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Development and validation of a simple model to predict functionally significant coronary artery disease in Chinese populations: A two-center retrospective study

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ABSTRACT

Objectives: This study sought to derive and validate a simple model combining traditional clinical risk factors with biomarkers and imaging indicators easily obtained from routine preoperative examinations to predict functionally significant coronary artery disease (CAD) in Chinese populations.
Methods: We developed five models from a derivation cohort of 320 patients retrospective collected. In the derivation cohort, we assessed each model discrimination using the area under the receiver operating characteristic curve (AUC), reclassification using the integrated discrimination improvement (IDI) and net reclassification improvement (NRI), calibration using the Hosmer-Lemeshow test, and clinical benefit using decision curve analysis (DCA) to derive the optimal model. The optimal model was internally validated by bootstrapping, and external validation was performed in another cohort including 96 patients.
Results: The optimal model including 5 predictors (age, sex, hyperlipidemia, hs-cTnI and LVEF) achieved an AUC of 0.807 with positive NRI and IDI in the derivation cohort. Moreover, the Hosmer-Lemeshow test showed a good fit, and the DCA demonstrated good clinical net benefit. The C-statistic calculated by bootstrapping internal validation was 0.798, and the calibration curve showed adequate calibration (Brier score = 0.179). In the external validation cohort, the optimal model performance was acceptable (AUC = 0.704; Brier score = 0.20). Finally, a nomogram based on this model was constructed to facilitate its use in clinical practice.
Conclusions: A simple model combined clinical risk factors with hs-cTnI and LVEF improving the prediction of functionally significant CAD in Chinese populations. This attractive model may be a choice for clinicians to risk stratification for CAD.

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1. Introduction

Cardiovascular diseases are the leading cause of mortality in China. Coronary artery disease (CAD) is one of the frequently occurring cardiovascular diseases, posing a serious threat to people's lives and a great economic burden to society [1]. Invasive coronary angiography (ICA) is the gold standard for the diagnosis of CAD. However, Patel et al. revealed only 41% obstructive coronary lesions in patients who were scheduled for ICA with clinical indication [2]. Furthermore, the severity of coronary artery stenosis does not exactly match myocardial ischemia, and percutaneous coronary intervention (PCI) for stenotic coronary arteries that have not caused myocardial ischemia can increases the incidence of adverse cardiovascular events [3]. In contrast, the functional significance of coronary stenosis assessed by fractional flow reserve (FFR) allows accurate determination of myocardial ischemia, which leads to better guide interventions and less waste of resources [4,5]. Unfortunately, the invasive nature and high cost of FFR restricted its application in clinical practice. Therefore, a noninvasive and practical method is needed to identify patients with functionally significant CAD.

More recently, several models combining clinical risk factors with circulating biomarkers and imaging indicators to predict anatomic CAD (coronary stenosis >50%) have shown improved performance compared to classical CAD prediction models [6–8]. Nevertheless, these models do not identify functionally significant CAD associated with high prognostic risk. On the other hand, some of these biomarkers and imaging parameters cannot be obtained with routine examinations, which may increase the financial burden on patients. Thus, we aimed to develop and validate a simple model combining traditional clinical risk factors with biomarkers and imaging indicators easily obtained from routine preoperative examinations to predict functionally significant CAD in Chinese populations.

2. Methods

This study, developing, validating, and comparing multivariable prediction models, was constructed according to Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement [9].

2.1. Study population

We retrospectively enrolled patients with stable CAD and unstable angina (UA), and referred for ICA at the Second Affiliated Hospital of Harbin Medical University from November 2020 to September 2021 as the derivation cohort. The following patients were excluded: (1) previous history of myocardial infarction; (2) atrial fibrillation; (3) significant (≥moderate) valvular disease; (4) cardiomyopathy; (5) more than 10% of the missing data; and (6) unable to calculate quantitative flow ratio (QFR) (Fig. 1). From March 2022 to August 2022, we enrolled patients at Guangdong Provincial People's Hospital Southern Medical University as an external validation cohort using the same inclusion and exclusion criteria. Finally, the derivation cohort and external validation cohort were comprised of 320 and 96 patients, respectively. The research protocol was approved by the institutional review boards of the Second Affiliated Hospital of Harbin Medical University (sydwgzr2020-030) and Guangdong Provincial People's Hospital Southern Medical University (KY-Z-2021-2149-01). Given its retrospective design, patient written consent was waived.
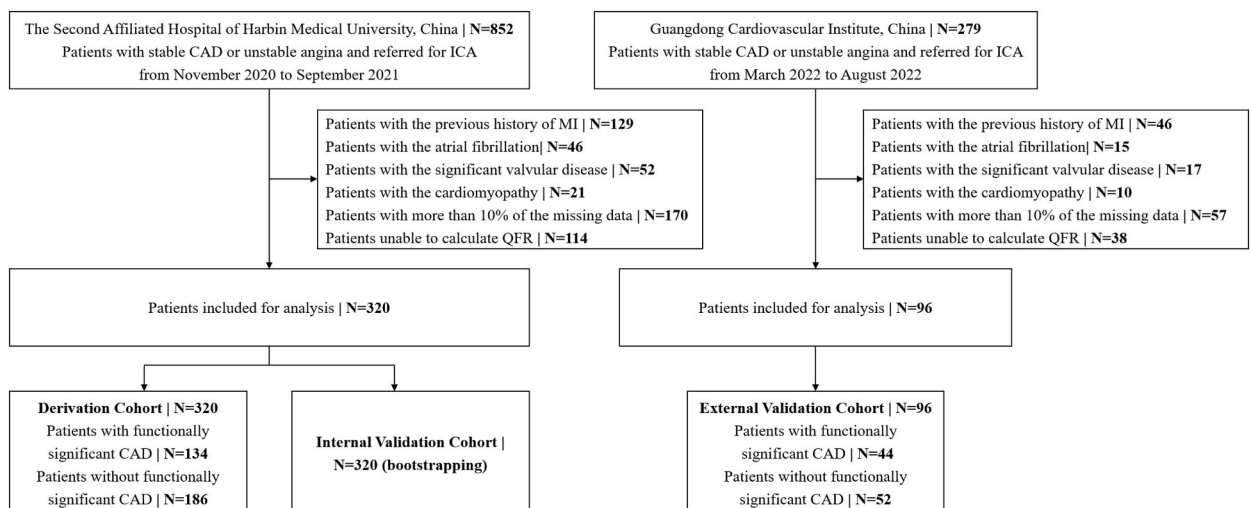

Fig. 1. Flow diagram for derivation and validation cohorts.
Abbreviation: CAD, coronary artery disease; ICA, invasive coronary angiography; MI, myocardial infarction; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio.

2.2. Data collection and clinical definitions

The date of the ICA procedure was defined as the index date. Detailed demographic, clinical characteristics and the results of relevant examinations were recorded from the electronic medical record system at the time of the procedure. Body mass index (BMI) was defined as weight (kg)/height (m^2). Hypertension was defined as a history of hypertension and the use of antihypertensive medication. Diabetes mellitus was defined by a diagnosis of diabetes mellitus in their medical history, use of an antidiabetic treatment, and fasting glucose levels over 7 mmol/L. Hyperlipidemia was defined as total cholesterol of ≥220 mg/dL, low-density lipoprotein cholesterol of ≥140 mg/dL, fasting triglycerides of ≥150 mm/dL, or the use of lipid-lowering medication. Smoking was defined as current smoking or having quit smoking for less than 1 year. The hs-cTnI level was based on the first detection on admission. Patients underwent transthoracic echocardiography examination and were measured LVEF within 48 h before ICA.

2.3. Outcome: functionally significant CAD

As the gold standard for determining functionally significant CAD, FFR is an invasive procedure that is complex and requires the vessels to be in a hyperemic state [10]. QFR has been proven to be consistent with FFR and can be calculated by the QFR system through an algorithm without hyperemic state [11]. Hence, based on the ICA and QFR results of patients [12], we defined functionally significant CAD as the presence of at least one of the following:

a) >50% stenosis of the left main coronary artery or proximal left anterior descending coronary artery (or both) or left circumflex coronary artery, or right coronary artery, with QFR ≤0.80.

b) >90% stenosis in a major coronary vessel.

2.4. Quantitative flow ratio analysis

The QFR was offline analyzed after ICA in the target vessel. The measurement of QFR required the selection of two parts with an end-diastolic projection angle ≥25° and no shortening or overlap. The lumen contours were automatically delineated by extensively validated algorithms. If the angiographic image quality was sub-optimal, a manual correction was permitted according to a standard operating procedure. QFR was analyzed by two experienced observers in the Angiography Laboratory of Guangdong Provincial People's Hospital who were blinded to the study using the Pulse Medical software (Pulse Medical Imaging Technology Shanghai, Shanghai, China).

2.5. Predictor variables

We sought out repeatedly reported predictors of functionally significant CAD in clinical studies and systematic reviews, which are easily accessible in different clinical settings [6,13–16]. For the development of predictive models, a minimum of 10 outcome events per predictor variable (EPV) is recommended [17]. The outcome event was functionally significant CAD in this study, and we had 134 participants with functionally significant CAD after inclusion and exclusion criteria. To avoid overfitting during model building, we finally included 10 candidate variables (age, sex, BMI, hypertension, diabetes mellitus, hyperlipidemia, smoking, previous coronary percutaneous intervention, hs-cTnI, and LVEF). For simplicity, age, LVEF and hs-cTnI were coded as dichotomous variables. Age was transformed into a binary variable according to the best cut-off value used to diagnose functionally significant CAD. LVEF was transformed into a binary variable with a cut-off value of 55% according to the British Society of Echocardiography guideline [18], meanwhile, LVEF 55% was also the best cut-off value used to diagnose functionally significant CAD. And the elevated hs-cTnI was defined when it is above the upper limit of the 99th percentile for the healthy population (34.2 ng/L for men, 15.6 ng/L for women).

2.6. Statistical analysis

Normally distributed continuous data were reported as mean ± SD and compared using Student t-test, whereas nonnormally distributed continuous data were described with medians and IQRs and compared using Mann-Whitney U-tests. Categorical variables were expressed in frequencies and percentages, and the comparison between groups was expressed by χ^2 test.

Variables with missing data ≤10% were imputed by the multiple imputation method. Variables with $P < 0.10$ in univariable analysis, as well as hs-cTnI and LVEF, were entered in multivariable model. Then, multivariate stepwise regression was performed according to the Akaike information criterion (AIC) to develop the final model. Multicollinearity among variables was assessed by the variance inflation factor (VIF) (VIF > 10 was considered strong collinearity) [19].

Model discrimination was evaluated by calculating the area under the receiver operator characteristic curve (AUC). AUCs were compared using the DeLong method [20]. As the AUC is relatively insensitive to model improvements, we also assessed continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) [21]. Continuous NRI assesses any upward or downward reclassification and values >0 correspond to improved reclassification. IDI takes into account the situation at different cut-off values and is usually used to reflect the overall improvement of a prediction model. Calibration was assessed using the Hosmer-Lemeshow (H-L) goodness of fit test ($P > 0.05$ indicates a good fit) or calibration curve (the predictions should fall on a 45° diagonal line in a well-calibrated model). Furthermore, we calculated the Brier score as a measure of overall performance. The Brier score can range from 0 to 1, and useful prediction models have Brier scores <0.25. Finally, the clinical usefulness and net benefit were estimated with decision curve analysis (DCA). The DCA is a measure that the relative impact of true-positive and false-positive results

given a threshold probability (or clinical preference) was accounted to yield the net benefit of each model [22]. The net benefit of each model over a specified range of threshold probabilities of outcome is graphically displayed as a decision curve.

We constructed other four models based on statistical results and clinical significance to compare with the final model. The discrimination, calibration, reclassification and clinical net benefit of the five models were compared in the derivation cohort to assess the optimal model. A nomogram based on the optimal model was constructed to facilitate its use in clinical practice. Internal validation of the optimal model was performed using bootstrap with 1000 replicates to obtain an optimism-corrected C-statistic and calibration curve. External validation of the optimal model was performed using AUC, H-L goodness-of-fit test and DCA. All statistics were performed using R software (version 4.2; R Foundation for Statistical Computing). Statistical significance was defined as $P < 0.05$.

2.7. Sensitivity analyses

To assess the robustness of the optimal model, we conducted two sensitivity analyses in the derivation cohort and external validation cohort, respectively. Using the optimal cut-off value determined by the Youden index of the derivation cohort, we calculated AUC, sensitivity, and specificity with the optimal model in patients with (1) stable CAD and UA, and (2) men and women, respectively.

3. Results

3.1. Patient characteristics

The baseline characteristics of the development cohort are summarized in Table 1. The mean age was 58 years, 200 (62.5%) were male, and 134 patients (41.9%) were functionally significant CAD. The variables except for BMI and previous PCI differed significantly between the functionally significant CAD and non-functionally significant CAD groups ($P < 0.05$). In the external validation cohort, the mean age was 59.3 years, 65 (67.7%) were male, and 44 patients (45.8%) were functionally significant CAD (Table S1). Patients with functionally significant CAD were older, more likely to be male, and had elevated hs-cTnI, decreased LVEF, and a higher prevalence of hyperlipidemia. Comparison of the baseline characteristics of the derivation cohort and external validation cohort (Table S2) shows that except for diabetes mellitus, previous PCI and LVEF, the other variables were balanced and comparable between the two cohorts.

3.2. Development of new prediction models

Table 2 shows the results of univariate and multivariate logistic regression analyses. Age ≥55 years, male sex, diabetes mellitus, hypertension, hyperlipidemia, smoking, LVEF <55%, and elevated hs-cTnI were univariate significant predictors of functionally significant CAD. The final model (Model E) retaining age, sex, hyperlipidemia, elevated hs-cTnI, and LVEF was established after stepwise multivariate logistic regression analysis. Next, we constructed other four models. Model A consisted of only significant clinical variables in the univariate analysis including age, sex, hypertension, diabetes mellitus, hyperlipidemia, and smoking. Models B and C added LVEF and hs-cTnI to model A, respectively. Model D added both LVEF and hs-cTnI to model A. The VIF values confirmed no multicollinearity between variables (all VIF < 2).

Table 1
Baseline characteristics of the derivation cohort.

Characteristic	Derivation Cohort			
	Total (N = 320)	Functionally significant CAD		*P* Value
		Yes (N = 134)	No (N = 186)	
Age, years	58.0 (8.5)	58.6 (8.5)	57.5 (8.6)	0.272
Age ≥55 years	211 (65.9)	99 (73.9)	112 (60.2)	**0.011**
Male	200 (62.5)	103 (76.9)	97 (52.2)	**<0.001**
BMI	24.8 (2.9)	25.0 (2.7)	24.7 (3.1)	0.435
Hypertension	153 (47.8)	75 (56.0)	78 (41.9)	**0.013**
Diabetes mellitus	69 (21.5)	40 (29.9)	29 (15.6)	**0.002**
Hyperlipidemia	108 (33.7)	69 (51.5)	39 (21.0)	**<0.001**
Smoking	95 (29.6)	48 (35.8)	47 (25.3)	**0.042**
Previous PCI	22 (6.9)	10 (3.1)	12 (3.8)	0.724
hs-cTnI, ng/L	7.7 (6.0–22.1)	9.1 (7.2–31.3)	6.2 (4.7–12.8)	**<0.001**
Elevated hs-cTnI	36 (11.3)	33 (10.3)	3 (0.9)	**<0.001**
LVEF, %	65.9 (62.0–70.0)	65.3 (60.3–70.0)	66 (62.8–70.0)	0.247
LVEF <55%	16 (5.0)	13 (9.7)	3 (1.6)	**0.001**

Data are mean (standard deviation), median (IQR), or value (%).
Abbreviation: BMI, body mass index; CAD, coronary artery disease; hs-cTnI, high-sensitivity cardiac troponin I; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

Table 2

Logistic regression analysis for predictor of functionally significant coronary artery disease in the derivation cohort.

	Univariate	Multivariate				
		Model A	Model B	Model C	Model D	Model E
Age ≥55 years	1.87 (1.16, 3.06)	2.22 (1.29, 3.89)	2.29 (1.31, 4.06)	2.26 (1.26, 4.15)	2.36 (1.30, 4.38)	2.49 (1.40, 4.57)
Male sex	3.05 (1.88, 5.05)	3.40 (1.95, 6.06)	3.18 (1.81, 5.70)	3.22 (1.78, 5.97)	3.08 (1.70, 5.71)	3.37 (1.91, 6.11)
Hypertension	1.76 (1.13, 2.76)	1.20 (0.71, 2.01)	1.23 (0.72, 2.09)	1.24 (0.71, 2.16)	1.25 (0.71, 2.19)	–
Diabetes mellitus	2.30 (1.35, 3.99)	1.47 (0.78, 2.75)	1.36 (0.72, 2.57)	1.36 (0.70, 2.64)	1.30 (0.67, 2.54)	–
Hyperlipidemia	4.00 (2.47, 6.58)	3.82 (2.22, 6.67)	3.91 (2.27, 6.87)	3.88 (2.19, 7.00)	3.95 (2.22, 7.15)	4.25 (2.47, 7.46)
Smoking	1.65 (1.02, 2.68)	1.34 (0.76, 2.37)	1.34 (0.76, 2.39)	1.40 (0.77, 2.57)	1.40 (0.76, 2.58)	–
LVEF <55%	6.55 (2.06, 29.02)	–	5.73 (1.70, 26.27)	–	3.98 (1.01, 19.92)	4.18 (1.06, 21.01)
Elevated hs-cTnI	19.93 (6.93, 84.30)	–	–	18.62 (6.18, 80.96)	17.05 (5.56, 74.89)	17.26 (5.62, 75.86)
AIC	–	382.79	376.42	348.28	346.40	343.09
H-L P Value	–	0.15	0.33	0.76	0.60	0.31

Except for AIC and H-L test, data are odds ratio (95% CI). Model A = age + sex + hypertension + diabetes mellitus + hyperlipidemia + smoking; Model B = Model A + LVEF; Model C = Model A + hs-cTnI; Model D = Model A + LVEF + hs-cTnI; Model E = age + sex + hyperlipidemia + hs-cTnI + LVEF.

Abbreviation: AIC, Akaike information criterion; CAD, coronary artery disease; hs-cTnI, high-sensitivity cardiac troponin I; LVEF, left ventricular ejection fraction.

3.3. Comparison of new models in the derivation cohort

Fig. 2 presents the ROC curves of all models in the derivation cohort. The AUC value of Model E (0.807, 95% CI: 0.760–0.855) was significantly higher than Model A (0.750, 95% CI: 0.697–0.803, $P < 0.01$) and Model B (0.766, 95% CI: 0.713–0.818, $P < 0.01$), but it was similar to model C (0.806, 95% CI: 0.758–0.855, $P = 0.9067$) and Model D (0.812, 95% CI: 0.764–0.860, $P = 0.4322$). The continuous NRIs and IDIs of all models are compared in Table 3. Compared to Model A, the risk reclassification for functionally significant CAD was improved by the addition of the LVEF alone (Model B, NRI = 0.238, $P < 0.001$), by hs-cTnI alone (Model C, NRI = 0.460, $P < 0.0001$), and by LVEF and hs-cTnI together (Model D, NRI = 0.518, $P < 0.0001$). Model E which only contained age, sex, hyperlipidemia, hs-cTnI, and LVEF significantly also improved the continuous NRI (0.564, $P < 0.0001$) and IDI (0.107, $P < 0.0001$) compared with model A. While there was no significant difference in the comparison of both continuous NRI and IDI between Model D and Model E (all $P > 0.05$). Calibration was adequate in all models as shown by the H–L goodness-of-fit test (all $P > 0.05$; Table 2). In the DCA, compared with models A and B, models C, D and E had a greater net benefit in the 25%–95% range of probability of functionally significant CAD, and net benefit curves for models C, D and E overlapped considerably across relevant probability thresholds (Fig. 3). Compared with other models, Model E demonstrated good discrimination, calibration, reclassification and clinical net benefit with the least number of variables.
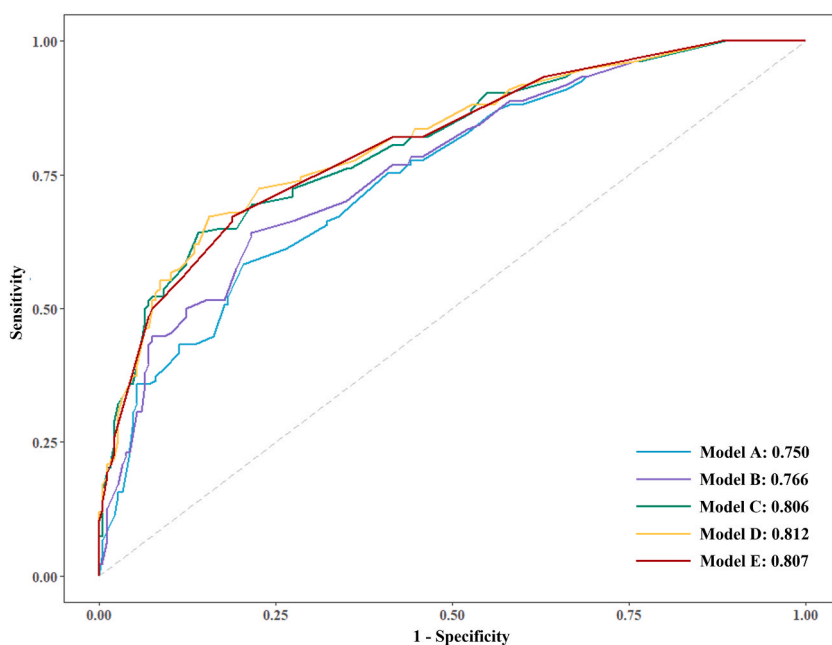

Fig. 2. Comparison of five models by receiver operating characteristic curve in the derivation cohort.

Table 3

Integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI) for five models in the derivation cohort.

	Model A	Model B	Model C	Model D	Model E
Model A	–	−0.024 (−0.043, −0.006), $P = 0.011$[a]	−0.098 (−0.135, −0.061), $P < 0.0001$[a]	−0.107 (−0.146, −0.069), $P < 0.0001$[a]	−0.100 (−0.140, −0.060), $P < 0.0001$[a]
Model B	0.238 (0.104, 0.373), $P < 0.001$[b]	–	−0.074 (−0.112, −0.035), $P < 0.001$[a]	−0.083 (−0.117, −0.048), $P < 0.0001$[a]	−0.076 (−0.112, −0.040), $P < 0.0001$[a]
Model C	0.460 (0.310, 0.611), $P < 0.0001$[b]	0.460 (0.310, 0.611), $P < 0.0001$[b]	–	−0.009 (−0.021, 0.003), $P = 0.124$[a]	−0.002 (−0.018, 0.013), $P = 0.793$[a]
Model D	0.518 (0.3566, 0.680), $P < 0.0001$[b]	0.460 (0.310, 0.611), $P < 0.0001$[b]	0.038 (−0.123, 0.199), $P = 0.644$[b]	–	0.007 (−0.002, 0.017), $P = 0.120$[a]
Model E	0.564 (0.392, 0.737), $P < 0.0001$[b]	0.450 (0.264, 0.636), $P < 0.0001$[b]	−0.075 (−0.296, 0.147), $P = 0.509$[b]	−0.054 (−0.276, 0.168), $P = 0.635$[b]	–

A value in any cell indicates the value (95 % CI) of the horizontal model compared to the vertical model.
[a] IDI with corresponding P value.
[b] Continuous NRI with corresponding P value.

The Model E was presented in the form of a nomogram (Fig. 4). To simplify the operation, a dynamic nomogram was exhibited at https://shenwenqian.shinyapps.io/DynNomapp/. Table 4 shows the actual prevalence of functionally significant CAD and the frequency of revascularization according to quartiles of nomogram score. The prevalence of functionally significant CAD was gradually increasing according to the nomogram score quartiles, and the prevalence was approximately 7.5 times higher in the highest quartile than in the lowest quartile. Likewise, the frequency of revascularization gradually increased from the first to the fourth quartiles. What is noteworthy is that the frequency of revascularization exceeded the probability of functionally significant CAD in almost all score ranges.

3.4. Model internal and external validation

In the internal validation, the C-statistic and calibration curve of Model E was obtained after 1000 bootstrap resamples. As shown in Fig. 5, the optimism-corrected C-statistic of Model E was 0.798, the Brier score was 0.179, and the calibration curve showed good calibration. In the external validation of Model E, AUC was 0.704 (95% CI: 0.570–0.838), the H-L test value was 0.165, and the Brier score was 0.20. In the DCA, Model E had a higher net benefit than "All line" or "None line" for ≥15% of the probability of functionally significant CAD (Fig. S1).

3.5. Sensitivity analyses

As shown in Table S3, the results of the two subgroup analyses were similar to those of all patient analyses (main analysis) in each cohort, both in the derivation cohort and the external validation cohort.
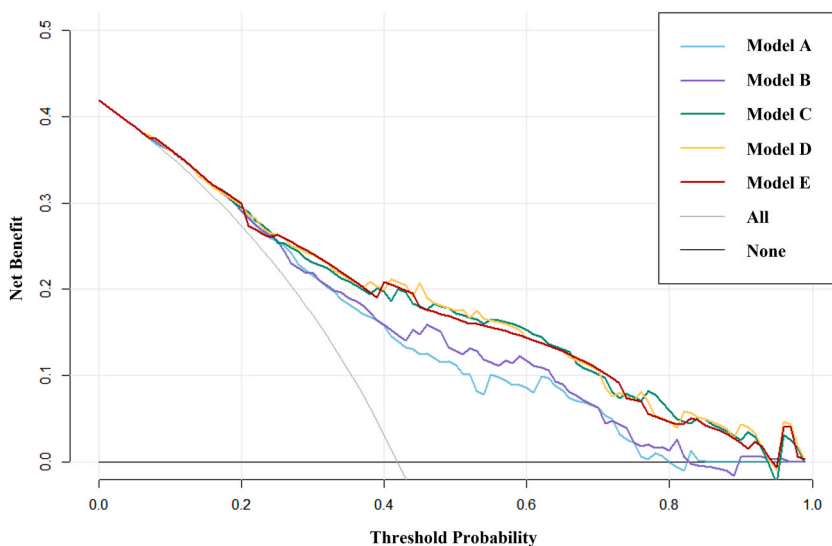

Fig. 3. Decision curve analysis of five models in the derivation cohort.
The black line was "none line" which indicates the net benefit when no patients are considered to be with functionally significant CAD; the grey line was "all line", the net benefit when all the patients are considered to be with functionally significant CAD.
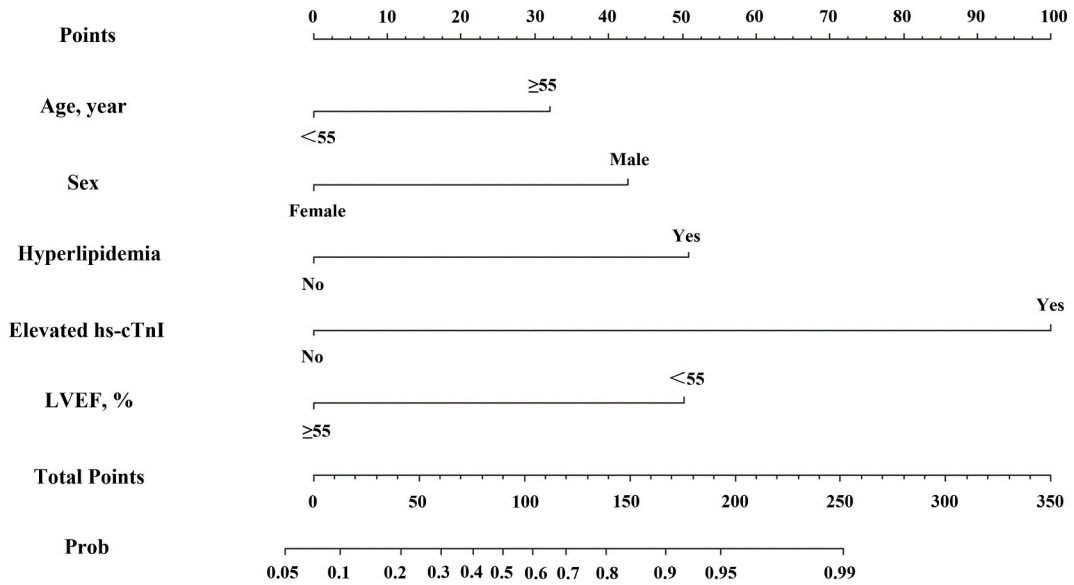
Fig. 4. Nomogram for Model E to predict the probability of functionally significant coronary artery disease.
Abbreviation: hs-cTnI, high-sensitivity cardiac troponin I; LVEF, left ventricular ejection fraction.

Table 4
Prevalence of functionally significant coronary artery disease and frequency of revascularization in derivation cohort according to quartiles of nomogram score for the model.

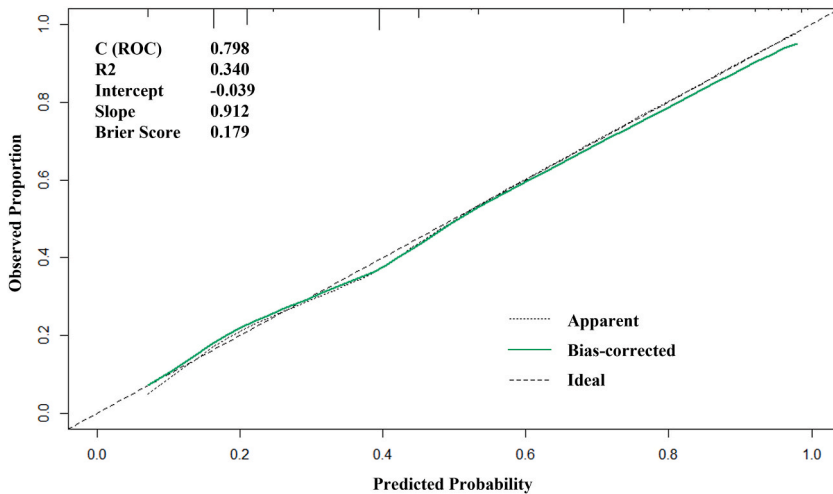| Nomogram score	<42.66 (Q1)	42.66–74.75 (Q2)	74.75–124.95 (Q3)	≥124.95 (Q4)
n	78	117	44	81
Functionally significant CAD, n (%)	9 (11)	35 (30)	23 (52)	67 (83)
Revascularization, n (%)	13 (17)	37 (32)	25 (57)	65 (80)

Abbreviation: CAD, coronary artery disease.

Fig. 5. The calibration curve for internal validation of Model E using bootstrap with 1000 replicates.
Abbreviation: ROC, receiver operator characteristic curve.

4. Discussion

In this study, we developed five models to predict functionally significant CAD in Chinese populations. Discrimination, reclassification, calibration and clinical benefit of five models were compared in the derivation cohort, and the final model consisting of age, sex, hyperlipidemia, hs-cTnI and LVEF manifested more satisfactory. The model also performed well in internal and external validation. For ease of clinical application, the final model is presented as a nomogram.

Currently, the performance of most CAD prediction models was unsatisfactory in Chinese populations. In the external validation of Duke clinical score, a study from the Chinese population showed lower predictive performance [8]. Similarly, several of the externally validated studies of the CAD consortium clinical score and Diamond-Forrester model with low predictive ability were also from the Chinese population [8,23]. The main reason may be that the models are developed based on the European and American populations, and the disease characteristics of the population are different from Chinese populations. On the other hand, these models were used to predict obstructive CAD (coronary anatomical stenosis >50%) rather than functionally significant CAD (FFR ≤ 0.80) which are associated with inducible ischemia and poor outcomes [24]. Hence, we developed the model to predict functionally significant CAD based on the Chinese population.

According to multiple logistic regression analyses, hs-cTnI has a significantly higher OR value than other factors. Cardiac troponins, an important component of myocardial contraction, are a complex of troponin T, troponin I and troponin C. Troponins regulate the interaction between actin and myosin, thereby promoting myocardial contraction, and have been proven to correlate with the severity of CAD [25–27]. The emergence of highly sensitive methods has made it easier to detect previously undetectable levels of cardiac troponins [28]. Evidence demonstrates that hs-cTnI has independent prognostic value regarding acute coronary syndromes, heart failure, and even stable CAD [29–33]. Similarly, LVEF was also preserved in multivariable logistic regression analyses. LVEF measured by echocardiography provides a real-time, non-invasive assessment of left ventricular systolic function and is a routine examination indicator before ICA in patients with CAD. Further, an echocardiographic assessment of LVEF before discharge helps to stratify the risk of CAD patients after revascularization. Recently, a large cohort study based on the Chinese population exploring the association between LVEF and mortality or cardiovascular events in CAD patients showed that all-cause mortality or major adverse cardiovascular and cerebrovascular events risk increased significantly below an LVEF of 55%, and patients with LVEF <55% had a more than 3.5-fold higher mortality than those with LVEF ≥55% [34]. Yong Liu et al. showed that the inclusion of LVEF in the predictive model improved the ability to diagnose obstructive CAD [16]. Hence, we used a cut-off value of 55% to transform LVEF into a binary variable for inclusion in the model to predict functionally significant CAD. Some other new makers, such as kidney injury molecule-1, adiponectin, epicardial fat volume, and perivascular fat attenuation index also have been found to predict CAD [6,7,35]. Yet, LVEF and hs-cTnI are usually routinely available before ICA without additional financial burden to the patient.

Compared to other models, Model E with the least number of variables demonstrated the best discrimination, calibration, and clinical net benefit in the development cohort. In internal validation, the discrimination (C-statistic = 0.798) and calibration (Brier score = 0.179) of Model E still performed well. Given the prediction ability of models may be influenced by distinct risk conditions in different regions, we conducted an external validation in a southern Chinese population. In the external validation, the AUC value and Brier score of Model E were 0.704 and 0.20, respectively, which indicated that the performance of the model decreased slightly but still acceptable. It may be that there are differences in demographic characteristics due to the large environmental differences between the North and South. Of note, Model E performed similarly to the main analysis in the sensitivity analysis. Therefore, it is reliable and general to use this promising model to predict functionally significant CAD.

Currently, patients without evidence of ischemia often undergo revascularization only based on the degree of anatomical stenosis of coronary artery disease. We found for patients who underwent ICA, the probability of revascularization was higher than functionally significant CAD. In our study, the ultimate goal of the whole diagnostic process is the recognition of patients with functionally significant stenosis causing myocardial ischemia, who have a higher risk of adverse cardiovascular events in the future and are more likely to benefit from invasive examinations and revascularization. Simultaneously, the DCA confirmed that our model has a favourable clinical net benefit. Accordingly, considering the current rising costs of cardiovascular health care, downstream diagnostic and treatment decisions guided by such a simple model may be an attractive strategy for clinical cardiology practice.

5. Limitations

Several limitations of this study should be considered. First, this study was subjected to the limitation of its retrospective design, other variables that have been demonstrated to be associated with functionally significant CAD, such as classification of chest pain and resting ECG changes, might have provided additional information but were not available in the present study. Besides, the hs-cTnI level in the derivation cohort and external validation cohort may be biased by different assay methods and assayers, and there may be inter-operator variability in the measurement of LVEF. Second, for easy interpretation and operation in routine clinical practice, the three continuous variables were transformed into dichotomous variables may result in under-exploitation and under-utilization of the predictive value of the variables. This needs to be explored further in the future. Third, this is a preliminary study with a small sample size. While our model was externally validated at a hospital in a different region, the generalization of our model needs to be further validated by a multicenter study with a large sample size.

6. Conclusions

We derived and validated a simple model only based on five routinely available variables to predict functionally significant CAD in Chinese populations. This attractive strategy may reduce unnecessary invasive examinations for patients. A large-scale prospective study is needed to validate the effectiveness of this predictive model in the management of patients with CAD.

Statement of ethics

The research protocol was approved by the institutional review boards of the Second Affiliated Hospital of Harbin Medical University (sydwgzr2020-030) and Guangdong Provincial People's Hospital Southern Medical University (KY-Z-2021-2149-01).

Funding statement

Author contribution statement

Wen-Qian Shen: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. Guo-Qing Du: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper. Xin Duan: Yi-Tong Li: Shuang Chen: Yu-Ming Huang: Jun-Qing Yang: Li-Wen Li: Contributed reagents, materials, analysis tools or data. Jing-Yi Xue: Conceived and designed the experiments. Jia-Wei Tian: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20643.

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