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# The predictive value of coronary artery calcium score combined with traditional risk factors for obstructive coronary heart disease in young people

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## Abstract

**Objectives** This study attempts to compare the predictive effects of several prediction models on obstructive coronary artery disease (OCAD) in young patients (30–50 years old), with a view to providing a new evaluation tool for the prediction of premature coronary artery disease (PCAD).

**Methods** A total of 532 hospitalized patients aged 30–50 were included in the study.All of them underwent coronary computed tomography angiography (CCTA) for suspected symptoms of coronary heart disease.Coronary artery calcium score (CACS) combined with traditional risk factors and pre-test probability models are the prediction models to be compared in this study.The PTP model was selected from the upgraded Diamond-Forrester model (UDFM) and the Duke clinical score (DCS).

**Results** All patients included in the study were aged 30–50 years. Among them, women accounted for 24.4%, and 355 patients (66.7%) had a CACS of 0. OCAD was diagnosed in 43 patients (8.1%). The CACS combined with traditional risk factors to predict the OCAD area under the curve of receiver operating characteristic (ROC) ($AUC = 0.794, p < 0.001$) was greater than the PTP models ($AUC_{UDFM} = 0.6977, p < 0.001$; $AUC_{DCS} = 0.6214, p < 0.001$). By calculating the net reclassification index (NRI) and the integrated discrimination index (IDI), the ability to predict the risk of OCAD using the CACS combined with traditional risk factors was improved compared with the PTP models ($NRI\&IDI > 0, p < 0.05$).

**Conclusion** The predictive value of CACS combined with traditional risk factors for OCAD in young patients is better than the PTP models.

**Keywords** Premature CAD, CACS, Obstructive CAD, PTP models, Young doubts

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## Introduction

Premature coronary artery disease (PCAD) is widespread, affects large numbers of people, and a large proportion of the population has a poor prognosis [1]. This is because there is a lack of effective screening tools to catch young patients who may develop coronary artery disease (CAD) [2]. A number of studies have shown that young patients (aged 30–50 years) with traditional atherosclerotic cardiovascular disease (ASCVD) risk assessment as low risk have an underestimated potential coronary heart disease (CHD) risk [3–5]. Age figures prominently in various risk assessment tools [6], so there is a lack of effective models or predictive tools to assess PCAD risk. It is particularly important to develop screening methods and develop early prevention strategies for younger populations.

Evaluating pre-test probabilities can assist patients with suspected coronary heart disease to select appropriate testing options.Currently, the upgraded Diamond-Forrester model (UDFM) and Duke clinical score (DCS) are mainly used for pre-test probability (PTP) assessment [7, 8]. The guidelines also recommend the use of PTP models to assess high-risk groups.However, in both prior probability models, age plays a dominant role in model construction. Its predictive role in younger patients (30–50 years old) still needs further validation.

The ACC/AHA guideline states that it is reasonable to improve the risk assessment of premature coronary artery disease in younger populations by evaluating coronary artery calcium (CAC) with non-contrast computed tomography (CT). Different from coronary CT angiography (CCTA), is a non-invasive examination method and is more suitable for young people. Our study attempts to evaluate the predictive value of coronary artery calcium score (CACS) combined with traditional risk factors for obstructive coronary artery disease (OCAD) in young patients and compare it with existing PTP models. To provide new modeling tools for risk assessment of premature coronary artery disease.

## Methods

### Study population

The population of this study was from the First Affiliated Hospital of Dalian Medical University.A total of 1960 inpatients who underwent CCTA examinations from August 2015 to June 2021 were screened, and all of them underwent this examination because of suspected coronary heart disease symptoms.1352 patients were excluded because they were older than 50 years.The main exclusion criteria were: previous history of coronary heart disease, severe liver and kidney insufficiency, malignant diseases such as tumors, and lack of clinical data. Finally, 532 patients were included in this study, and they were grouped according to CACS, as shown in Fig. 1.All patients gave informed consent and were approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University.

### CCTA acquisition and measurement of CACS

All CCTA and post-imaging reconstructions and evaluations were performed by three experienced radiologists and judged in strict accordance with guidelines.CCTA was performed with a Siemens Somatom Force CT scanner (Siemens Healthineers, Forchheim, Germany).Sublingual nitroglycerin 0.25 mg was administered 5 min before the examination, and the scanning range was from the level of the tracheal carina to the diaphragmatic surface of the heart.First, the calcium scoring scan (unenhanced scan) was performed in the prospective ECG-gated sequence scan mode with a slice thickness of 3 mm.Second, three-phase injection was accomplished through the antecubital vein using an Ulrich twin-cylinder high-pressure injector (Germany).The scan parameters were as follows.Scan modo: prospective ECG-gated sequence; rotation speed: 0.25 s/r; detector collimation: 2×96×0.6 mm; tube voltage and tube current: auto mAs and auto kV; matrix: 512×512; slice thickness: 0.75 mm; interval: 0.7 mm.

The acquired CCTA images were sent to Siemens Syngo. via a VB10 post-processing workstation (Siemens Healsineers, Forchheim, Germany).OCAD can be diagnosed if the degree of stenosis of any one of the LM, LAD, LCX, and RCA is greater than or equal to 50% by coronary computed tomography angiography.Non-contrast CCTA imaging was used for post-processing of calcification integration, the threshold was 130HU, and the calcification quality correction factor was preset.After the extent of calcification was determined, CACS was automatically calculated using the Agatston method, and CACS were grouped as 0, 1-100, or >100 Agatston Units (AU) [9].

### Evaluation of ASCVD risk factors

All enrolled patients were assessed for ASCVD risk factors, and information was obtained during the clinical visit accompanied by CAC testing.Traditional risk factors included in this study were identified based on existing ASCVD risk assessment tools.Lipid status can be judged by previous clinical diagnosis, laboratory results, or use of lipid-lowering therapy.The diagnostic criteria for dyslipidemia were as follows: low-density lipoprotein cholesterol≥160 mg/dL, hypertriglyceri demia≥150 mg/dL, and/or high-density lipoprotein cholesterol<40 mg/dL in men, <50 mg/dL in women [10]. Diabetes (without distinction between types of diabetes) and hypertension were defined based on previous clinical diagnosis or reported use of antihypertensive or hypoglycemic drugs.

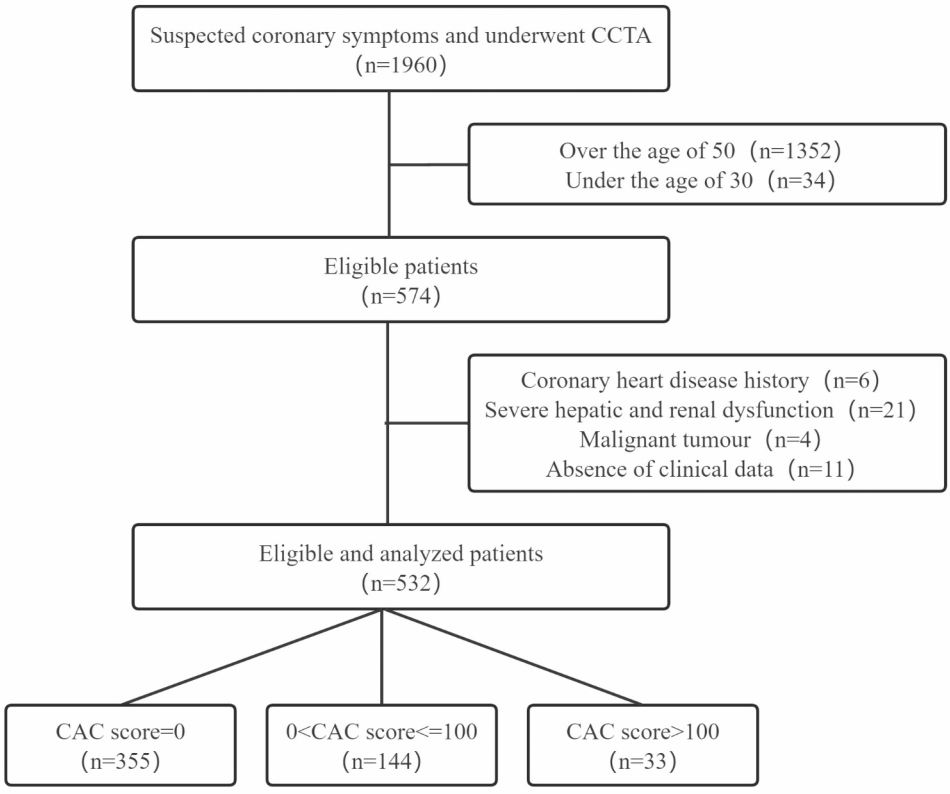


**Fig. 1** Study flow chart. Abbreviations:CCTA,coronary computed tomography angiography;CAC,coronary artery calcification

Information such as smoking was obtained from patient self-reports.

### Calculation of pre-test probability

The upgraded Diamond-Forrester model and Duke clinical score were used as the pre-test probability evaluation model.The former is mainly based on age, gender and type of chest pain for pre-test probability assessment of patients with coronary heart disease, and is only designed for patients between 30 and 70 years old.The types of chest pain are divided into typical angina, atypical angina, and nonspecific chest pain.Angina pectoris is characterized by (1) characteristic nature and location (retrosternal chest pain); (2) induced by exertion, physical activity, or emotional agitation; (3) relieved by rest or nitrates [11]. Atypical angina is defined as having both of the above criteria. Nonspecific chest pain was defined if one or none were present.The Duke clinical score takes into account diabetes, smoking, hyperlipidemia, old myocardial infarction, and ECG changes on the basis of the above [12]. After that, the calculation of the a priori probability is carried out through the a priori probability model provided by each.

### Statistical analysis

Categorical variables were presented as numbers and relative frequencies (percentages) and were compared using the chi-square test or Fisher's exact test.For normally distributed variables, continuous variables were expressed as mean ± SD; for non-normally distributed data, continuous variables were expressed as median (interquartile range), and were compared using analysis of variance or nonparametric tests.The odds ratio (OR) and 95% confidence interval (CI) of obstructive coronary heart disease were analyzed by multivariate Logistic regression analysis of age, gender, traditional risk factors, CACS, and pre-test probability model.In the model, the logarithm of the calcium integral and the pre-test probability was used.The area under the receiver operating characteristic curve was calculated to evaluate the ability of calcification score combined with traditional risk factors and pre-test probability model to identify obstructive coronary heart disease.Take Youden's index (the maximum value of [sensitivity + specificity − 1]) as the critical value.Reclassification performance was compared using relative integrated discrimination rate improvement (IDI) and continuous net reclassification index (NRI).All p-values reported in this study were two-sided and $p < 0.05$ was considered statistically significant.Statistical analysis was performed using R (version 4.1.2).

## Results

### Demographic characteristics

The clinical baseline characteristics of 532 patients were analyzed and grouped according to calcium score. The baseline characteristics of the patients are shown in Table 1.Patients in the two groups with higher CACS had a higher age, and men, diabetes, current smoking and dyslipidemia accounted for a higher proportion.Patients with OCAD were more concentrated in the group with higher CACS.Serum creatinine was higher in groups with higher CACS.However, there were no statistical differences in left ventricular hypertrophy, left ventricular ejection fraction, and high-sensitivity C-reactive protein among different CACS groups.

### Relationship between traditional risk factors, CACS, PTP models and OCAD

As shown in Supplementary Fig. 1, single-factor logistic regression analysis was performed on traditional risk factors, CACS, and PTP models.Because the data of the CACS were not normally distributed, they were logarithmically transformed.The results of the prior probability were calculated after multiplying by 100, because before this, their results were extremely small.Gender, diabetes, dyslipidemia, and current smoking are all independently associated with the development of OCAD.The PTP calculated using the upgraded Diamond-Forrester model to predict the risk of OCAD (OR, 1.163; 95% CI, 1.100–1.230; $p<0.001$) and the PTP calculated using the Duke Clinical Score to predict the risk of OCAD (OR, 1.045; 95% CI, 1.003–1.089; $p<0.001$) are similar.However, they are all lower than CACS in predicting the risk of OCAD (OR, 2.788, 95% CI, 2.027–3.835; $p<0.001$).

After adjusting for age, sex, diabetes, dyslipidemia, hypertension, and current smoking, CACS and PTP models were still independently associated with the occurrence of OCAD.Model 1 adjusted for age and gender, and Model 2 adjusted for traditional risk factors based on Model 1.In Model 1 (OR, 2.725; 95% CI, 1.948–3.854; $p<0.001$) and Model 2 (OR,2.580; 95% CI, 1.821–3.695; $p<0.001$), the risk of OCAD calculated by CACS was still higher than the two PTP models. See Table 2.

### Comparison of prediction models

The results of single-factor and multi-factor regression analysis showed that the predictive ability of CACS for OCAD was better than the PTP models.After combining the CACS with traditional risk factors, its predictive ability is even more obvious. See Fig. 2. The AUCS of the two PTP models for predicting OCAD were 0.697 ($p<0.001$) and 0.621 ($p=0.003$) respectively. The AUC of the joint model of CACS and traditional risk factors was 0.794 ($p<0.001$).The comparisons between models are still statistically significant, with p values less than 0.05.

By calculating the NRI and the IDI, it was clear that the ability to predict the risk of OCAD using the CACS combined with traditional risk factors was improved compared with the PTP models. See Supplementary Fig. 2. Compared with $PTP_{UDFM}$, the net reclassification index (NRI, 0.2576; 95%CI, 0.009–0.506; $p=0.042$) of the joint model is statistically significant.However, the integrated discrimination index was not statistically significant.

**Table 1** Baseline characteristics of groups according to coronary artery calcium score

| | ALL | CACS = 0 | 0 < CACS < = 100 | CACS > 100 | *p*.overall | *p*.trend |
|---|---|---|---|---|---|---|
| | *N* = 532 | *N* = 355 | *N* = 144 | *N* = 33 | | |
| Age, years | 41.6 (6.04) | 40.7 (6.14) | 43.2 (5.47) | 44.7 (4.90) | < 0.001 | < 0.001 |
| Gender, male | 402 (75.6%) | 252 (71.0%) | 121 (84.0%) | 29 (87.9%) | 0.002 | 0.001 |
| Hypertension | 511 (96.1%) | 340 (95.8%) | 140 (97.2%) | 31 (93.9%) | 0.515 | 0.915 |
| Diabetes Mellitus | 75 (14.1%) | 38 (10.7%) | 28 (19.4%) | 9 (27.3%) | 0.003 | 0.001 |
| Current Smoker | 208 (39.1%) | 119 (33.5%) | 74 (51.4%) | 15 (45.5%) | 0.001 | 0.001 |
| Dyslipidemia | 303 (57.0%) | 188 (53.0%) | 89 (61.8%) | 26 (78.8%) | 0.006 | 0.002 |
| **Laboratory Data** | | | | | | |
| Hs-CRP, ng/ml | 1.19 [0.57;2.44] | 1.16 [0.56;2.44] | 1.10 [0.58;2.44] | 1.51 [0.99;4.82] | 0.108 | 0.287 |
| Cre,μmol/L | 72.0 [62.0;82.0] | 71.0 [58.0;81.0] | 72.0 [64.0;85.0] | 76.5 [72.0;88.0] | 0.008 | 0.002 |
| LVH | 40 (7.52%) | 24 (6.76%) | 13 (9.03%) | 3 (9.09%) | 0.568 | 0.381 |
| LVEF | 59.0 [58.0;60.0] | 59.0 [58.0;60.0] | 59.0 [58.0;59.0] | 58.0 [56.0;59.0] | 0.004 | 0.002 |
| **CCTA** | | | | | | |
| LM stenosis > = 50% | 2 (0.38%) | 0 (0.00%) | 1 (0.69%) | 1 (3.03%) | 0.037 | 0.009 |
| RCA stenosis > = 50% | 20 (3.76%) | 4 (1.13%) | 8 (5.56%) | 8 (24.2%) | < 0.001 | < 0.001 |
| LAD stenosis > = 50% | 28 (5.26%) | 10 (2.82%) | 9 (6.25%) | 9 (27.3%) | < 0.001 | < 0.001 |
| LCX stenosis > = 50% | 21 (3.95%) | 5 (1.41%) | 7 (4.86%) | 9 (27.3%) | < 0.001 | < 0.001 |
| Obstructive CAD | 43 (8.08%) | 13 (3.66%) | 16 (11.1%) | 14 (42.4%) | < 0.001 | < 0.001 |

Note: Values are presented as mean ± SD, number (percentage), or median (interquartile range)

Abbreviations: CACS, coronary artery calcium score; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; LM, Left main coronary artery; RCA, right coronary artery; LAD, left anterior descending branch; LCX, left circumflex artery; CAD, coronary artery disease

**Table 2** Multivariate logistic regression results

| | Model 1 | | Model 2 | |
|---|---|---|---|---|
| | **OR(95%CI)** | ***p*-value** | **OR(95%CI)** | ***p*-value** |
| Log(CACS + 1) | 2.725(1.948–3.854) | < 0.001 | 2.580(1.821–3.695) | < 0.001 |
| $PTP_{UDFM}$ | 1.594(1.350–2.109) | < 0.001 | 1.567(1.323–2.083) | < 0.001 |
| $PTP_{DCS}$ | 1.273(1.169–1.396) | < 0.001 | 1.309(1.138–1.549) | 0.001 |

Note: model 1,adjusted for age, gender; model 2,adjusted model 1 + diabetes, dyslipidemia, current smoking and hypertension

Abbreviations: Log(CACS + 1),add 1 to the coronary artery calcium score and take the logarithm value; $PTP_{UDFM}$,pre-test probability calculated by upgraded Diamond-Forrester model; $PTP_{DCS}$,pre-test probability calculated by the Duke clinical score

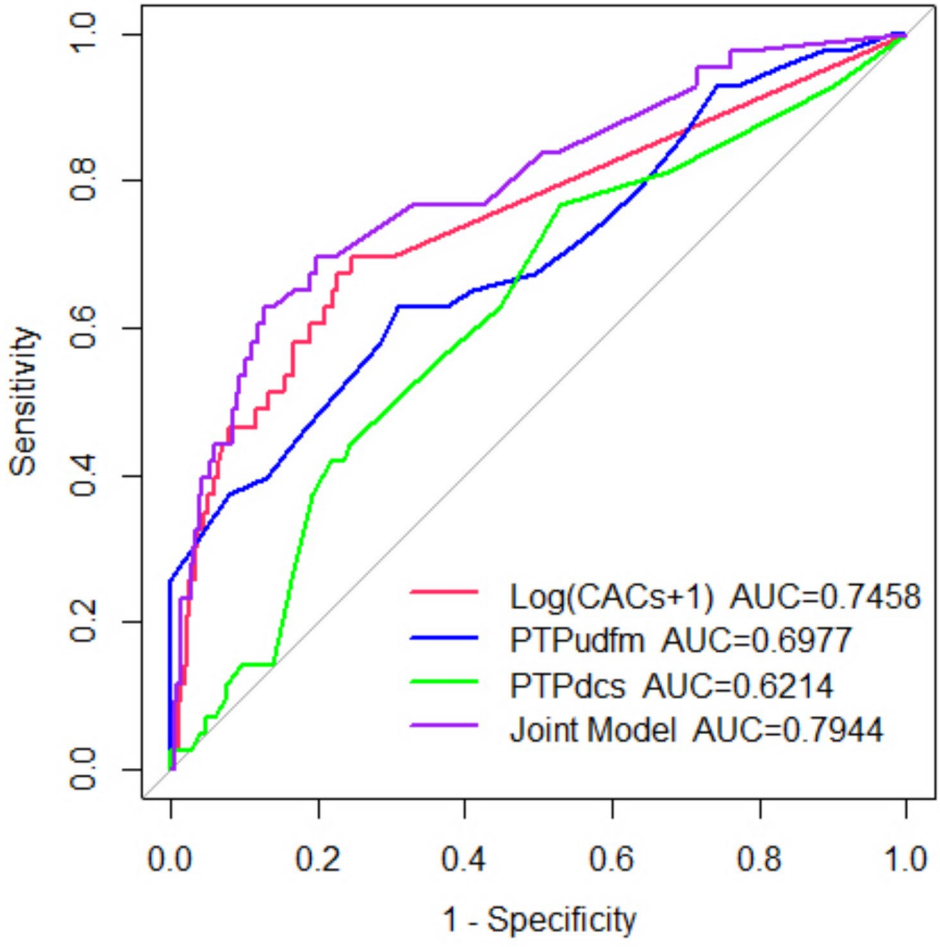


**Fig. 2** Receiver operating characteristic curves showing the incremental value of joint model, coronary artery calcium score and pre-test probability models. Abbreviations:Log(CACS+1),add 1 to the coronary artery calcium score and take the logarithm value;PTPUDFM,pre-test probability calculated by upgraded Diamond-Forrester model;PTPDCS,pre-test probability calculated by the Duke clinical score

When comparing the joint model with $PTP_{DCS}$, both the net reclassification index (NRI,0.5119;95%CI,0.3319–0.6918;$p < 0.001$) and the integrated discrimination index (IDI,0.140;95%CI,0.088–0.192;$p < 0.001$) were statistically significant.

## Discussion

There is a lack of effective assessment of the risk of coronary heart disease in young patients (age 30–50 years old). This study analyzed this group of patients.Our study found that: (a)CACS still has a good predictive value for obstructive coronary heart disease in young patients; (b) The predictive ability of CACS combined with traditional risk factors is better than the PTP models.

Few studies have evaluated coronary heart disease risk in young patients.Current guidelines recommend that adults with an ASCVD risk between 5% and 19.9% should consider CAC scoring [6]. The CAC score mainly depends on coronary artery calcification, which is affected by multiple factors such as genetics and

environment. The exact molecular mechanism is still unclear. Most scholars believe that endothelial cells play an important role in vascular calcification, and β2-AR signaling pathway, calcium regulation, endothelial progenitor cells, inflammation, oxidative stress, neurohumoral regulation, etc. can all accelerate the calcification process by affecting endothelial cells [13–15]. The above mechanism shows that vascular calcification is greatly affected by age. And age plays an important role in previous ASCVD assessment systems, and the ASCVD risk of young patients is mostly<5%.In multiple cohort studies of carotid intima-media thickness [16], younger patients (age younger than 50 years), especially men, who were uncertain about their risk management, had lower estimated 10-year risks. A prospective study of coronary heart disease risk in young patients found that approximately 10% of 3043 young patients had coronary atherosclerosis.Over the subsequent 12 years of follow-up, the risk of coronary heart disease in this group of patients increased five-fold [17]. Therefore, the risk of premature coronary heart disease deserves attention, and early and simple risk assessment for young patients will help reduce the risk of long-term disease.

ACC/AHA recommends using pre-test probability models to predict people at high cardiovascular risk [18]. However, research by James K. M et al. shows that in women and younger age subgroups, the evaluation performance of the pre-test probability model is poor [19]. In the classic Framingham risk assessment model and the traditional coronary heart disease risk assessment model, as age increases, the risk increases exponentially, which is related to the characteristics of its model construction [20, 21]. Therefore, these traditional models have certain shortcomings for risk assessment in young patients.A 12.5-year follow-up study mentioned that patients younger than 50 years old can be selectively screened for CAC as long as they have risk factors to further guide prevention strategies.In this study, approximately 33% of young patients had CACS>0 [17]. Although they also have hypertension, the risk of obstructive coronary artery disease remains underestimated.This result confirms the necessary value of CACS in young patients.

The predictive ability of CACS combined with traditional risk factors for OCAD has been significantly improved.In this study population, its AUC was 0.794, which was significantly better than the pre-test probability models, which provides a new idea for early prevention of young patients with low risk factors.As a non-invasive examination technology, non-contrast computed tomography has attracted much attention in the prediction, diagnosis and treatment of coronary heart disease [22]. Guidelines suggest that CACS can be used to guide preventive treatment in asymptomatic patients at intermediate risk.For low-risk patients, the joint model better reassessed risk, and patients who were previously significantly underestimated were identified so that preventive treatment could be started as early as possible. Corresponding preventive strategies remain to be confirmed by further research.

Crucially, when CACS are classified according to levels, people with a CACS>0 have a significantly higher risk of obstructive coronary heart disease than those with a CACS=0.This reminds us that calcium scores have different predictive roles in people of different ages.CACS>0 deserves high vigilance in young patients because of the exponential nature of the risk increase. In addition, CACS=0 does not exclude atherosclerosis.Therefore, after taking traditional risk factors into account in our combined model, future studies could consider adding other imaging or assessment indicators.

Our study has several limitations. First, the sample size was small and it was a single-center retrospective study. Secondly, the proportion of hypertension and dyslipidemia in the study population is extremely high, and referral bias is unavoidable. Third, the severity of the risk factors cannot be determined. For example, almost all people have high blood pressure, but the duration of the disease cannot be determined. Fourth, patients with severe renal impairment were excluded, which may play a role in long-term risks. Fifth, the guidelines recommend assessing cardiovascular risk every 5 years, so follow-up of this group of patients will provide a better understanding of long-term risks, which will be conducted in subsequent studies.

## Conclusion

Even if the risk of ASCVD is low in young patients (30–50 years old), further examination is necessary.The predictive value of calcium score combined with traditional risk factors for obstructive coronary heart disease is better than the pre-test probability model.Performing non-contrast computed tomography scans on these patients can help identify potential risks to further guide early prevention.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04166-6.

**Supplementary Figure 1** Forest plot of single factor regression. Abbreviations:Log(CACS+1),add 1 to the coronary artery calcium score and take the logarithm value;PTPUDFM,pre-test probability calculated by upgraded Diamond-Forrester model;PTPDCS,pre-test probability calculated by the Duke clinical score.

**Supplementary Figure 2** NRI results comparing joint model and PTP models. a) NRI results of joint model compared with PTPUDFM. b) NRI results of joint model compared with PTPDCS.

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This study is a retrospective study based on clinical data and has not been registered on clinical trial.

**Author contributions**
A.Ronglin Sun, Yongkui Ren and Da Yin made substantial contributions to the conception and design of the study. B.Ronglin Sun and Weili Pan participated in the study design, and drafted the manuscript. C.Minxian Wang, and Xiaohong Chen participated in the collection and analysis of data. All authors have approved the final version of the manuscript.

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**Data availability**
All data generated or analysed during this study are included in this manuscript. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## Declarations

**Ethics approval and consent to participate**
This study was granted an exemption from requiring ethics approval by the First Affiliated Hospital of Dalian Medical University Ethics Committee because this study was a retrospective observational study.In order to comply with the standardization of the research, this research was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University and the approval number was PJ-XJS-2022-21.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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## Publisher's note