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RESEARCH

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The correlation between coronary artery, aortic, and mitral valve calcification in patients with coronary atherosclerosis

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Abstract

Background Atherosclerosis is the underlying process causing coronary artery calcification. Pathophysiology of aortic and mitral valve calcification has several similarities with coronary atherosclerosis, but their correlation has not been clear, especially in patients with coronary atherosclerosis.

Purpose This study aims to investigate the correlation between the calcium score of the coronary arteries, aortic, and mitral valves in patients with coronary atherosclerosis.

Methods This was a cross-sectional, correlation study. Stratified randomization was done based on the coronary artery calcium score category. The calcium score was calculated using Agatston technique. Statistical tests were done to look for the correlations between the coronary artery and aortic valve calcium score, coronary artery and mitral valve calcium score, as well as coronary artery and aortic + mitral valve calcium score.

Results There are ninety-seven subjects (coronary calcium score "mild" 34 subjects, "moderate" 30 subjects, "severe" 33 subjects) with a mean age of 63.85 (± 9.80) years old. The median coronary artery calcium score was 158.7 (Agatston Unit (AU; 1–3917.7), aortic valve 12.6 AU (0–3747), and mitral valve 0.1 AU (0–1247.5 AU). There was a very weak correlation between coronary artery calcium score with aortic, mitral, and aortic + mitral valve calcium score.

Conclusions There was no statistically significant correlation between the calcium score of the coronary artery and the calcium score of the aortic valve, as well as the calcium score of the mitral valve in patients with coronary atherosclerosis. However, the secondary analysis showed a correlation between them varied depending on the severity of coronary artery calcification, which could shed light on a better understanding of the atherosclerotic process in the coronary artery, aortic, and mitral valve.

Keywords Aortic valve, Atherosclerosis, Calcification, Calcium score, Computed tomography, Coronary artery, Mitral valve

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Background

Coronary heart disease is one of the major causes of death globally. Atherosclerosis is the underlying mechanism of coronary heart disease, leading to calcified plaque formation. The coronary atherosclerosis burden is quantitatively measured by calcium scoring, which has become a routine parameter in computed tomography (CT) of the coronary arteries and has proven to be an independent predictor for morbidity and mortality [1–6].

Calcification can also occur in aortic and mitral valves, which can be quantified by CT calcium scoring technique. However, aortic and mitral valve calcium score is not routinely assessed in coronary CT study, despite their potentially hazardous effect. Aortic valve calcium score is reported to correlate well with the degree of aortic stenosis [5]. Aortic stenosis is the third most common cardiovascular disease after coronary heart disease and hypertension, whose prevalence has been increasing steadily in Asia and other regions along with the increased life expectancy of the population. Mitral valve calcification is reported to be associated with the risk of atrial fibrillation, stroke, and cardiovascular death [7–14]. Pathophysiology of aortic and mitral valve calcification is still the subjects of research. However, studies have found similar risk factors between these valve calcification and coronary atherosclerosis [7–11]. Coronary atherosclerosis is based on endothelial dysfunction and chronic inflammation. In connection with this, histopathological studies have found endothelial damage and lymphocyte infiltration accompanied by increasing inflammatory activities on calcified aortic and mitral valves [7, 15].

Coronary artery, aortic, and mitral valve calcification may share a similar mechanism. Koulaozidis et al. [11] have studied the correlation between them but did not include patients with a history of coronary heart disease. The correlation between coronary artery, aortic, and mitral valve calcification in those with coronary atherosclerosis is not clear, even though the calcification of these three structures had some similarities in the literature. The presence of their correlation could impact how radiologists report coronary CT studies including the evaluation of aortic and mitral valve calcification. Furthermore, these evaluations might affect the patient's treatment plan due to the prognostic value of mitral valve calcification. Therefore, we aimed to investigate the correlation between coronary artery, aortic, and mitral valve calcification, as measured quantitatively by calcium score, in patients with coronary atherosclerosis.

Methods

Study design and population

A cross-sectional study was conducted using secondary data obtained from coronary CT studies stored in the Picture Archiving and Communication System (PACS) from March 2012 to June 2020. All adult patients with a coronary calcium score > 0 AU were included. The presence of calcification in these patients meant that they already had coronary atherosclerosis, which led to the formation of calcified plaques. Exclusion criteria were suboptimal image quality; prior intervention/surgery in the coronary artery, aortic, or mitral valve; prior valve disease, endocarditis, or cardiomyopathy; congenital heart defects; and abnormal morphology of aortic or mitral valve. The patient's history and comorbid diseases, such as hypertension, were obtained from medical records or study comments on PACS.

Left ventricular ejection fraction (LVEF) was obtained from echocardiography studies (documented in medical records). We used the classification by Zsuzsanna et al. [6] to divide the LVEF into normal (> 55%), intermediate (50–55%), and impaired (< 50%).

The minimal sample size was 85 subjects calculated from the formula $n = \left[\frac{(z\alpha+z\beta)}{0{,}5\ln[(1+r)/(1-r)]}\right]^2 + 3$ with 95% confidence interval and 80% statistical power, using estimated correlation coefficient ($r = 0.3$) from Koulaozidis et al. [11]. We added 10–15% to the minimal sample size, increasing it to 94–98 subjects. We selected our subjects by stratified randomization, which were based on coronary calcium score written in radiology reports, categorized according to Society of Cardiovascular Computed Tomography (SCCT) classification [16]: "mild" (1–99 AU), "moderate" (100–299 AU), and "severe" (≥ 300 AU).

CT imaging protocol and post-processing

All studies were performed using a 256-slice CT scanner with synchronized electrocardiogram triggering, 3 mm slice thickness, image acquisition in craniocaudal direction with 1.5 mm increment, kV 120, kernel B35f, 280 ms gantry rotation time, and field of view 190 mm (scan range from the carina to inferior border of the heart). Coronary calcium scores in the selected subjects were re-calculated. Aortic and mitral valve calcium score measurements were done separately, and the examiners were blinded to the coronary calcium score. All calcium scores were calculated using the Agatston method, measured semiautomatically by Syngo.via software (*Siemens Healthineers; PA, USA*). Coronary calcium score was defined as the sum of calcium scores from the left main, left anterior descending, left circumflex, and right coronary arteries and their branches (Fig. 1). The aortic

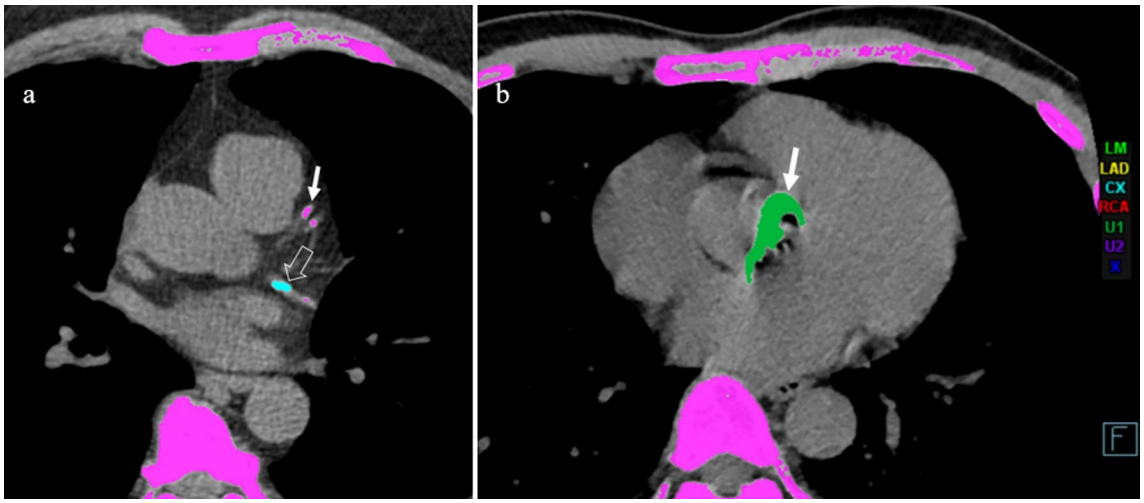

Fig. 1 Post-processing example images for **a** coronary artery calcium score, consisting of left anterior descending (*solid arrow*) and left circumflex arteries (*open arrow*), and **b** aortic valve calcium score (*solid arrow*)

valve calcium score was calculated from the sinotubular junction to aortic valve leaflets, including the left ventricular outflow tract [5]. The mitral valve calcium score was calculated in the region between the left atrium and left ventricle, including the mitral valve leaflets [12]. The sum of the aortic and mitral valve calcium scores (aortic + mitral valve calcium score) was also calculated for each subject. All calcium scores measurement was confirmed by a senior radiology consultant with more than ten years of experience in cardiac imaging (IS).

Statistical analysis

We used SPSS 20.0 software. Categorical data were presented as a number and percentage (%). Numerical data variables were presented as median and range if data are not normally distributed, or mean and standard deviation if data are normally distributed. p value < 0.050 was considered statistically significant. The associations between hypertension, diabetes mellitus, and left ventricular ejection fraction with calcification in the aortic and mitral valves were evaluated with Fisher's exact test. The correlation between coronary calcium score with aortic, mitral, and aortic + mitral valve calcium score was assessed using Spearman's rank correlation.

Results

There were 551 subjects, 244 of which met the inclusion criteria. After stratified randomization, we obtained 97 subjects, consisting of 34 with "mild" coronary calcium score, 30 with "moderate," and 33 with "severe." All subjects were of Asian ethnicity, and most of them were male (59.8%) and elderly (67%) with a mean age of 63.85 (±9.80) years old and mean LVEF of 66.98 (±16.95) %. Most subjects did not have hypertension (74.2%) or diabetes mellitus (74.2%) (Table 1). The median coronary calcium score was 158.7 AU (0.9–3917.7 AU), the aortic valve 12.6 AU (0–3747 AU), and the mitral valve 0.1 AU (0–1247.5 AU).

There was no association between hypertension with aortic valve calcification ($p = 0.563$) and mitral valve calcification ($p = 0.180$). Diabetes mellitus also had no association with aortic valve calcification ($p = 0.383$) and mitral valve calcification ($p = 0.958$). No association was found between the LVEF and aortic valve calcification ($p = 0.571$), as well as mitral valve calcification ($p = 0.064$).

There was no significant correlation between coronary calcium score with the aortic valve, mitral valve, and aortic + mitral valve calcium score. Secondary analysis in each coronary calcium score category showed a statistically significant correlation ($r = 0.52$, p 0.004) between coronary calcium score with aortic and aortic + mitral valve calcium score in the "moderate" category. There was no significant correlation between the "mild" and "severe" categories (Table 2).

Discussion

Demographic characteristics

Our study did not find any association between LVEF with aortic and mitral valve calcification. However, the proportion of LVEF impairment was increased in those with severe coronary calcification compared to other groups. Myocardial ischemia was more likely to exist in severe coronary atherosclerosis, which could be the cause of left ventricle impairment.

In the "severe" category, there is a larger percentage of male and elderly participants compared to the "mild"

Table 1 Demographic data

Characteristics	Coronary calcium score categories			Total ($n=97$)
	Mild ($n=34$)	Moderate ($n=30$)	Severe ($n=33$)	
Sex				
Male	19 (55.9%)	13 (43.3%)	26 (78.8%)	58 (59.8%)
Female	15 (44.1%)	17 (56.7%)	7 (21.2%)	39 (40.2%)
Age group				
< 60 years old	16 (47.0%)	6 (20.0%)	8 (24.2%)	30 (30.9%)
≥ 60 years old	18 (53.0%)	24 (80.0%)	25 (75.8%)	67 (69.1%)
Hypertension				
Yes	11 (32.4%)	7 (23.3%)	7 (21.2%)	25 (25.8%)
No	23 (67.6%)	23 (76.7%)	26 (78.8%)	72 (74.2%)
Diabetes mellitus				
Yes	12 (35.3%)	9 (30.0%)	4 (12.1%)	25 (25.8%)
No	22 (64.7%)	21 (70.0%)	29 (87.9%)	72 (74.2%)
LVEF				
Impaired	4 (11.8%)	3 (10.0%)	7 (21.2%)	14 (14.4%)
Intermediate	2 (5.9%)	0 (0.0%)	1 (3.0%)	3 (3.1%)
Normal	28 (82.3%)	27 (90.0%)	25 (75.8%)	80 (82.5%)

Table 2 Correlation between coronary with aortic, mitral, and aortic + mitral valve calcium score

Coronary calcium score	Aortic valve calcium score		Mitral valve calcium score		Aortic + mitral valve calcium score	
	r	*p* value	*r*	*p* value	*r*	*p* value
All subjects ($n=97$)	0.25	0.012	0.11	0.288	0.25	0.012
Categories						
Mild ($n=34$)	− 0.15	0.413	0.09	0.604	0.08	0.643
Moderate ($n=30$)	0.52	0.003	0.09	0.630	0.52	0.004
Severe ($n=33$)	0.25	0.156	0.20	0.278	0.25	0.164

category. These findings were in accordance with the multiethnic study of atherosclerosis (MESA), which found that incidence and progression of coronary artery calcification were strongly correlated with traditional risk factors for atherosclerosis, such as older age, male sex, obesity, hypertension, diabetes mellitus (DM), and family history [17]. On the other hand, the proportion of hypertensive and diabetic subjects in our study was relatively small in all coronary calcium score categories. The observed trend may appear contradictory to the conventional understanding of risk factors for atherosclerosis. However, recent studies showed that blood pressure and glucose control have an impact on the progression of coronary artery calcification, and Gronewold et al. [18] found that hypertensive subjects with well-controlled blood pressure have a similar risk to non-hypertensive subjects for the progression of coronary artery calcification. Snell-Bergeron et al. [19] found that in young adults with type 1 DM, the risk for progression of coronary artery calcification was not increased in subjects with well-controlled blood glucose, while it was increased in the poorly controlled group. Our study was conducted in a national referral hospital, and subjects were most likely given adequate treatment for hypertension and DM—this could explain why the proportion of both diseases was relatively low, even in "severe" coronary calcium score. Demographic characteristics in our study affirmed that atherosclerosis is a complex and multifactorial process, and therefore, its progression cannot be accurately predicted based only on conventional risk factors.

Correlation between coronary artery, aortic, and mitral valve

Overall, there was no significant correlation between coronary artery with aortic, mitral, and aortic + mitral valve calcium scores. Our findings were similar to Koulaozidis

et al. [11] who found only a modest correlation between coronary artery calcium score with aortic and mitral valve calcium score. However, no previous study has ever done correlation analysis in each subgroup of coronary calcium score. Further analysis of our subjects showed no significant correlation between coronary and aortic valve calcium scores in the "mild" category. A low coronary calcium score indicated a low systemic atherosclerosis burden, and thus, it was not surprising that aortic valve calcification was very low or non-existent. In the "moderate" category, there was a statistically significant correlation between coronary artery with aortic valve calcification (r 0.052, p value 0.003). It could indicate that coronary artery and aortic valve calcification were parts of the systemic atherosclerosis process, and their progression aligned with each other. However, in the "severe" category, there was no correlation between them, which might seem contradictory to our previous findings. It indicated the presence of other factors influencing aortic valve calcification, which were different from the coronary artery.

The risk of developing aortic stenosis generally increases with age. It is most commonly observed in individuals over the age of 65, with the incidence of the condition rising sharply in those over 75 [20]. In the "severe" category, we observed that < 60-year-old subjects mostly had very low aortic, as well as mitral, valve calcium scores (< 1 AU), while ≥ 60-year-old subjects tended to have higher aortic and mitral valve calcium scores. These findings were following Allison et al. [21], which found that age was independently correlated with aortic valve calcification.

We found that hypertension was independently associated with aortic valve calcification. This might be secondary to increased sheer stress on valve in hypertension [21]. The difference in histological structure between the heart valve and blood vessel might also cause different progression mechanisms of calcification in these two structures, even if both of them were based on atherosclerosis. Henein et al. showed coronary artery calcium score had a stronger correlation with the aortic root calcium score (both had the same histological structures), compared to the aortic valve calcium score [22].

Additionally, recent studies found that the progression of aortic valve calcification had two phases. The first phase was similar to atherosclerosis, strongly associated with hyperlipidemia and inflammation. It was consistent with pathological findings in early calcification of the aortic valve, which found oxidized lipoprotein and inflammatory cell infiltration. The second, advanced phase, consisted of calcium accumulation leading to ossification, which was not associated with cardiovascular risk factors, and calcium deposits would grow faster along with increasing calcium load. Calcification in this phase was surrounded by osteoblastic cells, and its progression was independent of lipid profile [23]. This might explain why in severe coronary artery calcification, there was no correlation between the aortic valve and coronary artery calcium score.

No statistically significant correlation was found between the coronary artery and mitral valve calcium score in all categories. Our findings were similar to a previous study [21]. It could indicate the influence of other factors on mitral valve calcification. Similar to the aortic valve, older age and hypertension were independently associated with mitral valve calcification [21], possibly due to decreased valve flexibility and increased shear stress, respectively. Aortic stenosis is strongly associated with the progression of mitral valve calcification [12], possibly because it caused increased shear stress on the mitral valve. Additionally, the difference in histological structure might also influence the progression of mitral valve calcification. Previous pathology study found that atheroma plaques in the mitral valve had different compositions compared to those in the coronary artery and aorta [24]. In terms of lipid deposition, atheromas in the mitral valve had a good correlation with atheromas in the coronary artery and aorta. However, atheromas in the mitral valve usually consisted of lipids only, while atheromas in the coronary artery and aorta also had calcification, thrombus, fibrosis, and ulceration. Therefore, atheromas in the coronary artery and aorta had a bigger size and number compared to the mitral valve. It could indicate that the atherosclerosis process in the mitral valve rarely causes calcified plaques, except in elevated shear stress on the mitral valve surface, e.g., severe aortic stenosis. In other words, calcification in the mitral valve would appear later than the coronary artery and aortic valve, even if their basic mechanism were the same. This could explain why there was no correlation between the coronary artery and mitral valve calcium scores in all categories. We also found that the correlation coefficient between the coronary artery and aortic + mitral valve calcium score was the same as the coronary artery and aortic valve calcium score since the mitral valve calcium score does not correlate with the coronary artery calcium score.

Potential application of aortic and mitral valve calcium score

The presence of aortic or mitral valve calcification could have a prognostic value or become a risk factor for cardiovascular events, and therefore, they might influence the patient's treatment. Mitral calcification had been shown to increase the risk of atrial fibrillation (1.4-fold), independent of left atrial size, and

associated with increased risk of severe coronary heart disease and stroke (2.1-fold), as well as cardiovascular death (1.6-fold) [14, 21]. Evaluation of mitral valve calcium score on coronary CT could be beneficial for clinicians to consider more aggressive treatment.

A previous study found that the correlation between the aortic valve and coronary artery calcium score was independent of cardiovascular risk factors [25]. It indicated that the aortic valve calcium score was not only an indicator of a degenerative process but could also be an indicator of systemic atherosclerosis burden. A combination of the aortic valve and coronary artery calcium score might be a better predictor for cardiovascular events compared to coronary calcium score alone, and potentially better for directing a patient's treatment.

Aortic valve calcification had different progression for men and women. Men had significantly higher calcium load than women. However, women had a significantly faster progression of aortic valve calcification than men, and women more frequently developed aortic stenosis symptoms than men [26]. Radiologists could suggest shorter follow-up intervals with echocardiography to evaluate the presence of aortic stenosis for female patients if they noticed aortic valve calcification on coronary CT, and calcium score could help to determine the degree of stenosis in low flow low gradient status. Early detection of aortic valve calcification could be important for preventing its progression. Pharmacological treatment with a statin to prevent calcification progression had inconsistent results [23], probably due to its two phases of progression. Statin treatment in the early phase might have good results, while in the advanced phase, it might not be beneficial, since calcification progression would be independent of lipid profile and inflammatory activity.

Study limitations

First, our subjects were selected based on medical records and PACS data, while echocardiography results for valve evaluation were not always listed in them. Therefore, a small possibility existed that subjects with aortic/mitral stenosis or regurgitation were included in our study. Hypertensive and diabetic subjects were not further differentiated based on disease control, duration, or medications. Our study also did not differentiate the aortic valve calcium score into leaflet and annular calcifications. Lastly, our study did not include non-calcified plaques, and atherosclerotic disease that had not produced calcified plaques was not evaluated.

Conclusions

Overall, there was no significant correlation between coronary artery calcium score with aortic, mitral, and aortic + mitral valve calcium score in patients with coronary atherosclerosis. However, our study indicated that the correlation between them could vary depending on the severity of coronary artery calcification and pointed out possible explanations for these findings, which could shed light on a better understanding of the atherosclerotic process in the coronary artery, aortic, and mitral valve. Aortic and mitral valve calcium scores could be an addition to coronary CT assessment. They had potential benefits (both in clinical and radiological settings) and could be easily measured at the same time with coronary calcium score.

Abbreviations

AU	Arbitrary unit
CT	Computerized tomography
DM	Diabetes mellitus
MESA	Multiethnic study of atherosclerosis
PACS	Picture archiving and communication system
SCCT	Society of cardiovascular computed tomography

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Author contributions

BMS contributed to concepts, design, definition of intellectual content, literature search, data acquisition, manuscript preparation, manuscript editing, and manuscript review. IS was involved in concepts, design, definition of intellectual content, data acquisition, manuscript editing, and manuscript review. L contributed to concepts, design, definition of intellectual content, manuscript editing, and manuscript review. JP was involved in design, definition of intellectual content, data analysis, statistical analysis, and manuscript review.

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Availability of data and materials

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

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (Protocol Number 20-05-0540). Before CT examination, all patients signed informed consent to anonymously use their imaging for research purposes.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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