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RESEARCH ARTICLE

Model for Patients with Multivessel Coronary Artery Lesions in the Highlands Region (Qinghai Province, Northwest China)

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Abstract

Objective: The severity and prognosis of coronary artery disease are closely associated with treatment strategy choice. To achieve timely, accurate, early selection of a suitable treatment plan and assess patients' prognosis, we developed an effective predictive model for early identification of high-risk patients according to lesion severity.

Methods: Among the 510 patients with chest pain admitted to the Qinghai Red Cross Hospital between August 2018 and October 2019, 386 had coronary artery disease detected by coronary angiography. A total of 24 demographic characteristics and serum markers were analyzed in study participants. Least absolute shrinkage and selection operator regression was used to select variables, and multivariate logistic regression was used to build predictive models by using nominal plots. The discriminatory power of the models was evaluated with the area under the receiver operating characteristic curve (AUC). Predictive models were calibrated with calibration plots and the Hosmer–Lemeshow test. Their clinical validity was evaluated via decision curve analysis.

Results: Data were randomly divided (7:3) into training (358 cases) and test (152 cases) sets. The predictive model included sex, age, smoking status, heart rate, systolic blood pressure, diastolic blood pressure, albumin, urea nitrogen, creatinine, uric acid, total cholesterol, and high-density lipoprotein cholesterol as predictors. The AUCs for the training and test sets were 0.793 and 0.732, respectively. The predictive model showed a good fit, and decision curve analysis indicated the clinical validity of the predictive model.

Conclusions: We developed an effective risk predictive model with good clinical value for predicting multivessel disease. Smoking cessation, lowering creatinine, and increasing HDL cholesterol concentrations might decrease the risk of developing multivessel disease, thereby avoiding severe disease.

Keywords: coronary heart disease; multivessel disease; predictive model; highland region

Abbreviations: AUC, Area under the curve; HDL-C, High-density lipoprotein cholesterol; LASSO, Least absolute shrinkage and selection operator.

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Background

Coronary heart disease is the most common cardiovascular system disease worldwide. With increases

in life expectancy, cardiovascular disease in Asia has increased rapidly in past decades [1], and the prevalence and population-attributable fraction for mortality from cardiovascular disease have also grown [2]. Coronary atherosclerotic lesions appear more tortuous and diffuse with increasing age, and present higher plaque loads [3]. Thus, multivessel disease can independently predict long-term mortality in patients with coronary artery disease [4]. Multivessel disease is a severe coronary artery disease type strongly associated with an increase in cardiovascular events and poorer prognoses [5]. Herein, we developed and validated a predictive model based on clinical biomarkers and risk factors for a population from the highlands region, to quickly and accurately identify high-risk patients and improve clinical outcomes through early diagnosis and treatment.

Methods

Study Design

A total of 510 patients with chest pain treated between August 2018 and October 2019 at Qinghai Red Cross Hospital, including patients with Han, Hui, Tibetan, and Salar ethnicity, were identified. The medical ethics committee approved this study. Trained researchers retrieved patient demographic characteristics, serum biomarkers, and coronary angiography data from the hospital's electronic medical record system. Data were submitted to the Department of Science and Education for verification in spreadsheet format. The Qinghai Red Cross Hospital approved all experiments. The study complied with the TRIPOD statement [6], and written informed consent was obtained from all participants before the study.

Study Participants

All patients with chest pain were hospitalized and underwent coronary angiography, and at least two senior interventionalists confirmed the results. Coronary artery disease was confirmed in 386 of 510 patients, according to the criteria recommended by the European Society of Cardiology [7], with a diagnosis of ST-segment or non-ST-segment elevation myocardial infarction or unstable angina pectoris. The study exclusion criteria were ① history of previous coronary intervention or acute decompensated heart failure; ② malignancy, end-stage disease, severe liver disease, or coagulation abnormalities; ③ multiple organ failure or renal failure on dialysis; ④ history of cerebral hemorrhage or gastrointestinal bleeding within the prior 6 months; and ⑤ immune diseases and psychiatric abnormalities. All patients or their family members agreed and signed the informed consent form.

Candidate Predictors

We aimed to develop a predictive model for multivessel coronary artery lesions by using clinically accessible indicators. Multivessel coronary disease is defined by the presence of two or more major epicardial vessels with more than 70% diameter stenosis, involving at least two separate coronary regions, without left main coronary artery disease [8]. We collected patient demographic variables including age, sex, history of hypertension, history of diabetes mellitus, history of stroke, and history of smoking. Heart rate, systolic blood pressure, diastolic blood pressure, weight, height, body mass index (kg/height m^2), ultrasensitive C-reactive protein, cystatin C, albumin, urea nitrogen, creatinine, uric acid, fasting glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured after admission. The test methods involved collection of blood from patients' veins into a vacuum sodium citrate anticoagulation tube in the early morning on the day after admission to the hospital, while the patients were fasting. The collected blood samples were then submitted to the professional and technical personnel at the hospital's testing center for analysis of the aforementioned biochemical indexes with an automated biochemical analyzer.

Statistical Analysis

Normally distributed continuous variables are expressed as means ± standard deviations, and categorical variables are expressed as percentages. To build and validate the predictive models, we randomly selected 70% of patients as the training set and the other 30% as the validation set. A least absolute shrinkage and selection operator (LASSO)

regression was used to select variables for the predictive model. We developed the predictive models by applying multivariate logistic regression. A predictive model for the risk of multivessel coronary artery lesions in patients with coronary artery disease was developed with nominal plots. The predictive model's discriminative power, calibration power, and clinical validity were evaluated. Discriminative capacity was assessed with the area under the receiver operating characteristic curve (AUC). Calibration capacity was assessed with calibration plots and the Hosmer–Lemeshow test, and clinical validity was evaluated with decision curve analysis. All tests were two-tailed, and P-values < 0.05 were considered statistically significant. Statistical analyses were conducted in R software (version 3.5.1).

Results

Participant Characteristics

Data were randomly divided into training (n = 358) and test (n = 152) sets. The comparison of clinical data (including general and biochemical data) between populations showed no statistically significant differences ($P > 0.05$, Table 1), thus indicating comparability between the groups.

LASSO Regression and Multivariate Logistic Regression Analysis

In the training data, variables were screened with LASSO regression and subsequently included in the multivariate logistic regression model (Figure 1). The application of multivariate logistic regression to analyze the aforementioned risk factors revealed that age, sex, smoking status, serum creatinine (Scr), and HDL-C were predictors of multivessel disease in patients with chest pain (Table 2).

Establishment of a Nomogram Predictive Model

The five aforementioned independent risk factors were included, and an individualized nomogram predictive model for multivessel disease in patients with chest pain was successfully established (Figure 2).

Validation of the Predictive Model

We calculated AUC values to assess the discriminatory ability of the predictive model by examining the occurrence of multivessel disease in patients with chest pain through the test and training data. As shown in Figure 3A and B, the predictive model yielded an AUC of 0.732 (95% CI = 0.630–0.833), with a specificity of 0.845 and sensitivity of 0.643, for the test data, and an AUC = 0.793 (95% CI = 0.739–0.848), with a specificity of 0.732 and sensitivity of 0.742, for the training data. The test data indicated that the nomogram had good discriminatory ability and predictive value, and correctly identified multivessel disease.

A calibration plot and Hosmer–Lemeshow test were used to calibrate the predictive model. From the calibration curves, the predictive model and the training data showed a very good degree of fit (Figure 4).

Decision curve analysis was used to evaluate the clinical validity of the predictive model. From the decision curves, the net benefits of the predictive model for the internal validation set were significantly higher than those of the two extreme cases, indicating that the nomogram model had the superior net benefit and predictive accuracy (Figure 5).

Discussion

This study focused on a predictive model for patients with chest pain in the highland region, where numerous other models for the risk of multivessel coronary heart disease have not been adequately validated. We developed a model with strong predictive power (AUC of 0.732) by plotting columnar lines; the model also had a high degree of calibration and clinical validity. The clinical characteristics of patients with chest pain in this model, such as age, sex, smoking status, HDL, and creatinine levels, were used in the predictive model for patients with coronary artery disease with multiple lesions. Therefore, in clinical settings, the probability of combined multivessel disease can be predicted by quickly obtaining the medical history, lifestyle habits, and biochemical indicators of patients with chest pain. Consequently, the risk level can be determined early in treatment, to aid in rational clinical

Table 1 Participant Characteristics.

Variables	Test data (n = 152)	Training data (n = 358)	P
Multi, n (%)			0.781
0 = without multi	110 (72.4)	265 (74.0)	
1 = with multi	42 (27.6)	93 (26.0)	
Sex, n (%)			0.712
1 = male	112 (73.7)	271 (75.7)	
2 = female	40 (26.3)	87 (24.3)	
Age, y	59.9 ± 10.4	58.7 ± 10.6	0.240
Hypertension, n (%)			0.842
0 = no	65 (42.8)	148 (41.3)	
1 = yes	87 (57.2)	210 (58.7)	
Diabetes, n (%)			0.592
0 = no	115 (75.7)	261 (72.9)	
1 = yes	37 (24.3)	97 (27.1)	
Cerebral, n (%)			0.999
0 = no	136 (89.5)	322 (89.9)	
1 = yes	16 (10.5)	36 (10.1)	
Smoking, n (%)			0.925
0 = no	95 (62.5)	227 (63.4)	
1 = yes	57 (37.5)	131 (36.6)	
Heart rate, median (IQR)	76.0 (68.0, 80.0)	77.0 (70.0, 82.0)	0.166
SBP, median (IQR)	126.5 (115.0, 140.2)	129.0 (116.0, 141.0)	0.638
DBP, median (IQR)	77.0 (70.8, 86.0)	79.0 (71.0, 87.0)	0.340
Weight, median (IQR)	74.0 (66.8, 82.0)	75.0 (68.0, 84.0)	0.219
Height, median (IQR)	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	0.42
BMI, median (IQR)	26.1 (24.0, 28.3)	26.3 (24.1, 28.9)	0.385
Scrp, median (IQR)	1.7 (0.8, 4.6)	1.9 (0.9, 5.1)	0.689
Cysc, median (IQR)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.831
Alb, median (IQR)	39.8 (37.4, 42.1)	39.6 (37.4, 41.5)	0.412
BUN, median (IQR)	5.4 (4.3, 6.7)	5.4 (4.3, 6.5)	0.773
Scr, median (IQR)	71.9 (61.4, 83.1)	71.5 (61.4, 81.2)	0.755
eGFR, median (IQR)	95.5 (81.5, 113.5)	95.6 (82.4, 115.0)	0.632
UA, median (IQR)	339.9 (281.8, 390.2)	338.9 (271.2, 403.0)	0.833
FBG, median (IQR)	4.9 (4.2, 5.8)	4.8 (4.3, 5.9)	0.759
Triglycerides, median (IQR)	1.5 (1.1, 2.0)	1.5 (1.1, 2.0)	0.914
Total cholesterol, median (IQR)	3.9 (3.3, 4.6)	4.0 (3.4, 4.8)	0.367
HDL-C, median (IQR)	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)	0.109
LDL-C, median (IQR)	2.4 (1.7, 2.9)	2.4 (1.9, 3.1)	0.218

diagnosis, and guide decisions regarding treatment strategy and intensity.

The accumulation of combined cardiovascular risk factors in terms of number and severity increases the risk of cardiovascular events with advancing age [9]. Particularly in older patients, coronary vascular lesions tend to be more complex, and are easily combined with multiple or even diffuse lesions, with a poor prognosis and a high risk of cardiovascular events [10]. In this study, the mean age was relatively older, at close to 60 years. The analysis revealed that 39.3% of patients younger than 60 years had multivessel lesions, whereas 60.7% of patients older than 60 years had multivessel lesions; therefore, with age, the probability of coronary lesions increases, and complexity

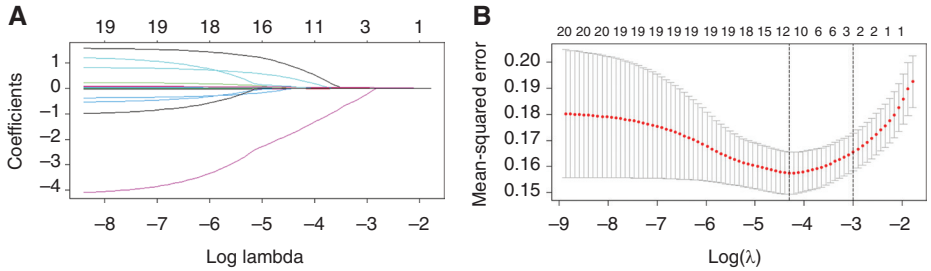

Figure 1 Variables Selected by the LASSO Logistic Regression Model.
(A) According to the logarithmic (lambda) sequence, a coefficient profile was generated, and non-zero coefficients were produced by the optimal lambda. (B) The optimal parameter (lambda) in the LASSO model was selected via ten-fold cross-validation with minimum criteria. The partial likelihood deviation (binomial deviation) curve relative to log (lambda) was plotted. A virtual vertical line at the optimal value was drawn with one SE of the minimum criterion (the 1-SE criterion).

Table 2 Multivariate Logistic Regression Analysis of Training Data.

Variables	OR	95% CI	P
(Intercept)	0	0–0.001	0 < 0.001
Sex	5.281	2.16–13.475	0 < 0.001
Age	1.055	1.026–1.086	0 < 0.001
Smoking	2.337	1.21–4.628	0.013
Scr	1.081	1.058–1.108	0 < 0.001
HDL-C	0.086	0.018–0.367	0.001

OR, odds ratio; CI, confidence interval.

may become more common. Consequently, age may be considered an important predictor of complex coronary lesions.

Incorporating sex into the final predictive model can enable more reliable, personalized clinical decision-making and care [11]. Previous studies have found that non-obstructive lesions and plaque erosion are more predominant in women than men with acute coronary syndrome [12–18]. Although plaque erosion causes less stenosis than ruptured plaques, recent data suggest that cardiovascular disease mortality is significantly higher in women than in men [19] and might be associated with more comorbidities in women in early stages after acute coronary syndrome onset [20–23]. However, in a cross-sectional study with 3501 patients, including 67% women, female patients with young myocardial infarction were more likely to have comorbidities than men. The

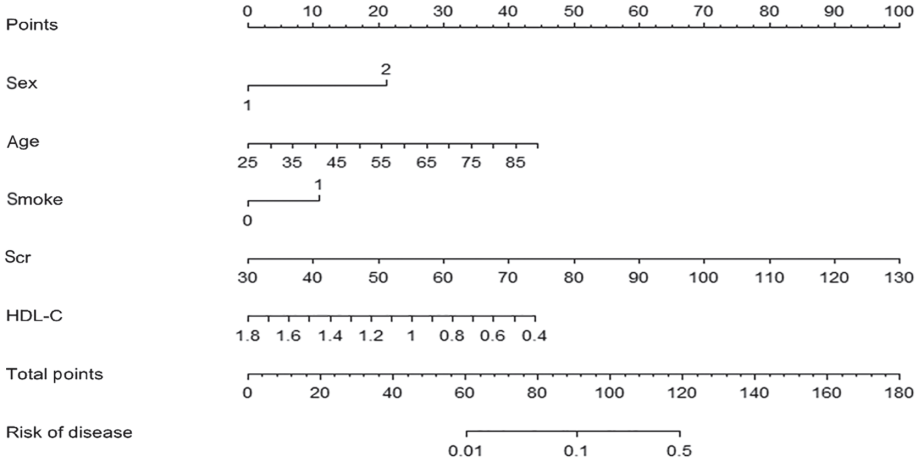

Figure 2 Nomogram for Predicting the Probability of Multivessel Disease in Chest Pain Patients.
The nomogram is used by scoring each variable on its corresponding score scale. The scores for all variables are then summed to obtain the total score, and a vertical line is drawn from the total point row to indicate the estimated probability of multivessel disease in patients with chest pain. HDLC, high-density lipoprotein cholesterol; Scr, serum creatinine.

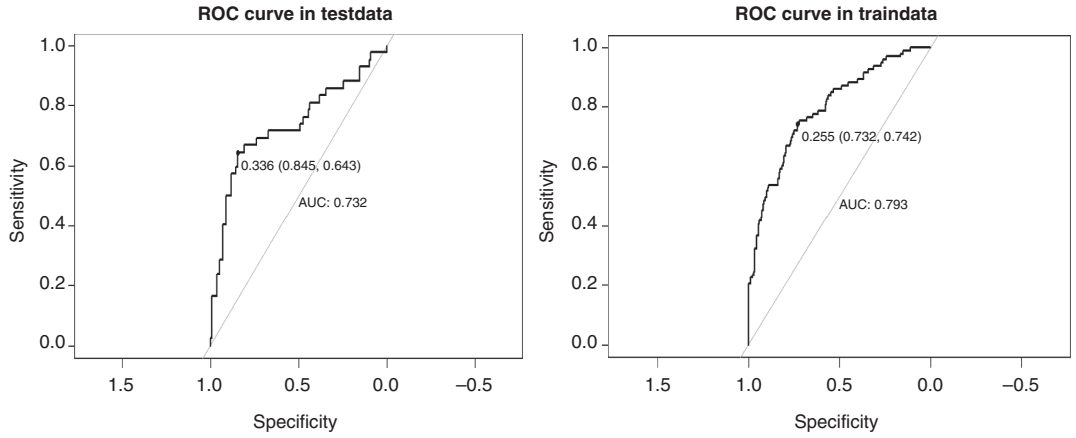

Figure 3 Receiver Operating Characteristic Curves from the Test Data and the Training Data.

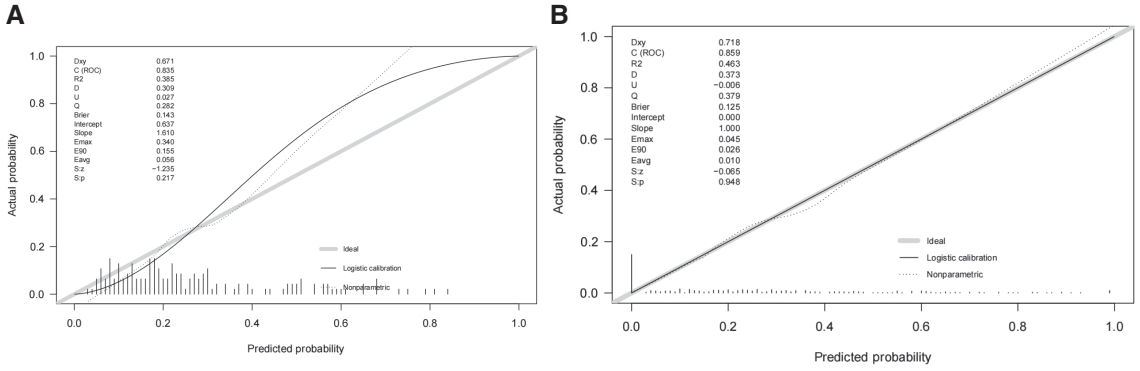

Figure 4 Calibration Plots.
The shadowed line represents perfect prediction by an ideal model, and the dotted line shows the performance of the test data (A) and training data (B).

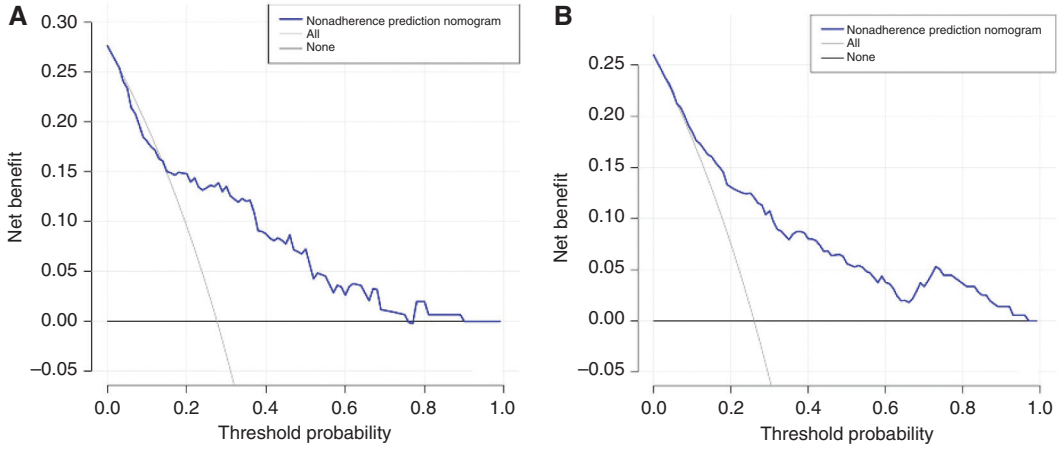

Figure 5 Decision Curve Analysis.
The black solid line represents the net benefit. The black solid line indicates that all samples are negative, and all were not treated. The gray solid line indicates that all samples were positive and were treated (A) from the test data and (B) from the training data.

general mean health scores were also significantly lower in young women with myocardial infarction compared to male patients [24]. We have drawn a similar conclusion in our study, women also had significantly higher rates of comorbidities, including hypertension (66%) and stroke (13%), than men (56% and 9%), but no significant difference in diabetes (24% vs. 27%).

Smoking is a major risk factor for coronary heart disease and has a significant dose-response relationship with coronary heart disease development and death [25]. Both active and passive smoking can increase the incidence of atherosclerosis [26]. The tar and carbon monoxide chemicals in tobacco can cause tissue hypoxia, induce inflammatory mediators that elicit inflammatory responses, activate platelets, increase blood viscosity, and provide conditions facilitating thrombosis [27, 28]. Moreover, nicotine excites the sympathetic nerves, increases heart rate and myocardial contractility, leads to coronary spasms, and aggravates myocardial ischemia and heart failure [29, 30]. Caralis et al. have shown that smoking is an independent risk factor for coronary artery spasms, increasing the risk by approximately 4.2 times [31, 32]. A recent study has suggested that smokers have longer and more diffuse coronary artery lesions [33]. More than 100,000 people die each year in China from smoking-associated diseases; approximately 316 million adults older than 15 years of age smoke, thus resulting in a prevalence of 27.7%, and women account for 2.7% of smokers. The present study found that smoking patients, compared with nonsmokers, had 1.14 times more multiple coronary lesions, and a greater proportion had diabetes. Thus, smoking and other cardiovascular disease risk factors might synergistically amplify the pathogenic utility of other risk factors and increase the probability of coronary heart disease, in agreement with Liu's findings [34]. Smoking is an important causative factor that can be prevented, and the above results suggest that persuading patients to quit smoking early is clinically important in preventing coronary artery spasms and decreasing cardiovascular events.

High LDL-C and low HDL-C concentrations are considered risk factors for atherosclerotic heart disease [35], and the ability of HDL to promote macrophage cholesterol efflux is strongly negatively correlated with subclinical atherosclerosis and obstructive coronary artery disease. Moreover, HDL particle size and concentration are among the main factors influencing the ability of cell-cholesterol efflux. Low plasma concentrations of HDL-C have been identified as a cardiovascular risk factor. Lower HDL might also be a non-specific indicator of poor general health status [36]. However, several studies have found a U-shaped association between HDL concentrations and cardiovascular events [37, 38]. This study also indicated 2.47 times more patients with patients with low HDL-C than with normal values; the former group of patients were also older and heavier, and had more combined hypertension.

Creatinine levels reflect renal function, and the cardiovascular risk is proportional to renal insufficiency [39]. In a study of renal insufficiency in acute coronary syndromes, a significant negative correlation has been found between 180-day prognosis and creatinine clearance; after adjustment for co-morbidity differences, low creatinine clearance remained an independent correlate of increased all-cause mortality. In many studies, patients with rather than without mild renal insufficiency are considered to have poorer clinical baseline characteristics. Typically, these patients are older and more often have comorbid diabetes, hypertension and severe coronary risk factors [40–43].

Renal insufficiency is a factor accelerating coronary atherosclerosis, even in patients without cardiovascular risk factors [44]. Patients in the abnormal creatinine group were older and had a higher proportion of combined hypertension than those in the normal group.

BMI has been identified as a risk factor for cardiovascular disease [45]. However, in this study, we found no statistically significant differences in BMI between patients with single and multiple lesions, in both the training and test sets. In the training data, we derived an AUC of 0.795 (95% CI: 0.741–0.849) with the inclusion of BMI, and an AUC of 0.793 (95% CI: 0.739–0.848) without inclusion of BMI, thus resulting in a P-value of 0.407. These findings suggested that the addition of BMI did not improve the predictive power of the model. Several potential explanations for these results exist. First, comorbidities, confounders, and selection bias in the population might have weakened

the association between BMI and multibranch coronary disease. Retrospective studies often fail to account for unmeasured or unexplained variables that might influence the relationship between BMI and multibranch disease in patients with cardiovascular disease. Second, assessing overweight through BMI alone has limitations, because BMI does not account for body composition and fat distribution, or differentiate between muscle and fat mass. These factors can affect the conclusions drawn from the analysis. Measuring waist circumference may provide a more accurate identification of obese patients at risk of cardiovascular disease. Third, obese individuals may be more likely to have other conditions, such as increased attention to personal health care or the use of nonsteroidal drugs or statins for obesity management. In addition, they might generally invest more in managing their weight, thus potentially attenuating the effect of BMI in the model.

Limitations

Our study also has several limitations. First, the study population was selected to represent patients from the highland region, which tends to have older demographics. This aspect might have introduced some selection bias into the study findings. In the future, we plan to conduct a more comprehensive study in a younger patient group to further enhance our research. Second, this was a cross-sectional study reflecting exposure and disease status simultaneously, and causal inferences could not be made. The conclusions regarding use of predictive models for coronary heart disease, a chronic disease with generally stable pre-onset combined risk factors, remain relevant. Third, this study was a single-center study in an under-represented population.

Conclusions

In conclusion, we established and verified a nomogram model for prediction of multi-vessel disease in patients with chest pain. Our nomogram model, combining age, sex, smoking status, Scr, and HDL-C, was verified internally as a useful tool for risk assessment. The application of this model is expected to aid in screening patients with high risk of coronary heart disease.

Data Availability Statement

The data used in this study is available from the first author on the basis of appropriate request.

Ethics Statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Qinghai Red Cross Hospital (reference number: KY-2020-30). This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. The patients/participants provided their written informed consent to participate in this study.

Author Contributions

Tuersunjiang Naman contributed to the conception and design. JL and HXQ contributed to the data analysis, drafted the manuscript, and performed interpretation. JPZ, GQM, SZ, YSM, and XKM contributed to the data acquisition. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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