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Prevalence of Coronary Artery Disease in Patients Undergoing Valvular Heart Surgery

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ABSTRACT

Background: The risk of coronary artery disease (CAD) in different valve dysfunction has been unclear.

Methods: We reviewed patients, who underwent valve heart surgery and coronary angiography from 2008 to 2021, at our center.

Results: A total of 7,932 patients were included in the present study, and 1,332 (16.8%) had CAD. The mean age of the study cohort was 60.5±7.9 years, and 4,206 (53.0%) were male. CAD was 21.4% in aortic disease, 16.2% in mitral valve disease, 11.8% in isolated tricuspid valve disease, and 13.0% in combined aortic and mitral valve disease. Patients with aortic stenosis were older than those with regurgitation (63.6±7.4 years vs. 59.5±8.2 years, $P < 0.001$), and the CAD risks also were higher (28.0% vs. 19.2%, $P < 0.001$). The age difference was minimal (60.6±8.2 years vs. 59.5±6.7 years, $P = 0.002$) between patients with mitral valve regurgitation and stenosis, but the risks of CAD were twice high in regurgitation (20.2% vs. 10.5%, $P < 0.001$). When the type of valve impairment was not considered, non-rheumatic etiology, advanced age, male sex, hypertension, and diabetes were independent predictors of CAD.

Conclusion: In patients undergoing valve surgery, the prevalence of CAD was influenced by conventional risk factors. Importantly, CAD also was associated with the type and etiology of valve diseases.

INTRODUCTION

In patients undergoing valvular heart surgery, the underlying coronary artery disease (CAD) may significantly increase perioperative and long-term complications and mortality if left untreated. Numerous studies have proved the benefit of concomitant coronary artery bypass grafting (CABG) for patients undergoing valve surgery with CAD [Bruno 2020]. Screening and identification of patients with high risks of CAD are pivotal. Current consensus guidelines recommend coronary angiography for men aged >40 years and postmenopausal women [Writing Committee Members 2022]. Due to the complex etiology, the prevalence of CAD varies along with age and comorbidities. The risk of CAD also may differ among centers, due to socioeconomic factors and geographic influence.

Despite the ongoing studies on CAD, there has been limited data on the risk of CAD in different types of valve disease. The etiology behind the valve dysfunction may confer unique risks for atherosclerosis. Patients with calcification-related valve stenosis may be more likely to have CAD than patients with accidental leaflet prolapse. Moreover, the abnormal hemodynamics induced by valve stenosis or regurgitation may affect coronary artery consumption/supply balance. These may result in different prevalences of CAD in patients with valvular heart disease. In the present study, we sought to investigate the probabilities of undergoing CABG in patients undergoing valvular heart surgery and clarify the impact of the type of valve disease on the risk of CAD.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of Anzhen Hospital. The study was done in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study. We reviewed patients who underwent valve surgery and coronary angiography at our hospital from 2008 to 2021. Patients whose primary diagnosis was coronary artery disease were excluded from the study cohort. The present study's definition of coronary artery disease was derived from whether patients underwent concomitant CABG, which the surgeons decided, according to the preoperative coronary angiography. The diagnosis was made based on a comprehensive evaluation of patient history, preop serum studies (antibodies, erythrocyte sedimentation rate, c-reactive protein, and other tests), imaging manifestation, intraoperative observation, and finally pathological verification. Almost all removed valves underwent pathological examinations. The data on hypertension, diabetes, rheumatic valve disease, and atrial fibrillation were extracted from discharging diagnosis.

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The types of valve disease were further classified based on the valve involved and the hemodynamics of impairment. In the present study, mitral valve patients included those who underwent mitral valve surgery with or without concomitant tricuspid valve procedure, and so were the aortic valve patients. Tricuspid valve patients only included those who underwent isolated tricuspid valve procedures with or without concomitant non-valve operations. The mixed valve patients included patients who had aortic valve surgery and mitral valve surgery. Patients also were divided into the stenosis group, regurgitation group, and mixed pathophysiology group (having both stenosis and regurgitation).

Continuous variables were reported as mean ± standard deviation if normally distributed and median (interquartile) if skewed distributed. The normality was examined with the single-sample Kolmogorov–Smirnov test. Continuous data were compared with the independent t-test for normal data and Kruskal-Wallis test for skewed data. Discrete variables were reported as numbers (%) and were compared with the Chi-square test. In the multivariable logistic model, an LR forward stepwise analysis with an entry probability of 0.05 and a removal probability of 0.10 was performed. Statistical analyses and plotting were performed with IBM SPSS Statistics (version 25; IBM Software, IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 8.0; GraphPad Software, San Diego, CA, USA). Results with a P-value <0.05 were interpreted as statistically significant.

Table 1. Baseline characteristics of patients undergoing coronary angiography before valve heart surgery

Variables	Values (*N* = 7932)
Age	60.5±7.9
Male	4206 (53.0)
Diabetes	754 (9.5)
Hypertension	2276 (28.7)
Atrial fibrillation/flutter	3231 (40.7)
Concomitant CABG	1332 (16.8)
Rheumatic valve disease	2549 (32.1)
Aortic valve operation	2068
Stenosis	462
Regurgitation	872
Mixed and others	734
Mitral valve operation	4049
Stenosis	515
Regurgitation	2179
Mixed and others	1355
Isolated tricuspid valve operation	85
Aortic and mitral valve operation	1730

RESULTS

A total of 7,932 patients were included in the present study, including 2,068 patients undergoing aortic valve surgery, 4,049 patients undergoing mitral valve surgery, 85 patients undergoing isolated tricuspid valve surgery, and 1,730 patients undergoing combined aortic valve and mitral valve surgery. The mean age was 60.5±7.9 years, and 4,206 (53.0%) were male. Among the study subjects, 1,332 (16.8%) underwent concomitant CABG and were classified as patients with CAD. The baseline characteristics are shown in Table 1. (Table 1)

The association between CAD and conventional risks was first analyzed. There was an increasing trend of CAD as age increased (Figure 1A). (Figure 1) Men also had significantly increased risks of CAD compared with women of the same age (Figure 1B). As expected, hypertension (Figure 1C) and diabetes (Figure 1D) also were associated with increased risks of CAD. Interestingly, rheumatic heart disease (Figure 1E) and atrial fibrillation (Figure 1F) were associated with reduced risks of CAD when only age was controlled.

As shown in Figure 2A, there were minimal differences in age among patients with different impaired valves. (Figure 2) The etiology of the valve impairment, however, seemed quite different. Over 40% of the mitral valve disease found in patients was caused by rheumatic heart disease, including those with mixed mitral valve and aortic valve disease. In contrast, only approximately 5% of aortic valve disease and tricuspid valve impairment were due to rheumatic heart disease (Figure 2B). The prevalence of CAD also was different among the four groups, which was highest in patients with aortic valve disease (21.4%) and lowest in patients with tricuspid valve disease (11.8%) (Figure 2C). Although the difference in age between patients with aortic valve disease and mitral valve disease was only 1 year (61.3±8.2 years vs. 60.4±7.7 years, $P < 0.001$), the difference in CAD risk was 5% (21.4% vs. 16.2%, $P < 0.001$).

To clarify the impact of valve impairment on CAD prevalence, we further performed a multivariable logistic regression analysis. The results show that age (per year increment OR: 1.037, 95% CI: 1.028 - 1.045, $P < 0.001$), female sex (OR: 0.464, 95% CI: 0.406 - 0.529, $P < 0.001$), diabetes (OR: 1.940, 95% CI: 1.623 - 2.319, $P < 0.001$), rheumatic heart disease (OR: 0.781, 95% CI: 0.669 - 0.911, $P = 0.002$), hypertension (OR: 1.631, 95% CI: 1.432 - 1.857, $P < 0.001$), and the valve impaired ($P = 0.008$) were associated CAD in patients undergoing valve surgery. When aortic valve disease was chosen as the reference, mitral valve disease had a similar risk (OR: 0.993, 95% CI: 858 - 1.150, $P = 0.930$), but isolated tricuspid valve (OR: 0.653, 95% CI: 0.330 - 1.294, $P = 0.222$) and mixed aortic-mitral valve disease (OR: 0.762, 95% CI: 0.633 - 0.918, $P = 0.004$) seemed to have reduced CAD risk. It should be noted that, however, the stenosis/regurgitation category was not included in the regression model due to data complexity and this might affect the results.

In the 2,068 patients undergoing aortic valve surgery, there was no difference in age (62.0±6.9 years vs. 61.3±8.2 years, $P = 0.270$) and CAD risk (18.4% vs. 21.6%, $P = 0.422$) between rheumatic causes and non-rheumatic causes (Figure

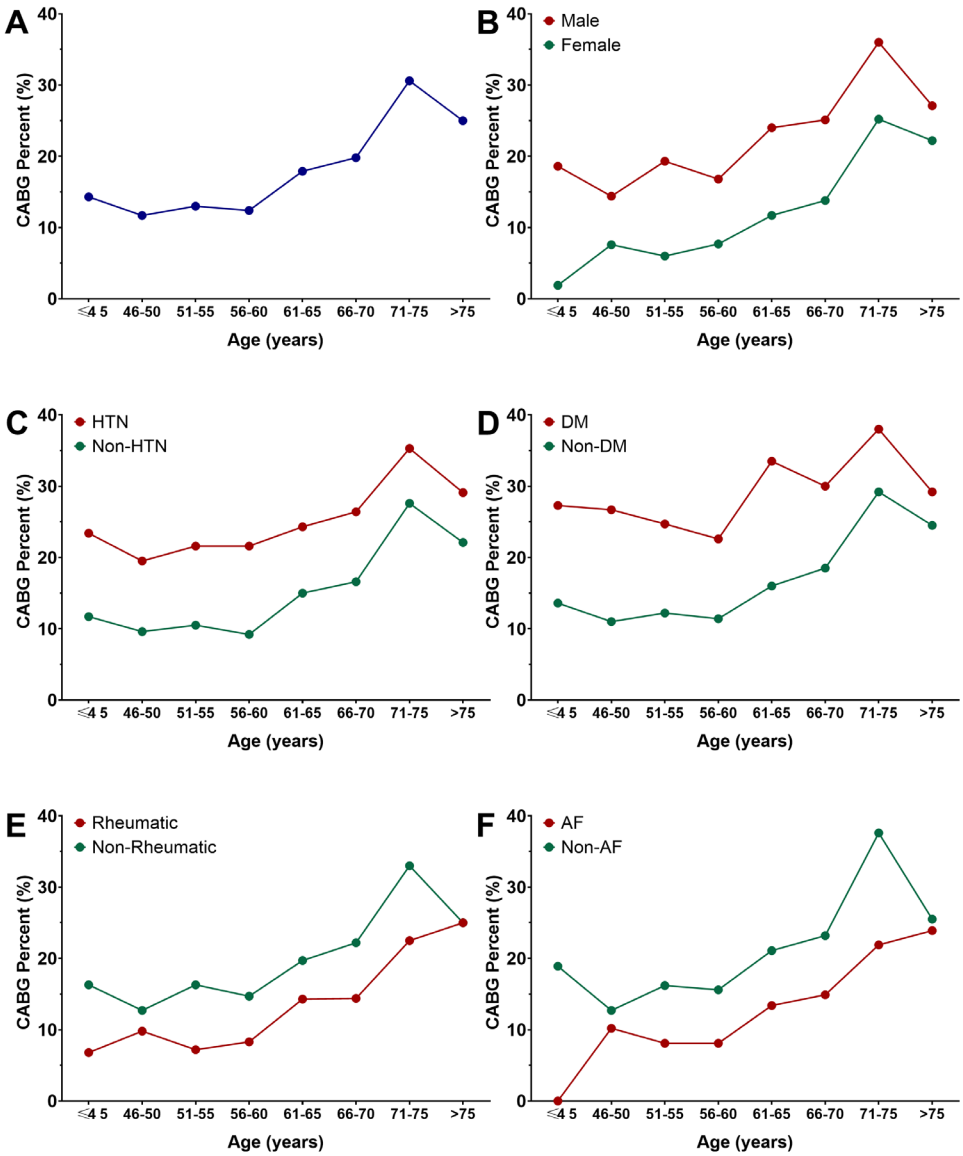

Figure 1. Prevalence of coronary artery disease stratified by conventional risk factors in patients undergoing valvular heart surgery. The prevalence of CAD increases as age increases (A). In addition, CAD is more common in men (B), patients with hypertension (C), patients with diabetes (D), non-rheumatic heart disease, and no atrial fibrillation (F).

3A). (Figure 3) We further identified 1334 patients with relatively simple impairment, including 872 with regurgitation and 462 with stenosis. Patients with aortic stenosis were significantly older than those with regurgitation (63.6±7.4 years vs. 59.5±8.2 years, $P < 0.001$), and the CAD risks also were higher (28.0% vs. 19.2%, $P < 0.001$) (Figure 3B). In patients with aortic valve regurgitation, 141 underwent aortic root replacement due to root dilation. They were younger than others (58.0±7.4 years vs. 59.8±8.4 years, $P = 0.019$) and had a trend of decreased CAD risk (14.9% vs. 20.0%, $P = 0.161$) (Figure 3C).

In 4,049 patients undergoing mitral valve operation, there was a minimal difference in age between rheumatic causes and non-rheumatic causes (60.0±7.1 years vs. 60.6±8.2 years, $P = 0.011$). The risks of CAD, however, were significantly different (12.1% vs. 19.2%, $P < 0.001$) (Figure 4A). (Figure 4) We further identified 2,179 patients with regurgitation and 515 patients with stenosis. Similarly, the age difference was minimal (60.6±8.2 years vs. 59.5±6.7 years, $P = 0.002$), but the risks of CAD were twice high in patients with regurgitation (20.2% vs. 10.5%, $P < 0.001$) (Figure 4B). To clarify the natural causes of CAD development, the analysis of regurgitation/stenosis was stratified by etiology. In patients with rheumatic heart disease, CAD was 14.3% in those with regurgitation and 11.0% with stenosis ($P = 0.235$) (Figure 4C). In patients with non-rheumatic valve impairment, the age was

comparable between regurgitation and stenosis (60.7±8.3 years vs. 59.1±7.6 years, P = 0.092); the CAD was 20.9% in regurgitation and only 7.5% in stenosis (P = 0.004) (Figure 4D).

DISCUSSION

In the present study, we investigated the prevalence of CAD in patients undergoing valvular heart surgery. The overall probability of undergoing concomitant CABG was 16.8% in this cohort with a mean age of 60. Coronary artery disease was more common in patients with conventional risks, including advanced age, male sex, hypertension, and diabetes. Notably, the risk of CAD also was significantly affected by the types and etiology of valve disease. This finding implicates the impact of hemodynamic abnormalities and left ventricular burdens on the development of CAD.

The conventional risks of atherosclerosis play an important role in the development of CAD in patients with valve diseases [Cazelli 2017; Hasselbalch 2017; Xu 2018]. The risk of CAD was steady in patients <60 years old, but increased sharply thereafter. The abnormal trends in patients <45 years and patients >75 years might be due to patient selection. We do not routinely use angiography for CAD screening in patients <50 years. Those young patients who underwent angiography generally had high risks for CAD. Moreover, many septuagenarians and octogenarians with combined valve disease and CAD may choose transcatheter valve replacement and percutaneous coronary intervention. Sex, hypertension, and diabetes are still high risks for CAD, suggesting the necessity of strict management of blood pressure and blood sugar. The interesting risk stratification by atrial fibrillation may be due to the type of valve disease. Generally, atrial fibrillation is more likely to be associated with mitral valve diseases other than aortic valve diseases.

An interesting finding in the present study was that CAD risks varied along with the type of valve disease as previously reported [Emren 2014; Sonmez 2002]. Thalji and colleagues found that patients with aortic valve diseases were more likely to have CAD than those with mitral valve diseases [Thalji 2013], which also was observed in our investigation. The direct comparison suggested aortic valve disease was associated with increased CAD. The multivariate regression, however, showed a similar CAD risk between aortic valve disease and mitral valve disease. The difference may be due to the interaction between mitral valve disease and rheumatic etiology. Of note, there were differences in the prevalence of CAD between valve regurgitation and valve stenosis. Mitral valve regurgitation was associated with a higher prevalence of CAD than mitral valve stenosis. This may be due to the increased afterload burden of the left ventricle and more coronary blood flow in aortic valve impairment and mitral valve regurgitation. We also found that CAD was more common in aortic valve stenosis than in aortic valve regurgitation. This was supported by prior studies worldwide [Atalar 2012; Manjunath 2014; Matta 2019; Narang 2009]. It is unclear if the

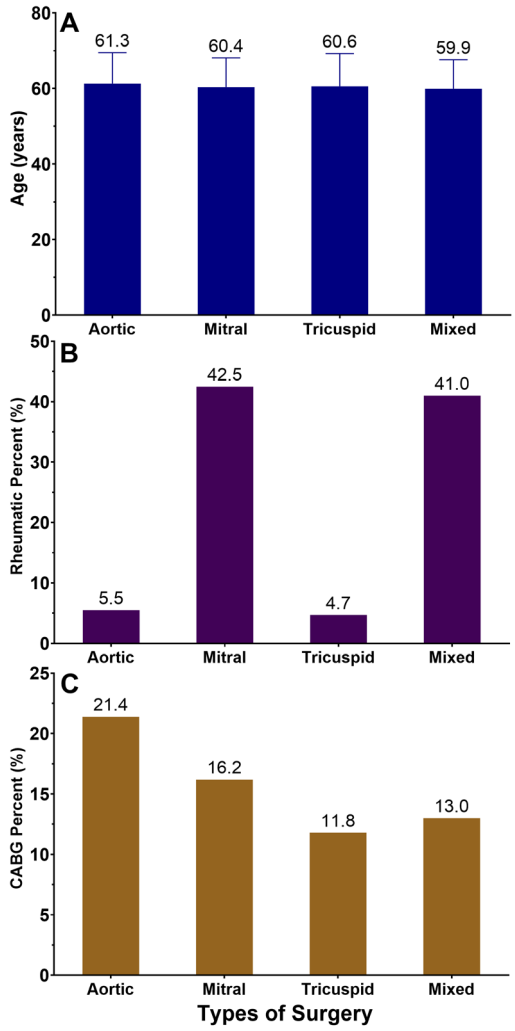

Figure 2. The age, etiology, and prevalence of coronary artery disease in patients undergoing different valvular heart surgeries. The difference in age is minimal (A). The etiology of valve disease (B) and the prevalence of coronary artery disease (C) vary significantly.

complex perfusion hemodynamics of coronary arteries in the aortic root impacts CAD development. It suggests that, however, valvular heart disease and coronary artery disease are not independent of each other. Ischemic heart disease can lead to functional mitral valve regurgitation. On the other hand, valve dysfunction can intervene in the course of CAD development. Some types of valve dysfunction, such as aortic valve stenosis, may accelerate the progress of CAD. The timing of invasive intervention should be more comprehensively decided in patients with valve disease and CAD. It should be noted that, however, the association between CAD and the type of valve dysfunction also may be due to selection bias. Patients with CAD and aortic stenosis are more likely to have severe ischemic symptoms and therefore be referred to surgery.

Another point regarding CAD in patients with valve disease is the etiology of valve dysfunction. Prior studies reported

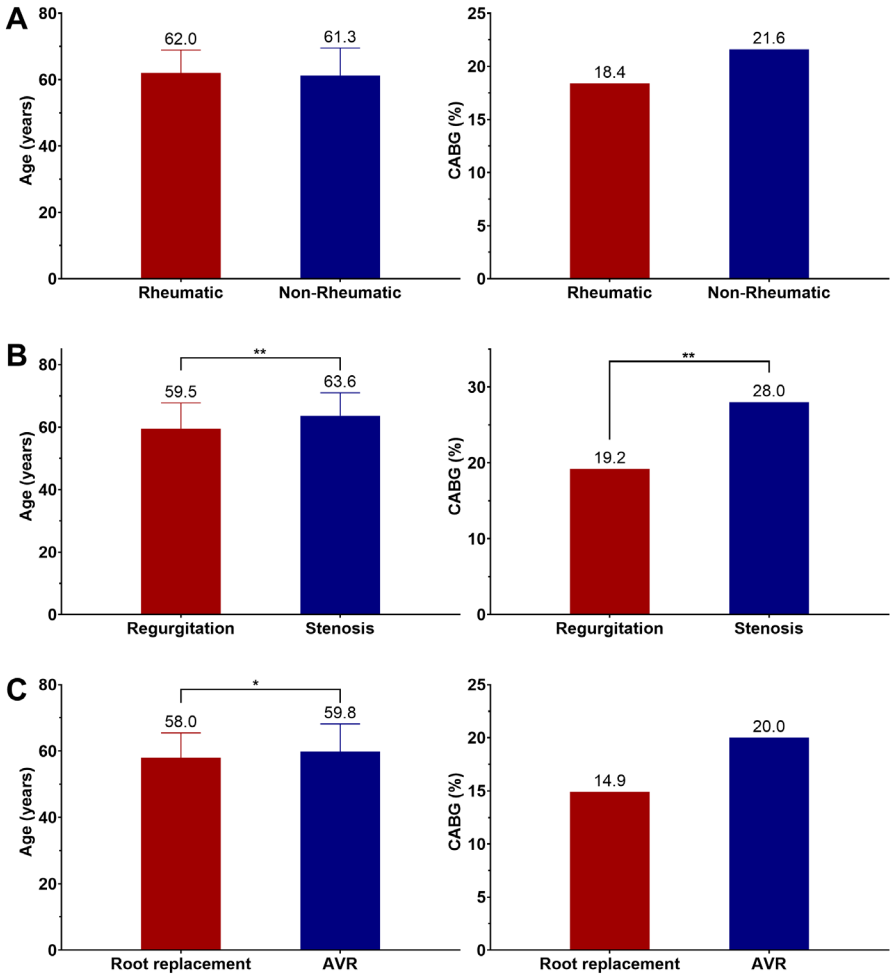

Figure 3. Age and the prevalence of coronary disease in patients undergoing aortic valve surgery. A) There is no difference in age and CAD prevalence. B) patients with aortic stenosis are older than those with regurgitation and the CAD risks also are higher. C) patients undergoing aortic root replacement are younger and have a trend of decreased CAD compared with patients undergoing isolated aortic valve replacement.

that rheumatic heart disease was associated with reduced CAD risk [Kruczan 2008; Manjunath 2014]. Rheumatic valve disease and degenerative valve disease have distinct mechanisms of valve damage. The cellular and molecular dysregulation in valve damage may also play roles in endothelial pathogenesis [Konst 2020]. Moreover, valve prolapse/chordae rupture represents a different etiology and clinical course compared with leaflet/annulus calcification. As shown in the present study, there was a trend of reduced CAD in patients with aortic root dilation compared with those with isolated aortic valve disease. It is reasonable that passive valve insufficiency due to root dilation is associated with fewer vascular lesions compared to calcification-induced valve insufficiency. Although we find a lower CAD presence in patients with rheumatic valve disease compared to others in the regression, it is hard to determine if the difference was due to rheumatic pathophysiology or a high proportion of mitral valve stenosis. Due to the limited study volume and unclear classification of the etiology, we were not able to identify the extent of the impact of etiology on CAD development. Further studies are warranted to investigate the association between the etiology of valve disease and CAD development.

There were limitations in the present study. The study was conducted in a single center, and we only included patients who had coronary angiography at our institute, which may introduce a slight selection bias to the study cohort. The definition of CAD was made by concomitant CABG and analyzed qualitatively. The degree of coronary obstruction was not available and the prevalence of mild CAD may be different from the results in the present study.

CONCLUSION

In patients with valvular heart disease undergoing surgery, the prevalence of CAD was influenced by conventional risk factors including age, sex, hypertension, and diabetes. Importantly, CAD also was associated with the type of valve disease, implicating the impact of hemodynamic impairment and the etiology of valve diseases on the coronary artery.

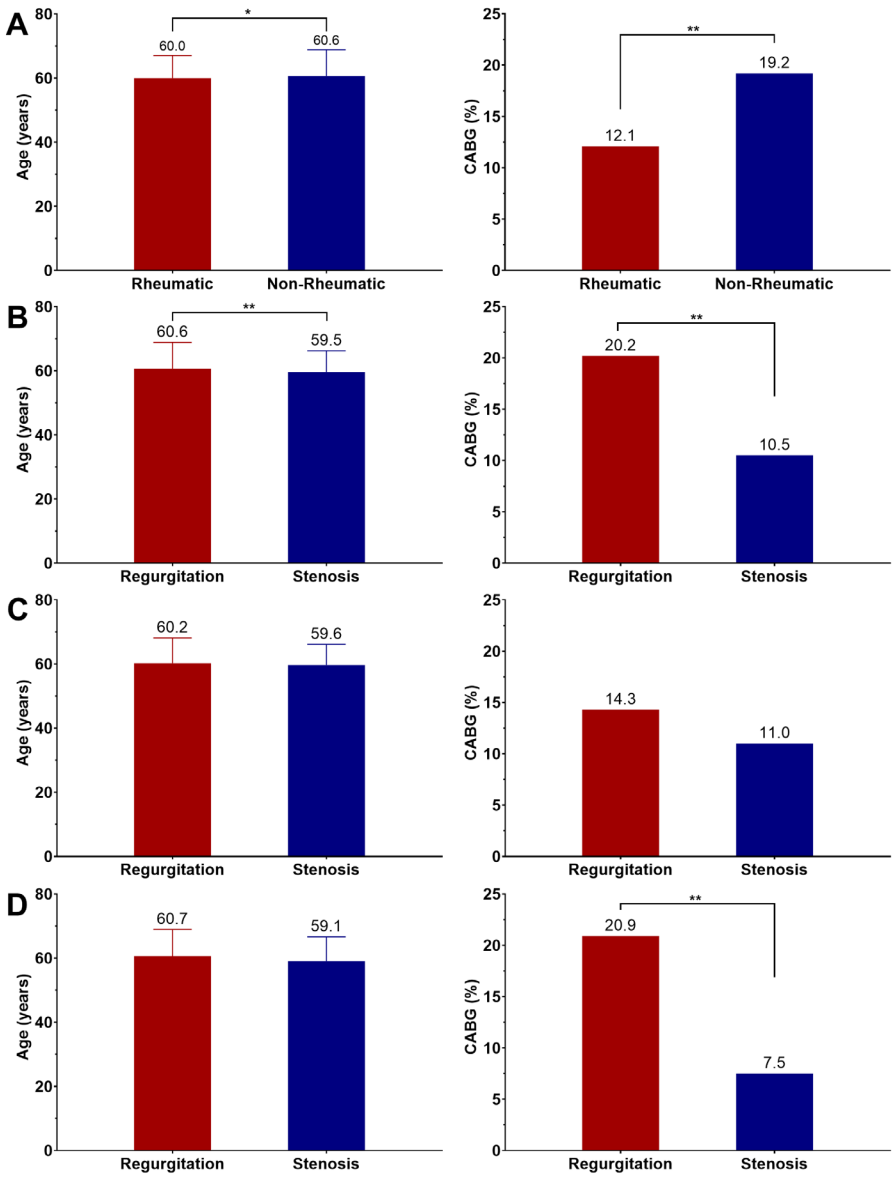

Figure 4. Age and the prevalence of coronary disease in patients undergoing mitral valve surgery. A) The difference in age between rheumatic causes and non-rheumatic causes is minimal but CAD is significantly different. B) The age difference is minimal but the CAD is twice more in regurgitation compared with stenosis. C) In patients with rheumatic heart disease, there is a trend of increased CAD in those with regurgitation. D) in patients with non-rheumatic valve impairment, the age is comparable between regurgitation and stenosis but the CAD is significantly higher in regurgitation.

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