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Predictive value of the perivascular fat attenuation index for MACE in young people suspected of CAD

Yani Yu[1,2†], Dongkai Shan[1†], Xi Wang[1], Zinuan Liu[1], Guanhua Dou[3], Junjie Yang[1], Yuqi Liu[1,2*] and Yundai Chen[1,2*]

Abstract

Objective The perivascular fat attenuation index (FAI) evaluated by coronary computed tomographic angiography (CCTA) has been reported to have strong prognostic value, but few studies have focused on young people. This study aimed to assess the predictive value of the perivascular FAI in young people suspected of having coronary atherosclerotic disease (CAD).

Method A retrospective analysis was performed on adults aged ≤ 45 years who underwent CCTA due to suspected CAD between 2015 and 2016 and who were followed up for at least 5 years following their visit ($n = 503$). The perivascular FAI at the proximal segment of the right coronary artery (RCA) was measured and grouped into high FAI and low FAI according to the optimal cut-off value, and the association between a high FAI and major adverse cardiac events (MACE) was evaluated by Cox hazard regression. K–M survival analysis was conducted to assess the prognostic value of the perivascular FAI and improvement over traditional risk factor prediction methods.

Results The event-free survival of patients in the high FAI group (FAI≥-75.2 HU) was significantly lower than that of patients in the low FAI group (FAI<-75.2 HU) at a median follow-up of 72.7 months (93.9% vs. 99.7%, $P < 0.001$). A high FAI (HR = 19.257, 95% CI: 2.504-148.107, $P = 0.004$) showed a significant correlation with an increased risk of MACE in young people. The prediction accuracy of MACE can be improved by including a high FAI on the basis of the traditional risk factor model, and the area under the curve (AUC) increased from 0.728 to 0.845 ($P < 0.001$). Moreover, the new model revealed significant improvements in integrated discrimination (IDI = 0.033, 95% CI: 0.009–0.103, $P = 0.014$) and the net reclassification index (NRI = 0.597, 95% CI: 0.000-0.699, $P = 0.024$).

Conclusion The high perivascular FAI at the proximal segment of the RCA is significantly associated with an increased risk of long-term MACE and may be a potential tool for cardiovascular risk stratification in young people suspected of CAD.

†Yani Yu and Dongkai Shan contributed equally to this work.

*Correspondence:
Yuqi Liu
ametuofo980869@163.com
Yundai Chen
cyundai@vip.163.com

Full list of author information is available at the end of the article

Keywords Perivascular fat attenuation index, Young people, Coronary computed tomographic angiography, Major adverse cardiac events

Introduction

The perivascular fat attenuation index (FAI), an indicator measured by coronary computed tomographic angiography (CCTA), has recently been determined to be an important vascular inflammation and cardiovascular residual risk marker. Previous evidence suggests that the perivascular FAI differs significantly between patients with obstructive coronary artery disease (CAD) and patients with nonatherosclerotic vessel disease, and it can be applied to identify and monitor unstable plaques [1]. Notably, the proximal right coronary artery (RCA) has been reported to be a stable inflammatory marker and is easy to quantify because of its stable position in the right coronary sulcus with abundant surrounding adipose tissue and the absence of nonfatty structures such as side branches or coronary veins. Therefore, the perivascular FAI of 10–50 mm at the proximal segment of the RCA can be used for the quantification of coronary artery inflammation at the individual patient level. The CRISP-CT study explored the predictive value of the perivascular FAI, and a threshold of -70.1 HU around the proximal RCA was defined as the optimal cut-off for evaluating cardiac prognosis, above which the perivascular FAI was related to a 6-9-fold increased risk for fatal heart attacks and a 5-fold increased risk for nonfatal myocardial infarction [2]. Although several reports have focused on the prognostic influence of perivascular FAI, most of them were restricted to middle-aged and elderly people with chest pain suspected of having CAD, and few studies have explored the prognosis of young people with CAD in terms of vascular inflammation. However, to the best of our knowledge, the incidence rate of acute coronary syndrome (ACS) in young people is increasing annually, and the prognosis is unacceptable; moreover, there are no reliable indications available to help predict the prognosis of young ACS patients. Compared with elderly patients with long disease progression and a large proportion of chronic pathological changes such as fibrosis and neovascularization, the role of acute exacerbation of vascular inflammation in the development of ACS in young patients needs further verification [3]. Therefore, the purpose of this study was to explore the association between the perivascular FAI and major adverse cardiac events (MACE) in young people suspected of having CAD to evaluate the ability of the perivascular FAI to predict MACE in young people and its value-added effect on the predictive efficacy of traditional risk factors.

Method

Study population

This study is a post hoc analysis of data from previous cohort that included patients no more than 45 years old who underwent CCTA examination at the Chinese PLA General Hospital between 2015 and 2016 due to suspected CAD, such as chest tightness and chest pain. Patients who were unable to provide follow-up information or who did not want to participate in the study were excluded from the study. Other exclusion criteria included previous percutaneous coronary intervention, coronary artery bypass graft history, myocardial infarction, inability to interpret serious artifacts on CCTA images, severe diffuse calcification or an RCA length less than 40 mm. This study was approved by the Chinese PLA General Hospital's Institutional Review Board (No. S2018-059-03), and also complied with the Declaration of Helsinki. All participants signed written informed consent prior to their CCTA scans. There is no clinical trial registration in this study.

According to the findings of the derivation cohort study by Evangelos K Oikonomou et al. [17], with a median follow-up duration of 72 months, the survival rate in the low FAI control group was approximately 0.94, while the high FAI observation group exhibited a hazard ratio (HR) of 2.55. Assuming a sample size ratio of 2:3, $\alpha = 0.05$, $\beta = 0.2$, an enrollment interval of 48 months, and a follow-up period of 72 months, with an assumed attrition rate of 10%, calculations using the PASS software indicate that an overall sample size of 485 cases is needed, which should be distributed with 195 cases in the observation group and 290 cases in the control group.

Follow-up and endpoint

The patients were followed up by telephone from the time they received the CCTA examination until December 2021. The follow-up information was collected, and the events were adjudicated by a trained clinician unaware of the clinical data. The primary study endpoint, MACE, was defined as follows: all-cause mortality, cardiac death, non-fatal myocardial infarction, non-fatal stroke, unplanned revascularization, and hospital readmission due to unstable angina. Survival time was defined as the time from the beginning of follow-up to the occurrence of any defined endpoint or to the last follow-up.

Clinical data collection

All clinical data is collected and recorded according to unified standards. Demographic data and clinical characteristics, including sex, age, body mass index (BMI),

smoking history, family history of CAD, diabetes, hypertension and hyperlipidemia, were collected systematically. Smoking history included current smoking or previous smoking history. A family history of CAD was defined as the first-degree relatives of the patients who were diagnosed with CAD. Diabetes was defined as a random blood glucose level ≥ 11.1 mmol/l, a fasting blood glucose level ≥ 7.0 mmol/l, and/or a 2-hour blood glucose level after an oral glucose tolerance test (OGTT) ≥ 11.1 mmol/l or treatment with hypoglycemic drugs. Hypertension was defined as a systolic blood pressure (SBP) ≥ 140 mmHg, a diastolic blood pressure (DBP) ≥ 90 mmHg or receiving antihypertensive treatments. Hyperlipidemia was defined as fasting total cholesterol ≥ 6.2 mmol/l, low-density lipoprotein cholesterol (LDL-C) ≥ 3.4 mmol/l, triglyceride ≥ 1.7 mmol/l, or treatment for dyslipidemia. Unfortunately, as all the patients we have included are outpatient patients, we are unable to obtain laboratory test results for all patients.

CCTA acquisition

CCTA scanning procedure

All included patients underwent 64 multislice dual-source spiral CT scans (Somatom Definition Flash, Siemens Medical Solutions, Forchheim, Germany). The CCTA scans included noncontrast and contrast-enhanced images. Before the procedure, the patients were trained to hold their breath to avoid artifacts caused by respiratory movement during scanning. The patients underwent continuous electrocardiogram monitoring during the whole examination. Before scanning, 0.5 mg nitroglycerin tablets were given under the tongue to dilate the coronary artery. Unless contraindications existed, all patients with a heart rate (HR) > 70 beats/min were intravenously injected with 50 ~ 100 mg of esmolol hydrochloride to control the heart rate. Nonionic contrast media (Ultravist®, 370 mgI/ml, Schering AG, Guangzhou, China) was intravenously injected via the anterior antecubital vein at a flow rate of 5.0 mL/s. The scanning parameters were as follows: detector collimation, 2 × 128 × 0.6 mm; tube voltage, 80 ~ 120 kV (according to BMI); tube current, 290 ~ 560 mAs/revolution; layer thickness, 0.7 mm; and gantry rotation time, 0.28 s. The scanning range was from the bifurcation of the pulmonary artery to 1 cm below the diaphragm, and the region of interest was positioned at the root of the ascending aorta. According to the heart rate control, prospective or retrospective electrocardiogram gated scan mode was applied necessarily and appropriately.

Postprocessing of coronary artery images

All CCTA images were transmitted to a dedicated workstation (Syngo.via VB10B, Siemens Healthcare, Siemens, Germany) to analyse CCTA images in axial and multiplanar reconstruction views. Two experienced researchers who were blinded to the clinical data of the patients analysed the images. All coronary arteries ≥ 2 mm in diameter were analysed according to the 17-segment modified AHA classification [4]. The segmental involvement score (SIS) was the total number of segments with any plaque. The segmental stenosis score (SSS) was the sum of the stenosis degree scores of each segment [5]. Each segment was scored according to the presence of plaque (0 = absent, 1 = present) and the degree of lumen stenosis [0 = no stenosis, 1 = minimal stenosis (< 25%), 2 = mild stenosis (25-49%), 3 = moderate stenosis (50-69%), 4 = severe stenosis (70-99%), 5 = occlusion (100%)] [6]. The SIS and SSS were used to evaluate the extent and severity of CAD. The data collection protocol did not include specific measurements of coronary calcification scores, plaque volume, or epicardial adipose tissue volume due to the retrospective nature of the study and the limitations of the available imaging data.

FAI quantification

Perivascular FAI analysis was performed on a dedicated postprocessing workstation (Anythink CT, Coronary Artery Analysis, version 1.01, CREALIFE, China). The proximal segment of the RCA (10–50 mm from the RCA ostium), which is located within a radial distance from the outer vessel wall equal to the diameter of the respective vessel, was traced as previously described [1]. The CT attenuation threshold of adipose tissue was set from -190 to -30 HU. The perivascular FAI was defined as the mean CT attenuation of adipose tissue within the defined region of interest (Supplement Fig. 1). The perivascular FAI at the proximal segment of the RCA can be used as a noninvasive imaging biomarker representing global coronary inflammation at the patient level [7]. Our study did not distinguish patients with different dominant types, given the lack of evidence regarding its influence on global coronary inflammatory measurements. If the length of the RCA was < 50 mm, the distance from the RCA ostium was properly adjusted during the perivascular FAI measurement, and the patient was excluded in rare cases where the RCA length was < 40 mm [8]. Major disagreements between the two investigators were resolved by negotiating the measurement method and location.

Statistical analysis

Data analysis was performed using R studio (1.4.1106 vision) software. Descriptive data were generated for all variables. The continuous variables were tested for normality by the Shapiro–Wilk method and then described by "mean ± standard deviation" or "median (interquartile range)", while the categorical variables were described by "frequency (percentage)". The Student's t test was

Table 1 Comparison of baseline characteristics between MACE group and non-MACE group

Characteristic	MACE (*n* = 13)	Non-MACE (*n* = 490)	*P* value
Age, year	42.00(34.00, 43.5)	42.00(38.00, 44.00)	0.496
BMI, kg/m^2	27.29 ± 2.63	25.89 ± 3.48	0.150
Male, %	12(92.31%)	374(76.33%)	0.155
Hypertension, %	7(53.85%)	178(36.33%)	0.158
Diabetes, %	1(7.69%)	34(6.94%)	0.063
Hyperlipidemia, %	6(46.15%)	139(28.37%)	0.139
Smoking history, %	8(61.54%)	176(35.92%)	0.057
CAD family history, %	5(38.46%)	119(24.29%)	0.195
Perivascular FAI, HU	-69.42 ± 7.34	-77.73 ± 7.76	**< 0.001**
SIS	4.00(1.50, 5.00)	0.00(0.00, 1.00)	**< 0.001**
SSS	9.00(5.00, 14.50)	0.00(0.00, 2.00)	**< 0.001**
CADRADS category			**< 0.001**
0	0(0.00%)	307(62.70%)	
1	0(0.00%)	44(9.00%)	
2	3(23.10%)	86(17.60%)	
3	4(30.80%)	27(5.50%)	
4	6(46.20%)	23(4.70%)	
5	0(0.00%)	3(0.60%)	

Table 2 Comparison of baseline characteristics between high FAI group and low FAI group

Characteristics	High FAI (*n* = 197)	Low FAI (*n* = 306)	*P* value
MACE, %	12(6.09%)	1(0.33%)	**< 0.001**
Age, year	42.00(37.00, 44.00)	42.00(38.00, 44.00)	0.608
BMI, kg/m^2	27.14 ± 3.63	25.14 ± 3.13	**< 0.001**
Male, %	172(87.31%)	214(69.93%)	**< 0.001**
Hypertension, %	92(46.70%)	93(30.39%)	**< 0.001**
Diabetes, %	20(10.15%)	17(5.56%)	0.054
Hyperlipidemia, %	64(32.49%)	81(26.47%)	0.146
Smoking history, %	90(45.69%)	94(30.72%)	**0.001**
CAD family history, %	54(27.41%)	70(22.88%)	0.249
Perivascular FAI, HU	-70.02 ± 4.39	-82.34 ± 5.42	**< 0.001**
SIS	0.00(0.00, 2.00)	0.00(0.00, 1.00)	**< 0.001**
SSS	0.00(0.00, 3.00)	0.00(0.00, 2.00)	**< 0.001**
CADRADS category			**0.034**
0	104(52.80%)	203(66.30%)	
1	21(10.70%)	23(7.50%)	
2	38(19.30%)	51(16.70%)	
3	16(8.10%)	15(4.90%)	
4	17(8.60%)	12(3.90%)	
5	1(0.50%)	2(0.70%)	

used to compare continuous variables with normal distribution, while the Mann–Whitney U test was used to compare continuous variables with non-normal distribution. Categorical variables were compared by the χ^2 test or Fisher's exact test. Cox hazard regression was used to evaluate the association between perivascular FAI and MACE, and an optimal cut-off value was determined according to the Youden index. K–M event–free survival curves and event accumulation curves of all subjects were generated. Stratification was carried out according to perivascular FAI ≥ cut-off value, and the difference in event-free survival rate between groups was tested. Cox hazard regression and time-dependent receiver operating characteristic (ROC) analysis were used to evaluate the effect of the perivascular FAI on the predictive efficacy of traditional risk factor models, and bootstrap repeated sampling was used to verify the model. The integrated discrimination improvement (IDI) and net reclassification index (NRI) were calculated to further evaluate the discrimination ability. All the statistical tests were two-sided. A P value < 0.05 was considered significant.

Results

Basic clinical data

The sample consisted of 503 participants, with an average age of 40.18 years. The median follow-up time was 72.7 (70.55, 75.77) months, and 13 patients experienced MACE. The clinical baseline characteristics and CCTA characteristics are shown in Table 1. As shown in the table, the perivascular FAI was significantly greater in the MACE group than in the non-MACE group (-69.42 ± 7.34 HU vs. -77.73 ± 7.76 HU, $P < 0.001$), and there was also a significant difference in the CADRADS category, SIS and SSS ($P < 0.001$). However, no significant difference in other cardiovascular risk factors was observed between the two groups.

To investigate the diagnostic value of the perivascular FAI in young people, we conducted ROC curve analysis, and the results revealed that the area under the curve (AUC) was 0.783 (95% CI: 0.677–0.889), and the Youden index was 0.531. Based on the ROC analysis, the optimal cut-off value corresponding to the perivascular FAI was -75.2 HU; accordingly, the sensitivity was 0.923, and the specificity was 0.614 (Supplement Fig. 2).

Association between perivascular FAI and MACE in young people suspected of CAD

Among the enrolled participants, 197 (39.17%) were categorized into the high FAI group (perivascular FAI≥-75.2 HU), and 306 (60.83%) were categorized into the low FAI group (perivascular FAI<-75.2 HU). As shown in Table 2, the incidence of MACE in the high FAI group was significantly greater than that in the low FAI group (6.10% vs. 0.33%, $P < 0.001$), and the participants with high FAI had a greater BMI (27.14 ± 3.63 vs. 25.14 ± 3.13, $P < 0.001$), were more likely to be males (87.31% vs. 69.93%, $P < 0.001$), and had a greater proportion of hypertension (46.70% vs. 30.39%, $P < 0.001$) and smoking history (45.69% vs30.72%, $P < 0.001$), but were similar in age and proportion of diabetes, hyperlipidemia, and CAD family history. An increase in CAD severity, such as in the

CADRADS category, SIS and SSS, was observed in the high FAI group ($P<0.05$).

Univariate Cox hazard regression models were used to investigate the associations between a series of clinical parameters and MACE in young people. Due to the unique nature of outpatient patients, we focus on utilizing all available clinical demographic data, known cardiovascular risk factors, and measured imaging data in the process of model construction. As shown in Table 3, high FAI, SIS, SSS and diabetes were risk factors for MACE in young patients, with a high FAI yielding a HR of 19.257 (95%CI: 2.504-148.107, $P=0.004$). Although we also attempted multivariate analysis to adjust for potential confounders, and the results indicated that a high FAI continued to be significantly associated with an increased risk of MACE in young individuals (HR = 12.780, 95% CI = 1.649–99.029, $P=0.0150$) (Supplement Table 1), we acknowledge that the limited number of events ($n=13$) may compromise the statistical robustness of the multivariate analysis. Consequently, we do not report the results of the multivariate analysis in this manuscript, which also precluded the inclusion of additional CCTA findings such as coronary calcification scores, plaque volume, and epicardial adipose tissue volume.

Predictive value of perivascular FAI for MACE in young people suspected from CAD

The median 72.7-month event-free survival rate of 503 young patients was 97.4% (490/503), of which 93.9% (185/197) were in the high FAI group, which was significantly lower than the 99.7% (305/306) in the low FAI group (χ^2=15.974, $P<0.001$). K–M survival analysis revealed a statistically significant difference in MACE occurrence between the high FAI group and the low FAI group, and a high FAI was significantly associated with poor prognosis in this post hoc analysis (Fig. 1).

Using the Cox hazard regression model, according to clinical experience, demographic characteristics such as age + male + BMI were included in Model 1 Based on Model 1, risk factors such as smoking history and diabetes status were added to Model 2. Finally, a high FAI was added to Model 3. By comparing the C-statistics of the three models, it was found that the predictive value of Model 3, which had a high FAI, for long-term adverse cardiovascular outcomes was significantly greater than that of Model 2 and Model 1 (Supplement Table 1).

Table 3 Association between perivascular FAI and MACE analyzed by univariate cox hazard regression model

Characteristics	Univariable		
	HR	95%CI	*P* value
Age	0.962	0.865–1.070	0.478
BMI	1.116	0.962–1.294	0.149
Male	3.770	0.490-28.998	0.202
Hypertension	2.017	0.678–6.003	0.207
Diabetes	3.778	1.040-13.731	**0.043**
Hyperlipidemia	2.104	0.707–6.261	0.181
Smoking history	2.756	0.902–8.425	0.075
CAD family history	1.884	0.616–5.758	0.267
High FAI	19.257	2.504-148.107	**0.004**
SIS	2.060	1.646–2.578	**< 0.001**
SSS	1.249	1.173–1.331	**< 0.001**

According to the time-dependent ROC curve analysis, after 72 months of follow-up, compared to those of Model 1 and Model 2, the C-statistic of Model 3 for the prediction of MACE in young people significantly increased, with the C-statistic increasing from 0.667 (95% CI: 0.549–0.785) for Model 1 to 0.728 (95% CI: 0.620–0.837) for Model 2 ($P=0.407$) and to 0.845 (95% CI: 0.776–0.913) for Model 3 ($P=0.006$) (Supplement Tables 2 and Fig. 2). Further analysis revealed that a high FAI significantly improved the discrimination and risk classification of MACE in young people beyond traditional risk factors. After 72 months of follow-up, the IDI of Model 3 was 0.033 (95% CI: 0.009–0.103, $P=0.014$), and the NRI was 0.597 (95% CI: 0.000-0.699, $P=0.024$), which means that the traditional risk factor model combined with a high FAI has better performance in predicting long-term cardiovascular adverse events. To determine the stability of the new model, we employed bootstrap repeated sampling for internal verification of Model 3 at 72 months of follow-up. The C-statistic after repeated sampling internal verification calibration was 0.827, which was close to the C-statistic at 72 months for Model 3 ($P>0.05$), indicating that the discriminatory ability of Model 3 was strong. Furthermore, the calibration curve demonstrated that the model has excellent calibration because the actual risk and anticipated risk curves fit well together Supplement Fig. 3).

Discussion

The present study investigated the prognostic value of perivascular FAI in young people suspected of having CAD, and the main results revealed an association between high FAI and MACE in this specific population, which was found that the high perivascular FAI (FAI≥-75.2 HU) at the proximal segment of the RCA was significantly associated with the increased risk of MACE in young people suspected of having CAD. K–M survival analysis revealed that the event-free survival rate of patients in the high FAI group, with a median follow-up of 72.7 months, was significantly lower than that of patients in the low FAI group. However, it must be noted that due to the limited number of MACE in this study, we elected not to conduct multivariate analysis and instead focused on reporting the results of the univariate analysis. This decision was made because, with our limited sample size, multivariate analysis might not effectively adjust for

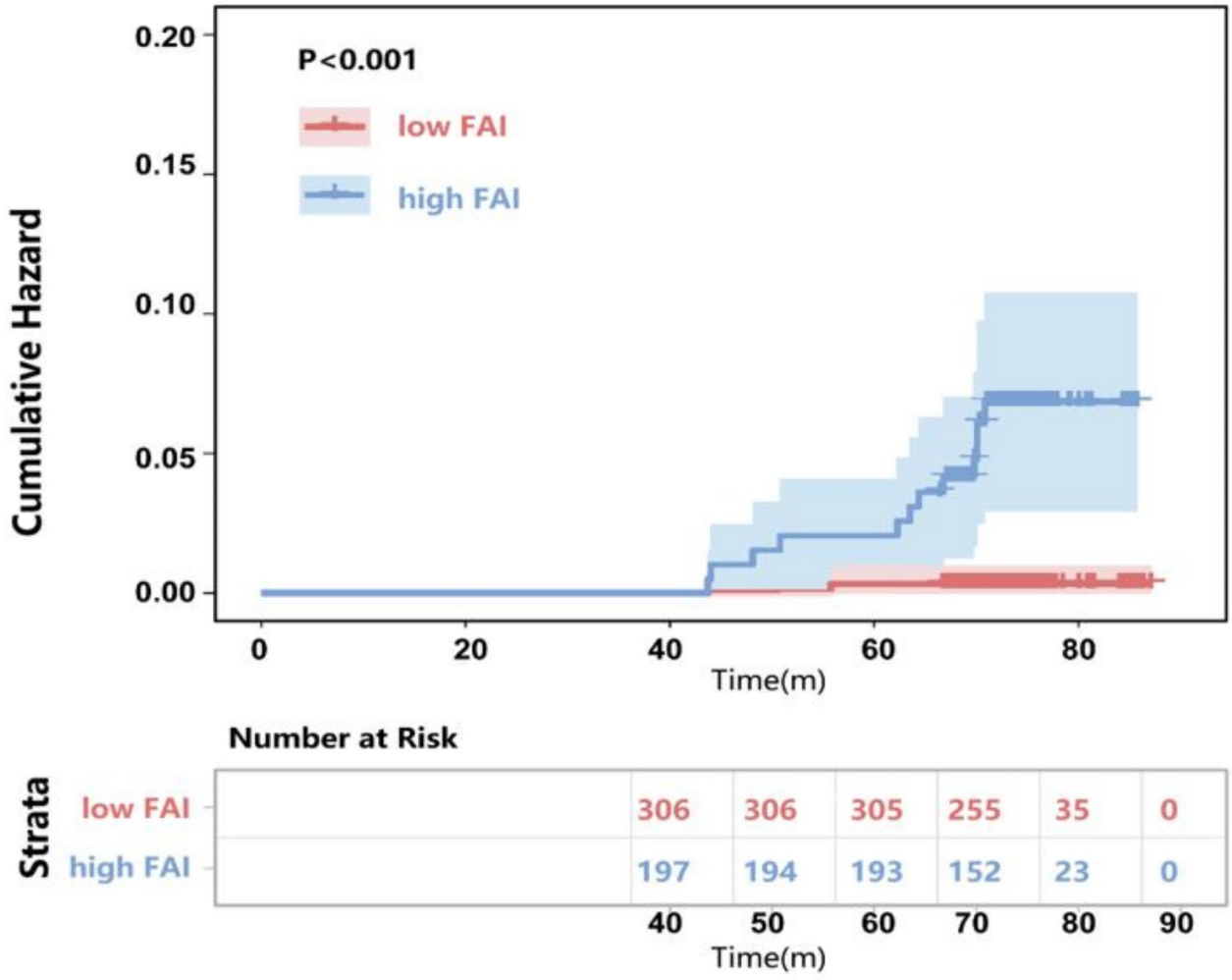

Fig. 1 Cumulative risk of median follow-up 72.7 months in young people stratification with -75.2HU cut-off value

potential confounders and could lead to overfitting. Consequently, our findings should be considered preliminary and require further confirmation with a larger prospective cohort study and investigation of the prognostic value of the perivascular FAI for other outcomes, such as the progression of coronary atherosclerosis.

FAI is a quantitative measure obtained through CCTA, which serves as an indicator of coronary artery inflammation by reflecting the biological alterations of the plaque composition. It has previously been observed that the perivascular FAI differs significantly between patients with obstructive CAD and patients with nonatherosclerotic CAD [1]. The study concluded that the perivascular FAI at the proximal segment of the RCA could represent the inflammation status throughout the coronary artery tree and is an independent predictor of the occurrence of MACE [1, 2, 9]. The CRISP-CT study demonstrated that a greater perivascular FAI at the proximal segment of the RCA increases the risk of all-cause and cardiac mortality, which is beyond traditional risk factors and CAD severity [1]. In fact, the cardiac mortality risk increased by 6-fold when high FAI and high-risk plaque features were present together [10]. Therefore, integrating the CCTA lumen, plaque feature assessment and PCAT biological phenotype can considerably improve cardiovascular risk prediction [11]. E.K. Oikonomou et al. reported that -70.1 HU around the proximal RCA was the critical value of the perivascular FAI, above which the perivascular FAI was associated with an increased risk for fatal heart attacks and nonfatal myocardial infarction [2]; moreover, the optimal cut-off value calculated by Masahiro Hoshino et al. was -73.1 HU [12], but they did not provide age information. The FAI for adverse outcomes seems to be established. However, no studies have yet tested its predictive power in different age groups, especially young individuals, who are of great interest due to their greater heart risk.

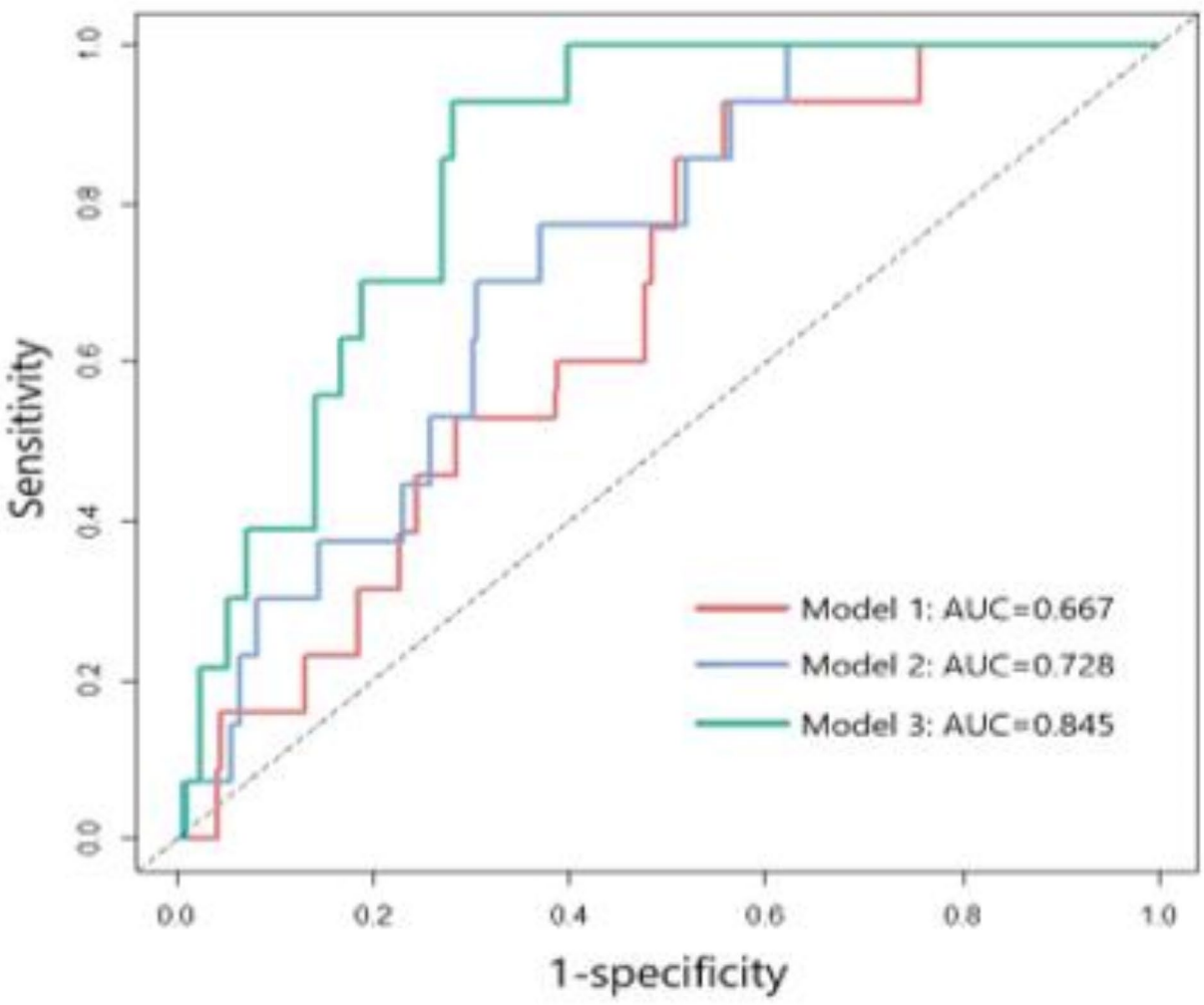

Fig. 2 Time dependent ROC analysis of effectiveness comparison of different prediction models at 72 months of follow-up

In recent decades, the incidence and death rate of CAD in young people [14] have dramatically increased [13]. In the past few decades, there has been a marked increase in the incidence and mortality of CAD among young individuals. However, the underlying mechanisms of this phenomenon in this population remain incompletely understood. Compared to middle-aged and older patients with CAD, younger patients exhibit a lower prevalence of traditional risk factors, present with acute symptoms, and may lack sufficient awareness of the disease, all of which can contribute to more severe clinical outcomes. Consequently, exploring new predictors beyond traditional risk factors to identify high-risk patients holds significant clinical importance. Inflammation may play a significant role in atherosclerotic progression and plaque rupture. Previous studies have suggested that ACS in young people is mostly caused by unstable plaque rupture when the compensatory mechanism and chronic structural changes are not fully developed [14]. However, elderly ACS patients may experience recurrent coronary ischemia, which prompts the body to develop compensatory mechanisms such as collateral circulation, while analogous processes occur in PCAT [3]. Therefore, acute exacerbation of the inflammatory response may play a crucial role in the occurrence of ACS in young people, whereas chronic alterations such as fibrosis and vascularity may have a greater impact on senior patients. A recent study conducted by Indira Deepthi Kitulwatte et al. also supported this viewpoint and reported that coronary atherosclerosis in young patients commonly showed an eccentric distribution with associated inflammation compared with that in elderly patients [15]. Moreover, the research to date has not evaluated the prognostic value of the perivascular FAI in young people. Our study is the first attempt to demonstrate that for young people suspected of having CAD, the perivascular FAI at

the proximal segment of the RCA could strongly predict long-term clinical adverse cardiovascular outcomes and may be a potential marker for cardiovascular risk stratification. Future studies may be required to conduct a more comparative analysis of the value of FA between young and elderly patients with CAD.

Despite a lower incidence rate, traditional cardiovascular risk factors retain considerable relevance in the etiology and prognostic prediction of CAD in young individuals. Smoking, in particular, is identified as one of the most prevalent risk factors among young CAD patients. The smoking prevalence and quantity among young patients suffering from acute myocardial infarction (AMI) significantly exceeds those among middle-aged and elderly patients, with persistent smoking emerging as the most potent independent predictor of long-term outcomes in early-onset AMI patients [16]. Furthermore, the association between diabetes and CAD is particularly pronounced in youthful demographic groups; research has shown that women with type 2 diabetes experience a risk of CAD that is increased by a factor of ten [17]. Although our study did not reveal a predictive role for smoking or BMI on adverse outcomes in young people, similar to the findings of Giacomo Tini and colleagues, we found that among traditional risk factors, only diabetes had prognostic value for long-term adverse outcomes in young CAD patients [18]. Our research also revealed that the inclusion of a high FAI in addition to traditional risk factors markedly enhanced the predictive power of the model, which underscores the importance of focusing on the application of CCTA in high-risk young individuals, particularly in conjunction with traditional risk factors.

In addition, the perivascular FAI may also assist in the dynamic monitoring of inflammation. Several randomized clinical trials initially suggested that the perivascular FAI measured around culprit lesions during ACS changes significantly as early as 5 weeks post-ACS and after optimal secondary preventative treatments [2]. This viewpoint was supported by Xu Dai et al., who reported that the perivascular FAI surrounding lesions of non-calcified and mixed plaques significantly decreases after statin therapy [19]. Similarly, Mancio J et al. reported that the perivascular FAI lost its strong predictive value for cardiac mortality after statin or aspirin treatment while maintaining it in untreated individuals [20]. A prospective study on psoriasis revealed that anti-inflammatory biological therapy may be significantly associated with decreased perivascular FAI, whereas no change was observed in those receiving local Ultraviolet B phototherapy [21]. This evidence seems to suggest a more significant role for the early diagnosis and warning prediction value of perivascular FAI in young people to promote the early implementation of positive interventions.

Another interesting point was that lesion-specific perivascular FAI was also associated with the hemodynamic significance of coronary artery stenosis, and a negative correlation was reported between perivascular FAI and fractional flow reserve (FFR) by Didi Wen et al. [22]. Dongkai Shan et al. suggested that the perivascular FAI in combination with the maximum area of stenosis (MAS) had a diagnostic predictive value of 0.818 for FFR, which was statistically equivalent to the computed tomography-derived FFR (CT-FFR) ($P = 0.076$) [23]. Shaowei Ma et al. also reported that the combination of the perivascular FAI and FFR exhibited diagnostic value similar to that of invasive coronary angiography in the assessment of stenosis severity (AUC: 0.820 vs. 0.839, $P = 0.39$) [24]. However, some evidence suggests that myocardial ischemia may develop more frequently as a result of functional coronary artery lesions, although further work is required to confirm whether perivascular FAI can improve the prognosis of patients with coronary functional ischemia and serve as an intervention therapy target.

Limitations

Firstly, our study was a single-center, observational and retrospective analysis of previously collected data with a low event occurrence rate, which precluded detailed subgroup analysis. For example, the participants in our study were overwhelmingly men, so the results might not be representative of patients managed in clinical practice, although we found no effect modification by sex in the Cox hazard regression. Secondly, due to the varying compliance among outpatient participants, our study did not adjust for the use of statins or aspirin, and the lack of baseline laboratory tests, specifically lipid profiles, may have resulted in an inaccurate assessment of cardiovascular risk. Although a history of hyperlipidemia provides some predictive value, it is not a complete substitute for actual measurements. Additionally, the unique characteristics of the outpatient cohort and the retrospective nature of the study precluded the definitive identification of all cases of familial hypercholesterolemia (FH), which is a significant risk factor for CAD in young individuals. This may have affected our comprehensive understanding of CAD risk factors and potentially limited the generalizability of our results. Therefore, we aim to include comprehensive laboratory testing, particularly lipid levels, and systematic diagnosis of FH in the design of future research to better comprehend the role of FH in young CAD patients and to enhance the precision of risk assessment. Thirdly, the CADRADS score was not included in the Cox regression analysis due to its uneven distribution. Another reason is that we believe that coronary atherosclerosis is a progressive disease, and compared with SSS, the CADRADS grade can only reflect the lumen with the heaviest stenosis. Moreover, the difference in CT

tube voltage was also not evaluated, but it was selected based on the patients' BMI, which was adjusted in our analysis, and repeated measurements by two researchers can also help reduce systematic error. Another limitation of our study is the absence of CCTA results, including coronary artery calcium (CAC) scoring, epicardial adipose tissue (EAT) volume, and low-attenuation noncalcified plaque burden. These parameters are known to be associated with cardiovascular risk, particularly the low-attenuation noncalcified plaque burden, which is considered the strongest predictor of fatal or non-fatal myocardial infarction. Consequently, our study may not fully capture their impact on the prediction of MACE. In future research, we should consider incorporating these metrics to provide a more comprehensive assessment of cardiovascular disease risk in young individuals [25, 26]. Fourthly, a low occurrence of MACE in natural conditions also affects young people as a whole. Our study revealed that there were only 13 MACE, and the incidence of MACE was only 2.58%, which limits us from conducting multi factor analysis to adjust for potential confounding factors. However, we conducted validation tests for the discrimination and calibration of the predictive model, and the results indicate that our model exhibits good stability. Finally, the study sample predominantly consists of Asian individuals, which may restrict the generalizability of the findings. Given that cardiovascular disease risk factors and manifestations can vary across different ethnicities, caution should be exercised when applying the results of this study to other racial or population groups. We recommend that future research be conducted within a more racially diverse context to evaluate the universality of the prognostic value of the FAI. Despite the aforementioned limitations, our research provides a promising perspective for the non-invasive evaluation of vascular inflammation in young people. It could serve as a new, more significant potential marker for the early diagnosis and prognosis prediction of young patients with CAD, thereby improving risk stratification.

Conclusion

As a non-invasive imaging marker reflecting coronary artery inflammation, the perivascular FAI at the proximal segment of the RCA is significantly associated with the risk of long-term MACE in young people suspected of CAD. A high FAI was significantly associated with a low event-free survival rate and could improve the prediction performance beyond traditional risk factors for MACE, which may be a potential tool for cardiovascular risk stratification in young people suspected of having CAD. Further multicenter, multiethnic studies would enhance the understanding of the prognostic role of the FAI across diverse populations.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Not applicable.

Author contributions
Y.Q. Liu and Y.D. Chen designed the research; Y.N. Yu and D.K. Shan performed the experiments and analysed the data; Y.N. Yu wrote the original draft; X. Wang, Z.N. Liu and G.H. Dou measured the data; D.K. Shan and J.J. Yang revised the article and prepared the figures. All authors reviewed and agreed to the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study complied with the Declaration of Helsinki and was approved by the Chinese PLA General Hospital's Institutional Review Board (No. S2018-059-03).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Human ethics and consent to participate declarations
All enrolled patients provided written informed consent.

Patient and public involvement
Not applicable.

Clinical trial registration
This study is a post hoc analysis without a clinical trial registration.

Author details
[1]Department of Cardiology, The Sixth Medical Center, Chinese PLA General Hospital, No. 6 Fucheng Road, Haidian District, Beijing 100142, China
[2]School of Medicine, Nankai University, No. 94 Weijin Road, Nankai District, Tianjin 300071, China
[3]Department of Cardiology, The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, Beijing 100853, China

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