ORIGINAL ARTICLE

Risk Stratification Model to Predict Concomitant Coronary Artery Disease in Preoperative Evaluation of Valvular Heart Surgery

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Background: Scarce data exist for a validated risk model to predict concomitant coronary artery disease (CAD) in patients undergoing valvular heart surgery.

Objective: Identify risk factors and develop a model to predict coexistent CAD in these patients.

Materials and Methods: This retrospective cohort study included patients who underwent preoperative coronary angiography (CAG) before valvular heart surgery from January 2015 to December 2018 at two tertiary care hospitals. Data from one hospital were analyzed to develop the predictive risk score, which was validated using data from the other hospital. A receiver-operating-characteristic curve was constructed to evaluate the score diagnostic ability.

Results: Of 690 patients, the prevalence of coexistent CAD was 11.4%. According to multivariate analysis, risk factors significantly associated with CAD were age (OR 1.04; 95% CI: 1.00 to 1.08), typical angina pain (OR 2.67; 95% CI: 1.24 to 5.73), family history of premature CAD (OR 5.51; 95% CI: 1.30 to 23.20), dyslipidemia (OR 2.11; 95% CI: 1.14 to 3.91), and diabetes (OR 2.98; 95% CI: 1.49 to 5.95). Factors significantly lowering the CAD risk were rheumatic heart disease (OR 0.21; 95% CI: 0.10 to 0.41) and aortic valve lesions (OR 0.32; 95% CI: 0.13 to 0.75). The predictive score created from these variables yielded a c-statistic of 0.84 (95% CI: 0.79 to 0.88) in the development and 0.64 (95% CI: 0.46 to 0.82) in the validation cohorts. Furthermore, at a 61.75 cutoff, this simplified predictive score exhibited 70.9% sensitivity, 80.7% specificity, 32.2% positive predictive value, and 95.5% negative predictive value.

Conclusion: In patients undergoing valvular heart surgery, traditional CAD risk factors were associated with concomitant CAD, whereas aortic valve lesions and rheumatic heart disease were the protective factors. Our predictive risk score can identify low-risk patients with concomitant CAD, which may avoid unnecessary CAG.

Keywords: Valvular heart disease; Coronary artery disease; Coronary angiography; Predictive risk score

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Patients with valvular heart disease require preoperative evaluation for concomitant coronary artery disease (CAD) to determine whether coronary artery bypass surgery should be performed as part of the operation. Current guidelines recommend performing coronary angiography (CAG) before valvular heart surgery in patients with a history of CAD, suspected myocardial ischemia based on chest pain symptoms or non-invasive testing, left ventricular systolic dysfunction, or a history of one or more cardiovascular risk factors. It is also recommended in men over 40 and postmenopausal women[1,2]. However, the breadth of these criteria may lead to many low-risk patients undergoing unnecessary invasive procedures.

Although the guidelines suggest stratifying patients by risk level to determine whether less invasive CAD investigation can be performed, there is no validated predictive risk model for such stratification. Previous studies aimed at developing such a risk score have lacked information regarding the etiology of valve dysfunction, which may be associated with the CAD risk level[3-6]. The

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incidence of coexisting CAD in degenerative valvular dysfunction is approximately 28%, whereas that in rheumatic valvular dysfunction is only 9.8%[3,5,7,8]. Thus, in the present study, we aimed to identify risk factors associated with CAD in patients undergoing valvular heart surgery, develop a predictive model to stratify these patients according to CAD risk, and validate this model.

Materials and Methods

Study population

In this retrospective cohort study, the authors included patients over 18 years old with degenerative or rheumatic valvular heart disease who underwent preoperative CAG before valvular heart surgery between January 2015 and December 2018 at two tertiary care hospitals, Queen Sirikit Heart Center of the Northeast and Srinagarind Hospital, in Thailand. Data from Queen Sirikit Heart Center of the Northeast was used as a development cohort, and data from Srinagarind Hospital was used as a validation cohort. The authors excluded patients if they (1) had undergone prior coronary artery bypass grafting or percutaneous coronary intervention, (2) required CAG due to acute coronary syndrome, (3) had CAG performed more than 12 months before the valvular operation, or (4) had incomplete clinical data. The present study was approved by the Khon Kaen University Institutional Review Board with the reference number: HE621139.

Operative definitions

Anginal pain was classified following the clinical criteria described in the European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines for chronic coronary syndromes[9,10]: (1) constricting discomfort in the front of the chest, neck, jaw, shoulder, or arm that was (2) precipitated by physical exertion and (3) relieved with rest. Chest pain that met all three criteria was classified as typical angina pain, while that which met only two criteria was classified as atypical angina pain. A family history of premature CAD was defined as a positive history of coronary heart disease in a first-degree male relative less than 55 years of age or a female relative younger than 65. Hypertension was defined as arterial blood pressure of greater than 140/90 mmHg or current treatment with antihypertensive medications. Patients were determined to have dyslipidemia if they met the criteria laid out by the National Cholesterol Education Program-Adult Treatment Panel-III (NCEP-ATP III) or were receiving lipid-lowering agents[11] and to have diabetes mellitus (DM) if they met the American Diabetes Association (ADA) criteria or were currently taking glucose-lowering drugs[12]. Chronic kidney disease (CKD) was defined as a glomerular filtration rate of less than 60 mL/min as calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation[13]. Significant CAD was defined as luminal narrowing of the left main coronary artery of greater than 50% or luminal narrowing of the left anterior descending, left circumflex, or right coronary artery of greater than 70%, as visually estimated by the interventional cardiologist performing CAG who was unaware of this study. The etiologies of valvular heart dysfunction were identified based on morphological echocardiographic and intraoperative findings. Significant aortic and mitral valvular lesions were defined as at least moderate severity degree using the criteria presented in the current ESC/AHA guidelines for valvular heart disease[1,2].

Sample size calculation

The estimated sample size for the predictive model development cohort was calculated based on the method proposed by Peduzzi et al. as 690 patients[14]. We planned to collect data regarding 14 independent variables, which required 140 instances of concomitant CAD. As a previous study found the prevalence of patients with coexisting CAD to be approximately 20.3%, we determined that a sample size of 690 patients would be necessary to guarantee adequate power to detect statistical significance[3-8]. For the validation cohort, all consecutive valvular heart disease patients who underwent operations between 2015 and 2018 in the other hospital were enrolled (n=62).

Statistical analysis

Categorical variables were expressed as frequency (percentage) and compared using the Pearson Chi-square or Fisher's exact test, as appropriate. Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range. They were compared using the Student's t-test or Wilcoxon rank-sum test, as appropriate.

Univariate and multivariate logistic regression analyses were used to identify variables associated with obstructive CAD. In the multivariate logistic regression analysis, the authors included known independent CAD risk factors[3-6] and variables with p-values of less than 0.25 according to univariate logistic regression analysis. We then performed multivariate logistic regression analysis using a backward elimination method to identify significant predictive factors for concomitant CAD. Independent predictors of obstructive CAD derived from multivariate logistic regression analysis were used to create a simplified risk score weighted by the regression coefficients. Then, a receiver-operating-characteristic (ROC) curve was constructed to determine the optimal cutoff value for the simplified risk score.

The predictive model derived from the development cohort was subsequently applied in the validation cohort to assess predictive accuracy by calculating the c-statistics of the ROC curves. Stata version 10.1 was used for all analyses

in this study. Factors with p-values of less than 0.05 were considered statistically significant.

Results

During the study period, we identified 1,339 consecutive patients undergoing valvular surgery in the hospital from which we recruited the development cohort, of whom 649 were excluded based on the exclusion criteria. The remaining 690 patients constituted our study population. The study flow diagram is shown in Figure 1.

Clinical characteristics of the patients

Concomitant CAD was detected in 79 (11.4%) patients. These patients were likely to be older, male, had anginal pain, and exhibited more traditional CAD risk factors compared to those without CAD. Patients without CAD were more likely to have mitral valve lesions and rheumatic heart disease. Details regarding baseline characteristics are provided in Table 1.

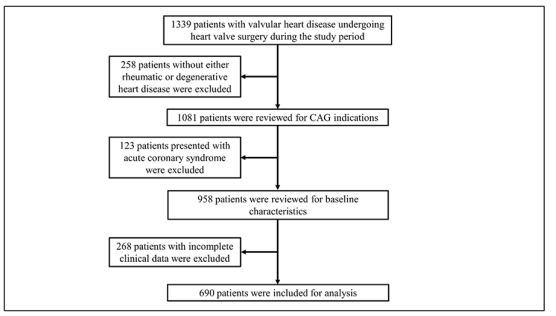

Figure 1. Study flow diagram.
CAG=coronary angiography

Logistic regression models and predictive score development

The clinical risk factors that predicted CAD were subjected to univariate analysis. The authors found that advanced age, male sex, chest pain, history of smoking, DM, hypertension, dyslipidemia, CKD, and family history of premature CAD were significant risk factors for CAD, whereas mitral valve lesions and rheumatic heart disease were protective factors according to univariate analysis. Variables that remained significantly associated with CAD after multivariate analysis were age (odds ratio (OR) 1.04; 95% confidence interval (CI) 1.00 to 1.08), typical angina pain (OR 2.67; 95% CI 1.24 to 5.73), family history of premature CAD (OR 5.51; 95% CI: 1.30 to 23.20), dyslipidemia (OR 2.11; 95% CI 1.14 to 3.91), and DM (OR 2.98; 95% CI: 1.49 to 5.95). In addition, significant risk-lowering factors for concomitant CAD were rheumatic heart disease (OR 0.21; 95% CI: 0.10 to 0.41) and aortic valve lesions (OR 0.32; 95% CI: 0.13 to 0.75). The results of the univariate and multivariate analyses are shown in Table 2.

The predictive risk score and ROC curve analysis

The simplified risk score is summarized in Table 3. It yielded a c-statistic of 0.84 (95% CI: 0.79 to 0.88) in the development cohort and 0.64 (95% CI: 0.46 to 0.82) in the validation cohort (Figure 2). With a cutoff score of 61.75, our model provided 70.9% sensitivity, 80.7% specificity, 32.2% positive predictive value, and 95.5% negative

Table 1. Baseline characteristics

	Patients without concomitant CAD (n=611)	Patients with concomitant CAD (n=79)	p-value
Age (years)	58.8±9.2	65.1±9.0	<0.001
Male	313 (51.2%)	52 (65.8%)	0.016
BMI (kg/m^2)	22.5±3.7	22.9±3.3	0.307
Chest pain characteristics			
Typical anginal pain	35 (5.7%)	18 (22.8%)	0.005
Atypical anginal pain	87 (14.2%)	18 (22.8%)	<0.001
Family history of premature CAD	5 (0.8%)	5 (6.3%)	0.001
Smoking history	211 (34.5%)	40 (50.6%)	0.006
Hypertension	161 (26.3%)	45 (56.9%)	<0.001
Diabetes	61 (10.0%)	25 (31.7%)	<0.001
Dyslipidemia	216 (35.4%)	56 (70.9%)	<0.001
Chronic kidney disease	99 (16.2%)	25 (31.7%)	0.001
Aortic valve lesion	319 (52.2%)	40 (50.6%)	0.792
Mitral valve lesion	476 (77.9%)	48 (60.8%)	0.001
Rheumatic heart disease	417 (68.2%)	18 (22.8%)	<0.001

Data are expressed as mean±SD, n (%).
BMI=body mass index; CAD=coronary artery disease.

Table 2. Univariate and multivariate analyses of predictive risk factors for concomitant CAD

	Univariate analysis		Multivariate analysis	
	Odd ratio (95% CI)	p-value	Odd ratio (95% CI)	p-value
Age (increase per year)	1.07 (1.04 to 1.10)	<0.001	1.04 (1.00 to 1.08)	0.025
Male sex	1.83 (1.12 to 3.00)	0.016		
BMI (kg/m^2)	1.03 (0.97 to 1.10)	0.307		
Chest pain characteristics				
Typical anginal pain	5.85 (3.06 to 11.18)	<0.001	2.67 (1.24 to 5.73)	0.012
Atypical anginal pain	2.35 (1.30 to 4.27)	0.005		
Family history of premature CAD	8.19 (2.32 to 28.95)	0.001	5.51 (1.31 to 23.20)	0.020
Smoking history	1.94 (1.21 to 3.12)	0.006		
Hypertension	3.70 (2.29 to 5.98)	<0.001		
Diabetes	4.17 (2.43 to 7.18)	<0.001	2.98 (1.49 to 5.95)	0.002
Dyslipidemia	4.45 (2.67 to 7.44)	<0.001	2.11 (1.14 to 3.91)	0.017
Chronic kidney disease	2.39 (1.42 to 4.03)	0.001		
Aortic valve lesion	0.94 (0.59 to 1.50)	0.792	0.32 (0.13 to 0.75)	0.009
Mitral valve lesion	0.44 (0.27 to 0.72)	0.001		
Rheumatic heart disease	0.14 (0.08 to 0.24)	<0.001	0.21 (0.10 to 0.41)	<0.001

BMI=body mass index; CAD=coronary artery disease; CI=confidence interval

Table 3. Simplified risk score for concomitant CAD prediction

Variable	Score
Age	1 point for each year
Chest pain characteristics	
Typical anginal pain	22
Atypical anginal pain	11.5
Family history of premature CAD	41.5
Diabetes	22.5
Dyslipidemia	19
Aortic valve lesion	-23
Rheumatic heart disease	-36.5

Patients with simplified risk scores <61.75 were defined as being at low risk of CAD.

CAD=coronary artery disease

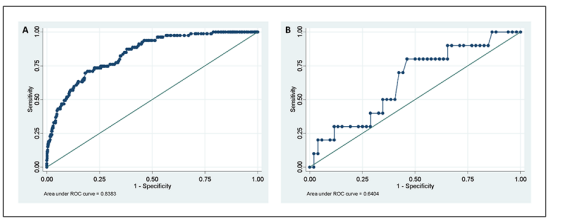

Figure 2. ROC curves analyses of a simplified predictive risk score for concomitant CAD. A) Development cohort, B) Validation cohort.

CAD=coronary artery disease, ROC=receiver operating characteristic

predictive value.

Discussion

The main findings of this study are as follows: 1) in patients undergoing valvular heart surgery, advanced age, typical angina pain, family history of premature CAD, dyslipidemia, and DM were significant risk factors for concomitant CAD, while rheumatic heart disease and aortic valve lesions were significant risk-lowering factors; 2) we created a predictive risk model, which exhibited high diagnostic accuracy and high negative predictive value. Thus, it should be beneficial to identify patients with a low risk of concomitant CAD.

The prevalence of coexisting CAD in our study was 11.4%, similar to those found in previous cohort studies in Asian populations but lower than in Western cohorts (approximately 20%)[3-6]. The lower rate of concomitant CAD in Asian populations might be explained partly by the larger proportion of rheumatic heart disease in these groups.

The findings of this study regarding risk factors for concomitant CAD were consistent with those from previous reports. Traditional risk factors for CAD were significant predictors after adjustment for confounding variables in the multivariate analysis. Furthermore, we found that rheumatic heart disease was a protective factor against concomitant CAD. This finding is different from the prior studies that found a lower prevalence of concomitant CAD in patients with rheumatic heart disease, but no significant association between rheumatic heart disease and CAD was previously detected. Although the authors did not find an adequate theory to explain this finding in the literature, degenerative and rheumatic heart disease may be associated with CAD in different degrees. In degenerative heart disease, age-related atheromatous plaque and calcification play a major role in developing obstructive CAD[15]. However, in rheumatic heart disease, CAD has been described as a consequence

of coronary artery inflammation, which may make its occurrence less likely[16] and result in a lower prevalence of CAD in patients with rheumatic heart disease. Furthermore, past antibiotic use as rheumatic fever prophylaxis may have resulted in anti-inflammatory effects and subsequently prevented the obstructive process of coronary arteries[17,18].

According to the multivariate analysis, the presence of aortic valve lesions was a protective factor for concomitant CAD, which contrasts with the findings of previous studies. There are some possible explanations for this finding. First, aortic valve lesions, especially aortic stenosis, share common risk factors as in CAD; thus, the high prevalence of coexisting CAD observed in patients with aortic stenosis[19] may be confounded by other cardiovascular risk factors[20]. Second, rheumatic heart disease, which was found to be a protective factor for CAD and was detected in 63% of our study population, was also one of the underlying etiologies of aortic valve dysfunction. Third, some patients with severe aortic stenosis presenting with chest pain were excluded from the present study, as they were diagnosed with acute coronary syndrome prior to CAG.

Preoperative evaluation of concomitant CAD in patients with valvular heart disease is crucial before open heart surgery, as missing a patient with coexistent CAD could result in catastrophic complications. Thus, the current patient selection guidelines for preoperative CAG tend to err on the side of performing the procedure[1,2]. Our risk stratification model has a high negative predictive value (95.5%) which can be useful to identify patients at low risk of concomitant CAD, may allow them to undergo less-invasive testing, and may avoid unnecessary CAG.

According to the guidelines for the management of valvular heart disease, coronary computed tomography angiography (CCTA) could be an alternative screening method for coexisting CAD in patients with low pretest probability[1,2]. A systematic review found that CCTA had a pooled sensitivity of 93%, a specificity of 89%, and a very strong negative likelihood ratio[7]. Thus, based on our model, performing CCTA in patients with a low risk of CAD should greatly reduce the chance of false-negative results, hospital costs, and CAG complications. This hypothesis should be evaluated in future studies.

Several limitations of the present study warrant consideration. First, this was a retrospective observational study in two tertiary care centers, and there may have been unexpected confounding factors that were accounted for in our analyses. However, we attempted to include all known potential risk factors in the multivariable model to mitigate the effects of these confounding factors. Second, the present study did not evaluate some novel CAD risk factors, such as high-sensitivity C-reactive protein, since they were not routinely obtained for preoperative evaluation. Third, the sample size in the validation cohort was small due to a higher proportion of infective endocarditis as well as the presentation of acute coronary syndrome in the validation hospital (hence the lower c-statistic in the validation cohort). However, the results from the development cohort exhibited strong internal validity with a c-statistic of 0.84 (95% CI: 0.79 to 0.88). Further external validation in a larger number of patients may be required in future studies. Fourth, the number of patients with CAD per adjusting variable in the multivariate analysis was <10 since the prevalence of CAD was smaller than expected. Thus, the results of OR should be carefully interpreted. Finally, since our study had a CAD prevalence of 11.4%, rheumatic heart disease of 63%, and included only degenerative and rheumatic valvular heart diseases, generalizing our study results on different populations has to be performed with caution.

Conclusion

In patients undergoing valvular heart surgery, traditional CAD risk factors were associated with concomitant CAD, whereas aortic valve lesions and rheumatic heart disease were the protective factors. Our predictive risk score can identify low-risk patients with concomitant CAD, which may avoid unnecessary CAG.

What is already known on this topic?

Current guidelines recommend performing CAG prior to valvular heart surgery in patients with risks or a history of CAD and in men over 40 and postmenopausal women. However, these criteria may lead to many low-risk patients undergoing unnecessary invasive procedures.

What this study adds?

In patients undergoing valvular heart surgery, traditional atherosclerotic risk factors were significantly associated with concomitant CAD, and rheumatic heart disease was associated with lower CAD risk. Our validated predictive risk score can identify low-risk patients with concomitant CAD, which may allow them to avoid unnecessary CAG.

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Conflicts of interest

The authors declare no conflict of interest.

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