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Novel lipid biomarkers and ratios as risk predictors for premature coronary artery disease: A retrospective analysis of 2952 patients

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Abstract

This study examined the associations between emerging lipid biomarkers (small dense low-density lipoprotein cholesterol [sdLDL-C), lipoprotein(a) [Lp(a)], and free fatty acids [FFA]), two ratios (sdLDL-C/LDL-C and the triglyceride–glucose [TyG) index), and the Gensini score (GS) in patients with premature coronary artery disease (PCAD) in relation to the extent of coronary stenosis. The authors evaluated a cohort of 2952 individuals undergoing coronary angiography (CAG), encompassing those with PCAD (n = 1749), late-onset coronary artery disease (LCAD; n = 328), and non-coronary artery disease (non-CAD; n = 575). Noteworthy differences were observed in the levels of the novel lipid biomarkers and ratio indexes among the PCAD, LCAD, and non-CAD groups ($p < .05$). Multiple logistic regression analyses pinpointed Lp(a) (OR = 2.62, 95% CI 1.22–5.63, $p = .014$) and the TyG index (OR = 2.53, 95% CI 1.08–5.93, $p = .033$) as independent risk factors for PCAD. Furthermore, these biomarkers and ratio indexes discerned substantial distinctions among PCAD patients with varying GS ($p < .05$). Consequently, these markers can proficiently anticipate the gravity of coronary artery stenosis (GS > 40) in PCAD patients, as evidenced by the ROC analysis. In conclusion, sdLDL-C, Lp(a), FFA, and the sdLDL-C/LDL-C and TyG indexes have considerable potential as risk and diagnostic markers for coronary artery stenosis in individuals afflicted with PCAD.

KEYWORDS
FFA, Lp(a), premature coronary artery disease, sdLDL-C, TyG index

1 | INTRODUCTION

Coronary artery disease (CAD) reduces the heart blood flow, myocardial ischemia, hypoxia, or necrosis due to coronary artery atherosclerosis or narrowing or even occlusion of the lumen. Based on pertinent research, CAD primarily contributes to mortality and premature demise in the Chinese population.[1] Premature CAD (PCAD) is a specific form of CAD, and approximately 3%–10% of all CAD cases involve younger people.[2] It is therefore believed that the poor diet and sedentary lifestyle of the youth have contributed to their increased incidence of PCAD in recent years.[3] Statistical reports have suggested that approximately 50% of all patients with PCAD develop substantive progression of coronary atherosclerosis within 10 years and 20% of patients with PCAD die prematurely.[4] Therefore, in recent years, increasing numbers of studies have been conducted on patients with PCAD.[5–8]

In 2019, the American College of Cardiology and the American Heart Association (ACC/AHA) proposed the guidelines for CAD risk assessment, which suggested that familial history, coronary artery calcification score, and serum high-sensitivity C-reactive protein serve as indicators for CAD diagnosis.[9] Additional research has demonstrated a correlation between the serum markers and the incidence, progression, and prognostication of CAD.[10] Despite the similarity in developing late-onset CAD (LCAD) and PCAD, a past study revealed distinct differences in plaque morphology and composition.[11] The present study suggested that the biomarkers of LCAD may not be used as biomarkers for PCAD. Therefore, biomarkers easily detected with high specificity and sensitivity should be identified for risk assessment and for distinguishing PCAD from LCAD.

Past research indicated that the level of lipoprotein(a) [Lp(a)] and the triglyceride–glucose (TyG) index are distinct factors that contribute to the development of CAD.[12–15] Multiple recent studies have suggested that the concentration of Lp(a) is linked to the existence and severity of PCAD.[7,8] An additional study indicated that the TyG index plays a crucial indicative function in assessing the risk levels and in implementing early clinical intervention for PCAD.[5,6] In different low-density lipoprotein cholesterol (LDL-C) subgroups, small dense low-density lipoprotein cholesterol (sdLDL-C) demonstrates the characteristics of small size, high density, wide contact area, a long plasma half-life, low affinity for liver LDL receptors, susceptibility to oxidation, and ease of deposition in the tunica intima.[16] Hence, sdLDL-C has a higher propensity to induce atherosclerosis. Previous research has indicated that sdLDL-C can worsen the development of atherosclerosis through the modulation of gene networks, monocytes, and enzyme activities.[17] Many fatty acids are stored as triacylglycerol (TAG) through esterification in the human body.[18] The breakdown of TAG through lipolysis serves as the primary source of free fatty acids (FFA). FFA predominantly attaches to albumin within the bloodstream for circulation.[19] Prior research has indicated that the FFA levels in the bloodstream increase in metabolic disorders, such as obesity, type 2 diabetes, and cardiovascular diseases. Increased FFA may promote ectopic lipid deposition and vascular and cardiac dysfunction.[20] However, the role of lipid biomarkers (sdLDL-C and FFA) in PCAD disease and severe stratification is unknown. We investigated the connection between lipid markers [sdLDL-C, Lp(a), and FFA] and two ratios (sdLDL-C/LDL-C and TyG index) along with the occurrence and development of PCAD and coronary severity in a large cohort of Chinese participants.

2 | MATERIALS AND METHODS

2.1 | Study participants

We included hospitalized patients who underwent coronary angiography (CAG) due to chest discomfort at the Anzhen Hospital from January 2018 to June 2019. The inclusion criteria for the study patients are as follows: for patients with PCAD: (1) male patients aged <55 years or female patients aged <65 years, and all patients aged >18 years; (2) CAG indicating that no more than one main coronary artery stenosis was >50%; (3) complete record and availability of clinical and biochemical indicators. For patients with LCAD: (1) male patients aged 55—65 years and female patients aged 65—75 years; (2) CAG indicated that no more than one main coronary artery stenosis was >50%; and (3) complete record and availability of clinical and biochemical indicators. For patients with non-CAD: (1) male patients aged <55 years or female patients aged <65 years, and all patients aged >18 years; (2) CAG indicated that no more than one main coronary artery stenosis was <50% or normal, and (3) complete record and availability of clinical and biochemical indicators. On the other hand, patients with PCAD and LCAD who fulfilled the following criteria were excluded from the study: (1) rheumatic heart disease, other organic heart diseases (such as cardiomyopathy, valvular heart disease, and pulmonary heart disease); (2) combined with serious infection and tumor; (3) severe chronic hepatic and renal dysfunction; (4) thyroid function disease (hyperthyroidism or hypothyroidism), autoimmune disease, major surgery or trauma, or burn occurred in the past two months, or any other major stress events; (5) previous application history of lipid-lowering and lipid-regulating drugs, non-steroidal anti-inflammatory, and analgesic drugs and antioxidants; (6) other potential inflammation-related factors; or (7) pregnancy. Furthermore, exclusion criteria for the non-CAD patients were as follows: (1) rheumatic heart disease; (2) combined with severe infection and tumor; (3) severe chronic hepatic and renal dysfunction; (4) thyroid function disease (hyperthyroidism or hypothyroidism), autoimmune disease, major surgery or trauma or burn occurred in the past 2 months, or other major stress events; (5) previous application history of lipid-lowering and lipid-regulating drugs, non-steroidal anti-inflammatory, analgesic drugs and antioxidant; (6) other potential inflammation-related factors; or (7) pregnancy. An ethical committee of Beijing Anzhen Hospital, Capital Medical University approved this study (Ethics number: 2023095X).

2.2 | Clinical parameters

We gathered demographic, clinical, and laboratory data from all participants. Blood samples were procured within 24 h of hospital admission,

specifically in the morning and while the patients were fasting. These samples were then analyzed within 4–6 h of collection using the Beckman AU5400 (US) automated biochemical analyzer to assess lipid parameters and other biochemical indices. The Sysmex XE-2100 was utilized for further blood analyses, all performed according to the manufacturer's guidelines. We upheld rigorous quality control standards, continuously monitoring all acquired data throughout the analysis. The TyG index was calculated using the follows formula: ln [fasting triglycerides (mmol/L) × fasting glucose (mmol/L)]/2. To gauge the severity of coronary artery stenosis in CAD patients, we referenced the Gensini score (GS) methodology, specifically employing the GS method.[21] Two interventional cardiologists independently reviewed the CAG outcomes, determining the severity of coronary artery stenosis. Subsequently, we sorted PCAD patients into three categories based on their GS scores: Group I, with a GS of less than 20; Group II, a GS ranging from 20 to less than 40; and Group III, showcasing a GS of 40 or higher.

2.3 | Statistical analyses

The data were analyzed with SPSS statistics version 26.0 (IBM Corp., Armonk, NY) software. All quantitative data were tested for normality. If the data conformed to the normal distribution, it was represented by mean ± standard deviation; if the data was skewed, it was represented by the median and quartile (25% and 75% Q). The Mann—Whitney—Wilcoxon test was used to compare the data between the two groups, while Chi-square tests were performed to compare the categorical data. The Kruskal–Wallis test with Dunn's post-hoc test was applied to compare the data from the three study groups. Quantitative data comparison was plotted using GraphPad Prism version 6.0 (Inc., San Diego, CA) software. Independent risk factors for PCAD were analyzed using the Hosmer Lemeshow test for multivariate logistic regression. Spearman's correlational analysis revealed the relationship between GS and serum biomarkers. The receiver operating characteristic (ROC) curve of SPSS 26.0 was used to select the cutoff values for sdLDL-C, Lp(a), FFA, sdLDL-C/LDL-C, and TyG index in order to compare the accuracy of these markers with the assessment of coronary artery stenosis. For these markers, the value with the highest Youden's Index score (sensitivity + specificity −1) was considered to indicate the cutoff point. $p < .05$ was considered to indicate statistical significance. The combined diagnosis ROC analysis was performed using MedCalc Statistical Software (Version 19.2.6).

3 | RESULTS

3.1 | Clinical data of patients

The baseline clinical characteristics and laboratory findings of PCAD, LCAD, and the non-CAD groups are displayed in Table 1. We enrolled 2952 patients in this study, including 1749 patients with PCAD, 628 with LCAD, and 575 with non-CAD. Significant differences were noted in the patients' clinical information, including age, male, body mass index (BMI), hypertension, diabetes mellitus, smoking, drinking, and family history of CAD among patients with PCAD, LCAD, and non-CAD ($p < .05$). Meanwhile, diabetes mellitus was only significantly different between the PCAD and non-CAD groups ($p < .05$) but not between the PCAD and LCAD groups. Family history of CAD was only significantly different between the PCAD and LCAD groups ($p < .05$) but not between the PCAD and non-CAD groups. Furthermore, the traditional lipid index [triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and LDL-C], novel lipid biomarkers [sdLDL-C, Lp(a), and FFA], and two ratio indexes (sdLDL-C/LDL-C and TyG index) indicated significant differences among patients with PCAD, LCAD, and non-CAD ($p < .05$) (Figure 1). FFA was only significantly different between the PCAD and non-CAD groups ($p < .05$) but not between the PCAD and CAD groups.

3.2 | Logistic analysis of PCAD

Table 2 illustrates the logistic analysis of the PCAD. According to the univariate logic analysis, only BMI was not a risk factor for PCAD, whereas all others were risk factors for PCAD ($p < .05$). Notably, sdLDL-C (OR = 4.65, 95% CI 3.39—6.38, $p < .0001$), Lp(a) (OR = 2.21, 95% CI 1.33—3.76, $p = .002$), FFA (OR = 3.34, 95% CI 2.13—5.23, $p < .0001$), sdLDL-C/LDL-C (OR = 6.20, 95% CI 3.05—12.60, $p < .0001$), and TyG index (OR = 8.28, 95% CI 3.63—18.90, $p < .0001$) were significantly associated with PCAD. According to the multiple logistic regression analyses, hypertension (OR = 2.24, 95% CI 1.62—3.09, $p < .0001$), diabetes mellitus (OR = 4.91, 95% CI 3.03—7.96, $p < .0001$), TC (OR = 1.78, 95% CI 1.47—2.15, $p < .0001$), Lp(a) (OR = 2.62, 95% CI 1.22—5.63, $p = .014$), and TyG index (OR = 2.53, 95% CI 1.08—5.93, $p = .033$) acted as independent risk factors for patients with PCAD after adjusting for sex, BMI, smoking, drinking, TG, TC, HDL-C, LDL-C, sdLDL-C/LDL-C, Lp(a), and FFA. Furthermore, age (OR = 0.90, 95% CI 0.88—0.92, $p < .0001$) and HDL-C (OR = 0.34, 95% CI 0.18—0.63, $p = .001$) were independent protective factors for patients with PCAD after adjusting for sex, BMI, smoking, drinking, TG, TC, HDL-C, LDL-C, sdLDL-C/LDL-C, Lp(a), and FFA.

3.3 | Comparison of clinical data and laboratory results among patients with PCAD having different GS

Clinical details and laboratory outcomes for PCAD patients with various GS are delineated in Table 3. A subset of clinical variables, including age, sex (male), hypertension, and smoking status, exhibited significant differences across groups I, II, and III ($p < .05$). Specifically, the variables of age, sex (male), and smoking displayed marked distinctions between groups I and II as well as between groups I and III. Conversely, considerable disparities were observed in clinical attributes such as sex (male) and hypertension between groups I and II and groups II and III. Notably, the BMI presented significant variation exclusively between

TABLE 1 Demographic, clinical characteristics, and laboratory findings among PCAD, LCAD, and non-CAD.

	Total patients ($n = 2952$)	PCAD ($n = 1749$)	LCAD ($n = 628$)	non-CAD ($n = 575$)	p value
Age (years)	54 (48–63)	51 (46–54)*,**	67.5 (63–72)	55 (50–62)	***<.0001***
Male, *n* (%)	1818 (61.6)	1176 (62.2)*,**	348 (55.4)	294 (51.1)	***<.0001***
BMI (kg/m^2)	25.78 (23.67–28.00)	26.14 (24.06–28.37)*,**	25.20 (23.38-27.35)	25.28 (22.98-27.18)	***<.0001***
Hypertension, *n* (%)	1659 (56.2)	1037 (59.3)*,**	417 (66.4)	205 (35.7)	***<.0001***
Diabetes mellitus, *n* (%)	797 (27.0)	529 (30.2)**	214 (34.1)	54 (9.4)	***<.0001***
Smoking, *n* (%)	954 (33.0)	808 (46.2)*,**	3 (0.5)	143 (27.4)	***<.0001***
Drinking, *n* (%)	685 (23.7)	560 (32.0)*,**	2 (0.3)	123 (23.6)	***<.0001***
Family history of CAD, *n* (%)	181 (6.2)	126(7.2)*	30 (4.8)	25 (4.8)	*.031*
TG (mmol/L)	1.44 (1.03–2.04)	1.57 (1.12–2.28)*,**	1.33 (0.97–1.89)	1.26 (0.9–1.68)	***<.0001***
TC (mmol/L)	4.11 (3.51–4.81)	4.20 (3.56–4.99)*,**	4.12 (3.47–4.83)	3.87 (3.45–4.40)	***<.0001***
HDL-C (mmol/L)	1.07 (0.92–1.26)	1.04 (0.90–1.21)*,**	1.12 (0.96–1.32)	1.13 (0.97–1.32)	***<.0001***
LDL-C (mmol/L)	2.42 (1.89–2.99)	2.50 (1.96–3.13)*,**	2.41 (1.83–3.00)	2.26 (1.85–2.66)	***<.0001***
Glu (mmol/L)	5.77 (5.14–7.32)	5.72 (5.14–7.24)*,**	6.18 (5.27–8.14)	5.47 (4.96–6.19)	***<.0001***
Hb (g/L)	140 (126–151)	141 (115–153)	139 (130–149.8)	139 (129–149)	.411
Cr (μmol/L)	67.4 (57.7–76.8)	67.4 (57.9–76.1)*	68.6 (59.2–78.8)	66.2 (55.9–77.6)	***.037***
TP (g/L)	70.2 (66.2–74.2)	70.7 (67.0–74.5)**	70.5 (66.1–74.2)	68.0 (64.1–72.5)	***<.0001***
sdLDL-C (mmol/L)	0.72 (0.52–1.01)	0.79 (0.57–1.06)*,**	0.68 (0.50–0.97)	0.59 (0.46–0.80)	***<.0001***
sdLDL-C/LDL-C	0.30 (0.24–0.38)	0.32 (0.25–0.39)*,**	0.29 (0.24–0.35)	0.26 (0.21–0.37)	***<.0001***
Lp(a) (nmol/L)	0.12 (0.05–0.29)	0.13 (0.05–0.28)*,**	0.15 (0.05–0.35)	0.10 (0.05–0.23)	***<.0001***
TyG index	1.11 (0.90–1.33)	1.15 (0.94–1.37)*,**	1.11 (0.88–1.32)	0.98 (0.79–1.14)	***<.0001***
FFA (mmol/L)	0.44 (0.31–0.61)	0.45 (0.31–0.62)**	0.45 (0.31–0.65)	0.39 (0.28–0.53)	***<.0001***

Italic bold values are statistically significant.

Abbreviations: BMI, body mass index; CAD, coronary artery disease; Cr, creatinine; FFA, free fatty acid; Glu, glucose ; Hb, hemoglobulin; HDL-C, high-density lipoprotein cholesterol; LCAD, late onset coronary artery disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCAD, premature coronary artery disease; sd-LDL-C, small dense low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; TP, total protein; TyG, Triglyceride-glucose.

*represent PCAD vs. CAD.

**represent PCAD vs. non-CAD.

groups I and III. Furthermore, traditional lipid indexes (TG, HDL-C, and LDL-C), novel lipid biomarkers [sdLDL-C, Lp(a), and FFA], and two ratio indexes (sdLDL-C/LDL-C and TyG index) were significantly different among patients of Group I, Group II, and Group III ($p < .05$) (Figure 2). In the pairwise comparisons, the novel lipid biomarkers [sdLDL-C, Lp(a), and FFA] and two ratio indexes (sdLD-LC/LDL-C and TyG index) were significantly different ($p < .05$). Furthermore, GS was significantly associated with novel lipid biomarkers [sdLDL-C, Lp(a), and FFA] and two ratio indexes (sdLD-LC/LDL-C and TyG index) (Table 4).

3.4 | ROC analysis of the novel lipid biomarkers and two ratio indexes (sdLDL–C/LDL-C and TyG index) for assessing coronary artery stenosis in patients with PCAD

Table 5 presents the results of the ROC curve analysis for the risk factors for GS >40 in patients with PCAD. The cutoff value of 0.535 mmol/L for sdLDL-C was employed to maximize the diagnostic efficacy for estimating coronary artery stenosis in patients with PCAD; the sensitivity was 100.0%, and the specificity was 33.3%. Furthermore, a cutoff point of 0.345 nmol/L for Lp(a) was used to maximize the diagnostic efficacy for assessing coronary artery stenosis in patients with PCAD; the sensitivity was 38.6%, and the specificity was 90.9%. A cutoff point of 0.385 nmol/L for FFA was adopted to maximize the diagnostic efficacy for assessing coronary artery stenosis in patients with PCAD; the sensitivity was 64.8%, and the specificity was 75.8%. Moreover, a cutoff value of 0.311 for sdLDL-C/LDL-C was used to maximize the diagnostic efficacy for assessing coronary artery stenosis in patients with PCAD; the sensitivity was 67.8%, and the specificity was 57.6%. Finally, a cutoff value of 0.204 for the TyG index was used to maximize the diagnostic efficacy for measuring coronary artery stenosis in patients with PCAD; the sensitivity was 77.8%, and the specificity was 43.0% (Figure 3). We performed a combined diagnosis involving five indicators and observed that the area under the ROC curve was 0.819, with a sensitivity of 75.1% and a specificity of

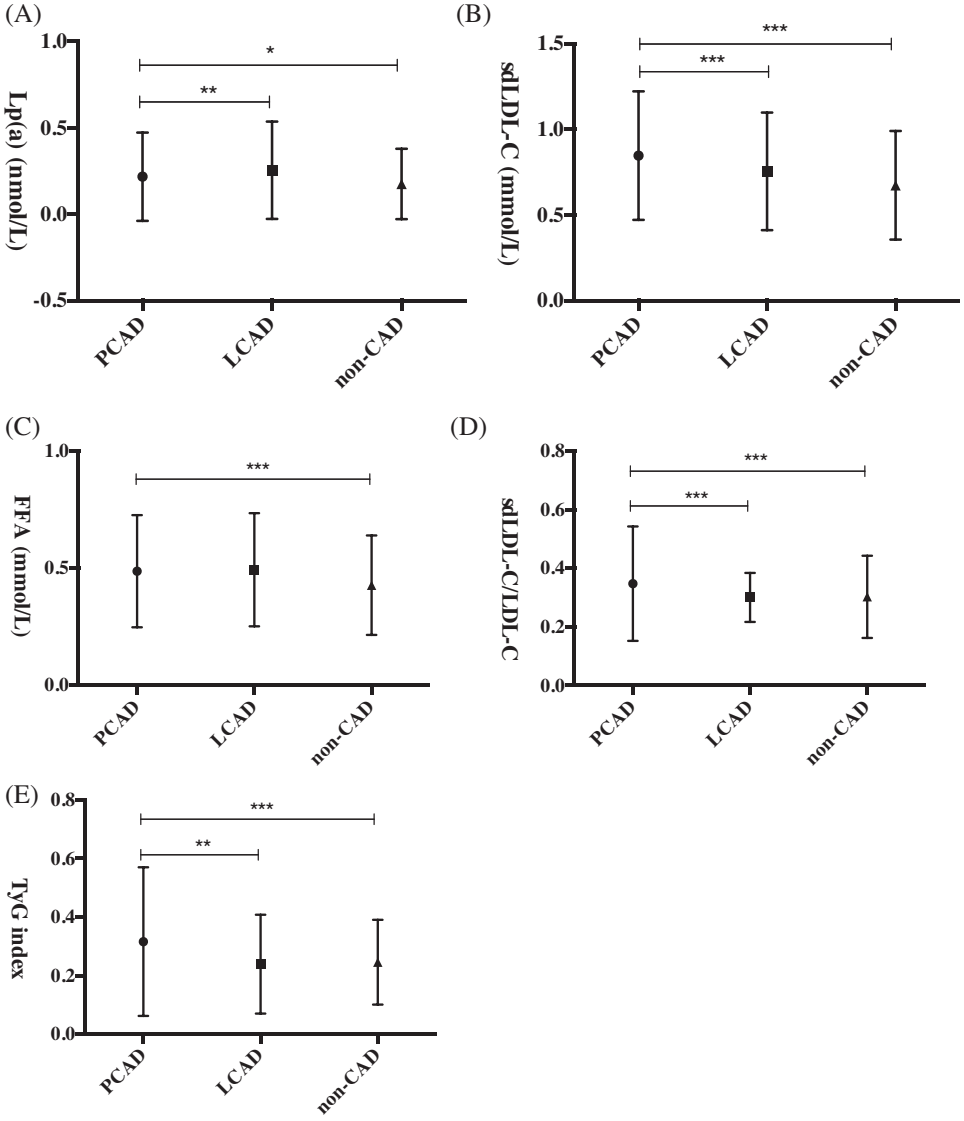

FIGURE 1 Comparison of novel lipid biomarkers [sdLDL-C, Lp(a), and FFA] and two ratio index (sdLDL-C/LDL-C and TyG index) among PCAD, LCAD, and the non-CAD patients. (A) Serum Lp(a) concentrations were significantly different among PCAD, LCAD, and the non-CAD patients; (B) Serum sdLDL-C concentrations were significantly different among PCAD, LCAD, and the non-CAD patients; (C) Serum FFA concentrations were significantly different among PCAD, LCAD, and the non-CAD patients; (D) The sdLDL-C/LDL-C was significantly different among PCAD, LCAD, and the non-CAD patients; (E) The TyG index was significantly different among PCAD, LCAD, and the non-CAD patients. * represent $p < .05$; ** represent $p < .01$;*** represent $p < .001$.

74.3% (Table 5; Figure 4). In summary, this joint diagnostic approach significantly enhances diagnostic efficiency.

4 | DISCUSSION

This study elucidated whether the novel lipid biomarkers sdLDL-C, Lp(a), and FFA and two ratio indexes sdLDL-C/LDL-C and the TyG index are related to PCAD. We found that the sample size was relatively large, and that angiography was employed to confirm whether the patients had PCAD or CAD. Our cumulative conclusions based on the present results are as follows: (1) sdLDL-C, Lp(a), FFA, sdLDL–C/LDL-C, and the TyG index are significantly different among patients with PCAD, LCAD, and non-CAD; (2) Lp(a) and the TyG index are independent risk factors for patients with PCAD; (3) sdLDL-C, Lp(a), FFA, and sdLDL-C/LDL-C and the TyG index positively correlate with PCAD severity assessed using GS, and GS is significantly associated with sdLDL-C, Lp(a), FFA, sdLD-LC/LDL-C, and the TyG index; and (4) sdLDL-C, Lp(a), FFA and sdLDL-C/LDL-C, and the TyG index might be better diagnostic predictors of coronary artery stenosis in patients with PCAD.

CAD is a potential disease that primarily occurs in the elderly population; however, CAD has become increasingly common in young people recently. Owing to the poor long-term prognosis, the possibility of recurrence after the first event is high,[22] often associated with adverse outcomes,[23,24] thereby incurring a huge burden to families and

TABLE 2 Univariate and multivariate logistic regression analyses of PCAD (compared to non-CAD).

Valuable	Univariate analysis, OR (95% CI)	*p* value	Multivariate analysis, OR (95% CI)	*p* value
Age	0.92 (0.91–0.93)	***<.0001***	0.90 (0.88–0.92)	***<.0001***
Male	1.96 (1.62–2.38)	***<.0001***	–	–
BMI	1.01 (0.99–1.03)	.354	–	–
Hypertension, *n* (%)	2.63 (2.16–3.20)	***<.0001***	2.21 (1.60–3.06)	***<.0001***
Diabetes mellitus, *n* (%)	4.18 (3.11–5.64)	***<.0001***	4.85 (2.99–7.87)	***<.0001***
Smoking	2.28 (1.84–2.82)	***<.0001***	–	–
Drinking	1.53 (1.22–1.92)	***<.0001***	–	–
TG	1.87 (1.63–2.14)	***<.0001***	–	–
TC	1.48 (1.34–1.64)	***<.0001***	–	–
HDL-C	0.27 (0.19–0.38)	***<.0001***	–	–
LDL-C	1.63 (1.43–1.84)	***<.0001***	1.74 (1.40–2.16)	*<.0001*
sdLDL-C (mmol/L)	4.65 (3.39–6.38)	***<.0001***	–	–
sdLDL-C/LDL-C	6.20 (3.05–12.60)	***<.0001***	–	–
Lp(a) (nmol/L)	2.21 (1.33–3.76)	***.002***	2.78 (1.28–6.04)	*.010*
TyG index	8.60 (5.52–13.38)	***<.0001***	3.75 (2.15–6.53)	*<.0001*
FFA (mmol/L)	3.34 (2.13–5.23)	***<.0001***	–	–

Italic bold values are statistically significant.

Abbreviations: BMI, body mass index; CI, confidence interval; FFA, free fatty acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); OR, odds ratio; PCAD, premature coronary artery disease; sd-LDL-C, small dense low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; TyG, Triglyceride-glucose.

society.[25] Our literature review revealed that research on PCAD risk factors mainly focuses on traditional cardiovascular risk factors.[4,26] Furthermore, only a few large-scale screening studies on PCAD have been conducted, and the existing screening tools often fail to distinguish young patients at risk of CAD.[27] Therefore, there is an urgent need to adopt rapid, accurate, and convenient methods to timely and accurately identify patients with PCAD in clinical settings and facilitate early detection and treatment.

Some studies have focused on traditional blood lipid indicators of PCAD,[28,29] however, these studies are outdated and have a limited sample size. Furthermore, some studies on novel blood lipid indicators of PCAD are available. However, the characteristics of these studies mainly include a single index or few markers.[5,8] This study aimed to recognize multiple novel lipid biomarkers for patients with PCAD in a large-sample Chinese population.

FFA is one of the substances produced by the hydrolysis of neutral fats. Elevated plasma FFA levels contribute to the development of metabolic syndrome, insulin resistance, and cardiovascular disease risk.[20] In a prospective cardiovascular cohort study, the authors elucidated the association between FFA levels and mortality and proposed that the FFA level can be an independent predictor of all-cause mortality and cardiovascular mortality in patients with CAD derived from angiography.[30] In another prospective cohort study, the authors explored whether fasting FFA levels can predict sudden cardiac death (SCD) in patients undergoing CAG. They observed a significant correlation between high FFA levels and mortality from all causes and cardiovascular causes, even after excluding patients with SCD; they demonstrated that a high plasma FFA level is an independent predictor for subsequent SCD in patients undergoing CAG.[31] The abovementioned two studies suggest that regulating of FFA uptake and/or metabolism can be a future treatment goal; however, the potential diagnostic utility of FFA is worth further analyses. Several studies have demonstrated that increased lipolysis in the adipose tissue is related to elevated plasma FFA levels in patients with chronic heart failure.[32,33] In experimental models of adipose-specific adipose triglyceride lipase knockout mice, the mice were immune to the effects of heart failure, which may be because of a decrease in plasma FFA levels.[34] Elevated FFA may impair cardiovascular diseases via several mechanisms, including metabolic syndrome or multiple heart tissue steatosis. Some studies have reported that increased FFA levels directly affect the vascular endothelium, resulting in endothelial dysfunction, which is manifested in the form of weakened vasodilation control,[35] possibly induced by ROS-mediated endothelial damage.[36] In the present study, we observed that the levels of FFA were significantly different among patients with PCAD, LCAD, and non-CAD. FFA is positively correlated with PCAD severity assessed using GS score, whereas GS is significantly associated with FFA. Furthermore, in patients with PCAD, FFA might be better diagnostic predictors of coronary artery stenosis. Therefore, we believe that health can be improved by decreasing the plasma FFA levels in individuals and through further studies on target identification and drug development for inhibiting plasma FFA so as to manage a healthy lifestyle.

SdLDL-C, a subgroup of LDL-C, is a specific indicator of atherosclerosis. sdLDL-C is more sensitive and specific than conventional blood

TABLE 3 Demographic, clinical characteristics, and laboratory findings of PCAD patients with different GS.

	PCAD ($n = 1749$)	Group I (588)	Group II (505)	Group III (656)	*p* value
Age (years)	51 (46–54)	52 (47–57)*	50 (46–54)	50 (46–54)**	***<.0001***
Male, *n* (%)	1176 (67.20)	348 (59.20)*	345 (68.30)	483 (73.60)**,***	***<.0001***
BMI (kg/m^2)	26.14 (24.06–28.37)	26.01 (24.00–28.08)	26.12 (23.93–28.12)	26.34 (24.21–28.71)**	.12
Hypertension, *n* (%)	1037 (59.30)	366 (62.20)*	273 (54.10)	398 (60.70)***	***.015***
Diabetes mellitus, *n* (%)	529 (30.20)	168 (28.60)	154 (30.50)	207 (31.60)	.52
Smoking, *n* (%)	808 (46.20)	232 (39.50)*	238 (47.10)	338 (51.50)**	***<.0001***
Drinking, *n* (%)	560 (32.00)	178 (30.30)	161 (31.90)	221 (33.70)	.43
Family history of CAD, *n* (%)	126 (7.20)	41 (7.00)	33 (6.50)	52 (7.90)	.64
TG (mmol/L)	1.57 (1.12–2.28)	1.49 (1.06–2.15)	1.57 (1.12–2.27)	1.66 (1.19–2.37)**	*.002*
TC (mmol/L)	4.2 (3.55–4.99)	4.2 (3.6–4.92)	4.13 (3.51–4.97)	4.22 (3.59–5.03)	.43
HDL-C (mmol/L)	1.04 (0.9–1.21)	1.09 (0.93–1.28)*	1.05 (0.91–1.2)	1.0 (0.87–1.15)**,***	***<.0001***
LDL-C (mmol/L)	2.5 (1.96–3.13)	2.39 (1.88–3.09)	2.48 (1.96–3.16)	2.59 (2.02–3.17)**	*.03*
Glu	5.72 (5.14–7.24)	5.97 (5.24–7.94)*	5.69 (5.08–7.17)	5.55 (5.05–6.65)**,***	***<.0001***
Hb (g/L)	141 (115–153)	139 (119.75–153)	141 (104.5–153)	141 (113–153)	.91
Cr (μmol/L)	67.4 (57.9–76.1)	63.35 (56.8–73.8)*	67.9 (58.9–76.6)	69.15 (58.83–78.0)**	***<.0001***
TP (g/L)	70.7 (67.0–74.5)	70.5 (66.9–74.3)	70.8 (66.9–74.8)	70.7 (67.33–74.6)	.77
sdLDL-C (mmol/L)	0.79 (0.57–1.06)	0.62 (0.44–0.82)*	0.79 (0.55–1.07)	0.97 (0.72–1.25)**,***	***<.0001***
sdLDL-C/LDL-C	0.32 (0.25–0.39)	0.28 (0.20–0.34)*	0.31 (0.26–0.38)	0.36 (0.29–0.45)**,***	***<.0001***
Lp(a) (nmol/L)	0.13 (0.05–0.28)	0.07 (0.03–0.16)*	0.11 (0.04–0.27)	0.22 (0.09–0.48)**,***	***<.0001***
TyG index	1.15 (0.94–1.37)	1.00 (0.81–1.21)*	1.14 (0.94–1.37)	1.29 (1.09–1.53)**,***	***<.0001***
FFA (mmol/L)	0.45 (0.31–0.62)	0.37 (0.24–0.52)*	0.46 (0.32–0.63)	0.51 (0.37–0.72)**,***	***<.0001***

Italic bold values are statistically significant.
Abbreviations: BMI, body mass index; Cr, creatinine; FFA, free fatty acid; Glu, glucose; GS, gensini score; Hb, hemoglobulin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCAD, premature coronary artery disease; TG, triglycerides; TC, total cholesterol; TP, total protein; sd-LDL-C, small dense low-density lipoprotein cholesterol; TyG, Triglyceride-glucose.
*represent Group I vs Group II.
**represent Group I vs Group III.
***represent Group II vs Group III.

TABLE 4 Correlations between the GS and cardiovascular risk factors.

Variables	Correlation coefficient (*r*)	*p* value
Lp(a)	0.385	***<.0001***
FFA	0.279	***<.0001***
sdLDL-C	0.437	***<.0001***
sdLDL-C/LDL-C	0.350	***<.0001***
TyG index	0.415	***<.0001***

Italic bold values are statistically significant.
Abrreviations: FFA, free fatty acid; GS, gensini; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); sd-LDL-C, small dense low-density lipoprotein cholesterol; TyG, Triglyceride-glucose.

lipid indicators and performs better in the clinical prediction of AS.[37] sdLDL-C mainly induces atherosclerosis via three aspects[16,17]: (1) sdLDL-C modulates lipid metabolism by influencing lipid transformations through the regulating lipid transformation-related factors. In addition, sdLDL-C exacerbates the onset and progression of atherosclerosis through its interaction with M2 macrophages; (2) sdLDL-C contributes to atherosclerosis by triggering inflammation, potentially influencing the inflammatory responses of monocytes. Furthermore, it exacerbates inflammation and amplifies atherosclerosis by suppressing the expression of activating transcription factor 3; (3) sdLDL-C promotes atherosclerosis by inducing endothelial damage, adhering to the vascular wall, and infiltrating vascular endothelial cells, thereby ultimately leading to endothelial injury and promoting atherosclerotic development. However, sdLDL-C has not been examined in patients with PCAD. Our study recorded that sdLDL-C and sdLD-LC/LDL-C were meaningfully different among patients with PCAD, LCAD, and non-CAD. Furthermore, sdLDL-C and sdLD-LC/LDL-C were associated with PCAD severity, as assessed by GS score, and GS was meaningfully associated with sdLDL-C and sdLD-LC/LDL-C. Moreover, sdLDL-C and sdLD-LC/LDL-C might be better diagnostic prediction ability of coronary artery stenosis in patients with

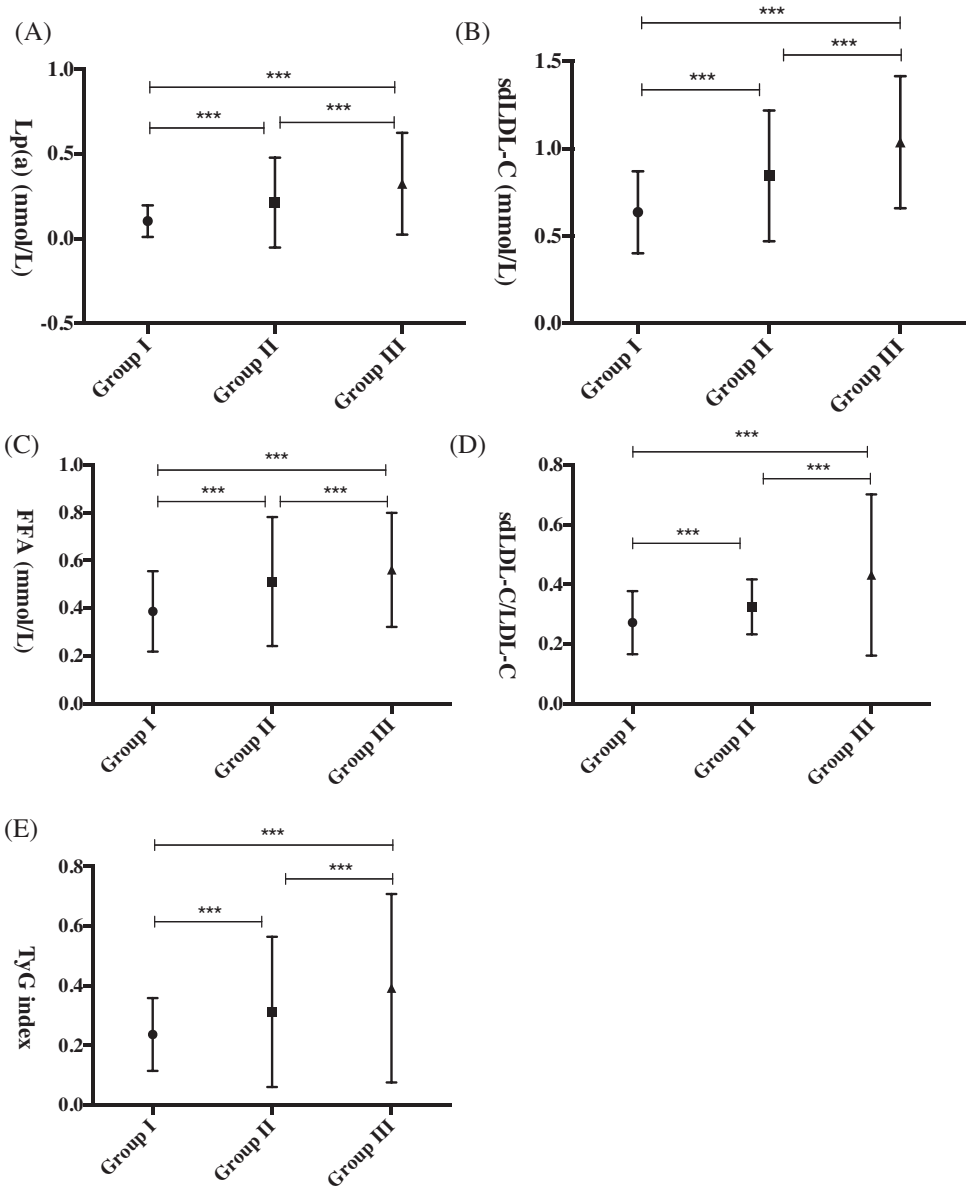

FIGURE 2 Comparison of novel lipid biomarkers [sdLDL-C, Lp(a), and FFA] and two ratio index (sdLDL-C/LDL-C and TyG index) among the different groups basing on GS. (A) Serum Lp(a) concentrations were significantly different among the different groups; (B) Serum sdLDL-C concentrations were significantly different among the different groups; (C) Serum FFA concentrations were significantly different among the different groups; (D) The sdLDL-C/LDL-C was significantly different among the different groups; (E) The TyG index was significantly different among the different groups. GS: Gensini score; Group I: GS < 20, Group II: 20 ≤ GS < 40, and Group III: GS ≥ 40. * represent $p < .05$; ** represent $p < .01$;*** represent $p < .001$.

PCAD. We applied effective methods to decrease the sdLDL-C levels, thereby decreasing the occurrence of cardiovascular events. Presently, there are two ways by which sdLDL-C levels can be decreased in the body[17]: (1) nonpharmacological interventions, including diet regulation and proper exercise, and (2) pharmacological interventions, including statins, beta drugs, and omega-3 fatty acids. Nevertheless, the specific mechanism of sdLDL-C in atherosclerosis remains unelucidated. Related studies will further explore the mechanism of sdLDL-C in CAD, possibly providing new directions for the clinical prevention, evaluation, and treatment of CAD; furthermore, it may provide new target information for preventing and treating CAD.

Lp(a) is an LDL variant similar to LDL cholesterol. The pathogenesis of Lp(a) primarily comprises the following three parts: promoting plaque formation, thrombosis, and proinflammatory effects. In 2022, the European Atherosclerosis Society issued an updated consensus statement regarding the role of Lp(a) in the pathogenesis of atherosclerosis and aortic stenosis. They recommend Lp(a) testing as an essential pillar of risk assessment for atherosclerotic cardiovascular disease (ASCVD).[38] High Lp(a) exhibits the strongest correlation with ASCVD[39] and aortic stenosis[40]; however, it weakly correlates with heart failure, ischemic, and peripheral artery disease. Genetics determines the Lp(a) levels in the plasma,[41] with non-genetic factors

TABLE 5 The sensitivity and specificity of risk indicators to increase coronary stenosis (GS ≥ 40) of PCAD.

	Cutoff point	Youden's index	AUC	Sensitivity (%)	Specificity (%)	95% CI	*p* value
Lp(a)	0.345	0.295	0.721	0.386	0.909	0.695–0.747	***<.0001***
FFA	0.385	0.2	0.648	0.758	0.442	0.62–0.677	***<.0001***
sdLDL-C	0.535	0.333	0.731	1.0	0.333	0.706–0.757	***<.0001***
sdLDL-C/LDL-C	0.311	0.254	0.677	0.678	0.576	0.65–0.705	***<.0001***
TyG index	1.017	0.298	0.725	0.85	0.448	0.699–0.750	***<.0001***
Combined factors	0.338	0.494	0.819	0.751	0.743	0.798–0.838	***<.0001***

Italic bold values are statistically significant.

Abbreviations: AUC, area under the ROC curve; CI, confidence interval; FFA, free fatty acid; GS, gensini; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCAD, premature coronary artery disease; sd-LDL-C, small dense low-density lipoprotein cholesterol; TyG, Triglyceride-glucose. Combined factors include Lp(a), FFA, sdLDL-C, sdLDL-C/LDL-C, and TyG index.

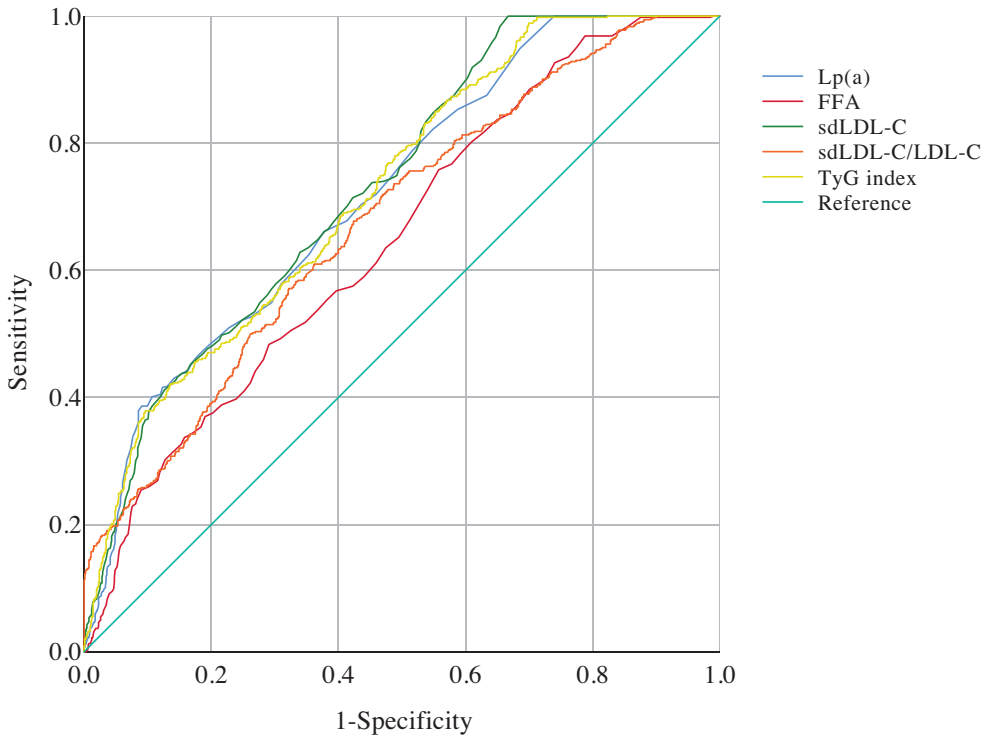

FIGURE 3 The ROC curves for novel lipid biomarkers [sdLDL-C, Lp(a), and FFA] and two ratio index (sdLDL-C/LDL-C and TyG index) of risk indicators to increase coronary stenosis (GS ≥ 40) of PCAD. ROC: receiver operating characteristics.

having a relatively small effect on Lp(a).[42] However, changing lifestyle factors such as diet and exercise did not significantly affect plasma Lp(a) levels.[43] In addition, elevated Lp(a) does not assure that someone will develop ASCVD, and it depends on other traditional risk factors. Several guidelines and consensus statements recommend that adults assess Lp(a) at least once in their lifetime.[38,44] Furthermore, the familial hypercholesterolemia guidelines recommend that children with genetic risk factors undergo Lp(a) testing once they are 10 years old.[45] If patients with elevated Lp(a) levels have a family history of CAD, the plasma Lp(a) levels of other family members should be measured.[46] Moreover, guidelines recommend managing other adjustable risk factors for asymptomatic patients with extremely elevated Lp(a) levels through lifestyle intervention and medical treatment.[38] Our study found that Lp(a) is significantly differs among PCAD, LCAD, and non-CAD patients. Furthermore, Lp(a) is an independent risk factor for patients with PCAD and is related to PCAD severity, as assessed using GS score. Moreover, GS is significantly associated with Lp(a). In addition, Lp(a) might be a relatively better diagnostic prediction ability of coronary artery stenosis in patients with PCAD. Therefore, early Lp(a) detection and increased healthcare are urgent issues, and personalized management of high Lp(a) levels via the available treatment strategies can decrease the risk of CAD.

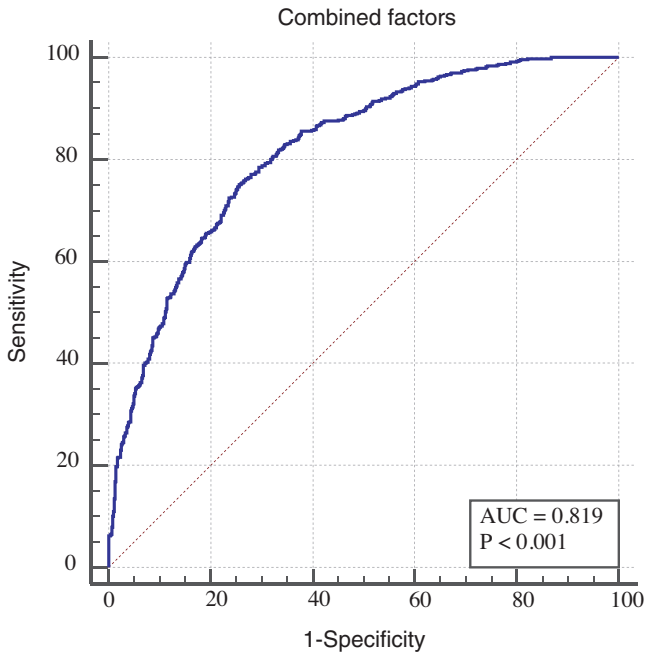

FIGURE 4 The ROC curves for the five combined factors (sdLDL-C, Lp(a), FFA, sdLDL-C/LDL-C, and TyG index) to increase coronary stenosis (GS ≥ 40) of PCAD.

The TyG index is a common and stable succedaneous marker for insulin resistance. The utilization of the TyG index in cardiovascular diseases involves several diseases, including stable CAD,[47] acute coronary syndrome,[48] in-stent restenosis,[49] arterial stiffness,[50] coronary artery calcification,[51] and heart failure.[52] Laura and colleagues. followed up a large sample of patients with vascular metabolic syndrome (median) for 10 years and proposed a positive correlation between the TyG index and cardiovascular disease for the first time, independent of the confounding factors.[53] Most studies on TyG and cardiovascular diseases have been conducted in middle-aged and older people. However, studies on the TyG index of patients with PCAD are limited. Wu and colleagues. conducted a clinical and laboratory data study on 526 patients with PCAD and followed them up (median) for 68 months. The authors observed that the TyG index independently predicted major adverse cardiovascular events in this patients.[6] Moreover, Wei and colleagues. retrospectively analyzed the clinical data of 2846 patients with PCAD and observed that the TyG index increased more frequently in premature or mature women with multivessel diseases.[5] In addition, in two studies, the TyG index was found to act as an effective auxiliary indicator of PCAD and cardiovascular diseases in the study population, which helped achieve early recognition of the severity of vascular disease and early intervention. The TyG index acts as a composite marker reflecting the changes in lipid and glucose metabolism. Various studies have explored its potential to predict cardiovascular risk, thereby highlighting its role in identifying individuals at risk for atherosclerosis-related outcomes.[54] However, the intricate mechanisms linking the TyG index, blood lipids, and atherosclerosis remain complex. Some theories propose the TyG index as an indicator of insulin resistance, contributing to dyslipidemia and endothelial dysfunction, which are the key factors in atherogenesis.[55,56] Comprehensive investigations are needed to clarify these pathways and potential synergistic effects on cardiovascular risk. Thus, the intricate associations between the TyG index, blood lipids, and their collective impact on atherosclerosis warrant thorough research. As a potential integrated marker of metabolic changes, the TyG index holds promise for unraveling complex interactions contributing to cardiovascular risk in individuals with PCAD. We observed that the TyG index is meaningfully different among patients with PCAD, LCAD, and non-CAD and that it is an independent risk parameter for patients with PCAD. The TyG index is positively correlates with PCAD severity assessed using GS, and the GS is meaningfully correlated with the TyG index. In addition, the TyG index might be as a better diagnostic predictor of coronary artery stenosis in patients with PCAD. However, the mechanisms of the TyG index in different types of cardiovascular diseases warrant further investigation. Furthermore, TyG index-guided targeted therapy for patients with cardiovascular diseases needs more in-depth verification.

In our study, age as a protective factor against PCAD raises several vital questions about the interplay between age-related changes in cardiovascular physiology and the pathogenesis of CAD.[57,58] One plausible explanation is the cumulative impact of arterial remodeling over some time.[59] Advanced age is associated with structural changes in the arterial walls, such as increased collagen deposition and reduced smooth muscle cell proliferation, which might confer a certain resistance level to atherosclerosis and plaque formation.[60] These structural modifications could contribute to the observed decrease risk in PCAD individuals. Individuals who reach an older age without manifesting PCAD may have a distinct genetic predisposition or healthier lifestyle habits that confer protection against the disease.[61] These factors could include better management of cardiovascular risk factors, regular physical activity, and adherence to prescribed medications. Notably, the interaction between age and other risk factors for PCAD must be considered. Older individuals might have a longer duration of exposure to risk-reducing interventions and lifestyle modifications, leading to a cumulative effect on their cardiovascular health. Moreover, comorbidities, such as hypertension or obesity, could modify the relationship between age and PCAD risk.[62,63] Incorporating these nuances into the analysis allows for a more comprehensive understanding of the intricate web of factors influencing PCAD development. However, notably, our study has its limitations, akin to those of a single investigation, including potential biases and confounders. Therefore, the protective effect of age against PCAD should be interpreted within the context of the broader research.

Our study has several limitations worth noting. Firstly, while our sample size is substantial, the research is anchored in a single-center retrospective analysis, potentially narrowing the findings' generalizability. Secondly, the delineation between PCAD and LCAD is primarily grounded on the age of the patients, even though other diagnostic criteria remained consistent. While age, as offers a valuable perspective on the divergent patterns of the disease, it should be acknowledged that the intricacies of atherosclerosis development are multifaceted, with genetics, lifestyle, metabolic factors, and environmental conditions playing pivotal roles. This aspect stands as a limitation in

interpreting our results. Thirdly, our objective was to unravel the nexus between lipid profiles and PCAD within the boundaries of our research scope. Unfortunately, the lack of detailed data on the usage of lipid-lowering medications precluded a thorough analysis of their effects on the observed lipid alterations. It would be prudent for subsequent research to delve into a holistic exploration of how pharmacological interventions influence lipid profiles to furnish exhaustive clinical recommendations. Fourthly, we recognize the potential for selection bias given that our participants, who underwent CAG, might not fully epitomize the wider PCAD demographic. Therefore, it is imperative to corroborate our findings through studies characterized by more heterogeneous and representative samples. Furthermore, we abstained from carrying out covariate adjustments and direct comparisons with LDL-C-based ROC curves during the diagnostic efficiency assessment via ROC curve analysis. This could potentially lead to inaccuracies in evaluating diagnostic performance. As a recommendation for future work, rigorous validation and affirmation through multicentric research endeavors, augmented sample sizes, and meticulous elimination of confounding variables are essential to fortify the integrity and applicability of our results.

5 | CONCLUSIONS

Enhancing the identification of individuals at an early risk of PCAD could substantially improve risk stratification and management of treatment modalities. Moreover, the systematic inclusion of the innovative lipid biomarkers sdLDL-C, Lp(a), and FFA, along with the two ratio indexes of sdLDL-C/LDL-C and TyG in the development of a clinical diagnosis and predictive models, has the potential to refine cardiovascular risk stratification. This approach could pave the way for personalized treatment and preventative strategies, fostering a more targeted and effective approach to patient care.

AUTHOR CONTRIBUTIONS

Si Chen, Xiaoli Zeng, Hui Yuan, and Yongzhe Li conceived and designed the research. Zhan Li and Haolong Li extracted data and conducted quality assessment. Si Chen analyzed the data and wrote the paper. All authors are accountable for all aspects of the study, and attest to the accuracy and integrity of the results. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

DATA AVAILABILITY STATEMENT

The data were able to be obtained through reasonable request on the corresponding author.

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