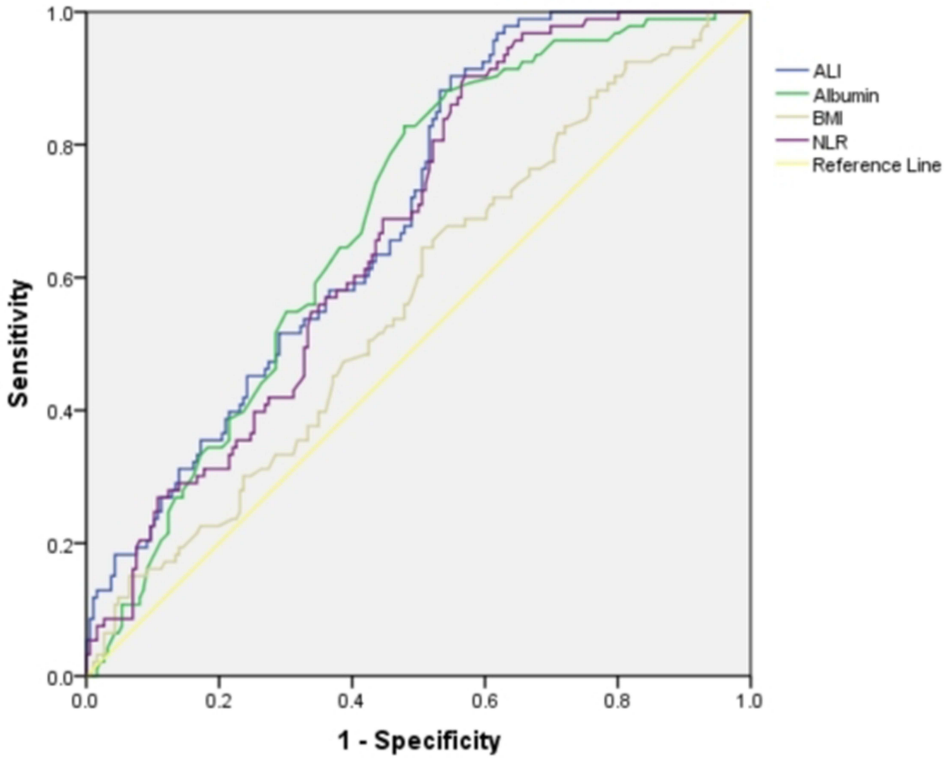

Figure 2 ROC curve showing the predictive value of risk factors for CSFP.

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Table 5 ROC Analysis of the Elated Parameters

	AUC	95% CI	P value
BMI, Kg/m^2	0.567	0.498–0.637	0.066
Albumin, g/L	0.687	0.625–0.749	<0.001
NLR	0.673	0.611–0.735	<0.001
ALI	0.694	0.633–0.755	<0.001

Abbreviations: BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; ALI, advanced lung cancer inflammation index.

Discussion

The incidence of CSFP in patients with ANOCA was 6.4%. Patients with CSFP have decreased ALI levels. Multivariable logistic regression analyses showed that a lower ALI was an independent predictor of CSFP in patients with ANOCA. Moreover, ALI showed reliable predictive value for the occurrence of CSFP in patients with ANOCA.

CSFP was first reported by Tambe et al and is characterized by slow blood flow with normal or nearly normal coronary arteries.[2] It was first recognized as an angiographic finding with undetermined clinical significance. However, with the rapid progress in interventional cardiology, the clinical significance of CSFP is increasingly being recognized. The findings of the affected coronary vessels or the number of vessels involved in CSFP were interesting in the present study. We found that the LAD artery was the most affected artery in patients with CSFP. In addition, all three affected vessels were predominant in the patients with CSFP. Multiple vessels may have a worse clinical prognosis. Further studies are required to confirm this hypothesis. In contrast to classic atherosclerotic cardiovascular disease, patients with CSFP tend to be younger and current smoking.[3,4] Moreover, the risk factors of CSFP remain unclear. The well-established cardiovascular risk factors have been inconsistent in previous studies. In the present study, we did not find any correlation among hypertension, diabetes, hyperlipidemia, and the presence of CSFP. We speculate that CSFP is a heterogeneous disease with a unique etiology. Therefore, exploring the predictors of CSFP is vital for risk stratification and the optimal management of these patients.

Inflammation has been suggested to be a potential pathogenesis of CSFP. Highly sensitive C-reactive protein has been suggested as a predictor of the presence of CSFP.[17] Li et al discovered that plasma interleukin-6 concentrations were positively correlated with TFC in patients with CSFP.[18] Moreover, in recent years, combined indicators derived from complete blood cell counts and biochemical indicators have been developed, providing a new perspective for understanding the etiology of CSFP. The NLR has been suggested as a significant marker of inflammation and has been demonstrated to be an independent predictor of CSFP occurrence.[16,19] Wang et al discovered that patients with CSFP had an increased systemic immune-inflammation index (platelet × neutrophil/lymphocyte ratio), which could serve as an independent predictor of CSFP.[5] More recently, the pan-immune-inflammation value (neutrophil count ×platelet count ×monocyte count × lymphocyte count) was proven to be a strong and independent predictor of CSFP.[20,21] In addition, the inflammatory burden index (CRP×NLR) and systemic inflammation response index (NLR×monocyte count) have been demonstrated to be reliable indicators for predicting CSFP.[7,8] These combined parameters comprise multiple indicators that can comprehensively reflect the degree of inflammatory response in different patients and may therefore provide a better predictive value in the presence of CSFP.

Plasma albumin is the most abundant protein in the human body and plays an important role in anti-inflammatory and antioxidant stress responses. It is well recognized that plasma albumin decreased as the inflammatory response increased.[22] A lower albumin level was associated with the occurrence of CSFP.[23] In recent years, combined indicators derived from albumin and other components have also been widely discussed for the prediction of CSFP. Yang discovered that the plasma fibrinogen-to-albumin ratio could serve as a valuable predictor of CSFP.[6] Zang et al suggested that the neutrophil-to-albumin ratio is closely related to CSFP.[9] In addition, the uric acid-to-albumin ratio[24] and C-reactive protein-to-albumin ratio[25] were suggested as novel predictors of CSFP.

BMI was used as a nutritional indicator in clinical practice. However, the role of BMI in CSFP remains to be elucidated. To date, only a few studies have demonstrated the predictive value of BMI for CSFP. They suggested that

higher BMI was associated with an increased risk of CSFP.[15] However, in the present study, we did not find any correlation between BMI and CSFP rate. We suggest that BMI in the previous study was significantly higher than that in the present study. The BMI was high as 33.9±8.2) in patients with CSFP in a previous study. Considering the significant association between BMI, NLR, albumin, and CSFP, we suggest that ALI (BMI×albumin/NLR) could provide a better predictive value for the presence of CSFP in patients with ANOCA. We found that patients with CSFP had lower ALI levels. Multivariable logistic regression analyses showed that a lower ALI was an independent predictor of CSFP in patients with ANOCA. Moreover, ALI showed reliable predictive value for the occurrence of CSFP in patients with ANOCA. This is the first time to report the correlation between ALI and CSFP. The significant association between ALI and CSFP can be interpreted as follows: First, ALI was calculated as BMI× albumin/NLR. It has been demonstrated that lower albumin levels and higher NLR are associated with an increased risk of CSFP due to an elevated inflammatory response. ALI may serve as a reliable indicator for predicting CSFP in patients with ANOCA. Secondly, as a new indicator for assessing inflammation, ALI has been suggested as a prognostic indicator for coronary artery disease. Wang et al suggested that an ALI score less than 334.96 could serve as a prognostic indicator for acute coronary syndrome after PCI.[11,12] ALI has also been demonstrated to be associated with all-cause death in hypertension,[14] heart failure[26,27] and ST-elevation myocardial infarction who underwent primary PCI.[13] A more recent study suggested that ALI is associated with the severity of coronary artery disease, as assessed using the SYNTAX score in patients with non-ST-elevation myocardial infarction.[28] Considering the well-established association between inflammation and cardiovascular disease, ANOCA is a subtype of coronary artery disease and we believe that ALI may participate in the initiation and development of CSFP in ANOCA patients. Atherosclerosis (as a chronic inflammatory diseases.[13] CSFP is an early phase of diffuse coronary atherosclerosis.[29] Therefore, it is reasonable to conclude that ALI and CSFP are correlated. As an easily calculated indicator in clinical practice, ALI is a reliable and accessible tool for the prediction and risk stratification of CSFP in ANOCA patients. ALI can comprehensively reflect the inflammatory and nutritional status, which may also serve as a promising indicator of prognosis. Although the real mechanism is still not fully understood, using this indicator, tailored treatments are performed in high-risk populations, which may improve the prognosis of these patients. Moreover, ALI could be used along with the existing risk scores so as to better identify the high risk patients.

Our study has several limitations. First, this was a single-center study with a limited sample size and we did not carry out a follow up. Second, ALI was calculated using indicators on admission. We did not record the data dynamically. Third, coronary angiography was performed by interventional cardiologists by using different angiographic projections. However, these factors did not significantly affect our results. Fourth, the study establishes associations, not causality, due to its observational design. Fifth, the study is cross-sectional, and external validation is lacking. So multicenter prospective validation studies are needed to confirm this results. Last, we did not perform a intra-coronary functional test, including the coronary flow reverse, index of microcirculatory resistance, or the provocation test, so we could not comprehensively understand the real etiology of CSFP.

Conclusion

We found that patients with CSFP had lower ALI levels. Multivariable logistic regression analyses showed that a lower ALI was an independent predictor of CSFP in patients with ANOCA. Moreover, ALI showed reliable predictive value for the occurrence of CSFP in patients with ANOCA. As an easily calculated indicator in clinical practice, ALI is a reliable and accessible tool for the prediction and risk stratification of CSFP in ANOCA patients, but further validation in diverse populations are needed.

Abbreviations

ALI, advanced lung cancer inflammation index; ANOCA, angina and nonobstructive coronary arteries; CSFP, slow coronary flow phenomenon; TIMI, thrombolysis in myocardial infarction; TFC: TIMI frame count.

Data Sharing Statement

Data supporting the conclusions of this article will be made available by the corresponding author upon request.

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Disclosure

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

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