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RESEARCH ARTICLE

Nomogram for Predicting the Severity of Coronary Artery Disease in Young Adults ≤45 Years of Age with Acute Coronary Syndrome

Xulin Hong[1a], Duanbin Li[1a], Xinrui Yang[2], Guosheng Fu[1], Chenyang Jiang[1], Wenbin Zhang[1]

[1]*Department of Cardiology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China*
[2]*Department of Cardiology, The Hangzhou Lin'an People's Hospital, Hangzhou, China*

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Abstract

Background: A non-invasive predictive model has not been established to identify the severity of coronary lesions in young adults with acute coronary syndrome (ACS).
Methods: In this retrospective study, 1088 young adults (≤45 years of age) first diagnosed with ACS who underwent coronary angiography were enrolled and randomized 7:3 into training or testing datasets. To build the nomogram, we determined optimal predictors of coronary lesion severity with the Least Absolute Shrinkage and Selection Operator and Random Forest algorithm. The predictive accuracy of the nomogram was assessed with calibration plots, and performance was assessed with the receiver operating characteristic curve, decision curve analysis and the clinical impact curve.
Results: Seven predictors were identified and integrated into the nomogram: age, hypertension, diabetes, body mass index, low-density lipoprotein cholesterol, mean platelet volume and C-reactive protein. Receiver operating characteristic analyses demonstrated the nomogram's good discriminatory performance in predicting severe coronary artery disease in young patients with ACS in the training (area under the curve 0.683, 95% confidence interval [0.645–0.721]) and testing (area under the curve 0.670, 95% confidence interval [0.611–0.729]) datasets. The nomogram was also well-calibrated in both the training (P = 0.961) and testing (P = 0.302) datasets. Decision curve analysis and the clinical impact curve indicated the model's good clinical utility.
Conclusion: A simple and practical nomogram for predicting coronary artery disease severity in young adults ≤45 years of age with ACS was established and validated.

Keywords: Acute coronary syndrome; risk factor; nomogram; Gensini score; Youth

Introduction

Acute coronary syndrome (ACS) has become a severe public health problem worldwide, including in China [1]. Although ACS occurs mainly in older populations, younger individuals ≤45 years of age

[a]These authors contributed equally to this research.
Corresponding authors: Wenbin Zhang and Chenyang Jiang, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University, No 3 East of Qinchun Road, Hangzhou, Zhejiang, 310000, P. R. China,
E-mail: 3313011@zju.edu.cn; cyjiang@zju.edu.cn

can also be affected, and the gradual increase in the incidence of ACS in young people has drawn substantial attention [2].

Younger patients with ACS frequently present with fewer and less complex coronary lesions, as estimated by the Gensini score [3], a strong predictor of short- and long-term adverse cardiovascular events [4, 5]. However, a major concern is that not all countries or areas can perform primary or early percutaneous coronary intervention [6], and even in experienced centers, approximately 50% of all young patients with myocardial infarction may not receive any reperfusion therapy because of late diagnosis [7]. Hence, a simple and rapid preoperative assessment tool is needed to aid in clinical decision-making.

Young patients with ACS have similar risk factors (RFs) to those of older patients [8]. Previous studies have indicated that young patients with coronary artery disease (CAD) already have multiple lifestyle-associated RFs, and conventional RFs (smoking, obesity, hypertension and hypercholesterolemia) have been reported to be highly prevalent in young Chinese men hospitalized for their first ACS events [2]. In addition, non-traditional RFs, such as hyperhomocysteinemia [9] and hyperuricemia [10], have also been suggested as predictors of the presence or severity of ACS in young Chinese patients. Various predictive models for CAD risk evaluation have been built on the basis of RFs, such as the Framingham risk score, the Systematic Coronary Risk Evaluation and Pooled Cohort Equations [11, 12], thus providing convenient, cost-efficient evaluation methods for clinicians in developing countries. However, very few models exist to predict the severity of CAD, particularly in young patients with ACS.

Thus, the purpose of our study was to evaluate the contributions of factors influencing the severity of ACS in young adults and to construct a model to aid in evaluation before coronary intervention.

Methods

Study Population

In the current retrospective dataset study, young adults ≤45 years of age who were diagnosed with ACS (a spectrum of disease comprising myocardial ischemia, including unstable angina, non-ST-segment elevation myocardial infarction and ST-segment elevation myocardial infarction [13]) for the first time, and who underwent coronary angiography (CAG) at Sir Run Run Shaw Hospital between January 1, 2010 and December 31, 2021, were enrolled. The study exclusion criteria were as follows: (1) missing data; (2) previous myocardial infarction; (3) previous percutaneous coronary intervention or coronary artery bypass grafting; and (4) myocardial infarction with non-obstructive coronary arteries. A total of 1,088 participants were included, who were then randomized into a training dataset (n = 763) and the testing dataset (n = 325) in a ratio of 7:3 (Figure 1). The Gensini scores of all patients were ranked: scores in the 50th percentile or below (≤ 32) were considered low, and those above the 50th percentile (>32) were considered high. The training and testing datasets were used to establish and validate the predictive nomogram, respectively.

This study was approved by the Institutional Ethics Committee of Sir Run Run Shaw Hospital. Informed consent was obtained from all participants at our institution.

Data Collection

Patients' demographic data including age, sex, body mass index (BMI), hypertension, diabetes, history of stroke, smoking, drinking and family history of CAD were obtained from electronic medical records. Baseline fasting venous blood samples were collected on admission, and laboratory indicators, such as triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, lipoprotein (a), homocysteine and C-reactive protein (CRP) were analyzed.

Hypertension was defined by blood pressure ≥140/90 mmHg or treatment with antihypertensive medications [14]. Diabetes mellitus was defined by symptoms of diabetes plus fasting plasma glucose ≥7.0 mmol/L, or random glucose ≥11.1 mmol/L or 2 h plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test [15], or a documented history of diabetes. Current smoking status was defined as smoking any cigarettes on one or more of the 30 days before admission [16]. Current drinking status was

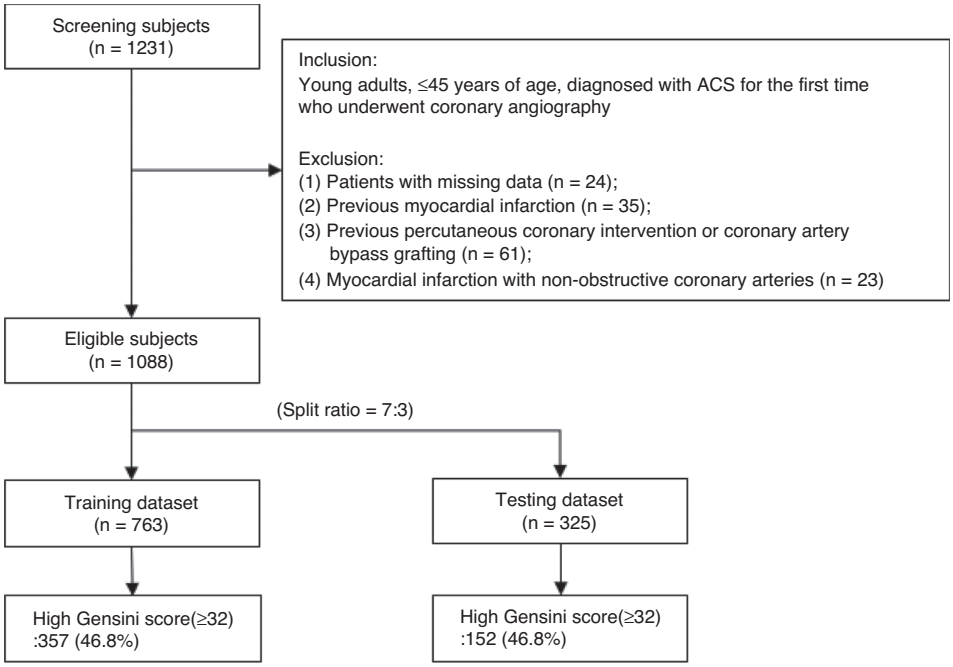

Figure 1 Flow Diagram of the Data Selection Process.
ACS: acute coronary syndrome.

defined as any alcohol consumption within the 30 days before admission [17]. NT-proBNP was age adjusted (>300 pg/mL is abnormal in those <45 years) [18]. eGFR was calculated with the MDRD formula.

All patients received coronary angiography via standard techniques. The coronary angiograms were analyzed by two experienced interventional cardiologists, and the severity of coronary artery stenosis was evaluated with the Gensini score [19].

Statistical Analysis

Statistical analyses were performed in IBM SPSS Statistics version 23.0 (SPSS Inc., Chicago, USA) and R 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were represented by median (interquartile range) and compared with Mann–Whitney U tests. Categorical variables were expressed as proportions, and compared with chi-square or Fisher's exact tests. Least Absolute Shrinkage and Selection Operator (LASSO) [20] and the Random Forest algorithm [21] were applied to determine optimal predictors. Intersective predictors of both algorithms were then assembled into a binary logistic regression model. A nomogram for evaluating the severity of CAD in young patients with ACS was eventually established. The predictive accuracy of the nomogram was assessed with calibration plots, and the performance was assessed with the receiver operating characteristic (ROC) curve, decision curve analysis (DCA) and the clinical impact curve (CIC). A two-sided $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

A summary of all patients' clinical characteristics is provided in Supplementary Table 1. Briefly, a total of 1088 patients met our inclusion and exclusion criteria, and were randomized into the training dataset (763 patients) and the testing dataset (325 patients) in a ratio of 7:3. No significant differences were observed in demographic characteristics, laboratory test results and the proportion of patients with a high Gensini score between the training group and the testing group (all $P > 0.05$). Table 1 displays the bivariate analyses according to Gensini score in the training dataset. Patients with high Gensini scores (>32) were more likely to be older ($P = 0.006$),

Table 1 Baseline Characteristics of the Patients in the Testing Dataset According to Gensini Score.

	Overall (n = 763)	Low Gensini score (n = 406)	High Gensini score (n = 357)	P value
Demographic characteristics				
Age ≥35 years, (%)	657 (86.1)	336 (82.8)	321 (89.9)	0.006*
Male, (%)	695 (91.1)	361 (88.9)	334 (93.6)	0.034*
Type 2 diabetes, (%)	139 (18.2)	48 (11.8)	91 (25.5)	<0.001*
Hypertension, (%)	337 (44.2)	152 (37.4)	185 (51.8)	<0.001*
BMI ≥24, (%)	592 (77.6)	296 (72.9)	296 (82.9)	0.001*
Prior stroke, (%)	10 (1.3)	3 (0.7)	7 (2.0)	0.245
History of smoking, (%)	428 (56.1)	225 (55.4)	203 (56.9)	0.743
History of drinking, (%)	274 (35.9)	151 (37.2)	123 (34.5)	0.477
Family history of CAD, (%)	25 (3.3)	11 (2.7)	14 (3.9)	0.463
UA, (%)	469 (61.5)	219 (53.9)	250 (70.0)	<0.001*
NSTEMI, (%)	144 (18.9)	76 (18.7)	68 (19.0)	0.982
STEMI, (%)	150 (19.7)	111 (27.3)	39 (10.9)	<0.001*
Laboratory testing				
Anemia, (%)	41 (5.4)	26 (6.4)	15 (4.2)	0.236
Platelet ≥300, (%)	85 (11.1)	54 (13.3)	31 (8.7)	0.056
MPV ≥10 fL, (%)	204 (26.7)	92 (22.7)	112 (31.4)	0.009*
NT-proBNP ≥300 pg/mL, (%)	225 (29.5)	116 (28.6)	109 (30.5)	0.608
Cardiac troponin I ≥0.02 ng/mL, (%)	415 (54.4)	218 (53.7)	197 (55.2)	0.735
CK-MB ≥24 IU/L, (%)	243 (31.8)	140 (34.5)	103 (28.9)	0.112
eGFR ≥90 mL/min/1.73 m^2, (%)	580 (76.0)	317 (78.1)	263 (73.7)	0.181
Total bilirubin ≥21 μmol/L (%)	109 (14.3)	60 (14.8)	49 (13.7)	0.756
Fibrinogen ≥4 g/L, (%)	175 (22.9)	76 (18.7)	99 (27.7)	0.004*
D-Dimmer ≥0.5 μmol/L (%)	97 (12.7)	57 (14.0)	40 (11.2)	0.287
LDL-C ≥3.9 mmol/L, (%)	104 (13.6)	40 (9.9)	64 (17.9)	0.002*
HDL-C ≥1.03 mmol/L, (%)	233 (30.5)	130 (32.0)	103 (28.9)	0.385
TG ≥1.7 mmol/L, (%)	388 (50.9)	198 (48.8)	190 (53.2)	0.248
Lipoprotein (a) ≥30 mg/dL, (%)	198 (26.0)	103 (25.4)	95 (26.6)	0.758
Homocysteine ≥15 μmol/L, (%)	215 (28.2)	108 (26.6)	107 (30.0)	0.341
CRP ≥5 mg/L, (%)	229 (30.0)	99 (24.4)	130 (36.4)	<0.001*
Preoperative BG ≥7 mmol/L, (%)	252 (33.0)	129 (31.8)	123 (34.5)	0.479
Angiographic data				
Gensini score (mean (SD))	38.49 (30.31)	17.21 (7.75)	62.70(28.18)	<0.001*

BG = blood glucose; BMI = body mass index; CAD = coronary artery disease; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MPV = mean platelet volume; NSTEMI = non-ST-segment elevation myocardial infarction; NT-proBNP = N-terminal of the prohormone brain natriuretic peptide; STEMI = ST-segment elevation myocardial infarction; TG = triglyceride; UA = unstable angina. *P < 0.05.

to be men (P = 0.034), and to have hypertension (P < 0.001) and diabetes (P < 0.001). Additionally, higher BMI (P = 0.001), mean platelet volume (MPV; P = 0.009), fibrinogen (P = 0.004), LDL-C (P = 0.002) and CRP (P < 0.001) were observed in the high Gensini score group.

Identification of Predictive Factors and Construction of Nomograms

LASSO regression was performed (Figure 2A, B), and eight predictive variables were determined: age, male sex, hypertension, diabetes, BMI, LDL-C, MPV and CRP. The Random Forest algorithm

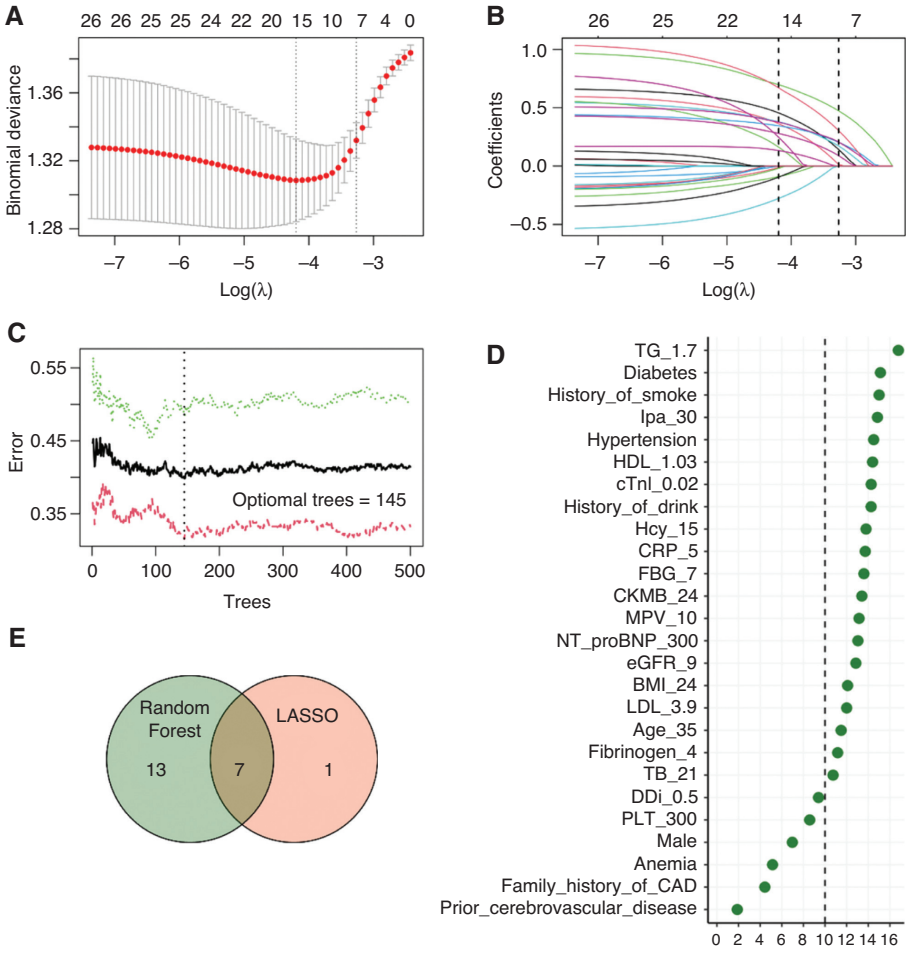

Figure 2 (A) Identification of the optimal penalization estimate of lambda in the LASSO regression. (B) LASSO estimate profile of predictive variables. (C) Error convergence curve of the RF model (500 trees). (D) Importance ranking of candidate predictors by mean decrease Gini index in the RF. (E) Venn diagram to show identical predictors from LASSO and RF algorithm. LASSO: least absolute shrinkage and selection operator; RF: random forest.

with fivefold cross-validation achieved a stable cross-validation error through construction of 145 decision trees (Figure 2C), and the relative importance of the candidate predictors was ranked according to the mean decrease in Gini index (Figure 2D). Thereafter, a total of seven identical predictors were determined with the LASSO algorithm (eight variables) and Random Forest algorithm (top 20 variables), as also demonstrated by a Venn diagram (Figure 2E). Eventually, these factors were assembled into a predictive model by a nomogram in the training dataset. A sum score was calculated as the total of the scores for related predictors with the risk of high Gensini score on the basal axis. For example, in a patient without hypertension and diabetes, with age ≥35 years, BMI <24 kg/m^2, MPV <10 fL, LDL-C <3.9 mmol/L and CRP≥5 mg/L, the total score was 201, and the high Gensini score probability was approximately 46.6% (Figure 3A). The estimate of each predictor was displayed in the forest plot (Figure 3B).

Discrimination, Calibration and Clinical Utility Assessment of the Established Nomograms

The discriminatory power of the nomogram was analyzed according to the area under the ROC curve in the training and testing dataset, respectively. In the training dataset, the area under the curve (with 95% confidence interval) was 0.683 (0.645–0.721), and that in the testing dataset was 0.670 (0.611–0.729; Figure 4). Good concordance was identified between the predicted and observed probabilities on the basis of the unreliability U test in the training dataset (P = 0.961, average error = 0.012, maximal error = 0.051) and the testing dataset (P = 0.302, average error = 0.045,

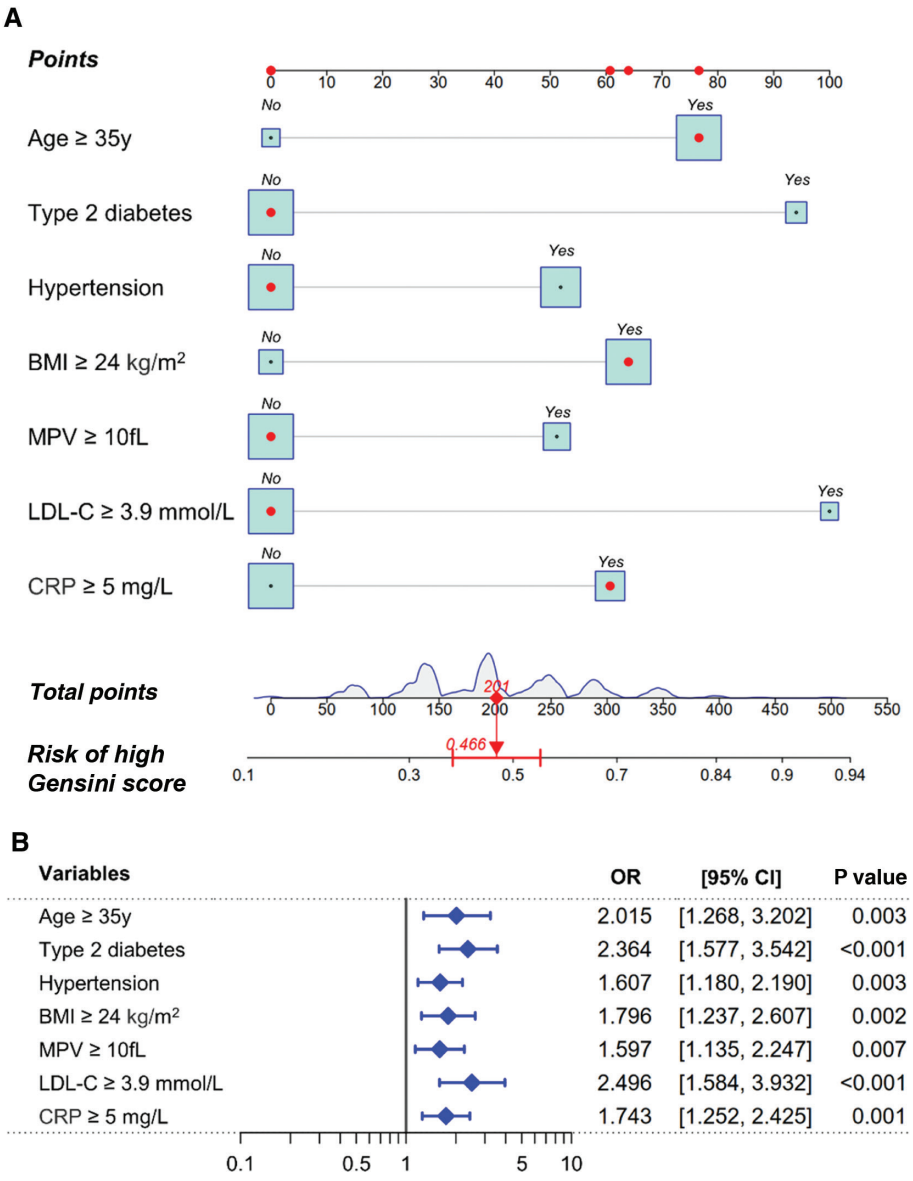

Figure 3 (A) Nomogram predicting the probability of high Gensini score. (B) The forest plot of nomogram predictors. BMI: body mass index; CRP: C-reactive protein; LDL-C: low-density lipoprotein cholesterol; MPV: mean platelet volume.

maximal error = 0.168; Figure 5). Furthermore, to assess the clinical utility of the established nomograms, we performed DCA and CIC. The DCA curve indicated that the nomogram had a significant positive net benefit when the threshold probability ranged from approximately 0.15 to 0.45. When the threshold probability was <0.15, the nomogram had no positive net benefit in predicting all patients without high Gensini scores. When the threshold probability was >0.45, the net benefit of the nomogram was not superior in predicting no patients with high Gensini scores (Figure 6A). The CIC of the nomogram indicated the predicted number of patients with high Gensini scores and true positive patients at different threshold probabilities (Figure 6B).

Discussion

This study successfully constructed and validated a nomogram predicting the probability of a high Gensini score in patients ≤45 years old with ACS. The nomogram incorporated seven factors: age, hypertension, diabetes, BMI, MPV, LDL-C and CRP. It demonstrated good discrimination,

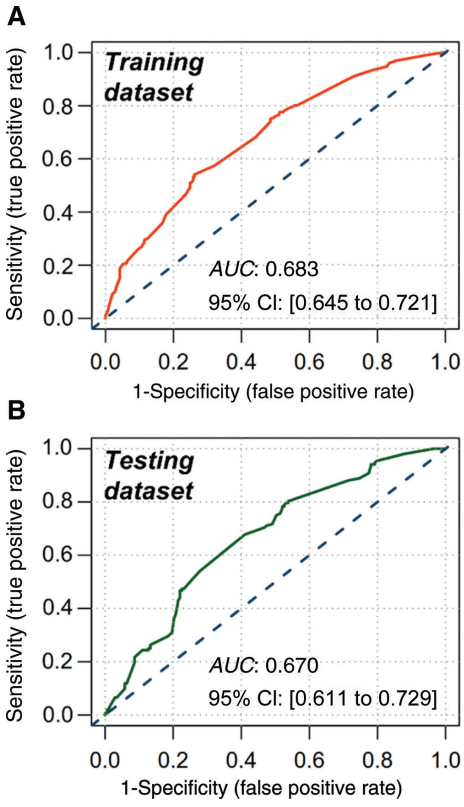

Figure 4 Receiver Operating Characteristic (ROC) Analyses of the Nomogram in (A) Training and (B) Testing Dataset.

calibration and clinical validity, thus making it a convenient and clinically valuable tool to identify young patients with ACS with severe coronary lesions.

With increased exposure to cardiovascular RFs, increased incidence of AMI in young adults has been observed. Data from observational epidemiological studies have demonstrated that the incidence of AMI increased by 37.4% from 2007 to 2009 in young adults 35–39 years of age [22]. Premature AMI in young patients can cause disability and death, and increase the burden on families and society [7]. High-risk patients with ACS usually require emergency coronary intervention, but in low-middle income countries and areas, CAG cannot be performed because of economic and workforce limitations. In addition, owing to the lack of awareness regarding CAD in young people [23], self-misinterpretation of angina symptoms and atypical electrocardiogram changes in some cases, the diagnosis of ACS in young people may be delayed, and preoperative assessment of the severity of ACS in young people is also inadequate. Furthermore, identifying the contribution of related factors for severe premature ACS is necessary for RF modification and for developing cost-effective primary and secondary prevention strategies in these patients. Thus, a non-invasive assessment tool before CAG may be valuable in these aspects.

Age is an independent predictor of severe CAD. Angiographic findings differ between younger and older patients. Younger patients frequently present with fewer coronary lesions and lower lesion complexity, as estimated by the Gensini score. Recently, young patients with ACS have been found to share the same RFs as older people. Conventional RFs, including smoking, hypertension, obesity, diabetes and high LDL-C, have been reported to be highly prevalent in young men 18–44 years of age who are hospitalized for first AMI events [2], and these factors are frequently incorporated into different models to predict severe CAD [24, 25, 12]. Nonconventional RFs—such as higher levels of homocysteine, fibrinogen and lipoprotein (a); abnormal platelet size and function; and increased inflammatory markers (CRP, leptin, interleukin-6 and tumor necrosis factor-α)—also contribute to the development of AMI in young adults [26]. Furthermore, previous studies have indicated that some nonconventional RFs are associated with the severity of coronary artery stenosis. Murat and colleagues have found a positive association between high levels of MPV and the severity of CAD, on the basis of the Gensini and Syntax scores [27], as also confirmed by Ekici et al. [28] and Vogiatzis et al. [29]. A recent mediation analysis has indicated that the increased risk of dyslipidemia on CAD was partly enhanced by elevated MPV levels, whose mediating effect was around 20% of the risk [30]. The relationship between inflammatory markers and the severity of CAD has also been widely studied. Tajfard et al. reported that elevated serum hs-CRP levels are significantly associated with the angiographic severity of CAD [31]. Oprescu et al. have also found that CRP positively correlates with coronary stenosis severity ($r = 0.3$, $P = 0.05$) [32]. However, the nonconventional RFs, such as lipoprotein (a) and homocysteine, were not associated with the severity of CAD in our study, possibly because of differences among participants involved in our study compared with prior studies.

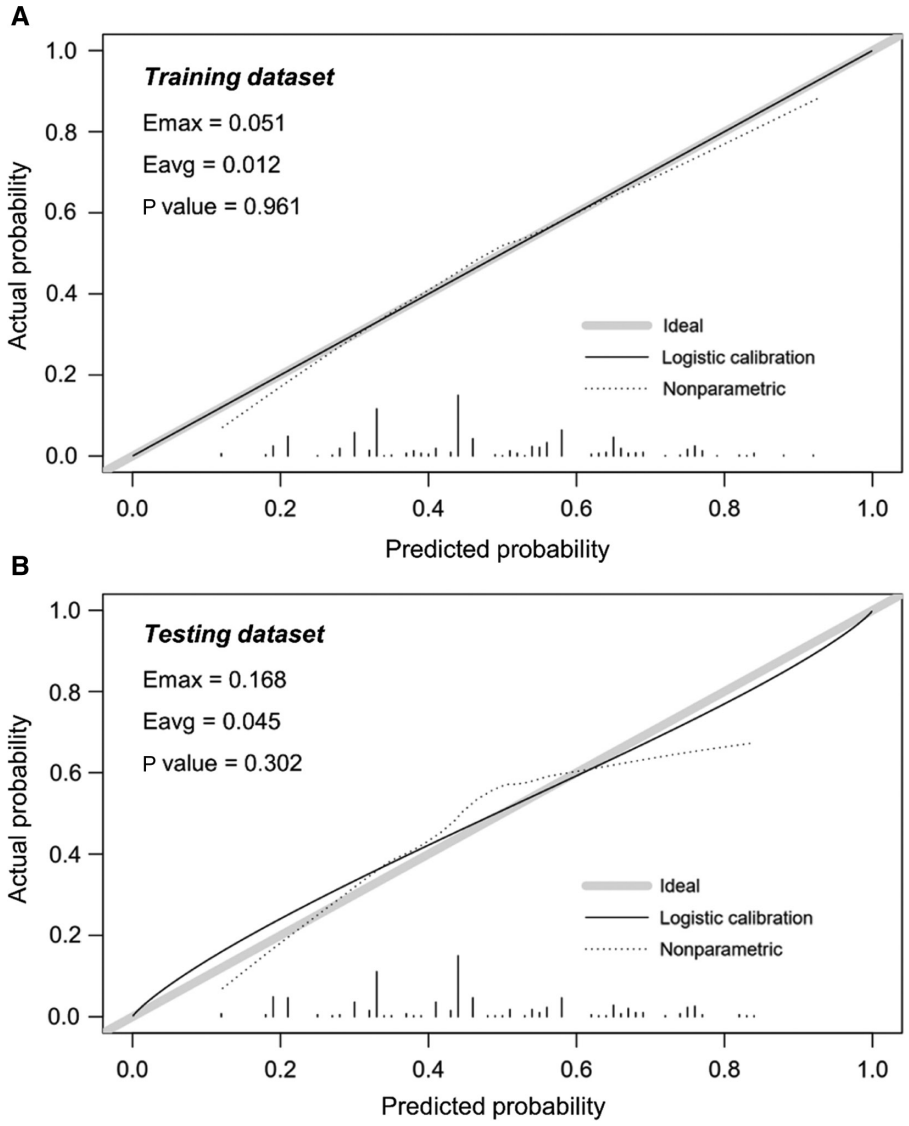

Figure 5 Calibration Plots in (A) Training and (B) Testing Dataset.

This study has some limitations that warrant consideration. First, this was a single-center retrospective study; moreover, most patients were from south China, and the results may not represent the full clinical picture in Chinese adults. Second, data on RFs were collected from medical records; therefore, potential influences such as genetic RFs and health behaviors (physical activity, sleep duration and stress) could not be assessed. Third, we obtained a ROC curve with moderate predictive power; however, more samples and parameters may be included to improve predictive ability in the future. Finally, the electrocardiogram data were incomplete, and the changes varied among ACS types, thus making their incorporation into the predictive model difficult. Our model cannot predict the coronary severity in different types of ACS.

Conclusion

A simple and practical nomogram for predicting the severity of CAD in young adults ≤45 years of age with ACS was established and validated. By using this tool, clinicians could rapidly evaluate patients before interventional therapy.

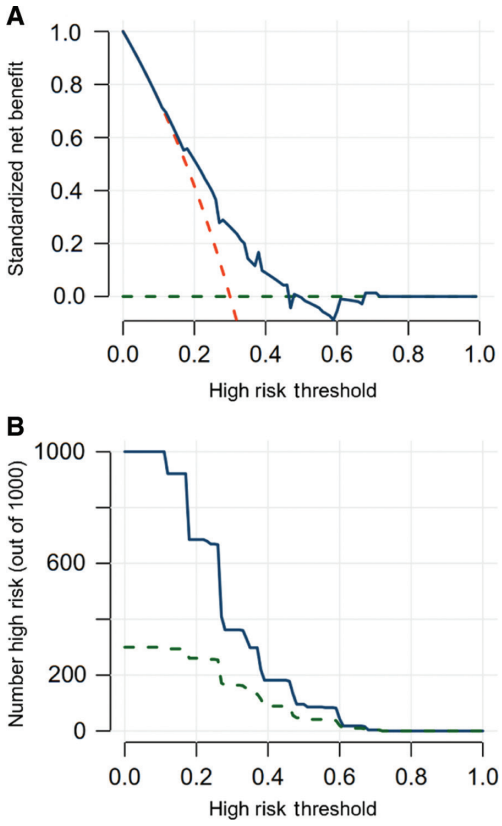

Figure 6 (A) Decision curve analysis. Blue solid line indicates the nomogram; red dashed line indicates the assumption that all patients have high Gensini score; green dashed line indicates the assumption that no patients have high Gensini score. (B) Clinical impact curves analysis. Blue solid line indicates the number of high-risk patients identified by nomogram; green dashed line indicates true positive patients at different threshold probabilities.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

This study was approved by the Institutional Ethics Committee of Sir Run Run Shaw Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflicts of Interest

The authors declare that they have no conflicts of interest to disclose with respect to this article.

Authors' Contributions

Dr. Zhang and Dr. Jiang contributed to conception and design. Dr. Fu provided administrative support, study materials and patients. Dr. Yang was involved in data collection and assembly. Dr. Li performed data analysis and interpretation. Dr. Hong contributed to manuscript writing. All authors approved the final manuscript.

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Supplementary Material: Supplementary material for this paper can be found at https://cvia-journal.org/wp-content/uploads/2022/10/CVIA_283_TABLE_S1.pdf