ORIGINAL ARTICLE

Prevalence and Risk Factors for Preoperative Coronary Artery Disease in Patients with Rheumatic and Non-Rheumatic Valvular Heart Disease

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Background: Traditional atherosclerotic risk factors have been used to guide preoperative coronary angiography (CAG) in patients with valvular heart disease (VHD) who required valve surgery. However, the prevalence of coronary artery disease (CAD) differed among etiologies of VHD.

Objective: To evaluate differences in the prevalence of CAD across VHD etiologies and predictive factors for CAD.

Materials and Methods: The authors retrospectively reviewed patients aged ≥18 years with VHD who underwent valve surgery between January 2015 to December 2019. Patients with previously diagnosed significant CAD were excluded. CAD was diagnosed based on CAG findings with ≥50% stenosis of the left main coronary artery or ≥70% stenosis of other major epicardial vessels. The etiologies of VHD were classified according to echocardiographic characteristics. Clinical characteristics, echocardiographic parameters, and CAG results were collected from medical records and electronic databases. Univariable and multivariable analysis were performed to identify predictive factors of CAD.

Results: Total 917 patients undergoing valve surgery, 714 patients (77.9%) had preoperative CAG and CAD was diagnosed in 34 patients (4.8%). Rheumatic VHD accounted for half of the present study population (457 patients, 49.8%). CAD prevalence was significantly lower in patients with rheumatic VHD compared to non-rheumatic VHD (1.9% vs. 7.6%; p<0.001). From multivariable analysis, age ≥60 years was a significant predictor of CAD (OR 2.90; 95% CI, 1.03 to 8.18; p=0.04), while rheumatic VHD was associated with lower risk of CAD (OR 0.30; 95% CI, 0.09 to 0.94; p=0.04).

Conclusion: The prevalence of CAD in patients with rheumatic VHD requiring valve surgery is low. Including rheumatic VHD in the decision-making algorithm for preoperative CAG appears to be reasonable.

Keywords: Valvular heart disease; Rheumatic heart disease; Coronary artery disease; Coronary angiography

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Valvular heart disease (VHD) is a common cardiac condition, affecting populations in both developed and developing countries. The etiologies of VHD varied among populations in different regions and age groups. Degenerative VHD was predominantly observed among elderly patients and in developed countries, whereas rheumatic VHD was more common in younger patients and in developing countries[1]. Regardless of the underlying etiology, mainstay treatments for symptomatic VHD include medications, percutaneous valve interventions, and valve surgery.

According to data from a study conducted in the United States[2], 45.9 to 64.2% of patients with aortic VHD who underwent preoperative coronary angiography (CAG) were diagnosed with significant coronary artery disease (CAD). These patients received coronary artery bypass graft (CABG) surgery in conjunction with valve surgery, which was associated with lower 30-day and 10-year mortality rates compared to those who did not. Therefore, current guidelines for the management of VHD recommend routine preoperative CAG in patients undergoing valve surgery to assess for concomitant CAD, in order to determine the necessity of concurrent CABG during valve surgery[3,4].

However, recent studies have found that the prevalence

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of CAD among VHD patients requiring valve surgery varies across populations and depends on several factors, including ethnicity, age, cardiovascular risk factors, and the etiologies of VHD (rheumatic vs. non-rheumatic). Therefore, the prevalence of CAD in different populations should be considered when deciding whether to perform preoperative CAG before valve surgery. A previous study in the Thai population reported a CAD prevalence of 16.7%, however, the present study included only 90 patients with aortic stenosis, which does not represent the majority of VHD patients in Thailand[5]. Until now, data regarding the prevalence and factors associated with CAD in patients with VHD are still limited.

Over the past decade, approximately 200 patients with VHD have undergone preoperative CAG annually at Srinagarind Hospital and Queen Sirikit Heart Center of the Northeast. However, the prevalence of CAD in this population has not been investigated. The present study aims to determine the prevalence of CAD and its associated factors among patients with rheumatic and non-rheumatic VHD in our region, with the goal of informing more proper indications for preoperative CAG.

Materials and Methods

Study design, settings, and target populations

This retrospective cohort study was conducted at Srinagarind Hospital and Queen Sirikit Heart Center of the Northeast. The authors included patients aged over 18 years old with VHD who underwent valve surgery and preoperative CAG between January 2015 and December 2019. Patients diagnosed with significant CAD from previous CAG or radionuclide cardiac imaging prior to valve surgery, as well as those who did not undergo surgery were excluded from the study. The present study protocol was approved by Office of the Khon Kaen University Ethics Committee in Human Research (HE631174).

Definitions

Rheumatic VHD was diagnosed based on echocardiographic criteria[6] as follows:

1) Pathological mitral regurgitation (MR) with at least one of the following morphological features:

- Anterior mitral valve leaflets thickening >3 mm
- Chordal thickening
- Restricted leaflet motion
- Excessive leaflet tip motion during systole

2) Mitral stenosis (MS) with a mean pressure gradient ≥4 mmHg

3) Pathological aortic regurgitation (AR) with at least one of the following morphological features:

- Irregular or focal thickening
- Coaptation defect
- Restricted leaflet motion
- Prolapse

4) Borderline disease of both aortic and mitral valves was also classified as rheumatic VHD

Degenerative VHD was diagnosed from echocardiographic findings demonstrating:

- Degenerative changes and calcification of the MV or AV
- Absence of morphological features indicative of rheumatic heart disease

Coronary artery disease was defined as the presence of ≥50% luminal narrowing in left main coronary artery or ≥70% luminal narrowing in any other major epicardial vessels, as determined by visual estimation on invasive coronary angiography[4].

Data collection

Demographic data and clinical characteristics including age, sex, body mass index (BMI), New York Heart Association (NYHA) functional class, family history of premature CAD, comorbidities (diabetes mellitus, hypertension, dyslipidemia, atrial fibrillation), history of congestive heart failure (CHF), history of stroke, estimated glomerular filtration rate (eGFR), and smoking history were retrospectively collected from medical records. Data regarding the etiology, type, and severity of VHD, left ventricular ejection fraction (LVEF), other echocardiographic parameters, and CAG results were obtained from transthoracic echocardiography and CAG electronic databases.

Statistical analysis

Categorical variables, including the prevalence of CAD, were summarized as frequencies (percentages) and compared using the Chi-square or Fisher's exact test. Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR), based on the distribution of data assessed by histogram inspection and Shapiro-Wilk's test. Student's t-test or Wilcoxon rank-sum test was used to compare the continuous variables, depending on the data distribution.

Factors associated with CAD were first assessed using univariable logistic regression. Variables with a significant association in the univariable analysis were then included in the multivariable logistic regression, using a stepwise backward selection method. The results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

All patients were followed until 30th September 2021. Patients were censored if they were lost to follow-up or the event of interest had not occurred. Survival time between patients with CAD, patients without CAD, and patients who did not undergo preoperative CAG were compared using

the Kaplan-Meier with statistical differences assessed by the Mantel-Cox log-rank test. A two-sided p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 28 (IBM corp., Armonk, NY, USA) and R program version 4.5.1.

Results

From January 2015 to December 2019, 917 patients underwent valve surgery at Srinagarind Hospital and Queen Sirikit Heart Center of the Northeast. 714 patients (77.9%) received preoperative CAG before valve surgery, including 360 with rheumatic VHD and 354 with non-rheumatic VHD. The demographic and baseline characteristics of the study population are presented in Table 1. Patients with CAD were significantly older than those without CAD (66 (60 to 72) vs. 58 (52 to 66) years; p<0.001). In both groups, most of the patients were classified as NYHA functional class II (78.2%). The prevalence of cardiovascular risk factors was higher among patients with CAD, including diabetes mellitus (17.6% vs. 9.0%; p=0.12), hypertension (50.0% vs. 33.7%; p=0.051), and dyslipidemia (47.1% vs. 20.6%; p<0.001). In contrast, atrial fibrillation was more frequent in patients without CAD (53.1% vs. 29.4%; p=0.007). No significant differences were observed regarding renal dysfunction (eGFR <60 mL/min/1.73 m^2), history of congestive heart failure, family history of premature CAD,

Table 1. Characteristics of the patients at baseline

Characteristics	Overall (n=714)	Patients with CAD (n=34)	Patients without CAD (n=680)	p-value[#]
Age (years)	58 (52,66)	66 (60,72)	58 (52,66)	<0.001
Male sex, n (%)	397 (55.5%)	25 (70.6%)	372 (54.7%)	0.069
Body mass index (kg/m^2)	22 (20,25)	22 (20,24)	22 (20,25)	0.99
NYHA functional class, n (%)				0.02
I	65 (9.1%)	1 (2.9%)	64 (9.4%)	
II	558 (78.2%)	27 (79.4%)	531 (78.1%)	
III	72 (10.1%)	2 (5.9%)	70 (10.3%)	
IV	9 (1.3%)	1 (2.9%)	8 (1.2%)	
Atrial fibrillation, n (%)	371 (52.0%)	10 (29.4%)	361 (53.1%)	0.007
Diabetes mellitus, n (%)	67 (9.4%)	6 (17.6%)	61 (9.0%)	0.12
Hypertension, n (%)	246 (34.4%)	17 (50.0%)	229 (33.7%)	0.051
Dyslipidemia, n (%)	156 (21.8%)	16 (47.1%)	140 (20.6%)	<0.001
History of smoking (current & ex-smoker), n (%)	193 (27.3%)	11 (32.4%)	182 (26.8%)	0.65†
Family history of premature CAD, n (%)	5 (0.7%)	0 (0%)	5 (0.7%)	>0.99†
History of stroke, n (%)	46 (6.4%)	1 (2.9%)	45 (6.6%)	0.72†
History of congestive heart failure, n (%)	279 (39.0%)	14 (41.2%)	264 (38.8%)	0.78
Baseline serum creatinine (mg/dL)	0.9 (0.8,1.2)	1.1 (0.8,1.3)	0.9 (0.8,1.1)	0.02
Baseline estimated GFR (mL/min/1.73 m^2)	77.5 (61.9,92.6)	69.2 (57.0,89.0)	78.0 (62.3,92.7)	0.09
Renal dysfunction (eGFR <60 mL/min/1.73 m^2), n (%)	160 (22.4%)	11 (32.4%)	149 (21.9%)	0.15
Type of VHD, n (%)				<0.001
Rheumatic VHD	360 (50.4%)	7 (20.6%)	353 (51.9%)	
Non-rheumatic VHD	354 (49.6%)	27 (79.4%)	327 (48.1%)	
Type of valvulopathy‡, n (%)				
Significant MS	285 (40.0%)	6 (17.6%)	279 (41.0%)	0.007
Significant MR	324 (45.4%)	11 (32.4%)	313 (46.0%)	0.12
Significant AS	219 (30.7%)	19 (55.9%)	200 (29.4%)	0.001
Significant AR	186 (26.1%)	7 (20.6%)	179 (26.3%)	0.46
Significant TR	299 (41.9%)	8 (23.5%)	291 (42.8%)	0.03
Baseline LVEF (%)	62.0 (51.2,70.0)	51.4 (46.1,69.0)	62.1 (51.8,70.0)	0.12
Presence of PH, n (%)	303 (42.4%)	10 (29.4%)	293 (43.1%)	0.12

[#] Comparison of baseline characteristics between patients with CAD vs. patients without CAD; † Fisher's exact test; ‡ Significant valvulopathy was classified as severity ≥ moderate grading

AR=aortic regurgitation; AS=aortic stenosis; CAD=coronary artery disease; eGFR=estimated glomerular filtration rate; LVEF=left ventricular ejection fraction; MR=mitral regurgitation; MS=mitral stenosis; NYHA=New York Heart Association; PH=pulmonary hypertension; TR=tricuspid regurgitation; VHD=valvular heart disease

or smoking history. Regarding valvular pathology, mitral regurgitation (MR) was the most prevalent valvular lesion in patients without CAD (46.0%), whereas aortic stenosis (AS) predominated among those with CAD (55.9%). Significant tricuspid regurgitation (TR) and pulmonary hypertension (PHT) occurred more frequently in patients without CAD.

CAD was observed in 34 patients (4.8%) of 714 patients who underwent preoperative CAG. The prevalence of CAD was significantly higher in patients with non-rheumatic VHD compared with those with rheumatic VHD (7.6% vs. 1.9%; p<0.001). In non-rheumatic VHD, CAD was most common in degenerative VHD (10.9%). The overall prevalence and type of CAD are summarized in Table 2. There were no significant differences in CAD types across different VHD etiologies, with single vessel disease (SVD) being the most common type.

Factors associated with CAD are presented in Table 3. In the multivariable analysis, age ≥60 years (OR 2.90; 95% CI, 1.03 to 8.18; p=0.04) was an independent predictor of CAD, while rheumatic VHD (OR 0.30; 95% CI, 0.09 to 0.94; p=0.04) was independently associated with a lower likelihood of CAD. In the univariable analysis, hypertension (OR 1.96; 95% CI, 0.98 to 3.93; p=0.05), dyslipidemia (OR 3.42; 95% CI, 1.70 to 6.89; p<0.001), and degenerative

Table 2. Details of coronary artery disease among patients who underwent coronary angiography according to etiology of valvular heart disease

Variable	All patients undergoing CAG (n=714)	Rheumatic VHD (n=360)	Non-rheumatic VHD (n=354)					p-value*
			Degenerative (n=156)	IE (n=40)	Bicuspid AV (n=34)	MVP (n=101)	Other VHD (n=23)	
CAD, n (%)	34 (4.8%)	7 (1.9%)	17 (10.9%)	3 (7.5%)	2 (5.9%)	2 (2.0%)	3 (13.0%)	<0.001
Type of CAD, n (%)								
LM	4 (11.8%)	0 (0%)	3 (17.6%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0.66
SVD	26 (76.5%)	6 (85.7%)	11 (64.7%)	2 (66.7%)	2 (100%)	2 (100%)	3 (100%)	0.95
DVD	7 (20.6%)	1 (14.3%)	5 (29.4%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)	
TVD	1 (2.9%)	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

* Rheumatic valvular heart disease vs. non-rheumatic valvular heart disease.

AV=aortic valve; CAD=coronary artery disease; CAG=coronary angiography; DVD=double vessel disease; IE=infective endocarditis; LM=left main; MVP= mitral valve prolapses; SVD=single vessel disease; TVD=triple vessel disease; VHD=valvular heart disease

Table 3. Univariable analysis and multivariable analysis of factors associated with coronary artery disease in patients with valvular heart disease

Variables	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age ≥60 years	4.11 (1.83 to 9.22)	<0.001	2.90 (1.03 to 8.18)	0.04
Male sex	1.98 (0.93 to 4.21)	0.07	1.48 (0.66 to 3.29)	0.33
BMI ≥25 kg/m^2	0.82 (0.36 to 1.85)	0.63	-	-
NYHA functional class III&IV	0.81 (0.24 to 2.75)	0.74	-	-
Atrial fibrillation	0.36 (0.17 to 0.78)	0.009	0.96 (0.39 to 2.35)	0.94
Diabetes mellitus	2.17 (0.86 to 5.45)	0.09	1.71 (0.61 to 4.80)	0.30
Dyslipidemia	3.42 (1.70 to 6.89)	<0.001	2.07 (0.98 to 4.39)	0.056
Hypertension	1.96 (0.98 to 3.93)	0.05	1.0 (0.45 to 2.20)	>0.999
History of stroke	0.42 (0.05 to 3.19)	0.40	-	-
History of heart failure	1.10 (0.54 to 2.22)	0.78	-	-
History of smoking (current & ex-smoker)	1.29 (0.61 to 2.71)	0.49	-	-
Renal dysfunction (eGFR <60 mL/min/1.73 m^2)	1.70 (0.81 to 3.57)	0.15	1.13 (0.50 to 2.45)	0.79
LVEF ≤40%	1.45 (0.54 to 3.87)	0.45	-	-
Rheumatic VHD	0.24 (0.10 to 0.55)	<0.001	0.30 (0.09 to 0.94)	0.04
Infective endocarditis	1.59 (0.46 to 5.43)	0.45	-	-
Degenerative VHD	3.75 (1.87 to 7.54)	<0.001	0.84 (0.33 to 2.14)	0.72
Bicuspid aortic valve	1.11 (0.25 to 4.85)	0.88	-	-
Mitral valves prolapse	0.33 (0.08 to 1.43)	0.14	0.21 (0.04 to 1.06)	0.06

eGFR=estimated glomerular filtration rate; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; VHD=valvular heart disease

VHD (OR 3.75; 95% CI, 1.87 to 7.54; p<0.001) were potential predictors of CAD, while atrial fibrillation (OR 0.36; 95% CI, 0.17 to 0.78; p=0.009) was associated with lower risk of CAD. However, these associations did not remain statistically significant in the multivariable analysis.

Overall survival was comparable between patients with rheumatic VHD and non-rheumatic VHD, with mean survival time (95% CI) was 69.1 (67.4 to 70.8) and 68.9 (66.5 to 71.3) months, respectively. The overall survival rate was 84.7%, with lower survival in patients with CAD (67.6%) compared with those without CAD (85.1%) or those who did not undergo preoperative CAG (86.2%). In the non-rheumatic VHD subgroup, survival differed significantly according to CAD status, with survival rate and mean survival time were 33.3% and 56.9 (44.5 to 69.3) months in patients with CAD, 86.5% and 70.0 (67.3 to 72.7) months in patients without CAD, 82.1% and 67.8 (62.9 to 72.7) months in patients who did not undergo preoperative CAG (p=0.02). In contrast, no significant difference was observed among these subgroups in patients with rheumatic VHD. Kaplan-Meier curves are illustrated in Figure 1.

Discussion

According to the current guidelines for VHD, routine preoperative CAG is recommended for assessing coexisting CAD before valve surgery, irrespective of patient characteristics or the etiology of VHD. However, previous studies have reported that a wide variation in CAD prevalence among patients undergoing valve surgery, ranging from 9% to 41%[7-14]. CAD is more common in patients with degenerative VHD, who are older and have multiple cardiovascular risk factors. In contrast, rheumatic VHD, still the predominant cause of VHD in developing countries, including Thailand, mainly affects younger individuals and is associated with lower prevalence of CAD[15]. Therefore, in patients with rheumatic VHD, particularly younger patients without significant atherosclerotic risk factors, preoperative CAG may be unnecessary, as the potential risks and complications could outweigh its benefits.

In the present study, the overall prevalence of CAD among patients with VHD who underwent preoperative CAG was 4.8%. CAD was more frequently observed in patients with non-rheumatic VHD, predominantly degenerative VHD, while its prevalence was markedly lower in those with rheumatic VHD. Compared with previous studies, the overall prevalence of CAD was considerably lower[11-13,16,17], while the higher prevalence in non-rheumatic VHD was consistent with prior studies[10,18]. Although, the prevalence of CAD among rheumatic VHD patients was notably lower than observed in earlier studies by Bai-Ling Li et al. (10.9%)[19], V Jacob Jose et al. (12.2%)[20], and Marchant E et al. (14%)[21].

In addition, the demographic data and clinical characteristics differed between patients with rheumatic VHD and non-rheumatic VHD, which may account for the observed difference in CAD prevalence between the two groups. Patients with CAD were older and had more cardiovascular risk factors including diabetes mellitus, hypertension, and dyslipidemia which are known as atherosclerotic risk factors[22]. Most of these patients had aortic stenosis as the underlying valve pathology. These findings are consistent with previous studies[16,17] and may

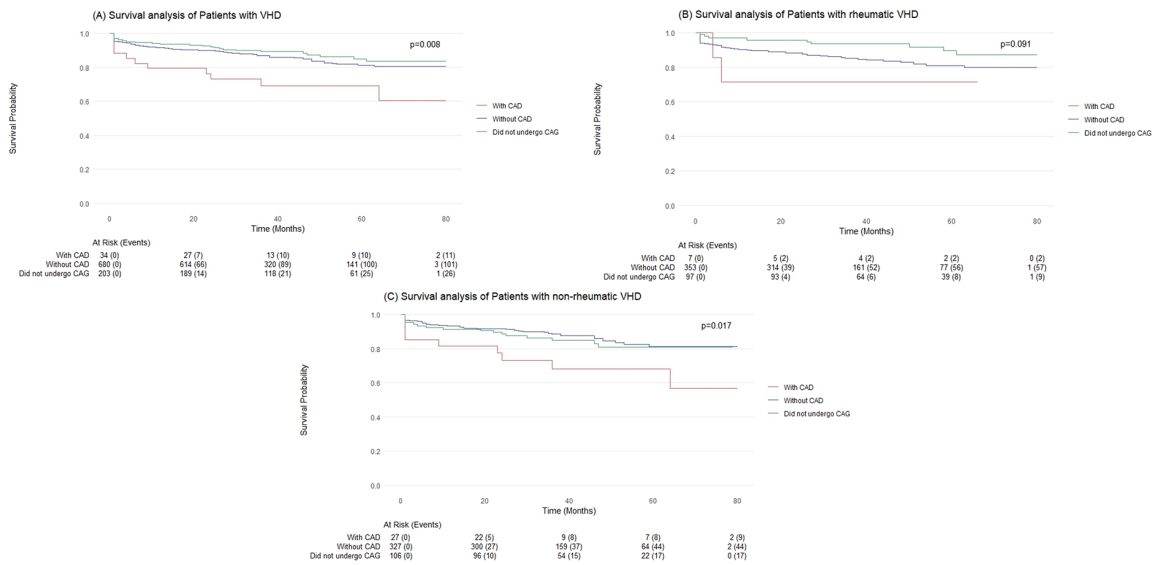

Figure 1. A) Survival analysis of patients with all valvular heart disease, B) rheumatic, and C) non-rheumatic valvular heart disease.

be explained by the fact that aortic stenosis commonly results from age-related degenerative calcification and atherosclerosis of the aortic valve. Conversely, atrial fibrillation, significant TR, and pulmonary hypertension were more common in patients without CAD. This is likely because most patients without CAD had rheumatic VHD, which typically involves the mitral valve, causing mitral valve abnormalities. In these patients, mitral valve disease can lead to elevated left atrial pressure, increased backward flow to the pulmonary circulation, pulmonary congestion, pulmonary vascular remodeling, and secondary TR. These pathophysiological changes ultimately predispose patients to the development of atrial fibrillation and pulmonary hypertension.

From the univariable analysis, age ≥60 years old, hypertension, dyslipidemia, and degenerative VHD are potential risk factors for CAD, while atrial fibrillation and rheumatic VHD are associated with lower risk of CAD among patients with VHD. However, in the multiple variable analysis, only advanced age remained independently associated with CAD. This finding is interesting and suggests that the underlying etiology of VHD should be considered when determining the need for preoperative CAG before valve surgery, although the results should be interpreted with caution given the small number of patients with CAD identified in the present study.

From the survival analysis, overall cumulative survival did not differ between rheumatic and non-rheumatic VHD. However, patients with concomitant CAD tended to have shorter survival compared with those without CAD in both groups, suggesting potential detrimental effects of CAD on the prognosis and treatment outcome of VHD. Though, evidence from previous studies remains. Zhiyong Xie et al.[23] reported that significant CAD was associated with higher risks of advanced acute kidney injury, longer ICU length of stay, and increased mortality, whereas Thomas M. Snow et al.[24] found no impact of concomitant CAD on both short- and long-term survival after transcatheter aortic valve implantation (TAVI) in patients with aortic stenosis. Further prospective studies are warranted to clarify the prognostic significance of CAD in patients with VHD.

The present study has several limitations. First, although a large numbers of patients with VHD were included, only 77.9% underwent preoperative CAG. Therefore, asymptomatic CAD in patients without CAG may have been undetected. More importantly, excluding patients who did not undergo preoperative CAG could introduce selection bias, and the factors influencing the decision to perform or omit preoperative CAG were not evaluated in the present study. Second, given the low prevalence of CAD, the results and associations observed in the present study should be interpreted with caution. In addition, some potential risk factors for CAD, particularly laboratory data, such as lipid profiles and fasting glucose were not measured or missing in most patients, which may have led to underestimation of their associations with CAD. Finally, as a single-center retrospective study, the findings may have limited generalizability and be subject to recall and selection bias. Future larger, multicenter, prospective studies are warranted to verify these results.

Conclusion

In the present study, only a small number of patients with VHD had concomitant CAD detected by preoperative CAG. The prevalence of CAD was significantly higher in patients with non-rheumatic VHD patients, especially degenerative VHD, compared to those with rheumatic VHD. Advanced age and cardiovascular risk factors were associated with increased risk of CAD, whereas rheumatic VHD and atrial fibrillation appeared to be protective. These findings suggest that both cardiovascular risk profiles and etiology of VHD should be considered when planning for preoperative CAG before valve surgery.

What is already known on this topic?

Assessment for coronary artery disease is generally recommended in patients with valvular heart disease who have atherosclerotic risks and are scheduled for valve surgery.

Prevalence of coronary artery disease among patients with valvular heart disease requiring valve surgery varies across patient ethnicity and the underlying etiology of VHD.

The etiology of valvular heart disease has never been considered as a factor in the decision to perform preoperative coronary angiography before valve surgery.

What this study adds?

Prevalence of coronary artery disease in large contemporary patients with valvular heart disease requiring valvular surgery is considerably low.

Patients with rheumatic valvular heart disease had significantly lower prevalence of coronary artery disease compared with patients with non-rheumatic valvular heart disease.

Rheumatic valvular heart disease is independently associated with a lower risk of coronary artery disease and should be considered in the decision-making algorithm for preoperative coronary angiography before valve surgery.

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Conflicts of interest

The authors declare no conflict of inrerest.

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