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To Explore the Influencing Factors of Pericoronary Adipose Tissue and Noninvasive Fractional Flow Reserve on the Progression of Coronary Heart Disease Based on 320-Slice Coronary CTA

ORIGINAL INVESTIGATION

ABSTRACT

Background: The objective of the study was to measure pericoronal adipose tissue parameters, fractional flow reserve with coronary artery computed tomographic angiography (CTA), and difference of fractional flow reserve with coronary artery CTA, by using high-performance 320-slice coronary CTA combined with semiautomatic quantitative software and explore the relationship between them and progression of coronary artery disease.

Methods: According to the inclusion criteria, 118 patients with complete data were selected. According to the results of coronary angiography during follow-up review, the patients were divided into coronary artery disease progression group (n = 43) and coronary artery disease stable group (n = 75), and the clinical baseline data, pericoronal adipose tissue volume, pericoronal adipose tissue fat attenuation index, fractional flow reserve with coronary artery CTA, and difference of fractional flow reserve with coronary artery CTA were compared between the 2 groups. According to univariate and multivariate logistic regression analyses, the risk factors related to coronary artery disease progression were screened out from pericoronal adipose tissue parameters and noninvasive hemodynamic characteristics (fractional flow reserve with coronary artery CTA and difference of fractional flow reserve with coronary artery CTA).

Results: There was no significant difference in baseline clinical data between the progression group and the stable group ($P > .05$). The left anterior descending artery-fat attenuation index-40 mm, left anterior descending artery-fat attenuation index-70 mm, left circumflex artery-fat attenuation index-70 mm, right coronary artery-fat attenuation index-70 mm, and difference of fractional flow reserve with coronary artery CTA in the progression group were higher than those in the stable group, while fractional flow reserve with coronary artery CTA was lower than that in the stable group, and the differences were statistically significant ($P < .05$). After adjusting for several factors, the results showed that left anterior descending artery-fat attenuation index-40 mm ($P = .002$; odds ratio = 1.237; 95% CI: 1.081-1.415), right coronary artery-fat attenuation index-70 mm ($P = .039$; odds ratio = 1.119; 95% CI: 1.006-1.246), fractional flow reserve with coronary artery CTA ($P = .001$; odds ratio = 0.708; 95% CI: 0.581-0.846), and difference of fractional flow reserve with coronary artery CTA ($P < .001$; odds ratio = 1.846; 95% CI: 1.394-2.445) were related to the progression of coronary artery disease. Compared with the above 5 indicators, the area under curve (AUC) of the above indicators combined is larger (0.897).

Conclusions: Quantitative pericoronal adipose tissue parameters and noninvasive hemodynamic characteristics based on 320-slice coronary CTA can be used as the basis for predicting the progression of coronary artery disease.

Keywords: Coronary artery disease, pericoronary adipose tissue, noninvasive hemodynamic characteristics, angiography

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INTRODUCTION

With the continuous innovation of image scanning equipment and the rapid development of artificial intelligence technology, the cognition of coronary artery disease (CAD), a common disease that seriously endangers human life and health, should not be limited to the diagnosis of vascular stenosis but should focus on exploring deeper related factors. Pericoronal adipose tissue (PCAT) is regarded as part of epicardial adipose tissue (EAT), and many studies suggest that PCAT contains more saturated fat than EAT, with faster fat production and metabolism ability.[1] Pericoronal adipose tissue directly connects with coronary artery vessels, which may be related to the pathophysiological evolution of coronary atherosclerosis by regulating inflammatory microenvironment and paracrine pro-inflammatory factors.[2,3] Noninvasive fractional flow reserve with coronary artery CTA (CCTA) (FFR_{CT}), as a noninvasive method to evaluate ischemic stenosis, has certain advantages in evaluating hemodynamic abnormalities.[4,5] Moreover, the difference of FFR_{CT} before and after coronary stenosis ($^{\Delta}FFR_{CT}$) has certain value in predicting the occurrence and development of acute coronary syndrome, which may provide additional information compared with FFR_{CT}.[6-8] However, whether PCAT parameters and noninvasive hemodynamic characteristics are related to the development of CAD remains to be unclear. Therefore, this study focuses on PCAT volume, PCAT-fat attenuation index (FAI), FFR_{CT}, and $^{\Delta}FFR_{CT}$ to explore the relationship between PCAT parameters and noninvasive hemodynamic characteristic parameters and the development of CAD, so as to provide a new idea for predicting the development of CAD.

METHODS

Research Objects and Grouping Criteria

From December 2020 to May 2021, patients with angina pectoris, chest pain, dyspnea, and other symptoms or with positive exercise test who have undergone CCTA scanning and coronary angiography (CAG) examination within a short period of time in hospital were selected to be included in the study. Among them, the exclusion criteria for the study patients were as follows: (1) history of previous coronary artery bypass grafting and stent surgery; (2) poor CCTA image quality, which seriously affected the accuracy of PCAT parameters and the extraction of noninvasive hemodynamic characteristic parameters; (3) severe anatomical variation of coronary artery vessels; (4) severe organic diseases; and (5) severe contrast agent allergy. Finally, 118 patients were selected as the research objects. All patients were followed up after 9-12 months. According to the results of the second CAG, the CAD progression group was defined as the group in which new lesions were found in the second CAG or the minimum lumen diameter increased by ≥0.4 mm or 20% in the second CAG reexamination.[9] The clinical data of the above subjects were also collected.

HIGHLIGHTS

- The study used the reexamination results of coronary angiography to define the progression group of coronary artery disease (CAD).
- In this study, parameters of pericoronal adipose tissue (PCAT) (volume and fat attenuation index) and noninvasive hemodynamic characteristics [fractional flow reserve with coronary artery CTA (CCTA) and the difference of fractional flow reserve with CCTA] are used to find out the related factors with the progression of coronary heart disease.
- Pericoronal adipose tissue parameters [left anterior descending artery-fat attenuation index (FAI)-40 mm, right coronary artery-FAI-70 mm] and noninvasive hemodynamic characteristics (fractional flow reserve with CCTA and the difference of fractional flow reserve with CCTA) can be used as the basis for predicting the progression of CAD.

Scanning Methods of Coronary Artery CTA

Coronary artery CTA scanning was conducted by the fourth-generation 320-slice 640-layer energy spectrum CT (Aquilion ONETSX-305A, Canon, Tokyo, Japan). Before image acquisition, patients took nitroglycerin orally to control their heart rate and hold their breath. The scanning range was 1-2 cm below the bifurcation of trachea to diaphragm. The scanning parameters were as follows: prospective electrocardiogram gating, reference tube current of 500 mAs, tube voltage of 120 V, automatic pitch adjustment, matrix of 512 × 512, rotation time of 0.28 s, and field of view is 320 mm × 320 mm. All CCTA images were reconstructed with 0.5 mm section thickness and 0.3 mm image interval and then transmitted to (Vitrea FX3.0, VitalEx tend) a digital semiautomatic image postprocessing workstation (CareSphere, TM, Perivascular Fat Analysis Tool) for analysis and evaluation. The enhanced scanning mode was as follows: the nonionic iodine contrast agent (370 mgI/mL, 50-60 mL) was injected through the elbow vein with a binocular high-pressure syringe at the rate of 5 mL/mL, and then an appropriate amount of normal saline was injected.

Coronary CTA Image Analysis and Coronary Angiography Result Analysis

Coronary artery CTA images of coronary artery were analyzed by 2 radiologists who have worked for more than 5 years on Vitrea FX3.0 (VitalEx tend), and CAG results were analyzed by 2 cardiac interventional physicians. The above opinions were evaluated by higher level physicians at the same time.

Pericoronal Adipose Tissue Parameters, FFR_{CT}, and ΔFFR_{CT} Measurement Methods

Two cardiovascular radiologists with more than 5 years of working experience who did not know the coronary atherosclerosis manifestation of patients used PCAT collection method prepared by Antonopoulos et al[10,11] for reference and pushed the original CCTA image to Shukun semiautomatic image postprocessing workstation (CareSphere, TM, Perivascular Fat Analysis Tool, China) to automatically outline the PCAT range and calculate the PCAT-FAI and volume of 3 coronary arteries. The PCAT acquisition threshold was set from −190 [Hounsfield (HU)] to −30 HU, and the acquisition profile distance was 4 mm from the adventitia of the vascular wall. In order to ensure the accuracy of the study, 2 lengths of interest (40 mm and 70 mm) were measured, namely the distance between left anterior descending artery (LAD) and left circumflex artery (LCX) was 40 mm and 70 mm from the beginning of blood vessels, and the determination

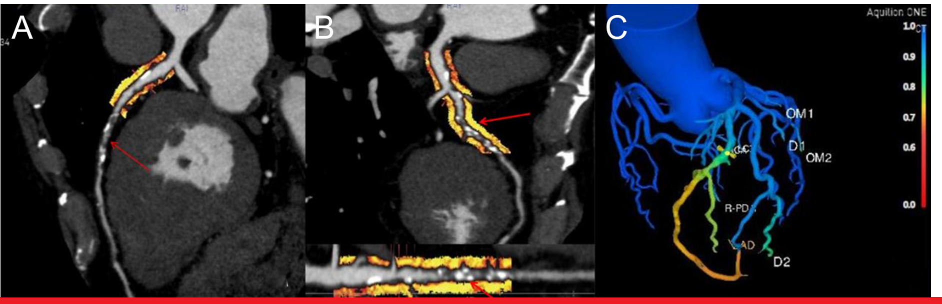

Figure 1. Schematic diagram of parameter capture. (A and B) Schematic diagram of PCAT capture for 2 acquisition lengths (40 mm and 70 mm). (C) Schematic diagram of capturing FFR_{CT} with reconstructed coronary artery tree. PCAT, pericoronary adipose tissue; FFR_{CT}, fractional flow reserve with coronary artery CTA

distance of right coronary artery (RCA) ranged from 10 mm from the beginning to 50 mm and 80 mm, as shown in Figure 1. Fat attenuation index was defined as the CT mean of the interested segment (PCAT). The calculation of FFR_{CT} was carried out through Shukun semiautomatic image post-processing workstations (CareSphere, TM, Perivascular Fat Analysis Tool, China). The calculation principle is to use the original CCTA images combined with the specific conditions of coronary artery lesions, calculate the fluid dynamic parameters in a reduced-dimension mode, and calculate the FFR_{CT} value by overall simulation. The lesion-specific FFR_{CT} value was measured at about 2 cm away from the distal end of the lesion. If there are multiple lesions, the FFR_{CT} value of the distal lesion shall prevail. $^{\Delta}FFR_{CT}$ value $=$ FFR_{CT} value before each lesion stenosis − FFR_{CT} value after each lesion stenosis, as shown in Figure 1.

Statistical Analysis

All statistical analyses were processed using a statistical software program (Statistical Package for Social Sciences Version 23.0, IBM, Chicago, Ill, USA). Measurement data with normal distribution were expressed as mean ± SD, measurement data with non-normal distribution were expressed as median (upper quartile, lower quartile), and counting data were expressed as (example, %). Kolmogorov-Smirnov test was used to evaluate the normality of continuous variables, and X^2 or Fisher's exact test was used to compare enumeration data between groups. The independent-sample test was used for the intergroup comparison of measurement data with normal distribution. The Mann–Whitney *U*-test was used for the intergroup comparison of measurement data with non-normal distribution. Logistic regression analysis was used to screen out the risk factors affecting CAD progress. The receiver operating characteristic (ROC) curve was drawn to evaluate the predictive value of related positive indicators on CAD progression. The difference was statistically significant with $P < .05$.

RESULTS

Analysis on Baseline Characteristics of Progression Group and Stable Group

Among the 118 patients included in this study, there were 43 patients (72.09% male) in the progression group and 75 patients (66.67% male) in the stable group. There were no significant differences in clinical data, related clinical disease history, related family history of vascular diseases, drug use, and related laboratory indexes between the 2 groups ($P > .05$) (see Table 1 for details).

Comparison and Analysis of Two Groups of Pericoronal Adipose Tissue Parameters and Noninvasive Hemodynamic Characteristics Parameters

In terms of PCAT parameters, LAD-FAI-40 mm, LAD-FAI-70 mm, LCX-FAI-70 mm, RCA-FAI-70 mm in the progression group were higher than those in the control group, with statistically significant differences (*P*-values were .03, .01, .04, and .01, respectively), but there was no statistically significant difference between the 2 groups in PCAT volume parameters ($P > .05$); in terms of noninvasive hemodynamic characteristics parameters, FFR_{CT} in the progression group was significantly lower than that in the stable group, and $^{\Delta}FFR_{CT}$ was significantly higher than that in the stable group ($P < .05$), as shown in Table 2.

Table 1. Comparison of Clinical Baselines Between the Progression Group and Stable Group

Variable	CAD Progression (n = 43)	CAD Stable (n = 75)	*P*
Age (year)	57.54 ± 9.17	57.05 ± 10.45	.80
Male [n (%)]	31 (72.09)	50 (66.67)	.54
BMI (kg/m²)	28.05 ± 3.92	27.57 ± 5.36	.62
Hypertension [n (%)]	26 (60.47)	48 (64.00)	.70
Diabetes [n (%)]	12 (27.91)	17 (22.67)	.53
Dyslipidemia [n (%)]	21 (48.84)	33 (44.00)	.61
Smoking [n (%)]	19 (44.19)	30 (40.00)	.66
Family history [n (%)]	17 (39.54)	20 (26.67)	.15
TC (mmol/L)	5.24 ± 0.68	5.19 ± 0.74	.72
TG (mmol/L)	1.66 ± 0.49	1.59 ± 0.35	.36
LDL-C (mmol/L)	3.96 ± 0.66	4.13 ± 0.43	.09
HDL-C (mmol/L)	2.07 ± 0.67	2.21 ± 1.04	.46
Antiplatelet [n (%)]	12 (27.91)	19 (25.33)	.76
Statin [n (%)]	10 (23.26)	26 (34.67)	.2
Beta blocker [n (%)]	8 (18.61)	15 (20.00)	.85
ACE-I or ARB [n (%)]	15 (34.88)	37 (49.33)	.26

BMI, body mass index; CAD, coronary artery disease; ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride

Table 2. Ratio of PCAT Parameters, FFR_{CT}, and ΔFFR_{CT} in the 2 Groups

	Variable	CAD Progression (n = 43)	CAD Stable (n = 75)	*P*
PCAT parameters		LAD-PCAT		
	Volume-40 mm (mm^3)	2064.59 ± 431.58	1964.10 ± 437.49	.23
	FAI-40 mm (HU)	−75.13 ± 6.66	−77.93 ± 6.90	.03
	Volume-70 mm (mm^3)	3800.49 ± 965.03	3652.51 ± 808.57	.35
	FAI-70 mm (HU)	−70.96 ± 6.64	−74.13 ± 5.76	.01
		LCX-PCAT		
	Volume-40 mm (mm^3)	1505.69 ± 296.26	1515.99 ± 394.91	.88
	FAI-40 mm (HU)	−76.60 ± 7.16	−77.78 ± 6.32	.35
	Volume-70 mm (mm^3)	3019.50 ± 616.61	3016.51 ± 835.23	.98
	FAI-70 mm (HU)	−76.75 ± 7.25	−79.53 ± 6.92	.04
		RCA-PCAT		
	Volume-40 mm (mm^3)	2230.90 ± 530.83	2129.88 ± 516.71	.31
	FAI-40 mm (HU)	−74.15 ± 7.04	−75.25 ± 7.32	.43
	Volume-70 mm (mm^3)	4283.50 ± 905.09	4109.50 ± 854.96	.30
	FAI-70 mm (HU)	−72.86 ± 4.38	−75.38 ± 5.68	.01
Noninvasive hemodynamic characteristics	FFR_{CT}	0.77 (0.74, 0.81)	0.79 (0.76, 0.84)	.006
	ΔFFR_{CT}	0.060 (0.030, 0.090)	0.017 (0.010, 0.031)	<.001

CAD, coronary artery disease; FAI, fat attenuation index; FFRCT, fractional flow reserve with coronary artery CTA; LAD, left anterior descending artery; LCX, left circumflex artery; PCAT, pericoronal adipose tissue; RCA, right coronary artery; ΔFFR_{CT}, difference of fractional flow reserve with coronary artery CTA.

Logistic Regression Analysis Results of Pericoronal Adipose Tissue Parameters and Noninvasive Hemodynamic Characteristics in Predicting Coronary Artery Disease Progression

Logistic regression analysis can be obtained. Left anterior descending artery-fat attenuation index-40 mm [*P* = .002; odds ratio (OR) = 1.237; 95% CI: 1.081-1.415], RCA-FAI-70 mm (*P* = .039; OR = 1.119; 95% CI: 1.006-1.246), FFR_{CT} (*P* = .001; OR = 0.708; 95% CI: 0.581-0.846), and ΔFFR_{CT} (*P* < .001; OR = 1.846; 95% CI: 1.394-2.445) were independent risk factors for predicting CAD progression (see Table 3).

Predictive Power of Indicators to Predict Coronary Artery Disease Progression

ROC curves were drawn for LAD-FAI-40 mm, RCA-FAI-70 mm, FFR_{CT}, and ΔFFR_{CT} to evaluate their predictive value for CAD progression. The results showed that compared with LAD-FAI-40 mm, RCA-FAI-70 mm, FFR_{CT}, and ΔFFR_{CT} , the AUC (0.897) of combined diagnosis was larger, and the difference was statistically significant (*P*-values were .0000, .0002, .0000, and .0475, respectively), as shown in Figure 2 and Table 4.

DISCUSSION

Under the trend of global population aging, the number of deaths due to CAD shows a gradual upward trend. Therefore, it is very meaningful to find out the factors affecting the progress of CAD disease and study them in advance when the fact that the incidence of CAD is increasing day by day is difficult to be reversed.[12]

For PCAT, current studies have shown that it can directly change the microenvironment around coronary vessels and accelerate the infiltration of macrophages in the process of lipid metabolism, which leads to the release of a large number of corresponding pro-inflammatory mediators. In addition, compared with fat components in other parts, it is more primitive and will accelerate the formation of

Table 3. Univariate and Multivariate Logistic Regression Analysis of PCAT Parameters and Noninvasive Hemodynamic Characteristics Parameters

		Univariate			Multivariate		
	Variable	*P*	OR	95% CI	*P*	OR	95% CI
PCAT parameters	LAD-FAI-40 mm (HU)	.037	1.066	1.004-1.132	.002	1.237	1.081-1.415
	LAD-FAI-70 mm (HU)	.01	1.089	1.021-1.161	.871	0.992	0.901-1.093
	LCX-FAI-70 mm (HU)	.044	1.058	1.002-1.117	.266	1.044	0.967-1.128
	RCA-FAI-70 mm (HU)	.017	1.1	1.017-1.189	.039	1.119	1.006-1.246
Noninvasive hemodynamic characteristics	FFR_{CT}, per 100	.009	0.893	0.821-0.972	.001	0.708	0.581-0.864
	ΔFFR_{CT}, per 100	<.001	1.686	1.374-2.067	<.001	1.846	1.394-2.445

FAI, fat attenuation index; FFRCT, fractional flow reserve with coronary artery CTA; LAD, left anterior descending artery; LCX, left circumflex artery; OR, odds ratio; PCAT, pericoronal adipose tissue; RCA, right coronary artery; ΔFFR_{CT}, difference of fractional flow reserve with coronary artery CTA.

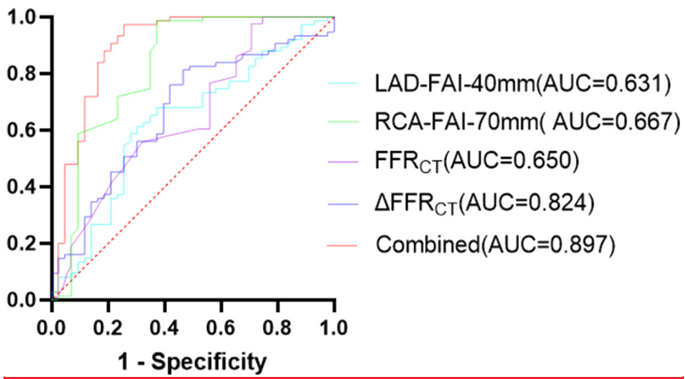

Figure 2. ROC curve of PCAT parameters, noninvasive hemodynamic characteristics, and various indicators combined. PCAT, pericoronary adipose tissue; ROC, receiver operating characteristic.

atherosclerotic plaque, which has a certain relationship with the development of coronary atherosclerosis.[13,14] Pericoronal adipose tissue-FAI can be regarded as a quantitative index of PCAT density changes; many studies believe that it has a certain relationship with major adverse cardiac events (MACEs) and that it can be used as a standard to measure the changes of perivascular inflammatory microenvironment.[15,16] It is believed that EAT may be related to the progression of coronary atherosclerotic plaque, but there are few studies related to the relationship between PCAT and coronary atherosclerosis. Therefore, this study got rid of the exploration of EAT. In order to ensure the accuracy of the experiment, PACT volume and FAI of 2 interested lengths were carefully measured for research.

Based on the above, the number of patients included in the study was 43 cases in the progression group and 75 cases in the stable group. Pericoronal adipose tissue volume and FAI around LAD, LCX, and RCA were compared between the 2 groups. Results showed that there were only differences among LAD-FAI-40 mm, LAD-FAI-70 mm, LCX-FAI-70 mm, and RCA-FAI-70 mm. Subsequent logistic regression analysis showed that LAD-FAI-40 mm and RCA-FAI-70 mm were independent risk factors for predicting the progression of CAD. To some extent, it can also be considered that the metabolic activity of LAD and PCAT around RCA is relatively strong when the disease of CAD patients has a progressive trend, which is similar to the result that RCA-FAI may be an independent risk factor for accelerating the formation of atherosclerosis by Ling et al.[17] However, there is no significant difference in PCAT-volume index between the 2 groups, which is similar to the research results of Wen et al.[18]

Noninvasive hemodynamic characteristics, another direction of this study, can be used as a highly reliable index to judge coronary functional stenosis and identify hemodynamic abnormalities, and it may be related to MACE.[19] Based on this, in order to explore the relationship between noninvasive hemodynamic characteristics and CAD progression, we measured FFR_{CT} and ΔFFR_{CT} and found that FFR_{CT} in the progression group was significantly lower than that in stable group, while ΔFFR_{CT} was significantly higher than that in the stable group. The difference between the 2 groups was statistically significant. Logistic regression analysis showed that FFR_{CT} and ΔFFR_{CT} were related to CAD progression. Combined with the results of this study, the following conclusions can be drawn: (1) Because FFR_{CT} reflects the myocardial blood flow reserve capacity, when the myocardium supplied by coronary vessels is ischemic, the ischemic myocardium is in a state of hypoxia, and the myocardial metabolic activity is reduced, which leads to the accelerated formation of coronary atherosclerotic plaque and CAD progression[20,21]; (2) ΔFFR_{CT} means that the pressure change before and after the lesion reflects the pressure gradient when the blood flows through the plaque. Therefore, the greater the pressure gradient is, the greater the external stress acting on the plaque is, which is more likely to cause plaque rupture and accelerated plaque formation, thus resulting in CAD progression.[22] The ROC curve was used to evaluate the predictive performance of each factor in predicting CAD progression, and the results showed that ΔFFR_{CT} had a good predictive value for CAD progression. Park et al[23] found that patients with higher ΔFFR_{CT} values had a higher risk of ACS, and the inclusion of ΔFFR_{CT} values had a certain predictive ability for the occurrence of ACS. Therefore, using noninvasive hemodynamic characteristics to predict CAD progression may provide a better risk stratification and treatment strategy.

Study Limitations

The limitations of this study are as follows: (1) The sample size in the progression group is relatively small, with bias. (2) In this study, some patients have very severe calcified plaques in coronary vessels, which will affect the calculation of FAI value because of its partial volume effect in image analysis and operation. (3) The values of FFR_{CT} and ΔFFR_{CT} in this study are calculated by simulation, but the real coronary vessels have the ability of elastic contraction when they are in functional state, so this study still needs to compare with invasive FFR as much as possible.

Table 4. Predictive Efficacy of Various Indicators in Predicting CAD Progression

	AUC	Sensitivity	Specificity	Yodon Index	*P*
LAD-FAI-40 mm	0.631	0.698	0.613	0.311	<.0001
RCA-FAI-70 mm	0.667	0.535	0.813	0.348	.0002
FFR_{CT}	0.650	0.977	0.293	0.27	.0001
ΔFFR_{CT}	0.824	0.628	0.987	0.615	.0475
Combined	0.897	–	–	–	–

CAD, coronary artery disease; FAI, fat attenuation index; FFRCT, fractional flow reserve with coronary artery CTA; LAD, left anterior descending artery; RCA, right coronary artery; ΔFFR_{CT}, difference of fractional flow reserve with coronary artery CTA.

CONCLUSIONS

In conclusion, LAD-FAI-40 mm, RCA-FAI-70 mm, FFR_{CT}, and ΔFFR_{CT} can be used as the basis for predicting CAD progression. Coronary CTA-based PCAT and noninvasive hemodynamic characteristics have certain value in predicting the progression of coronary heart disease, and the combination of the 2 may provide a new risk stratification and prevention strategy.

Ethics Committee Approval: This study was approved by the Medical Ethics Committee of the People's Hospital Affiliated to Hubei Medical University (no.: syrmyy2022-043).

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.M.L.; Design – S.M.L.; Supervision – S.M.L., S.L.; Literature search – S.M.L., H.Y.G.; Writing – S.M.L.; Critical review – S.M.L.

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Declaration of Interests: The authors declare that they have no competing interest.

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