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Association between the pan-immune-inflammation value and coronary collateral circulation in chronic total coronary occlusive patients

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Abstract

Background Inflammation and immunity play important roles in the formation of coronary collateral circulation (CCC). The pan-immune-inflammation value (PIV) is a novel marker for evaluating systemic inflammation and immunity. The study aimed to investigate the association between the PIV and CCC formation in patients with chronic total occlusion (CTO).

Methods This retrospective study enrolled 1150 patients who were diagnosed with CTO through coronary angiographic (CAG) examinations from January 2013 to December 2021 in China. The Cohen-Rentrop criteria were used to catagorize CCC formation: good CCC formation (Rentrop grade 2–3) and poor CCC formation group (Rentrop grade 0–1). Based on the tertiles of the PIV, all patients were classified into three groups as follows: P_1 group, PIV ≤ 237.56; P_2 group, 237.56< PIV ≤ 575.18; and P_3 group, PIV > 575.18.

Results A significant relationship between the PIV and the formation of CCC was observed in our study. Utilizing multivariate logistic regression and adjusting for confounding factors, the PIV emerged as an independent risk factor for poor CCC formation. Notably, the restricted cubic splines revealed a dose–response relationship between the PIV and risk of poor CCC formation. In terms of predictive accuracy, the area under the ROC curve (AUC) for PIV in anticipating poor CCC formation was 0.618 (95% CI: 0.584–0.651, $P < 0.001$). Furthermore, the net reclassification index (NRI) and integrated discrimination index (IDI) for PIV, concerning the prediction of poor CCC formation, were found to be 0.272 (95% CI: 0.142–0.352, $P < 0.001$) and 0.051 (95% CI: 0.037–0.065, $P < 0.001$), respectively. It's noteworthy that both the NRI and IDI values were higher for PIV compared to other inflammatory biomarkers, suggesting its superiority in predictive capacity.

Conclusions PIV was associated with the formation of CCC. Notably, PIV exhibited potential as a predictor for poor CCC formation and showcased superior predictive performance compared to other complete blood count-based inflammatory biomarkers.

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Keywords Pan-immune-inflammation value, Chronic total occlusion, Coronary collateral circulation

Introduction

Coronary artery disease (CAD) refers to the accumulation of atherosclerotic plaques and is a leading cause of mortality and morbidity worldwide [1]. CAD is caused by atherosclerosis which is a form of chronic inflammation. Chronic total occlusion (CTO) refers to the 100% coronary occlusion lasting for at least 3 months and the prevalence of CTO is nearly one-third in patients with CAD. CTO is a severe expression of advanced CAD and is associated with a worse prognosis [2]. Coronary collateral circulation (CCC) can serve as alternative bridge blood vessels to supply blood to the occluded segment of the distal myocardial ischemia area. Previous studies have shown that good CCC formation in patients with CTO can improve the survival and prognosis of patients [3, 4]. The CCC formation highly varies in different patients. The present methods for evaluating CCC formation, such as the Collateral Flow Index and intracoronary electrocardiogram are expensive and complex. Therefore, it is necessary to develop a simple and cost-effective biomarker to evaluate CCC formation.

The exact pathophysiology mechanisms of CCC formation are still not clearly identified. However, studies have revealed that inflammation can inhibit the collateral formation growth by interacting with new blood vessel formation. Studies have showed that the inflammatory biomarkers based on complete blood count, such as the platelet to lymphocyte ratio (PLR), and neutrophil to lymphocyte ratio (NLR) were associated with CCC formation and can serve as useful biomarkers to evaluate CCC formation [5–8]. The systemic immune-inflammation index (SII, platelet × neutrophil/lymphocyte ratioa) and the HALP score (hemoglobin, albumin, lymphocyte, and platelet) are also associated with inflammation [9, 10]. But, neither PLR nor NLR can comprehensively reflect the the complex immune and inflammatory contexture because they only evaluate the counts of two immune-inflammatory cells. Recently, the pan-immune-inflammation value (PIV) has emerged as a comprehensive immuno-inflammatory biomarker that can better reflect the immune and inflammatory status. The PIV incorporates all blood inflammatory cell types (e.g., neutrophils, lymphocytes, monocytes, and platelets). A recent study has shown that PIV was superior to NLR or PLR in predicting the prognosis of STEMI patients [11]. There are no relevant studies focusing on the role of PIV in predicting CCC formation. Therefore, the present study aimed to investigate the association between the PIV and CCC formation in patients with CTO and whether it is better than other inflammatory biomarkers in predicting CCC formation.

Materials and methods

Study population

This retrospective study enrolled 1150 patients who were diagnosed with CTO lesion in at least one major coronary artery(left anterior descending artery (LAD), left circumflex artery (LCA), and right coronary artery (RCA)) by coronary angiographic (CAG) examinations in the Department of Cardiology, Zhongnan Hospital of Wuhan University from January 2013 to December 2021. CTO lesion was defined as a total coronary artery occlusion of the coronary main vessel with thrombolysis in myocardial infarction (TIMI) 0 flow lasting for at least 3 months. Exclusion criteria: (1) congenital heart disease; (2) valvular heart disease; (3) history of old myocardial infarction or heart failure; (4) previous coronary artery bypass grafting or coronary intervention; (5) hematological diseases; (6) thyroid diseases infectious diseases; (7) malignant tumors; (8) severe hepatic or renal dysfunction; (9) autoimmune diseases; (10) treatment with hormones or immunosuppressants; (11) severe trauma or surgical operation within 3 months.

Laboratory measurement

All patients were required to fast for more than 10 h and then venous blood samples were obtained. Subsequently, laboratory parameters were measured, including platelet count (PLT), neutrophil count (NEUT), lymphocyte count (LYMP), monocyte count (MONO), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and lipoprotein(α) (Lp(α)). PIV, MLR, NLR, and PLR were calculated as follows: PIV=[neutrophil counts ($\times 10^9$/L) × platelet counts ($\times 10^9$/L) × monocyte counts ($\times 10^9$/L) / lymphocyte counts ($\times 10^9$/L)]; MLR=[monocyte counts ($\times 10^9$/L) / lymphocyte counts ($\times 10^9$/L)]; NLR=[neutrophil counts ($\times 10^9$/L) / lymphocyte counts ($\times 10^9$/L)]; PLR=[platelet counts ($\times 10^9$/L) / lymphocyte counts ($\times 10^9$/L)].

Assessment of outcome and data collection

The formation of CCC in patients with CTO was determined by coronary angiography (CAG), which was performed by two interventional experts based on the Judkin method through the radial or femoral artery. The Cohen-Rentrop criteria were used to assess grades of CCC formation [12]: Grade 0, without visible filling of any collateral artery; Grade 1, filling of the

side branches of the occluded artery but without filling of the epicardial arteries; Grade 2, filling of the epicardial artery partially; Grade 3, filling of the epicardial artery completely. The patients were divided into good CCC formation group (Rentrop grade 2–3) and poor CCC formation group (Rentrop grade 0–1). Additionally, the patients were divided into three groups according to the tertiles of the PIV. The name, age, sex, cardiovascular risk factors (smoking, hypertension and diabetes history) and CAG data of patients who met the criteria were collected.

Statistical analysis

Categorical, normal distribution, and non-normal distribution variables were presented as counts and percentages, mean and standard deviation, median and interquartile range, respectively. The Chi-square test was used to test categorical data. The Student's t-test was used for the analysis of quantified independent normal distribution data between the two groups, and the Mann–Whitney U-test was used when the Student's t-test conditions were not met. The one-way analysis of variance was used for the analysis of quantified independent normal distribution data between the three groups, and the Kruskal–Wallis test was used when the one-way analysis of variance conditions were not met. Spearmann's correlation was used for correlation analysis.

Logistic regression analysis was used to estimate the association of PIV with CCC formation (good or poor). Three models were constructed. Model 1 was the crude model. Model 2 adjusted for age, sex, smoking, hypertension, and diabetes, and model 3 further adjusted for TC, TG, LDL-C, and HDL-C. Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic value of PIV. DeLong's test was used to compare the the area under the curves (AUC). The net reclassification index (NRI) and the integrated discrimination index (IDI) were calculated to further evaluate the incremental diagnostic value of PIV. All analyses were conducted by SPSS 26.0 software (IBM Corp, Armonk, New York, USA) and R-studio software with R version 4.1.3. A two- tailed P value < 0.05 was considered statistical significance.

Results

Baseline characteristics

The average age of the 1150 patients was 61.78 ± 11.47 years, and 78.3% were men. According to the formation of CCC, they were divided into good CCC formation group (Rentrop grade 2–3, $n = 434$) and poor CCC formation group (Rentrop grade 0–1, $n = 716$). Table 1 shows the baseline characteristics of patients with good CCC formation and patients with poor CCC formation. The good CCC formation group had a higher proportion of multi-vessel lesions and higher HDL

Table 1 Baseline characteristics according to CCC formation (good CCC group vs. poor CCC group)

Variables	Total ($n = 1150$)	Good CCC ($n = 434$)	Poor CCC ($n = 716$)	*P* value
Age (years)	61.78 ± 11.47	62.70 ± 10.51	61.22 ± 11.99	0.034
Male (n, %)	900 (78.3)	342 (78.8)	558 (77.9)	0.729
Smoking	526 (45.7)	200 (46.1)	326 (45.5)	0.855
Hypertension (n, %)	685 (59.6)	247 (56.9)	438 (61.2)	0.154
Diabetes (n, %)	333 (29.0)	115 (26.5)	218 (30.4)	0.152
NEUT (×109/L)	5.44 (3.81,7.82)	5.00 (3.60,7.22)	5.70 (3.91,8.14)	< 0.001
LYMP (×109/L)	1.47 (1.10,1.90)	1.50 (1.10,1.93)	1.45 (1.12,1.89)	0.652
MONO (×109/L)	0.50 (0.39,0.66)	0.50 (0.40,0.68)	0.50 (0.39,0.65)	0.174
PLT (×109/L)	203.00 (158.25,245.00)	196.00 (150.75,236.00)	208.00 (166.00,253.00)	< 0.001
TC (mmol/L)	4.47 ± 1.11	4.33 ± 1.05	4.56 ± 1.13	0.001
TG (mmol/L)	1.43 (1.03,2.11)	1.41(0.95,1.99)	1.45 (1.05,2.23)	0.003
HDL-C (mmol/L)	1.03 ± 0.32	1.08 ± 0.42	0.99 ± 0.23	< 0.001
LDL-C (mmol/L)	2.81 ± 0.86	2.72 ± 0.79	2.87 ± 0.89	0.006
Lp(α) (mg/L)	133.80 (64.73,277.50)	145.00 (63.60,280.60)	128.30 (65.60,269.40)	0.105
Multi-vessel lesion (n, %)	136 (11.8)	86 (19.8)	50 (7.0)	< 0.001
Single-vessel lesion (n, %)	1014 (88.2)	348 (80.2)	666 (93.0)	< 0.001
Occlusive vessel (n, %)				
LAD (n, %)	398 (34.6)	143 (32.9)	255 (35.6)	0.357
LCX (n, %)	278 (24.2)	81 (18.7)	197 (27.5)	0.001
RCA (n, %)	499 (43.4)	221 (50.9)	278 (38.8)	< 0.001

Abbreviations: CCC: coronary collateral circulation; NEUT: neutrophil; LYMP: lymphocyte; MONO: monocyte. PLT: platelet; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Lp(α): lipoprotein(α); CTO: chronic total occlusion; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary arteries

levels, and lower levels of TC, TG, and LDL-C compared with the poor CCC formation group.

Table 2 shows the baseline characteristics according to tertiles of the PIV (P1 group, PIV ≤ 237.56; P2 group, 237.56< PIV ≤ 575.18; and P3 group, PIV > 575.18). Compared with the other two groups, the patients in P3 group had higher TC and HDL-C levels. There were no significant differences in age, sex, and history of smoking, hypertension and diabetes between the groups.

The correlations between the PIV and traditional cardiovascular risk indicators of CAD were examined. Figure 1 shows that the PIV was positively linked to TC and LDL-C levels.

Association between the PIV and CCC formation

The results of Spearman correlation analysis showed that the PIV (r=-0.099, P=0.001) was negatively correlated with CCC formation (good or poor). As shown in Fig. 2, the PIV of patients with poor CCC formation (median 406.50, IQR: 209.96–786.60) was significantly higher than those with good CCC formation (median 333.42, IQR: 161.87-616.65) (Fig. 2A). The proportion of poor CCC formation (55.7% vs. 63.5% vs. 67.5%, P=0.003) increased stepwise from the lowest PIV tertile to the highest one (Fig. 2B). Then, the groups were pairwise compared (P_1 vs. P_2, P_2 vs. P_3, P_1 vs. P_3) by using corrected alpha (α = 0.05/3 = 0.017). The prevalence of poor CCC formation in P_3 group was significantly higher than that in the P_1 group (P=0.001), but not P_2 group (P=0.244), and no significant difference between P_2 group and P_1 group (P=0.027).

Table 3 shows the OR and 95% CI of PIV for poor CCC formation based on the PIV tertiles. Unadjusted logistic regression analysis shows that using the P_1 group as a reference, the risk of Poor CCC formation for the P_2 and P_3 groups was 1.286-fold higher (OR 1.385, 95% CI 1.110–1.489; P=0.028) and 1.385-fold higher (OR 1.286, 95% CI 1.037–1.849; P=0.001), respectively (Model 1). After adjusting for age, sex, smoking, hypertension, diabetes, TC, TG, LDL-C, HDL-C, the P_2 group (OR 1.283, 95% CI 1.101–1.494, P=0.049) and P_3 group (OR 1.349, 95% CI 1.001–1.818, P=0.001) were also independently associated with poor CCC formation (Model 3).

The restricted cubic splines are presented in Fig. 3. A dose–response relationship between the PIV and risk of poor CCC formation was observed (non-linear P=0.585).

Evaluate the diagnostic and predicted incremental value of PIV for poor CCC formation

Figure 4 presents ROC curve of evaluating the diagnostic value of different models for poor CCC formation. The area under the ROC curve (AUC) of PIV was 0.618 (95% CI: 0.584–0.651, P<0.001) (Fig. 4A). The optimal cut-off point of PIV for poor CCC formation

Table 2 Baseline characteristics according to tertiles of the PIV

Variables	P_1(n=384)	P_2(n=384)	P_3(n=382)	P value
Age (years)	62.33 ± 10.18	62.34 ± 12.07	60.67 ± 12.00	0.068
Male (n, %)	296 (77.1)	300 (78.1)	304 (79.6)	0.702
Smoking	174 (45.3)	172 (44.8)	180 (47.1)	0.794
Hypertension (n, %)	215 (56.0)	241 (62.8)	229 (59.9)	0.158
Diabetes (n, %)	113 (29.4)	101 (26.3)	119 (31.2)	0.324
NEUT (×109/L)	3.37 (2.89,4.09)	5.56 (4.60,6.85)	8.85 (6.76,11.23)	< 0.001
LYMP (×109/L)	1.65 (1.35,2.05)	1.49 (1.15,1.91)	1.20 (0.90,1.62)	< 0.001
MONO (×109/L)	0.40 (0.32,0.50)	0.51 (0.42,0.63)	0.66 (0.50,0.83)	< 0.001
PLT (×109/L)	179.00 (140.00,213.50)	200.00 (159.00,242.00)	236.00 (192.00,271.00)	< 0.001
TC (mmol/L)	4.42 ± 1.11	4.42 ± 1.07	4.57 ± 1.13	0.085
TG (mmol/L)	1.50 (1.02,2.25)	1.51 (1.15,2.00)	1.33 (0.95,2.00)	0.011
HDL-C (mmol/L)	1.05 ± 0.40	0.98 ± 0.23	1.05 ± 0.30	0.003
LDL-C (mmol/L)	2.72 ± 0.87	2.78 ± 0.82	2.94 ± 0.87	0.001
Lp(α) (mg/L)	128.35 (58.60,255.43)	156.60 (77.90,309.50)	117.80 (58.55,253.15)	0.018
Multi-vessel CTO (n, %)	54 (14.1)	30 (7.8)	52 (13.6)	0.011
Single-vessel CTO (n, %)	330 (85.9)	354 (92.2)	330 (86.4)	0.011
Occlusive vessel (n, %)				
LAD (n, %)	112 (33.9)	120 (33.9)	122 (37.0)	0.634
LCX (n, %)	84 (25.5)	94 (26.6)	60 (18.2)	0.021
RCA (n, %)	134 (40.6)	140 (39.5)	148 (44.8)	0.336

Abbreviations: NEUT: neutrophil; LYMP: lymphocyte; MONO: monocyte. PLT: platelet; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; Lp(α): lipoprotein(α); CTO: chronic total occlusion; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary arteries

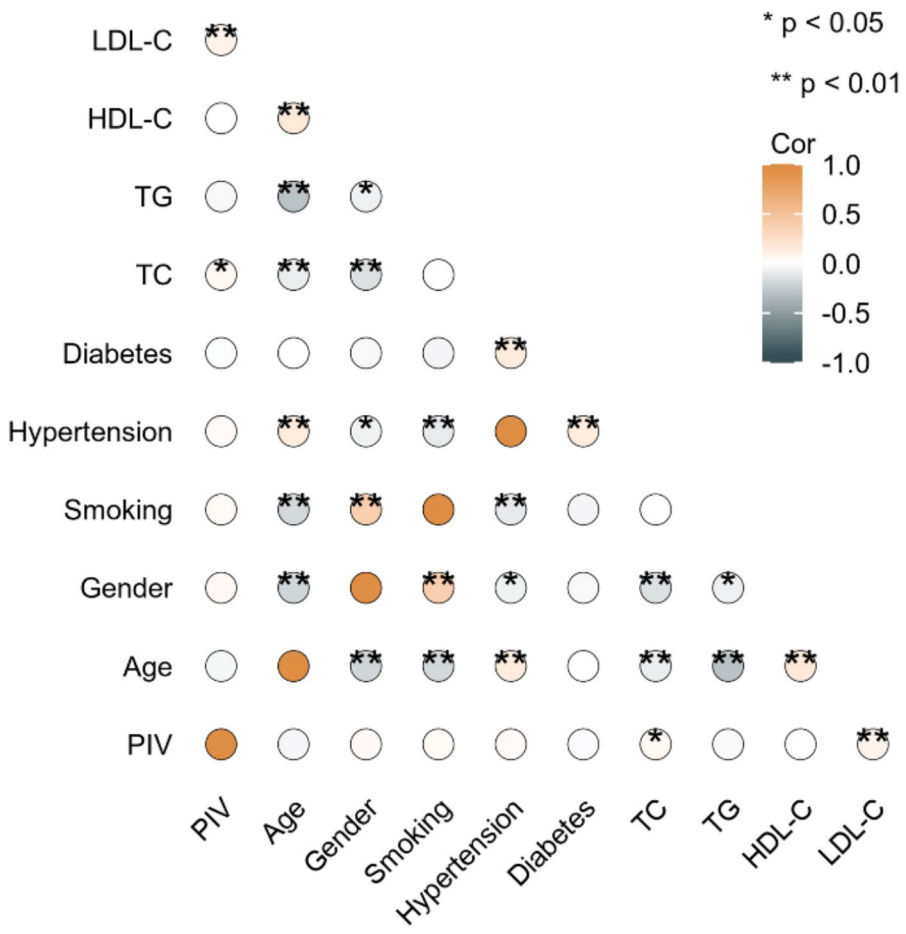

Fig. 1 Correlations between the PIV and traditional cardiovascular risk factors
Abbreviations: PIV: pan-immune-inflammation value; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

was 274.16, with 42.9% sensitivity and 76.0% specificity. Then, a baseline model was constructed using the risk factors that may be associated with poor CCC formation in the above analysis (i.e., age, sex, smoking, hypertension, diabetes, TC, TG, HDL-C, LDL-C and multi-vessel lesions). The improvement of the AUC for predicting poor CCC formation was most significant when adding the PIV to the baseline model (Fig. 4B). De Long test was used to compare if there was any statistical difference between the above 5 models. The results are presented in a Table 4. After inclusion of the PIV into baseline model, the NRI and IDI of PIV for predicting poor CCC formation were 0.272 (95% CI: 0.142–0.352, $P<0.001$) and 0.051 (95% CI: 0.037–0.065, $P<0.001$), respectively (Table 5). It's noteworthy that both the NRI and IDI values were higher for PIV compared to other inflammatory biomarkers, suggesting its superiority in predictive capacity. The NRI of poor and good CCC formation groups were 0.180 (95% CI: 0.078–0.263, $P<0.001$) and 0.093 (95% CI: 0.007–0.156, $P<0.001$), respectively.

Discussion

In our study, we found that PIV was an independent risk factor for poor CCC formation after adjusting for confounding factors, including sex, age, smoking, hypertension, diabetes, TC, TG, LDL-C, HDL-C. The proportion of poor CCC formation increased stepwise from the lowest PIV tertile (P_1 group) to the highest one (P_3 group). Additionally, PIV is a potential novel biomarker for predicting poor CCC formation and was superior to other complete blood count-based inflammatory biomarkers (i.e., NLR, MLR, PLR).

CCC exerts cardioprotective effect by restoring blood flow in the ischemic area of the myocardium. A well-developed CCC formation can improve ventricular function and reduce infarct size. Moreover, studies have shown that a well-developed CCC formation could decrease cardiovascular events, reduce mortality

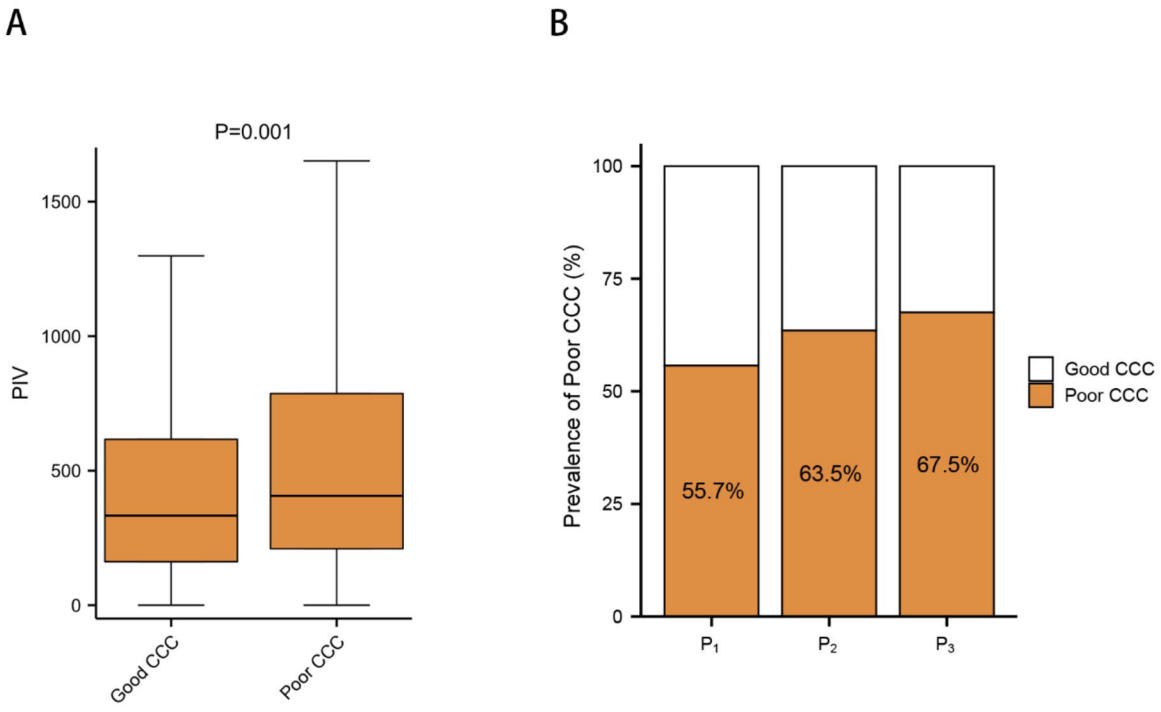

Fig. 2 (**A**) Comparison of the PIV between good CCC group and poor CCC group. (**B**) The prevalence of poor CCC according to the tertiles of the PIV
Abbreviations: CCC: coronary collateral circulation; PIV: pan-immune-inflammation value

Table 3 The OR and 95% CI of PIV for poor CCC formation

	Model 1		Model 2		Model 3	
	OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*
P_1	Reference		Reference		Reference	
P_2	1.286 (1.110–1.489)	0.028	1.268 (1.093–1.470)	0.027	1.283 (1.101–1.494)	0.049
P_3	1.385 (1.037–1.849)	0.001	1.388 (1.038–1.857)	0.002	1.349 (1.001–1.818)	0.001

Model 1: unadjusted

Model 2: adjusted for age + sex + smoking + hypertension + diabetes

Model 3: adjusted for Model 2 + TC + TG + LDL-C + HDL-C

Abbreviations: CCC: coronary collateral circulation; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; OR: Odds ratio; CI: Confidence interval

risk, and improve the prognosis of patients with CTO [13–15]. The process of CCC formation is complex involving angiogenesis and arteriogenesis. Several factors affect its development and inflammation is one of them. A variety of adhesion molecules and vascular endothelial growth factors (VEGF) secreted by different types of cells, in particular endothelial cells, play important roles in angiogenesis [16, 17]. Chronic inflammation affects the formation of CCC by leading to endothelial dysfunction in ways, such as through increasing the production of reactive oxygen species [18]. Both platelets and subtypes of leucocytes, such as neutrophils, lymphocytes and monocytes are effector cells of inflammation. Platelets contain a number of angiogenesis inhibitors and promoters to regulate new blood vessel growth in response to ischemia. Angiostatin, one of angiogenesis inhibitors, is especially important in the development of CCC. It has been reported that angiostatin could inhibit production of nitric oxide and reduce coronary angiogenesis, and the levels of angiostatin are negatively associated with CCC formation in patients who had undergone coronary bypass surgery [19]. Neutrophils release a large number of reactive oxygen species by promoting the production of inflammatory mediators and proteolytic enzymes, which directly cause damage to the vascular endothelium. High levels of neutrophil counts were associated with poor collateral development.

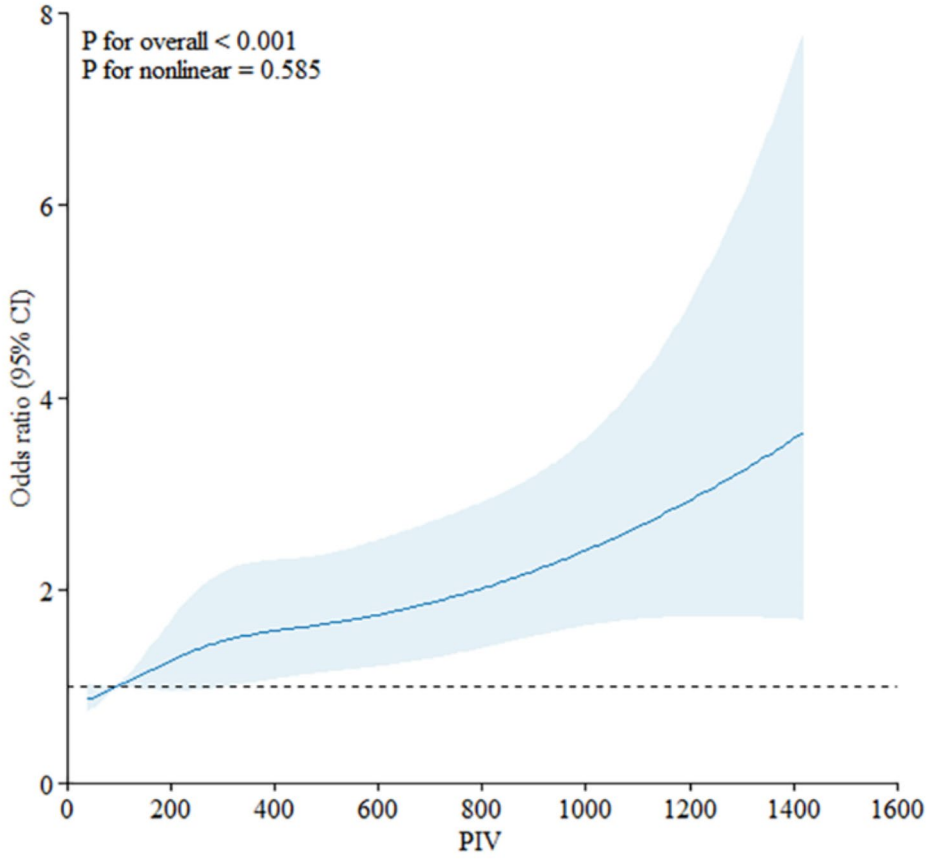

Fig. 3 Restricted cubic splines for the odds ratio of poor CCC formation
Abbreviations: CCC: coronary collateral circulation; PIV: pan-immune-inflammation value; CI: confdence interval

Monocytes promote angiogenesis. But, it is tissue resident monocytes rather than circulating monocytes that play an important role in arteriogenesis [20]. Monocytes also cause local ischemia and endothelial dysfunction. A study has shown that patients with poorly developed CCC had higher values of monocyte counts than patients with well-developed CCC [5]. The lymphocyte counts will reduce in response to inflammation. This decrease in lymphocytes can inhibit CCC formation by leading to reductions in VEGF and other factors related to collateral angiogenesis, and decreased vascular infiltration [21].

Table 4 Comparative analysis of AUC of different models in diagnosing poor CCC formation

Variables	AUC(95%CI)	*P* value
+PIV	0.645(0.612–0.679)	Reference
Baseline	0.578(0.544–0.612)	< 0.001
+MLR	0.624(0.590–0.658)	0.032
+NLR	0.633(0.599–0.666)	0.203
+PLR	0.534(0.600-0.668)	0.275

Abbreviations: CCC: coronary collateral circulation; PIV: pan-immune-inflammation value; PLR: platelet to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio; AUC: area under the receiver operating characteristic; CI: confidence interval

Based on the above, various inflammatory biomarkers based on peripheral immune cell have been developed which can serve as diagnostic markers for CCC formation in patients with CTO: neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR). All these inflammatory markers have been shown to be associated with the CCC formation in patients with CTO and can be predictors of the CCC formation [5–8]. But, None of them can comprehensively reflect the complex immune contexture because they only evaluate the counts of two immune-inflammatory cells. Thus, the PIV has been proposed as a comprehensive immuno-inflammatory biomarker that can better reflect the immune and inflammatory status because it incorporates all blood inflammatory cell types.

PIV was first proposed by Fuca et al. in 2020. Fuca et al. found that PIV was superior to other immune-inflammatory biomarkers in predicting survival outcomes in patients with metastatic colorectal cancer [22]. Since then, more and more studies about PIV

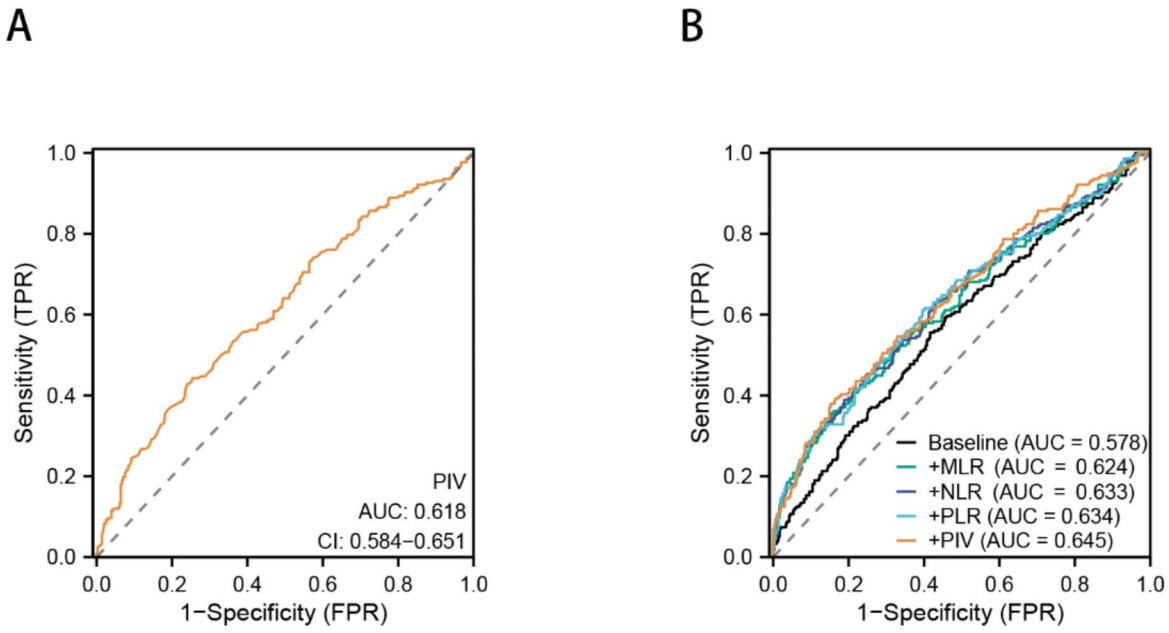

Fig. 4 ROC curve of evaluating the diagnostic value of different models for poor CCC formation. (**A**) the ROC curve of PIV for poor CCC formation. (**B**) The discriminative value of different models for evaluating poor CCC formation using ROC curve
Abbreviations: CCC: coronary collateral circulation; PIV: pan-immune-inflammation value; NLR: neutrophil to lymphocyte ratio; MLR: monocyte to lymphocyte ratio; PLR: platelet to lymphocyte ratio; ROC: receiver operating characteristic; AUC: area under the ROC curve; CI: confdence interval

have emerged and most of them focused on cancer [23]. There are only two studies that investigated the effect of PIV in cardiovascular disease so far. One study showed that PIV was superior to NLR or PLR in predicting early and late prognosis in STEMI patients [11]. Another study showed that PIV was an independent risk factor for long-term and all-cause cardiovascular mortality in hypertensive patients [24]. No study has explored the association between the PIV and CCC formation in patients with CTO. As far as we know, this is the first study to investigate the association between the PIV and CCC formation in patients with CTO.

However, there are some limitations in our study. First, the most important limitation of the study is that it is a retrospective study. So, we can not prove a causal relationship between the PIV and CCC formation. Second, we only collected the data from a single hospital. Third, the participants were only inpatients in a Chinese hospital. At last, the AUC of PIV was only 0.618 and the correlation between the PIV and CCC formation was weak. Therefore, multi-center, large-sample, prospective studies are needed to further explore the association between the PIV and CCC formation in patients with CTO.

Conclusions

PIV was associated with the formation of CCC. Notably, PIV exhibited potential as a predictor for poor CCC formation and showcased superior predictive

Table 5 Evaluate risk discriminative value of different models for poor CCC formation

	ROC analysis		Categorical NRI		IDI	
	AUC(95%CI)	*P*	Estimation(95%CI)	*P*	Estimation(95%CI)	*P*
Baseline	0.578 (0.544–0.612)		Reference		Reference	
+MLR	0.624 (0.590–0.658)	< 0.001	0.190 (0.086–0.287)	< 0.001	0.044 (0.030–0.057)	< 0.001
+NLR	0.633 (0.599–0.666)	< 0.001	0.174 (0.083–0.269)	< 0.001	0.042 (0.029–0.055)	< 0.001
+PLR	0.634 (0.600-0.668)	< 0.001	0.176 (0.079–0.274)	< 0.001	0.043 (0.030–0.056)	< 0.001
+PIV	0.645 (0.612–0.679)	< 0.001	0.272 (0.142–0.352)	< 0.001	0.051 (0.037–0.065)	< 0.001

Abbreviations: ROC: receiver operating characteristic; NRI: net reclassification improvement; IDI: Integrated discrimination improvement; AUC: area under ROC; CI: confidence interval; PIV: pan-immune-inflammation value; NLR: neutrophil to lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio; PLR: platelet to lymphocyte ratio; CCC: coronary collateral circulation

performance compared to other complete blood count-based inflammatory biomarkers.

Abbreviations

AUC	Area under the ROC curve
CAD	Coronary artery disease
CAG	Coronary angiography
CCC	Coronary collateral circulation
CI	Confdence interval
CTO	Chronic total occlusion
FPG	Fasting plasma glucose
HDL-C	High-density lipoprotein cholesterol
IDI	Integrated discrimination index
LAD	Left anterior descending
LCX	Left circumflex
LDL-C	Low-density lipoprotein cholesterol
LMR	Lymphocyte to monocyte ratio
Lp(α)	Lipoprotein(α)
LYMP	Lymphocyte
MLR	Monocyte to lymphocyte ratio
MONO	Monocyte
NEUT	Neutrophil
NLR	Neutrophil to lymphocyte ratio
NRI	Net reclassification index
OR	Odds ratio
PIV	Pan-immune-inflammation value
PLR	Platelet to lymphocyte ratio
PLT	Platelet
RCA	Right coronary arteries
ROC	Receiver operating characteristic
TC	Total cholesterol
TG	Triglycerides
VEGF	Vascular endothelial growth factors

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Author contributions
BZ and YL designed the research study. BZ and YL performed the research. AP, CL, and YF provided help and advice on data collecting. BZ analyzed the data. BZ, YL and JL wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors reviewed the manuscript.

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Data availability
All data generated or analyzed of this study are included in this article.

Declarations

Ethics approval and consent to participate
The study was approved by the ethics committee of Zhongnan Hospital (ethics approval number 2023188 K). The informed consent was obtained from all patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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