

Clinical predictive factors of coronary stenosis in patients with high-risk valvular heart disease who received diagnostic coronary angiography prior to cardiac valve surgery

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Abstract. Valvular heart disease (VHD) may lead to morbidities and mortality due to heart failure or sudden death. Concomitant coronary artery disease (CAD) is a crucial condition that needs to be explored in patients with VHD prior to cardiac valve surgery as it may increase morbidity and mortality. Patient age >40 years and mitral regurgitation are key risk factors for CAD in patients with VHD. The present study aimed to identify clinical risk factors for coronary stenosis in patients with high-risk VHD. The retrospective cohort study recruited patients aged >40 years who received cardiac valve surgery and coronary angiogram prior to cardiac valve surgery. Clinical factors predictive of coronary stenosis were computed by logistic regression analysis. There were 533 patients; 114 patients (21.38%) had coronary stenosis. Four factors were positively associated with coronary stenosis including age, male sex, mitral regurgitation and hypertension, while two factors were negatively associated with coronary stenosis, namely estimated glomerular filtration rate and rheumatic heart disease. Hypertension had the highest adjusted odds ratio at 2.596, while rheumatic heart disease had the lowest adjusted odds ratio at 0.428. Patient age >55 years showed a sensitivity and specificity of coronary stenosis of 80.70 and 37.47%, respectively. Clinical factors predictive of coronary stenosis in patients with high-risk VHD were age >55 years, male sex, mitral regurgitation and hypertension, while a high estimated glomerular filtration rate and presence of rheumatic heart disease were protective factors.

Introduction

Valvular heart disease (VHD) is a cardiac condition that may lead to morbidity and mortality due to heart failure or

sudden death (1-3). The prevalence of VHD is 3.1% in 1,818 Latinos/Hispanics individuals in the United States between October 2011 and June 24, 2014 (4). A report from South Korea found that incidence of non-rheumatic valvular heart disease increased from 70.6 to 110.3/100,000 individuals from 2006 to 2011 (5). Patients with VHD may require cardiac valvular surgery if symptoms are severe or left ventricle is dysfunction (6).

For those requiring surgical valvular treatment, the 2017 European Society of Cardiology (ESC) guidelines recommend coronary angiography prior to valvular surgery in the high-risk patients (7), including patients with evidence of coronary artery disease or severe mitral regurgitation and those aged >40 years. There are several cardiovascular risk factors that may contribute to coronary artery disease, such as atrial fibrillation, diabetes, obstructive sleep apnea or dyslipidemia (8-13).

Although coronary angiography is an invasive procedure with potential adverse side effects, it may be worthwhile as a means of identifying clinical factors associated with coronary artery stenosis. Additionally, a history of angina pain or non-invasive exercise testing for coronary artery disease may not be sensitive enough to detect stenosis. A study found that 40% of female patients with diabetes and coronary artery disease do not have angina chest pain and exercise testing for coronary artery disease has a sensitivity of 26% (14,15). Therefore, the present study aimed to evaluate which clinical factors are predictive of coronary artery stenosis in patients with high-risk VHD. By using clinical factors other than a history of angina pain or results from non-invasive tests for coronary stenosis, physicians may be able to recommend patients who require valvular heart surgery for coronary angiography prior to valvular surgery to test for coronary stenosis.

Materials and methods

Subjects. The present retrospective cohort study was conducted at University Hospital, Khon Kaen University, Thailand. There were 533 patients with a mean age of 59.86 (SD 9.64) and a proportion of male of 55.35% (295 patients). The inclusion criteria were patients aged ≥40 years who received cardiac valve surgery and coronary angiogram prior to cardiac valve surgery. Exclusion criteria included patients who had

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Table I. Clinical features of patients with valvular heart disease who underwent diagnostic coronary angiography prior to cardiac valve surgery categorized by the presence of CS.

Factor	No CS (n=419)	CS (n=114)	P-value
Mean age, years	58.64 (9.26)	64.31 (9.70)	<0.001
Male sex (%)	217 (51.79)	78 (68.42)	0.002
Mean body mass index	22.57 (4.08)	23.20 (3.78)	0.142
Mean eGFR, ml/min/1.73 m ²	76.81 (20.61)	68.47 (23.34)	<0.001
Co-morbidity (%)			
Atrial fibrillation	185 (44.15)	25 (21.93)	<0.001
Diabetes mellitus	39 (9.31)	25 (21.93)	0.001
Hypertension	79 (18.85)	54 (47.37)	<0.001
Dyslipidemia	61 (14.56)	27 (23.68)	0.023
Stroke/TIA	27 (6.44)	4 (3.51)	0.365
Heart failure	136 (32.46)	44 (38.60)	0.221
Smoker (%)	115 (28.47)	38 (34.23)	0.243
Valve abnormality (%)			
Aortic regurgitation	114 (27.21)	22 (19.30)	0.091
Aortic stenosis	155 (36.99)	43 (37.72)	0.913
Mitral regurgitation	158 (37.71)	60 (52.63)	0.005
Mitral stenosis	191 (45.58)	16 (14.04)	<0.001
Tricuspid regurgitation	149 (35.56)	28 (24.56)	0.033
Mean number of abnormal valves	1.83 (0.90)	1.48 (0.72)	<0.001
Causes of VHD (%)			
Ischemic	0 (0.00)	19 (16.67)	<0.001
Prolapse	33 (7.88)	6 (5.26)	0.421
Degenerative	98 (23.39)	40 (35.09)	0.016
Rheumatic heart disease	230 (54.89)	26 (22.81)	<0.001
Infective endocarditis	17 (4.07)	2 (1.75)	0.391
Medication (%)			
ACEI/ARB	77 (18.42)	34 (29.82)	0.009
Aspirin	114 (27.27)	65 (57.02)	<0.001
β blocker	142 (33.97)	42 (36.84)	0.580
Digoxin	115 (27.51)	14 (12.28)	0.001
Diuretic	268 (64.11)	51 (44.74)	<0.001
Warfarin	176 (42.11)	19 (16.67)	<0.001

CS, coronary stenosis; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker.

prosthetic valves, received emergency cardiac valve surgery or underwent a reoperation for cardiac valve surgery. Data were collected between January 2018 and January 2019. All eligible patients in the study received the standard clinical treatment for VHD.

Baseline characteristics, co-morbid disease, causes of VHD and current medications of eligible patients were recorded. Valvular abnormalities were recorded for those with severe regurgitation or stenosis by echocardiogram as proposed by a previous study (6) and causes of VHD were categorized as follows: Rheumatic heart disease, infective endocarditis, prolapse, ischemic and degenerative. Coronary stenosis was defined by a stenosis $\geq 50\%$ in any coronary artery prior to cardiac valve surgery.

Statistical analysis. Data are presented as the mean $\pm$ SD. Patients were categorized into two groups based on the presence of coronary stenosis. Clinical factors predictive of coronary stenosis were computed using univariate logistic regression analysis. Factors with $P < 0.20$ were used for stepwise multivariate logistic regression analysis. Factors with $P < 0.25$ were accepted into the final model. Hosmer-Lemeshow χ^2 was performed to evaluate goodness of fit for the final model. The significant numerical predictive factors were calculated for sensitivity and specificity using the area under a receiver operating characteristic (ROC) curve. The statistical analyses were performed using STATA software version 10.1 (College Station). $P < 0.05$ was considered to indicate a statistically significant difference.

Table II. Clinical factors predictive of coronary stenosis in patients with valvular heart disease patients who received diagnostic coronary angiography prior to cardiac valve surgery.

Factor	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Age	1.066 (1.041, 1.091)	1.038 (1.009, 1.068) ^a
Male sex	2.016 (1.300, 3.128)	2.210 (1.340, 3.646) ^a
Body mass index	1.038 (0.987, 1.092)	1.041 (0.981, 1.105)
eGFR	0.980 (0.970, 0.991)	0.985 (0.981, 0.997) ^a
Atrial fibrillation	0.355 (0.219, 0.576)	0.584 (0.321, 1.059)
Mitral regurgitation	1.835 (1.209, 2.786)	1.878 (1.160, 3.041) ^a
Hypertension	3.873 (2.490, 6.024)	2.596 (1.574, 4.280) ^a
Rheumatic heart disease	0.242 (0.150, 0.391)	0.985 (0.981, 0.997) ^a

^aP<0.05. eGFR, estimated glomerular filtration rate; Bold indicating significant factor.

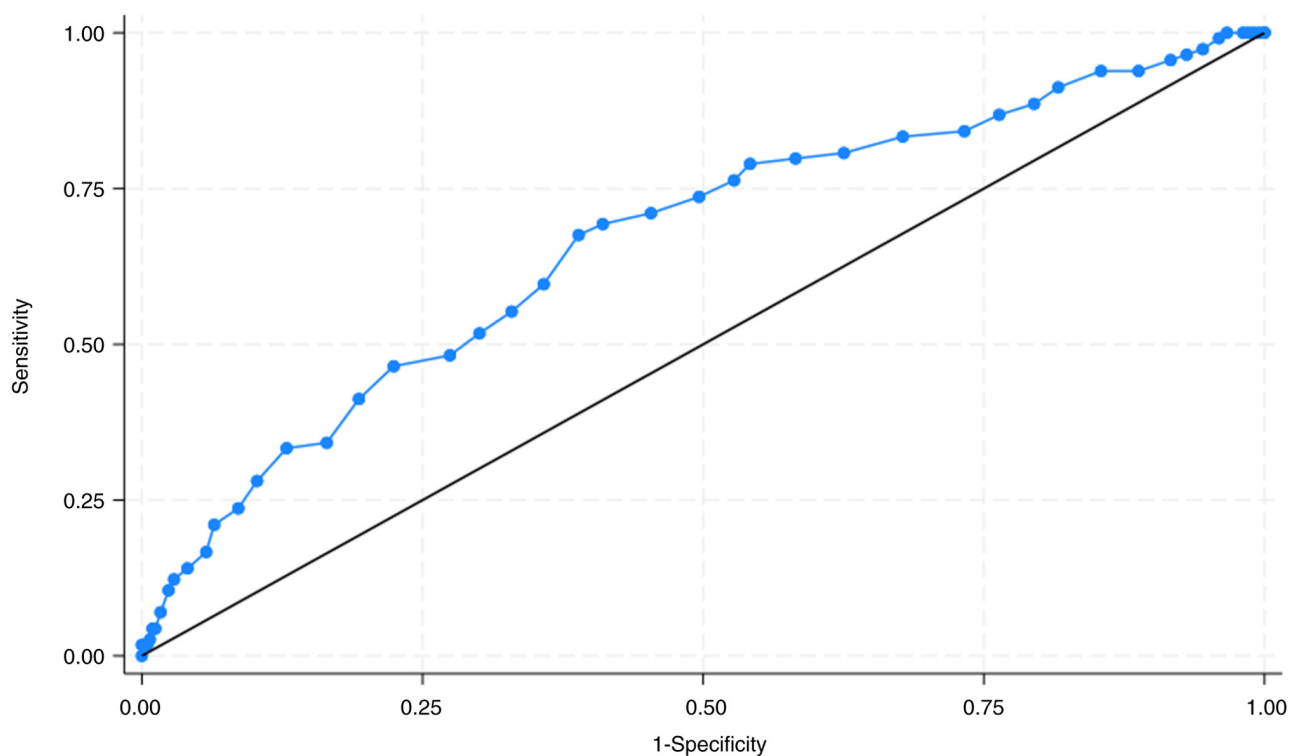


Figure 1. ROC curve of age in patients with coronary stenosis and valvular heart who received diagnostic coronary angiography prior to cardiac valve surgery. The area under the ROC curve was 66.45%. ROC, receiver operating characteristic.

Results

There were 533 patients who met the study criteria; 114 patients (21.38%) had coronary stenosis (Table I). The mean number of coronary arteries exhibiting stenosis was 2.2 ± 1.05 . Patients in the coronary stenosis group had significantly older mean age (64.31 vs. 58.64 years; $P < 0.001$) and significantly lower estimated glomerular filtration rate (68.47 vs. 76.81 ml/min/1.73 m²; $P < 0.001$) than the non-coronary stenosis group. Regarding co-morbid diseases, the coronary stenosis group had a higher percentage of diabetes and hypertension (21.93% vs. 9.31%; $P = 0.001$ and 47.37% vs. 18.85%; $P < 0.001$) but a lower proportion of atrial fibrillation (21.93% vs. 44.15%; $P < 0.001$) than the non-coronary stenosis group.

Coronary stenosis group had more patients with mitral regurgitation (52.63 vs. 37.71%; $P = 0.005$) but fewer patients with tricuspid regurgitation (24.56 vs. 35.56%; $P = 0.033$) and mitral stenosis (14.04 vs. 45.58%; $P < 0.001$) than the non-coronary stenosis group. The coronary stenosis group had a greater occurrence of degenerative causes of VHD (35.09%; $P = 0.016$), while the non-coronary stenosis group had more patients with rheumatic heart disease (54.89%; $P < 0.001$). The coronary stenosis group had a higher proportion of patients receiving angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) and aspirin therapy than the non-coronary stenosis group (29.82% vs. 18.42%; $P = 0.009$). Patients with rheumatic heart disease

had a significantly lower mean age than those without (56.07 vs. 63.35 years; $P < 0.001$), while patients with ischemic VHD had slightly older age than those with non-ischemic VHD (62.63 vs. 59.75 years; $P = 0.202$).

Factors included in the stepwise logistic regression analysis were age, sex, body mass index, estimated glomerular filtration rate, atrial fibrillation, diabetes mellitus, hypertension, dyslipidemia, rheumatic heart disease, mitral regurgitation, mitral stenosis, tricuspid regurgitation and history of smoking, heart failure and stroke/TIA. There were eight factors included in the final model predictive of coronary stenosis (Table II). A total of six factors were significant risk factors for coronary stenosis. Of these, four factors were positively associated with coronary stenosis, namely age, male sex, mitral regurgitation and hypertension, while two factors were negatively associated with coronary stenosis, namely estimated glomerular filtration rate and rheumatic heart disease. Hypertension had the highest adjusted odds ratio at 2.596 (95% confidence interval of 1.574, 4.280; $P < 0.05$), while both high estimated glomerular filtration rate and rheumatic heart disease had adjusted odds ratios of 0.985 (95% confidence interval of 0.981, 0.997; $P < 0.05$). The Hosmer-Lemeshow χ^2 value of the final model was 8.64 ($P = 0.374$; data not shown). Patient age > 55 years had a sensitivity and specificity of coronary stenosis of 80.70 and 37.47%, respectively. The area under ROC curve was 66.45% (95% confidence interval, 60.69, 72.21; Fig. 1).

Discussion

The present study showed a prevalence of coronary stenosis in patients with VHD of 21.38%, which was lower than a previous report from Lebanon (27.75%) (16). These differences may be due to a different study population (17). Unlike the report from Lebanon, the present study did not find significant differences in aortic stenosis. The aforementioned report showed that severe aortic stenosis is the most common form of VHD associated significant coronary stenosis (16). The present study found mitral regurgitation was the most common type of VHD associated with CAD and was independently associated with significant coronary stenosis, as previously reported (7).

Other than mitral regurgitation, the present study showed predictors for coronary stenosis in VHD were age, sex, estimated glomerular filtration rate, hypertension and rheumatic heart disease. Certain cardiovascular risk factors included in the analysis were not retained in the final model, such as atrial fibrillation, diabetes and dyslipidemia. As previously reported, age, male sex and hypertension were associated with coronary artery disease (18-21), while low glomerular filtration rate may increase risk of coronary artery disease (22). A previous study found that age and male sex have an adjusted odds ratio of 1.0560 and 2.6003, which were comparable to those found in the present study (23). The 2017 ESC guidelines recommend pre-operative coronary angiogram in patients with VHD aged > 40 years (7); here, patient age > 55 years had a sensitivity of 80%.

Rheumatic heart disease was negatively associated with coronary stenosis. Even though a previous study found that mitral regurgitation is the most common type of rheumatic heart disease (24), only 101 patients in the present study had mitral regurgitation from rheumatic heart disease (39.45%). The aforementioned negative association may be explained by

patient age since mitral regurgitation was negatively associated with age (coefficient of -0.188) (24). Patients with rheumatic heart disease may be younger and therefore at a lower risk for coronary artery disease. Here, patients with rheumatic heart disease had a significantly lower mean age than those without. A study from Brazil found that only 4% of patients with rheumatic heart disease have coronary artery disease compared with 33.61% of patients without rheumatic heart disease (25). A study from China found that patients with rheumatic heart disease undergoing valvular surgery for coronary artery disease are older than those without coronary artery disease (63 vs. 54 years; $P < 0.01$) (26). Although the mean age of the present study was comparable with the aforementioned studies, the present study found that rheumatic heart disease was protective factor for coronary stenosis in patients who underwent valvular surgery.

Risk factors for coronary stenosis in patients with VHD include male sex, age > 55 years, hypertension and low estimated glomerular filtration rate. Those with rheumatic heart disease may be at a lower risk of coronary artery disease. Finally, these risk factors were identified independently of chest pain or other non-invasive exercise testing for coronary artery disease. Physicians may consider these risk factors when deciding on pre-operative coronary angiography prior to cardiac valve surgery in patients with VHD who are aged > 40 years, regardless of history of angina pain or non-invasive exercise testing for coronary artery disease.

There are limitations in the present study. First, the present study population was a single, referral, university hospital resulting in small sample size. An interpretation of the results should be performed cautiously as the logistic model may lack sufficient power. The trace back power of the dataset was 99.7%. Second, certain factors for coronary artery disease were not included such as obstructive sleep apnea (27-34). Clinicians may use the model as a guide to evaluate the risk of coronary stenosis. Finally, the prevalence of rheumatic heart disease was high (48.03%). The results of this study may be applicable for populations with a similar prevalence of rheumatic heart disease. The primary outcome of this study was presence of coronary stenosis of $> 50\%$, not the percentage of coronary stenosis. The presence of significant coronary stenosis may be more clinical relevant than the percentage of coronary stenosis as the guideline recommends coronary bypass graft surgery prior to heart valve surgery if coronary stenosis is over 50% (7).

Clinical factors predictive of coronary stenosis in patients with high-risk VHD were age > 55 years, male sex, mitral regurgitation and hypertension, while high estimated glomerular filtration rate and rheumatic heart disease were protective factors. Patients who are identified as higher risk based on these risk factors should be considered for coronary angiogram prior to cardiac valve surgery.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

SW and KS conceived and designed the study. DK and VC interpreted data. KS performed statistical analysis. All authors have read and approved the final manuscript. SW and DK confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board at the Ethical Committee of Khon Kaen University, Thailand (approval no. HE591473.) The requirement for informed consent was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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