Prediction of Coronary Artery Disease in Patients Undergoing Operations for Rheumatic Aortic Valve Disease

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ABSTRACT

Background: We sought to develop and validate a logistic model and a simple score system for prediction of significant coronary artery disease (CAD) in patients undergoing operations for rheumatic aortic valve disease.

Hypothesis: The simple score model we established based on the logistic model was efficient and practical.

Methods: A total of 669 rheumatic patients (mean age 51 ± 9 years), who underwent routine coronary angiography (CAG) before aortic valve surgery between 1998 and 2010, were analyzed. A bootstrap-validated logistic regression model on the basis of clinical risk factors was developed to identify low-risk ($\leq 5\%$) patients, from which an additive model was derived. Receiver operating characteristic (ROC) curves were used to compare discrimination, and precision was quantified by the Hosmer-Lemeshow statistic. Significant coronary atherosclerosis was defined as 50% or more luminal narrowing in 1 or more major epicardial vessels determined by means of coronary angiography.

Results: Eighty-eight (13.2%) patients had significant coronary atherosclerosis. Independent predictors of CAD include age, angina, diabetes mellitus, and hypertension. A total of 325 patients were designated as low risk according to the bootstrap logistic regression and additive models. Of these patients, only 4 (1.2%) had single-vessel disease, and none had high-risk CAD (ie, left main trunk, proximal left anterior descending, or multivessel disease). The bootstrap logistic regression and additive models show good discrimination, with an area under the ROC curve of 0.948 and 0.942, respectively.

Conclusions: Our logistic regression model can reliably estimate the prevalence of significant CAD in rheumatic patients undergoing aortic valve operation, while the additive simple score system could reliably identify the low-risk patients in whom routine preoperative angiography might be safely avoided.

Introduction

Coronary artery disease (CAD) has a detrimental effect on long-term survival in patients undergoing aortic valve operations.¹ It is of great importance to detect the presence of coexistent CAD before aortic valve operations. It is impractical for every patient to undergo coronary angiography because of the low positive rate, the potential complications, and the cost. There is no validated approach and model for routine evaluation of possible CAD in these patients. The current American College of Cardiology/American Heart Association (AHA/ACC) practice guidelines² for presurgical coronary artery angiography (CAG) include the following: male patients 35 years of age or older; female patients who are postmenopausal or premenopausal and

35 years of age or older with coronary risk factors; and patients with chest pain, objective evidence of ischemia, 1 or more risk factors for CAD, previous CAD, or decreased left ventricular (LV) systolic function. However, the patients with aortic valve disease in China and many other developing countries were different from that of in the United States and other developed countries. For the former, the prevalent is rheumatic valve disease, and the latter, degenerative valve disease. In these patients, the risk of coexistent CAD is much lower^{3,4} and therefore the guideline might not be applicable for prediction. In this work, we sought to develop a new model to predict the risk of CAD in patients undergoing operation for rheumatic aortic valve disease.

Methods

The study was performed with protocols approved by the Ethics Committee in Research of Changhai Hospital.

Patient Selection

We retrospectively identified 902 consecutive patients from the Changhai Hospital who underwent operations for

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rheumatic aortic valve disease between 1998 and 2010. We excluded the patients who were diagnosed as CAD patients because of previous myocardial infarction. Among those patients, 207 did not undergo CAG at the discretion of the attending cardiologist and 26 patients with previous myocardial infarction were excluded. Thus, 669 patients were included in our study. Routine CAG was performed before valve surgery. The presence of significant coronary disease was defined as luminal narrowing of at least 50% of the diameter of a major coronary artery.

Risk Factor Selection

Risk factors for CAD were defined as follows: age, sex, family history of CAD (first-degree relative with a myocardial infarction before age of 50 years in men and before 60 years in women), smoking, diabetes mellitus, hypertension, hypercholesterolemia (defined as receiving medication for hypercholesterolemia or serum cholesterol of ≥ 5.8 mmol/L). In addition, the presence of ischemia changes on electrocardiogram (ECG) (defined as any resting ST-segment or T-wave abnormality), coexistent mitral valve lesion, abnormal LV function (defined as an ejection fraction of 50% or less by means of echocardiography or contrast ventriculography), C-reactive protein (CRP, defined as serum CRP ≥ 3.0 mmol/L), and New York Heart Association class III–IV were also designated as variables for analyses. Etiology was determined by echocardiography and histopathologic examinations.

Statistical Analysis

Logistic Regression Model Development: All the designate variables were entered into univariable analyses. The criterion for variable retention was significance of 0.2. Predictors of significant CAD in the univariable analyses were entered into a forward stepwise multivariable logistic regression model. Only independent predictors ($P < 0.05$) were included in the model:

$$\ln OR = \alpha + \chi_1\beta_1 + \chi_2\beta_2 + \chi_3\beta_3 + \chi_4\beta_4 + \dots + \chi_k\beta_k$$

($\ln OR$ is the natural logarithm of the odds ratio; α is a constant; $\chi_1 \dots$, and χ_k are independent predictors; $\beta_1 \dots$, and β_k represent respective parameter coefficients)

$$\text{Risk of significant CAD} = e^{\ln OR} / (e^{\ln OR} + 1)$$

The multivariable logistic model was validated and further refined by using the bootstrap technique,^{5–7} which used 1000 random resamplings to evaluate the stability of the odds ratio estimated with sampling variation.

Simple Additive Score Model: To simplify the calculation process of clinical risks and help the clinician assess the patients much more easily, a simple additive score model was established based on the bootstrap logistic regression model. We choose a probability of significant CAD of greater than 0.05 as a cutoff, which corresponded to a bootstrap logistic regression model score of -2.8 .

$$0.8 \times \text{interval age}^* + 6.7 \times \text{angina} + 1.5 \times \text{diabetes mellitus} + 1.2 \times \text{hypertension} - 6.9 > -2.8$$

*Interval age = (age – 35)/5; the youngest of our study population is 35 years old.

By multiplying each coefficient of the equation by 2, and rounding off the new coefficient to the nearest integer, a simple additive score model was established as follows:

$$2 \times \text{interval age} + 13 \times \text{angina} + 3 \times \text{diabetes mellitus} + 2 \times \text{hypertension} > 8$$

Comparing the Logistic Model with the Simple Additive Model: Model discrimination was examined by constructing receiver operating characteristic (ROC) curves for the logistic model and simple additive model. The Hosmer–Lemeshow goodness-of-fit statistic was used to describe the precision of the models.

Continuous variables are expressed as mean values $\pm$ standard deviation (SD). Categorical variables are expressed as frequencies, percentages, or both. All statistical analyses were performed with PASW statistics 18 software.

Results

Characteristics of the Study Population

Clinical characteristics of the study population are summarized in Table 1. Of these 669 patients, 88 (13.2%) had significant CAD, and 77 (11.5%) received concomitant coronary artery bypass graft surgery (CABG).

Logistic Regression Model

The univariable association between significant CAD and the risk factors evaluated as potential predictors are shown in Table 2. Family history, smoking, abnormal LV function, and ischemic changes on ECG did not reach the significance cutoff 0.2 for variable retention. Age, angina, diabetes mellitus, and hypertension were predictors in the logistic multivariable analysis, and further validated as predictive in the bootstrap-refined model as follows:

$$\begin{aligned} \text{Model score}(\ln OR) &= 0.823 \times \text{interval age} + 6.56 \\ &\times \text{angina} + 1.466 \times \text{diabetes mellitus} + 1.227 \\ &\times \text{hypertension} - 6.896 \end{aligned}$$

The comparisons between the original logistic regression model and the bootstrap logistic model on the odds ratio with confidence intervals are shown in Table 3. The odds ratios of the 2 models were of a high degree of similarity, and this confirmed the stability and validity of the model.

Simple Additive Model

The additive scoring system is listed in Table 4. A model score of 8 points corresponded to a risk of significant CAD of 0.05. We recommend CAG screening at 8 or more points. The score for age was 2 points for every 5 years above 35 years, and hypertension and diabetes mellitus yielded a score of 2 points and 3 points, respectively. The score of angina was 13 points more than 8 points, suggesting it was an independent risk factor of coexistence CAD. Because any

Table 1. Clinical Characteristics of the Study Population (n = 669)

Variable	
Age (years)	51 ± 9
Male (%)	396 (59.2%)
Hypertension (%)	99 (14.8%)
Diabetes mellitus (%)	19 (2.8%)
Hypercholesterolemia (%)	17 (2.5%)
Family history of CAD (%)	22 (3.3%)
Ischemia changes on electrocardiogram (%)	48 (7.2%)
Smoking (%)	89 (13.3%)
CRP (mg/L)	4.1 ± 1.8
NYHA class III or IV (%)	453 (67.7%)
Abnormal LV function (%)	583 (87.1%)
Atrial fibrillation (%)	175 (26.2%)
Angina (%)	49 (7.3%)
Concurrent MV replacement (%)	200 (29.9%)
Significant CAD (%)	88 (13.2%)
Concurrent CABG (%)	77 (11.5%)
Abbreviations: CAD, coronary artery disease; CABG, coronary artery bypass graft; CRP, C-reactive protein; LV, left ventricular; MV, mitral valve; NYHA, New York Heart Association.	

score more than 8 points would be an indication for CAG screening, the variable was reassigned a score of 8 points to simplify the scoring model system.

Comparisons Between Logistic Model and Simple Additive Model

The Hosmer-Lemeshow statistic revealed good fit with values of 6.3 ($P = 0.6$) and 7.0 ($P = 0.5$) for the logistic model and the simple additive model, respectively. The area under the ROC curve (AUC) of our logistic regression model was 0.948, and the similar discriminating ability was achieved by the simple additive model with an AUC of 0.942 (Figure 1).

Discussion

Aortic valve replacement (AVR) is recommended as a standard surgical procedure for most patients with symptomatic aortic valve disease.⁸ Concurrently combined with CAD as a risk factor for the prognosis of AVR, the independent predictors of impaired survival include advanced age, male sex, diabetes, noncongenital valvular pathology, or mixed valve disease, among others.⁹ It has been reported that concomitant CABG negates the effect of CAD on long-term survival.^{10,11} According to the AHA/ACC guidelines,² concomitant revascularization is recommended in patients with aortic valve disease. Treatment of CAD by CABG at the time of AVR improves long-term survival with acceptable morbidity and mortality.^{12–14} It is of great

Table 2. Univariable Associations With Significant Coronary Artery Disease

Variable	Coefficient	SE	OR	P
Age (years) ^a	0.882	0.090	2.416	<0.01
Male (%)	0.758	0.257	2.135	<0.01
Hypertension (%)	2.258	0.256	9.564	<0.01
Diabetes mellitus (%)	1.410	0.490	4.098	<0.01
Hypercholesterolemia (%)	1.596	0.507	4.935	<0.01
Family history of CAD (%)	−0.427	0.751	0.652	0.569
Ischemia changes on electrocardiogram (%)	0.030	0.226	1.030	0.997
Smoking (%)	0.141	0.325	1.152	0.663
High CRP (%)	0.563	0.299	1.755	0.06
NYHA class III or IV (%)	0.691	0.285	1.995	0.015
Abnormal LV function (%)	0.008	0.346	1.008	0.981
Atrial fibrillation (%)	0.258	0.250	1.295	0.301
Angina (%)	6.545	1.024	696.00	<0.01
Concurrent MV replacement (%)	−0.423	0.270	0.655	0.117
Abbreviations: CAD, coronary artery disease; CRP, C-reactive protein; LV, left ventricular; MV, mitral valve; NYHA, New York Heart Association; OR, odds ratio; SE, standard error. ^a For every additional 5 years.				

Table 3. ORs and CIs from the Original Regression Model and the Bootstrap Model

Variable	Original Model OR (95% CI)	Bootstrap Model OR (95% CI)
Age ^a	2.316 (1.784–3.005)	2.277 (1.746–2.968)
Hypertension	4.134 (1.939–8.817)	3.412 (1.557–7.477)
Diabetes mellitus	3.808 (1.067–13.588)	4.331 (1.172–16.002)
Angina	745.35 (82.785–6710.847)	777.480 (81.398–7426.166)
Abbreviations: CI, confidence interval; OR, odds ratio. ^a For every additional 5 years of age.		

Table 4. A Simple Additive Scoring System for the Prediction of Significant CAD

Variable	Score ^a
Age	2 points for each 5 years over the age of 35 years
Hypertension	2 points
Diabetes mellitus	3 points
Angina	8 points
Abbreviation: CAD, coronary artery disease. ^a A score equal to or more than 8 points is an indication for coronary angiography.	

importance to screen with CAG in patients with high risk of coexistence of CAD. The low specificity¹⁵ of the AHA/ACC

Figure 1. Comparison of ROC curves from the 2 models. The AUC of the bootstrap model and simple additive model were 0.948 (95% CI, 0.918–0.978) and 0.942 (95% CI, 0.911–0.973), respectively. Abbreviations: AUC, area under the ROC curve; CI, confidence interval; ROC, receiver operating characteristic.

guidelines for CAG screening limited the wide use of the guidelines, especially for patients with rheumatic aortic valve disease in China and other developing countries, due to low incidence of CAD, the cost, and possible the complications of CAG. If we applied the guidelines to our study population, we could find out that almost every patient should undergo CAG screening.

Several prior studies have concentrated on the predictive purely clinical models of significant CAD in symptomatic patients with chest pain.^{16–18} Based on established risk factor profiles, chest pain characteristics, and electrocardiographic criteria, Pryor et al¹⁷ developed and validated a model. Diamond and Forrester¹⁸ also built a model on the basis of age, sex, and nature of chest pain. These models excluded patients with typical or atypical angina, and applying these models to our patient population with rheumatic valve disease may be constrained by differences in baseline characteristics. To our knowledge, this is the first prediction model of significant CAD in patients undergoing operations for rheumatic aortic valve disease. We developed a logistic regression model and a simple additive model to better suit our population. In our study, both the models based on our rheumatic patients showed acceptable discriminative ability. With a probability of 0.05 as a cutoff, 325 patients were designated as having a low predicted risk for significant CAD. Of these patients, only 4 (1.2%) patients had single-vessel disease, and none had high-risk CAD (ie, left main trunk, proximal left anterior descending, or multivessel disease). Significant CAD was present in 84 (24.4%) of the 344 patients in the intermediate and high-risk groups.

There were 4 indicators of CAD in our model: age, angina, diabetes mellitus, and hypertension. Angina was reckoned as an independent indicator of significant CAD, and all the patients with angina who undergo AVR with rheumatic heart valve disease should receive CAG screening before surgery. The result was similar to that of other studies.^{19–21} Green

et al¹⁹ reported that about two-thirds of patients with severe aortic stenosis had angina pectoris, and that about one-half of these patients had CAD. Their study also found that 25% of the study patients without angina had angiographically significant CAD. In our study, 44 (89.8%) of 49 patients with angina had significant CAD. The prevalence of CAD in patients with angina in our rheumatic aortic population was much higher than that of prior studied populations. The result may be inferred by the size of the sample. It is necessary to expand the size of the sample in further studies to confirm the result. In some prior studies, angina was a less specific indicator of CAD in patients with valvular heart disease than in the general population because of increased wall stress or wall thickening with subendocardial ischemia,²² right ventricular (RV) chamber enlargement or hypertrophy,²³ and others, whereas some commonly considered risk factors, such as family history, gender, hypercholesterolemia, and smoking were not predictive in our study. Kruczan et al⁴ inferred that the difference could be due to the demographic and clinical characteristics. But the accurate reason was still unknown. We noted a high prevalence of single-vessel disease in our patients without angina but with significant CAD, and it has been reported that the presence of angina has been shown to be related to multivessel disease^{24,25}; therefore, it was not surprising that most patients with CAD but without angina had single-vessel disease. In some studies, CAG was performed only in patients with angina, but from the results of our study, the other 44 (7.0%) of 629 patients without angina also presented significant CAD. The absence of angina did not reliably exclude CAG screening.

Another useful approach to identify low-risk patients is computed tomography angiography (CTA). As a noninvasive option, the CTA could provide the clinician with a whole image of the coronary artery system, including the degree of narrowing of the major coronary artery. Several prior studies have reported that CTA could rule out the presence of significant CAD with acceptable sensitivity in patients undergoing valve surgery.^{26–29} However, the results of 16- or 64-slice CTA could be inferred by atrial fibrillation, which commonly occurred in patients with rheumatic valve disease. In our study population, 175 (26%) patients had atrial fibrillation, and 27 of these had significant CAD. As the technique continues to develop, a 320-slice or dual-source CT scanner might overcome the limitation, but the results should be tested with clinical trials. Because of the high cost, these instruments are not easily applied clinically, and there is still a strong demand for a simple prediction system for CAD in patients with rheumatic aortic disease.

Limitations

This retrospective study is based on a group of patients of a single center with rheumatic aortic valve disease. For that reason, the size of our study population was limited, and the results should be confirmed by a prospective, multicenter study. There are some differences between rheumatic valve disease and degenerative or calcific valve disease both in pathologic and clinical characteristics, the reason for the difference in indicators for CAD in these 2 types of disease still needs further studies.

Conclusion

Based on the rheumatic aortic valve population, we established a logistic model for the successful prediction of significant CAD in patients undergoing operations for rheumatic aortic valve disease, and furthermore we developed a simple additive score system to identify low-risk patients with simplicity and accuracy. Both the logistic model and the simple additive scoring system achieved acceptable sensitivity and specificity.

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