ORIGINAL ARTICLE

Prognostic value of mitral annular calcification in coronary atherosclerotic disease assessed by coronary computed tomographic angiography

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Background: There is a lack of evidence on the link between mitral annular calcification (MAC) and coronary atherosclerotic diseases. The present investigation was undertaken to detect the clinical and prognostic value of MAC in coronary atherosclerotic diseases in patients who underwent coronary computed tomographic (CT) angiography. **Materials and Methods:** Two hundred and five individuals with MAC and without it (n = 85 and 120, respectively) were included in the present cross-sectional study. Coronary artery disease-reporting and data system (CAD-RADS) at coronary CT angiography was used to define the severity of coronary atherosclerotic diseases. Patients were classified into no or non-significant CAD (CAD-RADS 0–2) and significant CAD (CAD-RADS 3–5) according to the severity of coronary atherosclerotic diseases. The association of MAC with two mentioned groups (no or non-significant CAD and significant CAD) was assessed using the Chi-squared test and logistic regression in crude and adjusted models. **Results:** Patients with MAC were significantly older (69.34 ± 8.20 vs. 60.64 ± 11.42, $P < 0.001$), had lower glomerular infiltration rate (69.67 ± 20.92 vs. 78.00 ± 20.23, $P = 0.005$), and higher coronary artery calcification score (352.87 ± 495.85 vs. 200.55 ± 426.13, $P = 0.05$) in comparison to those without MAC. However, the significant difference between the two groups regarding coronary artery calcification score disappeared after adjustment for confounders ($P = 0.14$). In addition, a statistically significant positive link between MAC and significant CAD was observed (odds ratio [OR] [95% confidence interval (CI)]: 1.96 [1.04–3.71], $P = 0.04$). Nevertheless, the association became statistically insignificant after adjustment for confounders (OR [95% CI]: 1.60 [0.78–3.28], $P = 0.2$). **Conclusion:** The findings of the study revealed that MAC has no independent prognostic value in coronary atherosclerotic diseases evaluated by coronary CT angiography.

Key words: Computed tomography angiography, coronary atherosclerosis, mitral valve stenosis

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INTRODUCTION

Mitral annular calcification (MAC) is a calcific degenerative process of the fibrous structure that supports the mitral valves (MVs).[1] MAC is a frequent finding of cardiovascular imaging with a frequency varying between 5% and 42% depending on the traits of the studied population and utilized imaging modality.[2] The etiology of MAC has not been fully understood; however, some factors including, increased age, female sex, chronic kidney disease, abnormal mineral metabolism, inflammation, hypertension, and aortic stenosis have been proposed as pathophysiological determinants of the condition.[3] MAC is of great clinical relevance since it accounts for a predictor of MV dysfunction (mitral stenosis and mitral regurgitations) and cardiovascular events.[4,5]

Previous research has found a significant link between MAC with cardiovascular morbidities and mortality.[6,7] Fox *et al*., over a follow-up duration of 16 years in the Framingham Heart Study, found that the fully adjusted risks of incident cardiovascular events and cardiovascular mortality were, respectively,

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50% and 60% higher in participants with MAC.[6] An investigation conducted on elderly individuals in the cardiovascular health study also reported similar results. Such that, MAC was related to higher adjusted risks of incident congestive heart failure (71%), angina (46%), and cardiovascular mortality (79%).[7] Furthermore, Kizer *et al*. in a population-based cohort of adults without clinical cardiovascular disease showed an independent association between MAC and strokes.[8]

Some indications suggest that MAC is a form of atherosclerosis, as the main cause of heart disease and stroke, in elderly individuals.[9,10] In addition, a growing body of evidence has shown that MAC and atherosclerosis have shared risk factors, including diabetes mellitus, hypertension, obesity, smoking, and hypercholesterolemia.[11,12] A correlation has also been found between MACand atherosclerotic diseases such as aortic atheroma,[13,14] carotid artery disease,[15,16] peripheral vascular disease,[17] and coronary artery disease (CAD).[18,19] Most of these studies that have been conducted in the past three decades used conventional modalities such as echocardiography with low sensitivity to investigate the presence and severity of coronary artery atherosclerotic disease. Moreover, the predictive value of MAC compared to traditional determinants of coronary atherosclerotic diseases is a matter of debate. Thus, the present study was designed to investigate the clinical and prognostic significance of MAC in coronary atherosclerotic diseases in a group of Iranian subjects who underwent coronary computed tomographic (CT) angiography.

METHODS

Study design and population

The present cross-sectional study was performed among patients who underwent coronary CT angiography at the request of a cardiologist at CT angiographic unit of Bonyan Medical Imaging Center between March 2020 and July 2021. To calculate sample size, the prevalence of severe coronary disease was considered as 88% and 68% in patients with and without MAC respectively based on previous studies {Atar, 2003 #35}. Considering a power of 90% and type I error of 0.05 the required sample size was estimated to be 85 in each group. The study subjects were classified into two groups of patients who had and patients who did not have MAC on CT. Exclusion criteria included a history of MV surgery, percutaneous coronary intervention, and coronary artery bypass graft surgery. The protocol of the study was approved by the Ethics Committee of Isfahan University of Medical Sciences (Research ID: IR.MUI.ME.REC.1399.810). Basic demographic and clinical traits of patients including, age, sex, current smoking, weight (kg), height (cm), plasma creatinine, glomerular infiltration rate (GFR), history of diabetes, and hypertension were gathered using a standard checklist from their medical electronic profile.

Coronary computed tomographic angiography

Coronary CT angiography has been performed by a 256-slice multidetector computed tomography scan (Brilliance TM 256, Philips Medical System, Cleveland, OH, USA) with the following scan parameters: slice thickness 0.67 mm, detector size 0.625 mm, rotation time 0.27 ms, tube voltage 120 Kv, and tube current-time 180–200 mAs. Oral beta-blocker medication (50–100 mg of metoprolol) was administered to patients with a heart rate more than of 75 beats/min 1 h before coronary CT angiography acquisition. To dilate coronary arteries, 0.4 mg sublingual nitroglycerine was also administered.

Images were analyzed on a dedicated workstation (Brilliance Workspace, Philips Healthcare, Cleveland, OH, USA) by a senior radiologist. The quantitative assessment of coronary artery calcification was performed by Agatston score. To identify calcification a threshold of 130 Hounsfield units was used. Agatston score >0 in any coronary arteries was considered as coronary artery calcification. To assess the severity of CAD, as a dependent variable, a score of CAD-reporting and data system (RADS) score was assigned to each patient. The CAD-RADS scores based on the severity of coronary stenosis were as follows: CAD-RADS 0 (defined as no plaque or stenosis), CAD-RADS 1 (defined as minimal or 1%–24% stenosis), CAD-RADS 2 (defined as mild or 25%–49% stenosis), CAD-RADS 3 (defined as moderate or 50%–69% stenosis), CAD-RADS 4 (defined as severe or 70%–99% stenosis), and CAD-RADS 5 (defined as total occlusion or 100% stenosis). Finally, patients were classified into no or non-significant CAD (CAD-RADS 0–2) and significant CAD (CAD-RADS 3–5) according to the severity of coronary atherosclerotic diseases.

Statistical analysis

The normality of continuous data was evaluated using Kolmogorov–Smirnov test and Q-Q plot. Positive skewed data (coronary artery calcification score) were subjected to logarithmic transformation. Continuous and categorical variables were reported as mean ± standard deviation (SD) (or median (minimum–maximum) for nonnormally distributed data) and frequency (percentage), respectively. Basic continuous and categorical data were compared between groups by using independent samples *t*-test and Chi-squared test, respectively. Comparing coronary artery calcification score between CAD groups was done using an independent samples test and using analysis of covariance after adjustment for confounders. The association of MAC with two mentioned groups (no or non-significant CAD and significant CAD) was assessed using the Chi-squared test and logistic regression in crude

and adjusted models. The results of logistic regression were reported as odds ratio (OR) and 95% confidence interval (CI) for OR. $P \leq 0.05$ was considered as statistically significant. Statistical analysis was performed using SPSS software version 26 (IBM Corp, Armonk, NY, US).

RESULTS

Two hundred and five subjects, comprising 85 with MAC and 120 without MAC, were included in the present study. The basic characteristics of individuals with MAC are compared to individuals without MAC [Table 1]. The mean age (69.34 ± 8.20 vs. 60.64 ± 11.42, $P < 0.001$) and GFR (69.67 ± 20.92 vs. 78.00 ± 20.23, $P = 0.005$) was significantly higher in patients with MAC as compared to those without MAC. The frequency of patients with significant CAD was significantly higher in patients with MAC compared to those without MAC (53.8% vs. 46.2%, $P = 0.036$). A significant difference was also observed between the two groups regarding the frequency of hypertension (47.9% vs. 52.1%, $P = 0.024$). No significant difference was found between two groups in terms of other basic variables ($P > 0.05$). A significantly higher coronary artery calcification score was observed in patients with MAC compared to those without (mean ± SD: 352.87 ± 495.85 vs. 200.55 ± 426.13, $P = 0.05$). However, after adjustment for confounding variables, the significant difference between the two groups disappeared (mean ± SE: 300.81 ± 51.39 vs. 238.79 ± 42.16, $P = 0.14$).

The basic characteristics of subjects across CAD groups are summarized in Table 2. Patients in the group of significant CAD had a significantly higher mean age (62.92 ± 11.43 vs. 68.15 ± 8.87, $P = 0.001$) and lower GFR (77.23 ± 20.45 vs. 66.63 ± 20.27, $P = 0.001$) compared to patients in the group of no or nonsignificant CAD. There was a significant difference between the two CAD groups regarding sex (0.046) and MAC ($P = 0.036$). No significant difference was found across CAD groups regarding other basic variables ($P > 0.05$). The crude model of logistic regression analysis showed a significant positive association between MAC and significant coronary atherosclerotic diseases (OR [95% CI]: 1.96 [1.04–3.71], $P = 0.04$). However, the association became statistically insignificant after adjustment for confounders (OR [95% CI]: 1.60 [0.78–3.28], $P = 0.2$).

Table 1: Comparing basic characteristics of patients with mitral annulus calcification and without mitral annulus calcification[a]

Variable	Mitral annular calcification		P[b]
	Yes (*n*=85)	No (*n*=120)	
Age (years)	69.34±8.20	60.64±11.42	<0.001
Weight (kg)	76.77±12.95	76.56±11.21	0.901
BMI (kg/m^2)	29.18±4.37	28.09±3.85	0.063
Sex, *n* (%)			
Females	41.1	58.9	0.888
Males	42.2	57.8	
Smoking (%)	46.2	53.8	0.723
Diabetes (%)	42.9	57.1	0.788
Hypertension (%)	47.9	52.1	0.024
CAD-RADS, *n* (%)			
0–2	37.3	62.7	0.036
3–5	53.8	46.2	
GFR	69.67±20.92	78.00±20.23	0.005
Calcium score	352.87±495.85 129 (0.00–2492.00)	200.55±426.13 40.90 (0.00–3550.00)	0.05

[a]Values in table are mean±SD for continuous variables, percentage for categorical variables, and median (maximum–minimum) for nonnormal distributed variables; [b]*P*-values were obtained from independent samples *t*-test for continuous variables and Chi-square test for categorical ones. BMI=Body mass index; GFR=Glomerular filtration rate; SD=Standard deviation; CAD-RADS=Coronary artery disease-reporting and data system

Table 2: Comparing basic characteristics of patients with across groups of coronary artery disease[a]

Variable	No or nonsignificant CAD (*n*=153)	Significant CAD (*n*=52)	P[b]
Age	62.92±11.43	68.15±8.87	0.001
Weight	77.48±11.39	74.23±13.16	0.090
BMI	28.84±4.13	27.65±3.90	0.071
Sex, *n* (%)			
Females	78.7	21.3	0.046
Males	65.6	34.4	
Smoking (%)	76.9	23.1	0.845
Diabetes (%)	66.7	33.3	0.081
Hypertension (%)	74.4	25.6	0.920
MAC (%)			
Yes	67.1	32.9	0.036
No	80.0	20.0	
GFR	77.23±20.45	66.63±20.27	0.001

[a]Values in table are mean±SD for continuous variables and percentage for categorical variables. [b]*P*-values were obtained from independent samples *t*-test for continuous variables and Chi-squared test for categorical ones. BMI=Body mass index; CAD=Coronary artery disease; GFR=Glomerular filtration rate, MAC=Mitral annular calcification; SD=Standard deviation

DISCUSSION

The results of the present study indicated that there is no independent association between MAC, assessed by coronary CT angiography, and the risk of coronary atherosclerotic diseases. However, the association was confounded by variables such as age, sex, GFR, and diabetes mellitus. To the best of our knowledge, no study has been conducted before on the association between MAC and coronary atherosclerotic diseases evaluated by CT angiography as an established tool for noninvasive assessment of coronary arteries.[20]

The relationship between MAC and cardiovascular risk factors such as age, female gender, diabetes mellitus, and increased body mass index has been shown in the multi-ethnic study of atherosclerosis.[21] Some other studies

have also shown the relationship between obesity and diabetes mellitus with MAC.[22,23] These findings largely explain the relationship between MAC and atherosclerotic diseases. In addition, a number of previous studies have investigated the relationship between MAC and cardiovascular events. Our results are in agreement with those of Bhatt *et al*. who found no independent association between MAC and the presence of lesions with severe stenosis in a retrospective cohort study of 481 patients based on cardiac catheterization and transthoracic echocardiograms.[24] However, some studies have reported contrary findings. Several studies have demonstrated that MAC is correlated with increased risk of CAD on echocardiography.[19,25] The differences in studies population and diagnostic criteria for coronary atherosclerotic diseases and MAC can partly explain the contradictory results. Moreover, these studies have used electrocardiography as a diagnostic method, which, compared to CT angiography, does not have sufficient sensitivity and specificity to detect MV and coronary artery calcification.[26-28] The results of a study by Tenenbaum *et al*. indicated that advanced MAC (calcium deposit thickness ≥ 5 mm), but not trivial MAC, is correlated with severe coronary calcification on spiral CT and CAD according to clinical data.[29] Although we did not assess the relationship between the severity of MAC and the risk of CAD; which needs to be investigated in future studies.

The present study has several limitations that should be acknowledged. This was a cross-sectional document-based study on a relatively small number of patients which might not be a good representation. Although a number of confounders such as age, sex, GFR, and diabetes mellitus have been controlled in the current study, the effect of uncontrolled covariates such as family history of coronary atherosclerotic diseases, dyslipidemia, renal dysfunction, and physical activity remained to be assessed. However, as far as we know, this is the first study that has investigated the association between MAC and coronary atherosclerotic diseases in patients who have examined with coronary CT angiography.

CONCLUSION

The findings presented in this study showed a significant association between MAC and severe coronary atherosclerotic diseases in patients who underwent CT angiography; however, the association was confounded by several factors including age, sex, GFR, and diabetes mellitus. Further prospective studies on large populations are required to confirm the findings.

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Conflicts of interest
There are no conflicts of interest.

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