Van Med J 31 (2): 102-111, 2024
DOI: 10.5505/vmj.2024. 43534

Mitral Annular Calcification as a Challenging Concomitant Factor for Patients Underwent TAVI

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Abstract

Introduction: Mitral annular calcification (MAC) is commonly observed in patients with cardiovascular diseases and has been associated with adverse clinical outcomes. This study aims to clarify the prevalence and impact of MAC on peri-procedural, in-hospital, and long-term outcomes in high-surgical-risk patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI).

Materials and Methods: 403 patients underwent TAVI for severe AS was retrospectively evaluated. MAC was identified on transthoracic-echocardiography and confirmed on computed-tomography in 45.4% of patients. Clinical outcomes, including in-hospital mortality and two-year follow-up mortality, were evaluated, and potential predictors of MAC and mortality were analyzed using logistic and Cox regression models.

Results : MAC was more prevalent in older, female patients with atrial fibrillation. Although the presence of MAC did not correlate with increased in-hospital (unadj OR: 1.77, 95% CI (0.88-3.54)) or long-term mortality (unadj OR: 0.73, 95% CI (0.40-1.33)), it was associated with a higher requirement for post-TAVI permanent pacemaker implantation (PPI) and moderate-to-severe paravalvular aortic regurgitation (PVAR). Multivariate analysis revealed left ventricular ejection fraction (adj HR: 0.97, 95% CI (0.94-0.99)), mean transvalvular gradient, (adj HR: 1.02, 95% CI (1.00-1.04)) systolic pulmonary artery pressure (adj HR: 1.04, 95% CI (1.01-1.0.6)) and severe PVAR (adj HR: 3.16, 95% CI (1.25-7.96)) as independent predictors of long-term mortality.

Conclusion: In patients with severe AS undergoing TAVI, MAC is a marker of complex cardiac pathology but does not independently predict mortality. However, its presence may increase the need for PPI and the incidence of PVAR, which warrants attention in postoperative management and follow-up.

Key words: Mitral valve; aortic valve stenosis; transcatheter aortic valve replacement; treatment outcome; aortic regurgitation.

Introduction

Mitral annular calcification (MAC) is a degenerative process characterized by dense calcium accumulation in mitral valve (MV) annulus. While its frequency increases with age, the prevalence in the general population varies between 8-15% (1). In elderly patients with known cardiovascular disease (CVD), the frequency can reach up to 42% (2). Although the pathophysiological mechanism behind the development of MAC is not entirely clear, the increased frequency of MAC observed in individuals with atherosclerotic CVD risk factors suggests that these two clinical conditions may arise in a similar manner (3,4). In parallel, the close relationship between MAC and both carotid and peripheral artery disease further corroborates this hypothesis (5). Additionally, clinical scenarios that induce increased left ventricular (LV) intracavitary pressure and LV hypertrophy, such as in hypertension or severe aortic stenosis (AS), may also induce the development of MAC (6). Beyond atherosclerosis, chronic kidney disease (CKD) has also been described as a contributor to tissue calcium accumulation and hence responsible for the pathogenesis of MAC (7). Lastly, large cohort studies refer female gender is a major risk factor for MAC (3,4,6). MAC is often incidentally detected, yet the diagnosis of MAC can be easily made with transthoracic-echocardiography (TTE). On TTE, MAC appears as a hyperechoic structure, with acoustic shadowing, situated in the atrioventricular groove and usually located in the posterior MV annulus (8,9). However, computed-tomography (CT) is not only superior to TTE in recognizing the presence of MAC, but also ensures the extent and degree (10,11). In daily practice, presence of MAC is associated with a series of clinically significant adverse events,

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Received: 02.01.2024, Accepted: 25.03.2024

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including increased cardiovascular mortality, MV functional abnormalities, and various arrhythmias, among which atrial fibrillation (AF) is predominant. Furthermore, the presence of MAC in patients undergoing surgery for MV dysfunction is associated with increased intraoperative complications and mortality (1). This study investigates the impact of the presence of MAC on peri-procedural, in-hospital, and postoperative 2-year long-term follow-up clinical outcomes in patients treated with transcatheter aortic valve implantation (TAVI).

Materials and Methods

Study population: nderwent TAVI using different transcatheter-heart valves (THV) in a single-center between 2015 and 2021, confirmed by TTE for symptomatic severe AS. Detailed pre-procedural clinical assessments and imaging procedures were conducted. Additionally, the majority of patients underwent diagnostic coronary angiography primarily via left-transradial approach, followed by angioplasty when necessary. Decision for revascularization was made according to the angiographic features of the lesions. After excluding 20 patients who had previous MV interventions, all analyses were performed on the remaining 403 patients (mean age 78.2±8.4, 205 (50.9%) female). Figure-1 describes the flow-chart of the study. The postoperative 2-year long-term clinical data of patients who reached the in-hospital survival endpoint were also evaluated. Preprocedural **Imaging and definition of MAC:** Detailed TTE evaluations within the last week prior to the procedure were carried out by experienced cardiologists using Vivid E9, GE, USA. The acquisition of echocardiographic measurements and confirmation of the diagnosis of severe AS adhered to the recommendations of the American Society of Echocardiography (12). To establish the presence and extent of MAC, which is a principal element of the study, pre-TAVI planning CT-angiographies with intravenous contrast (Omnipaque 350; GE Healthcare, USA) comprising 512-slices (SOMATOM Force, Siemens, Germany) were reviewed. Accordingly, MAC, identified as a hyperechoic structure with acoustic shadowing located at the posterior MV annulus of varying degrees, was observed in 205 (50.8%) of the 403 patients included in the study via TTE. Subsequently, CT images of these patients were evaluated in more detail in different sections to confirm the presence of MAC and to assess its distribution. Inspired by Carpentier's surgical classification, the presence of calcification extending to at least 1/3 of the posterior MV annulus on the transverse-plane CT image was accepted as the presence of MAC in this study (n=183, 45.4%) (13) (Figure-2).

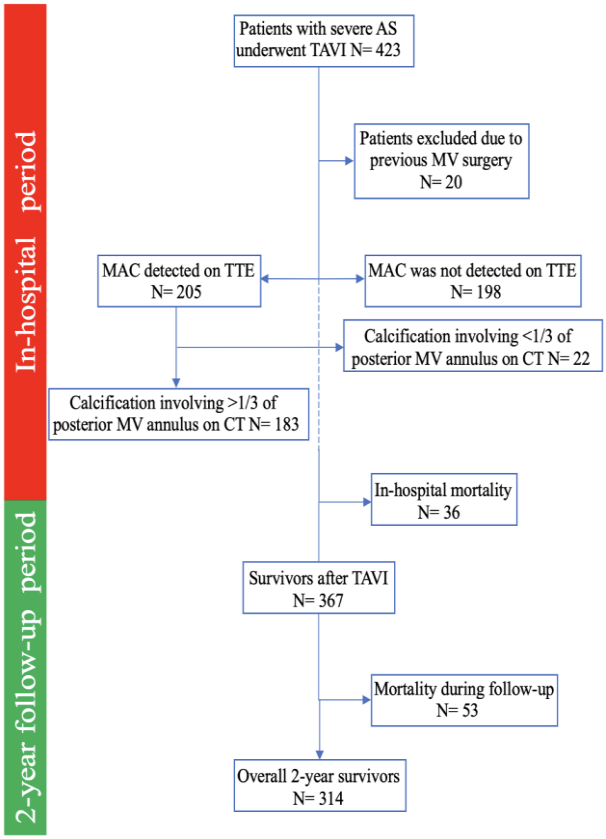

Figure 1: Flow-chart of the study according to timeline.

Application of TAVI and follow-up process: The TAVI procedures were executed through the transfemoral-route using four different THVs: balloon-expandable (S3 and XT™ from Edwards Lifesciences, CA, USA, and Myval™ from Meril, India) and self-expandable (CoreValve® Evolut™-R, Medtronic, Minneapolis, USA, and Portico, St. Jude Medical, Minneapolis, USA). These procedures were performed in line with the recommended techniques, under either general anesthesia or deep sedation. For hemostasis at the femoral access site, devices such as the ProGlide™ system (Abbott Vascular, CA, USA) and/or Angioseal® (St. Jude Medical, MN, USA) were utilized. In-hospital and long-term complications were evaluated based on the Valve Academic Research Consortium (VARC-3) criteria (14). Within the first month post-procedure, a TTE examination was repeated for every patient, followed by subsequent outpatient follow-ups in six-month intervals.

Study endpoints: The primary endpoints of the study are in-hospital mortality and mortality during the follow-up period.

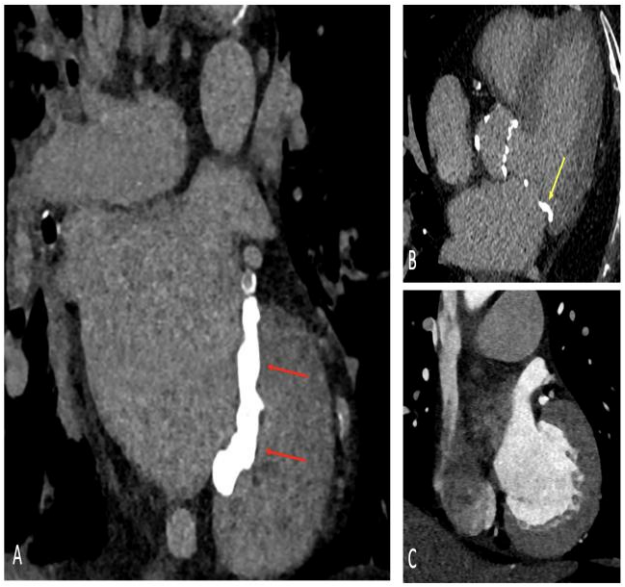

Figure 2: Severe mitral annular calcification (MAC) (red arrow), involving more than 1/3 of the posterior mitral valve annulus (A). Mild degree MAC (yellow arrow), in which less than 1/3 of the annulus is affected (B). Absence of calcification on the mitral valve annulus (C).

Data collection and ethics: Clinical data for the in-hospital period and the 2-year postoperative long-term follow-up were recorded using the hospital's digital archive and the Ministry of Health's Joint Electronic Database. Written consent was taken from all patients before interventions. The study approved from Medipol University's ethics committee (Approval Date: 12.10.2023, No:2023/841) and was conducted in the Declaration of Helsinki.

Statistical analyses: The normality assumption for continuous data was assessed using the Kolmogorov-Smirnov test and by examining the plotted histogram curves. Descriptive statistics for continuous data that were normally distributed are presented as mean±standard deviation within the article and tables, while non-normally distributed data are presented as median and interquartile ranges (25-75). Categorical data are expressed as counts and percentages. Comparisons between different groups, such as those with and without MAC, were made using independent sample t-tests, Mann-Whitney U tests, Chi-square tests, and Fisher's exact tests where appropriate. A p-value of 0.05 was set as the threshold for statistical significance. Variables associated with the presence of MAC and mortality during the follow-up among in-hospital survivors and their unadjusted odds ratios (ORs) and 95% confidence interval (CI) were determined by univariate binary logistic regression analysis. The independent predictors of these two outcomes and their adjusted ORs were determined by mutiple binary logistic regression analysis with the inclusion of variables that reached statistical significance in the univariate analysis. The variables associated with mortality during the follow-up period and their unadjusted hazard ratios (HRs) were determined by univariate Cox regression analysis. Accordingly, adjusted HRs and 95% CI were found by multivariate Cox regression analysis with variables that were found to reach statistical significance. Differences in long-term survival according to the presence of MAC and paravalvular aortic regurgitation (PVAR) were illustrated using Kaplan-Meier curves, and p-values were determined using the log-rank method. All mentioned analyses were performed using IBM SPSS Statistics-26 (IBM, NY, USA).

Results

Baseline features in terms of MAC: The comparison of baseline clinical, echocardiographic, procedural, and laboratory characteristics of the study population concerning the presence of MAC is summarized in Table-1. Demographic characteristics showed that patients with MAC were of advanced age and more frequently female, and they exhibited a higher prevalence of AF and lower glomerular filtration rates (GFR) ($p<0.05$ for all). No statistically significant differences were observed between the two groups in other demographic characteristics. Pre-procedural TTE revealed that patients with MAC had significantly higher mean and peak aortic valve gradients, systolic pulmonary artery pressure (sPAP), and a smaller aortic valve area ($p<0.05$ for all). While there was no difference between the two groups in terms of moderate-to severe aortic regurgitation, mitral and tricuspid regurgitations were more frequently observed in the MAC group. In terms of procedural features, slightly larger THVs were implanted in the non-MAC group. This can be explained by the increased LV hypertrophy and more extensive left ventricular outflow tract (LVOT) calcification in patients with MAC, resulting in a narrower aortic annulus diameter. Moreover, it was noted that, although not statistically significant, there was a more frequent need for pre and post-dilation in the patient population with MAC due to intense calcification.

Predictors of MAC: In the univariate-regression analysis, predictors that reached statistical significance for determining the presence of MAC were age, female gender, AF, peak and mean aortic gradient, aortic valve area, and GFR. These were subsequently included in the multivariate analysis, which identified AF (adjusted OR: 2.04, 95% CI (1.29-3.21), p=0.002), female gender

Table 1: Baseline clinical, echocardiographyc, procedural and laboratory characteristics of the study population regarding the presence of MAC

Variable	Without MAC (n=220, 54.6%)	With MAC (n=183, 45.4%)	Overall Group (n=403)	p value
Baseline Characteristics				
Age [Mean±SD]	76.5±9.1	80.3±6.9	78.2±8.4	0.001
Gender (female) [n(%)]	95 (43.2%)	110 (60.1%)	205 (50.9%)	0.001
BMI (kg/m²) [Mean±SD]	27.2±4.4	26.8±4.1	27±4.3	0.764
Hypertension [n(%)]	186 (84.5%)	162 (88.5%)	348 (86.4%)	0.247
Diyabetes [n(%)]	71 (32.3%)	73 (39.9%)	144 (35.7%)	0.112
Atrial Fibrillation [n(%)]	61 (27.7%)	82 (44.8%)	143 (35.5%)	0.001
COPD [n(%)]	82 (37.3%)	73 (39.9%)	155 (38.5%)	0.591
Previous CVA [n(%)]	10 (4.5%)	13 (7.1%)	23 (5.7%)	0.270
CAD [n(%)]	144 (65.5%)	131 (71.6%)	275 (68.2%)	0.188
Previous CABG [n(%)]	30 (13.6%)	33 (18%)	63 (15.6%)	0.226
STS score [median (min-max)]	9 (6-14)	8 (6-12)	8 (6-13)	0.249
Echocardiographyc Measures				
LVEF (%) [Mean±SD]	49.8±13.3	52±11	50.8±12.4	0.230
Max Aortic Gradient (mmHg) [Mean±SD]	70.7±19.4	76.6±21.2	73.4±20.5	0.006
Mean Aortic Gradient (mmHg) [Mean±SD]	45.5±12.7	49.2±14.2	47.2±13.5	0.007
Aortic Valve Area (m²) [Mean±SD]	0.74±0.14	0.68±0.15	0.71±0.15	0.001
Low-Flow Low-Gradient Severe AS [n(%)]	29 (13.2%)	16 (8.7%)	45 (11.2%)	0.159
Mean transmitral gradient (mmHg) [Mean±SD]	0.89±0.38	1.32±0.55	1.08±0.51	0.001
Moderate to severe AR [n(%)]	96 (43.6%)	91 (49.7%)	187 (46.4%)	0.222
Moderate to severe MR [n(%)]	128 (58.2%)	145 (79.2%)	273 (67.7%)	0.001
Moderate to severe TR [n(%)]	161 (73.2%)	151 (82.5%)	312 (77.4%)	0.026
sPAP (mmHg) [Mean±SD]	43±11.3	45±11	43.9±11.2	0.047
TAPSE (cm) [Mean±SD]	1.91±0.29	1.88±0.24	1.89±0.27	0.314
LA diameter (cm) [Mean±SD]	4.3±0.6	4.3±0.5	4.3±0.6	0.210
Procedural Features				
VIV TAVI [n(%)]	7 (3.2%)	10 (5.5%)	17 (4.2%)	0.256
General Aneshesia [n(%)]	39 (17.7%)	37 (20.2%)	76 (18.9%)	0.524
Type of THV				
• Sapien [n(%)]	87 (39.5%)	64 (35%)	151 (37.5%)	
• Corevalve [n(%)]	111 (50.5%)	106 (57.9%)	217 (53.8%)	0.303
• Portico [n(%)]	13 (5.9%)	10 (5.5%)	23 (5.7%)	
• Myvall [n(%)]	9 (4.1%)	3 (1.6%)	12 (3%)	
THV Size (mm) [median (min-max)]	29 (26-29)	26 (26-29)	27 (26-29)	0.006
THV Implantation Success [n(%)]	215 (97.7%)	180 (98.4%)	395 (98%)	0.650
Sheat size (F) [median (min-max)]	16 (14-18)	16 (14-18)	16 (14-18)	0.026
Predilatation [n(%)]	60 (27.3%)	62 (33.9%)	122 (30.3%)	0.151
Postdilatation [n(%)]	49 (22.3%)	50 (27.3%)	99 (24.6%)	0.241
Hospitalisation (days) [median (min-max)]	4 (3-7)	4 (3-7)	4 (3-7)	0.778
Laboratory				
Hemoglobin (g/dL) [Mean±SD]	11.6±1.5	11.8±7.6	11.7±5.2	0.019
Hematocrite [Mean±SD]	34.7±4.5	33.6±5.1	34.2±4.8	0.020
Creatinine (mg/dL) [median (min-max)]	1 (0.82-1.35)	1 (0.85-1.4)	1 (0.84-1.36)	0.387
GFR (mL/min/1.73 m²) [median (min-max)]	75.8 (53.7-90.3)	65 (46-83)	70.8 (49-88)	0.003

MAC: Mitral annular calcification, **BMI:** Body mass index, **COPD:** Chronic obstructive pulmonary disease, **CVA:** Cerebrovascular attack, **CAD:** Coronary artery disease, **CABG:** Coronary artery bypass graft, **STS:** Society of Thoracic Surgeons, **LVEF:** Left ventricle ejection fraction, **AS:** Aortic stenosis, **AR:** Aortic regurgitation, **MR:** Mitral regurgitation, **TR:** Tricuspid regurgitation, , **sPAP:** Systolic pulmonary artery pressure, **TAPSE:** Tricuspid annular plane systolic excursion, **LA:** Left atrium, **VIV TAVI:** Vale-in-valve transcatheter aortic valve implantation, **THV:** Transcatheter heart valve, **F:** French, **GFR:** Glomerular filtration rate, **SD:** Standard Deviation.

(adjusted OR: 1.8, 95% CI (1.16-2.78), p=0.008), and age (adjusted OR: 1.06, 95% CI (1.02-1.09), p<0.001) as the strongest predictors of MAC (Table-2).

Table 2: Univariate and multiple binary logistic regression analysis for predicting MAC

	Predictors of MAC			
	Univariate		Multiple	
	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age	1.06 (1.03 – 1.09)	0.001	1.06 (1.02 – 1.09)	0.001
Female sex	1.98 (1.33 – 2.95)	0.001	1.8 (1.16 – 2.78)	0.008
Atrial Fibrillation	2.11 (1.39 – 3.20)	0.001	2.04 (1.29 – 3.21)	0.002
Max Aortic Gradient (mmHg)	1.01 (1.00 – 1.02)	0.005	1.00 (0.97 – 1.03)	0.622
Mean Aortic Gradient (mmHg)	1.02 (1.00 – 1.03)	0.009	0.99 (0.95 – 1.04)	0.849
Aortic Valve Area (m^2)	0.06 (0.01 – 0.27)	0.001	0.09 (0.01 – 0.56)	0.009
GFR (mL/min/1.73 m^2)	0.98 (0.98 – 0.99)	0.004	0.99 (0.98 – 1.00)	0.130

MAC: Mitral annular calcification, **OR:** Odds ratio, **GFR:** Glomerular filtration rate

Table 3: In-hospital and long-term outcomes of the study population regarding the presence of MAC.

Variable	Without MAC n (%)	With MAC n (%)	Overall Group n (%)	p value
In-hospital mortality	15 (6.8%)	21 (11.5%)	36 (8.9%)	0.103
Mortality during follow-up	33 (15%)	20 (10.9%)	53 (13.2%)	0.229
Overall 2-year mortality	48 (21.8%)	41 (22.4%)	89 (22.1%)	0.888
Moderate to severe PVAR	31 (15.1%)	75 (46.3%)	106 (28.9%)	0.001
Moderate to severe MR	113 (55.1%)	118 (72.8%)	231 (62.9%)	0.001
Moderate to severe TR	117 (57.1%)	103 (63.6%)	220 (59.9%)	0.207
Permanent pacemaker implantation	12 (5.5%)	21 (11.5%)	33 (8.2%)	0.028
Major bleeding	31 (14.1%)	28 (15.3%)	59 (14.6%)	0.732
Minor bleeding	28 (12.7%)	34 (18.6%)	62 (15.4%)	0.105
Overall vascular complication	44 (20%)	45 (24.6%)	89 (22.1%)	0.269
Major vascular complication	23 (10.5%)	18 (9.8%)	41 (10.2%)	0.838
Minor vascular complication	20 (9.1%)	25 (13.7%)	45 (11.2%)	0.147
Periprocedural MI	2 (0.9%)	3 (1.6%)	5 (1.2%)	0.510
Periprocedural stroke	7 (3.2%)	5 (2.7%)	12 (3%)	0.791
Cardiac tamponade	3 (1.4%)	4 (2.2%)	7 (1.7%)	0.529
Need for urgent surgery	10 (4.5%)	5 (2.7%)	15 (3.7%)	0.338
	Mean ± SD	Mean ± SD	Mean ± SD	
LVEF (%)	51.1±12.8	54±10.1	52.4±11.7	0.107
Mean THV gradient (mmHg)	11.7±7.9	11.2±6	11.5±7.1	0.216
sPAP (mmHg)	39.4±9.9	40.3±10.6	39.8±10.2	0.483

MAC: Mitral annular calcification**, LVEF:** Left ventricle ejection fraction, **THV:** Transcatheter heart valve, **PVAR:** Paravalvular aortic regurgitation, **MR:** Mitral regurgitation, **TR:** Tricuspid regurgitation, **sPAP:** Systolic pulmonary artery pressure, **MI:** myocardial infarction.

In-hospital and long-term outcomes: In-hospital, post-discharge follow-up, and 2-year overall mortality rates among the 403 patients included in the study were 36 (8.9%), 53 (13.2%), and 89 (22.1%), respectively, with no relationship found between the presence of MAC and mortality. Furthermore, no statistically significant differences were seen between the two groups regarding peri-procedural adverse events such as major and minor bleeding, vascular complications, myocardial infarction, stroke, and tamponade. However, in patients undergoing TAVI, the rates of moderate-to severe PVAR and permanent pacemaker implantation (PPI), which are of significant prognostic importance, were found to be significantly higher in the population with MAC (p<0.001 and p=0.028, respectively) (Table-3). In patients who reached the endpoint of in-hospital survival (n=367, 91.1%), univariate-and multivariate-regression analyses investigating the predictors of deaths occurring during the 2-year follow-up period (n=53, 13.2%) are summarized in Table-4. The presence of MAC did not have a statistically significant effect on in-hospital mortality (unadjusted OR: 1.77, 95% CI (0.88-3.54), p=0.106) and was not a predictor of

mortality during the follow-up period (unadjusted OR: 0.73, 95% CI (0.40-1.33), p=0.311). Kaplan-Meier curves drawn according to the initial presence of MAC also did not reveal a difference

Table 4a: Univariate and multiple binary logistic regression analysis for mortality during follow-up among in-hospital survivors (n=367).

	Follow-up Mortality			
	Univariate		Multiple	
	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Age	1.04 (1.00 - 1.08)	0.031	1.04 (0.99 – 1.09)	0.066
LVEF (%)	0.96 (0.94 – 0.98)	0.002	0.96 (0.94 – 0.99)	0.018
GFR (mL/min/1.73 m²)	0.98 (0.97 – 0.99)	0.008	0.99 (0.98 – 1.01)	0.662
Mean THV Gradient (mmHg)	1.04 (1.00 – 1.09)	0.037	1.04 (1.00 – 1.08)	0.031
Moderate to severe PVAR	2.34 (1.28 – 4.25)	0.005	1.77 (0.87 – 3.57)	0.110
sPAP	1.06 (1.02 – 1.09)	0.001	1.05 (1.01 – 1.08)	0.009

OR: Odds ratio

Table 4b: Univariate and multiple binary logistic regression analysis for mortality during follow-up among in-hospital survivors regarding ordinal PVAR (n=367).

	Follow-up Mortality			
	Univariate		Multiple	
	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
No PVAR (reference)	-	-	-	-
Mild PVAR (categorical)	0.88 (0.40 – 1.93)	0.753	0.73 (0.29 – 1.80)	0.498
Moderate PVAR (categorical)	1.43 (0.61 – 3.35)	0.399	0.86 (0.30 – 2.42)	0.778
Severe PVAR (categorical)	5.43 (2.03 – 14.55)	0.001	3.86 (1.26 – 11.82)	0.018

[a]Multiple analyses were built adjusting for age, LVEF, GFR, mean THV gradient and sPAP. **OR:** Odds ratio, **LVEF:** Left ventricle ejection fraction, **GFR:** Glomerular filtration rate, **THV:** Transcatheter heart valve, **PVAR:** Paravalvular aortic regurgitation, **MAC:** Mitral annular calcification, **PPI:** Permanent pacemaker implantation, MR: Mitral regurgitation, **TR:** Tricuspid regurgitation, **sPAP:** Systolic pulmonary artery pressure.

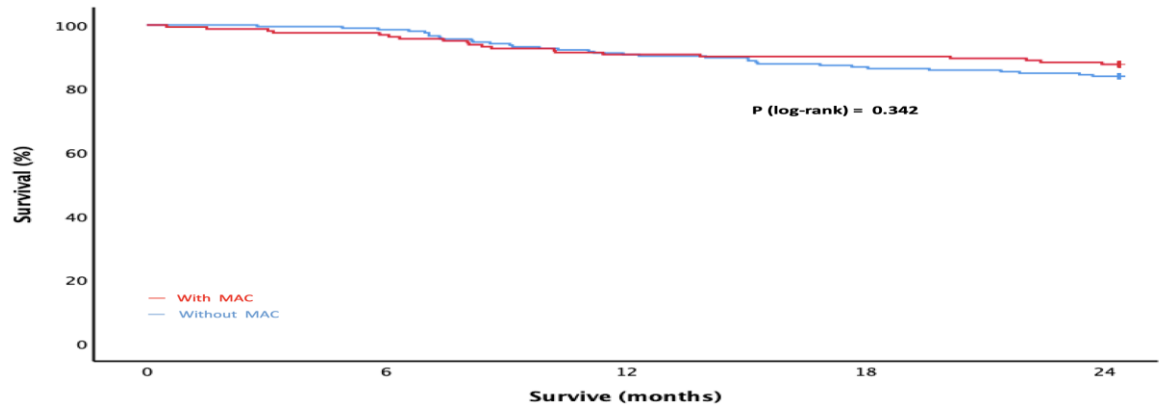

Figure 3: 24-month Kaplan-Meier survival plots in terms of mitral annular calcification.

between the two groups (Log-rank p=0.342) (Figure-3). According to the multivariate-Cox-regression analysis, which included age, LVEF, GFR, mean-THV gradient, moderate-severe PVAR, and sPAP, the independent predictors of mortality during the 2-year follow-up period were LVEF (adjusted HR: 0.97, 95% CI (0.94-0.99), p=0.015), mean-THV gradient (adjusted HR: 1.02, 95% CI (1.00-1.04), p=0.025), and sPAP (adjusted HR: 1.04, 95% CI (1.01-1.06), p=0.001) (Table-5a). Association of PVAR with MAC and its Impact on Long-term Prognosis Patients with

Table 5a: Univariate and multiple Cox regression analysis for mortality during follow-up among in-hospital survivors (n=367).

	Follow-up Mortality			
	Univariate		Multiple	
	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Age	1.04 (1.00 - 1.07)	0.035	1.03 (0.99 – 1.08)	0.069
LVEF (%)	0.96 (0.94 – 0.98)	0.002	0.97 (0.94 – 0.99)	0.015
GFR (mL/min/1.73 m²)	0.98 (0.97 – 0.99)	0.008	0.99 (0.98 – 1.01)	0.757
Mean THV Gradient (mmHg)	1.02 (1.00 – 1.04)	0.014	1.02 (1.00 – 1.04)	0.025
Moderate to severe PVAR	2.18 (1.27 – 3.76)	0.005	1.71 (0.94 – 3.13)	0.077
sPAP	1.05 (1.03 – 1.07)	<0.001	1.04 (1.01 – 1.06)	0.001

HR: Hazard ratio

Table 5b: Univariate and multiple Cox regression analysis for mortality during follow-up among in-hospital survivors regarding ordinal PVAR (n=367).

	Follow-up Mortality			
	Univariate		Multiple[a]	
	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
No PVAR (reference)	-	-	-	-
Mild PVAR (categorical)	0.87 (0.42 – 1.84)	0.733	0.73 (0.32 – 1.65)	0.456
Moderate PVAR (categorical)	1.39 (0.63 – 3.06)	0.403	0.92 (0.37 – 2.30)	0.872
Severe PVAR (categorical)	4.32 (1.90 – 9.81)	0.001	3.16 (1.25 – 7.96)	0.015

[a]Multiple analyses were built adjusting for age, LVEF, GFR, mean THV gradient and sPAP. **HR:** Hazard ratio, **LVEF:** Left ventricle ejection fraction, **GFR:** Glomerular filtration rate, **THV:** Transcatheter heart valve, **PVAR:** Paravalvular aortic regurgitation, **sPAP:** Systolic pulmonary artery pressure.

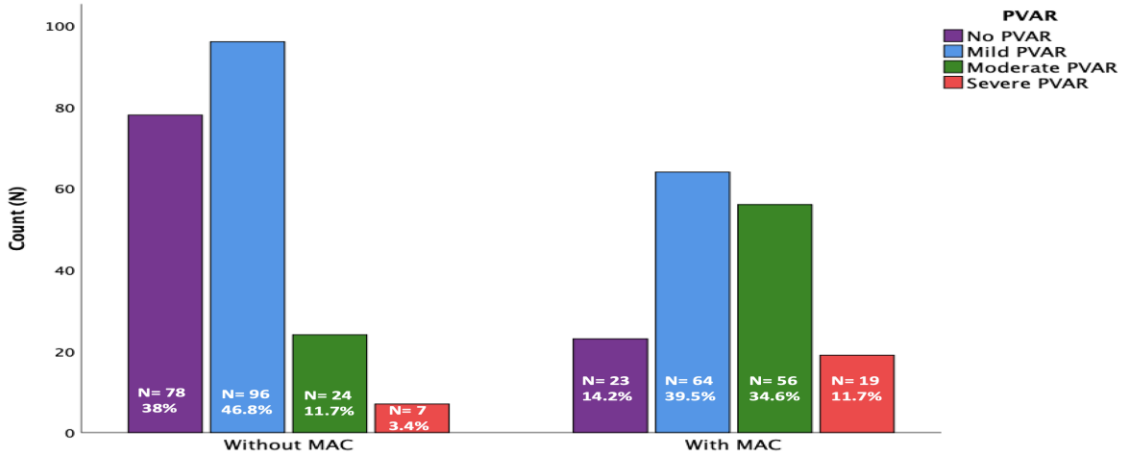

Figure 4: Bar graphs representing the frequency of different degrees of paravalvular aortic regurgitation (PVAR) in terms of mitral annular calcification (MAC).

preoperative MAC were found to have a higher incidence of moderate-to-severe PVAR during TTE follow-up after THV implantation (n=75, 46.3% vs n=31, 15.1%, p<0.001). Absolute numbers and percentages of postoperative PVAR grades in relation to the presence of MAC are provided in Figure-4. Notably, the rate of severe PVAR, which particularly affects long-term prognosis, was 11.7% (n=19) in patients with MAC, compared to 3.4% (n=7) in those without MAC. According to multivariate-Cox-regression analysis accounting for postoperative PVAR (categorized as mild-moderate-severe as ordinal variable), age, LVEF, GFR, mean-THV gradient,

and sPAP; mild and moderate PVAR had no prognostic effect on long-term mortality, whereas severe PVAR emerged as a clear independent predictor of long-term mortality (adjusted HR: 3.16, 95% CI (1.25-7.96), p=0.015) (Table-5b). Kaplan-Meier survival curves stratified according to PVAR grades also distinctly illustrate that patients with severe PVAR have a significantly increased risk of 2-year mortality (Figure-5).

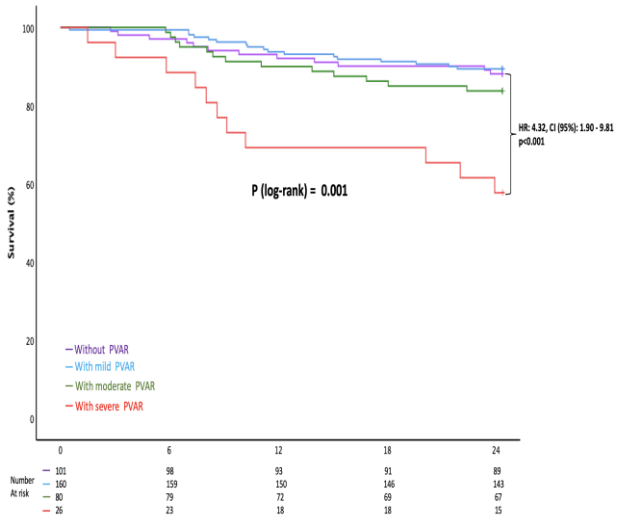

Figure 5: Four different 24-month Kaplan-Meier survival plots in terms of paravalvular aortic regurgitation (PVAR) degree.

Discussion

Current study investigating the determinants and prognostic importance of preoperative TTE-detected MAC, confirmed by CT in patients undergoing TAVI, the primary findings are as follows: 1-The strongest determinants of MAC in this patient cohort are age, GFR, and the presence of AF. 2-The presence of MAC has no impact on adverse perioperative outcomes such as in-hospital mortality, bleeding or intervention site complications. 3-Patients with MAC have a higher need for PPI in the early postoperative period. 4-According to long-term analyses, the frequency and severity of PVAR were significantly higher in the patient group with preoperative MAC. A subgroup of patients with severe PVAR showed a 3.8-fold increased risk of 2-year mortality compared to those without PVAR. 5-However, the presence of MAC alone is not a predictor of long-term mortality. 6-LVEF, mean-THV gradient, and sPAP are independent predictors of long-term mortality. This retrospective analysis of a single-center series showed that the prevalence of moderate-to-severe MAC extending to at least one-third of the posterior MV annulus in TAVI patients is comparable to current series in the literature at 45.4%, with a female predominance of 60.1%. Limited publications support the potential association between MAC and various adverse events in the general cohort, as well as in subgroups treated for severe AS. A meta-analysis of 2620 patients found significant MAC associated with increased periprocedural bleeding but no difference in in-hospital and long-term outcomes, including death and PPI (15). In a 761-patient, 36-month follow-up series reported by Abramowitz investigating the significance of concomitant MAC in severe AS patients treated with TAVI, the prevalence of mild, moderate and severe MAC was 30.4%, 9.5% and 9.5%, respectively (16). When the study cohort was divided into two groups for the presence of MAC, there was no difference in 30-day mortality and major complications. However, the subgroup with severe MAC had a statistically significant increased risk of long-term mortality compared to those without MAC (adjusted HR: 1.95, 95% CI (1.24-3.07), p=0.004). However, the effect of non-severe MAC on long-term prognosis could not be demonstrated (adjusted HR: 1.13, 95% CI (0.82-1.55), p=0.47) (16). In our series, PPI rates were 11.5% vs. 5.5% (p=0.028) in the groups with and without MAC, whereas 10.7% vs. 12.4% (p=0.53) was reported in Abramowitz's series. In a series of 423 patients documented by Ancona, using seven different types of self- and balloon-expandable THVs implanted via transfemoral route with a 24-month follow-up, 49.1% of patients had varying degrees of MAC and 17.7% had severe circumferential MAC. Further, female gender, peripheral artery disease, and LVEF were identified as independent predictors of MAC (17). In this series, in parallel to the Abramowitz, there was no difference between the groups in terms of MAC severity in 30-day all-cause mortality, stroke, myocardial infarction, bleeding and other vascular complications (17). Furthermore, similarly in this series, severe circumferential MAC was associated with increased 24-month cardiovascular mortality (adjusted HR: 2.94, 95% CI (1.32-6.52), p=0.034). Our current series aligns with Ancona and Abramowitz in that MAC does not affect in-hospital mortality but, uniquely, does not emerge as an independent predictor of long-term mortality. This discrepancy could be attributed to differences in categorizing MAC severity based on CT appearances. In both other series, only severe MAC increased long-term mortality, while mild and moderate severity did not. A noteworthy common point in both series is that LVOT calcification measured by preoperative CT was higher and the mean annulus area (mm^2) was narrower in the group with MAC (17,18). This

may indicate that increased intraluminal LV pressure and MV stress due to severe AS contribute to the development of MAC. As a result, it is noticeable that THV implantation was performed in a statistically significantly smaller size in the MAC group, similar to both the current series and the Ancona and Abramowitz series. However, the mean postoperative THV gradients did not differ significantly in all three series. While MAC prevalence is noted to approach 50% in CVD populations, it rarely leads to severe MV dysfunction (19). However, this study observed higher mean-transmitral gradients and frequencies of moderate-to-severe MV regurgitation in the MAC group. Post-TAVI severe MV regurgitation also persisted more frequently in patients with MAC. Additionally, early post-TAVI TTE assessments indicated significantly higher frequencies and severities of PVAR in patients with MAC. The presence of a narrow aortic annulus and more intense valvular and LVOT calcification in severe AS accompanied by severe MAC, as well as the relatively smaller size of THV implantation, may be considered as possible reasons that increase the frequency of PVAR. The prevalence of severe PVAR post-TAVI was noted as 11.7% in patients with MAC compared to 3.4% in those without. PVAR is a key marker of prognosis after TAVI (20). According to a meta-analysis of over 15.000 patients, the development of moderate to severe PVAR in patients undergoing TAVI is associated with at least a two-fold increased risk of all-cause mortality after one year (21). In the present study with a 2-year follow-up period, mild and moderate PVAR did not affect long-term mortality, whereas severe PVAR resulted in a 3.16-fold increased mortality risk, in line with established literature. Unlike the Ancona and Abramowitz series, the association between the presence of MAC and the frequency and grade of PVAR demonstrated in this study may be an indicator of poor prognosis after TAVI in patients with extensive MAC. Patients who are intended to undergo TAVI should be considered to have a high risk of postoperative PVAR in patients with MAC in the preoperative evaluation therefore adequate efforts should be made to reduce this risk. In conclusion, limited literature and findings from this study support the association of preoperative TTE or CT-detected and graded MAC with certain adverse outcomes in patients with severe AS undergoing TAVI. However, further research on larger, multi-center cohorts with multimodal imaging and extended follow-ups is warranted to explore this relationship further.

Study Limitations: Primary limitation of this study is its retrospective design and the absence of a control-cohort. Second, all patients treated only with TAVI method. It is speculated that treatment of similar patients with surgical valve replacement could yield different results, especially regarding postoperative PVAR. These conditions limit the generalizability of the study findings. Third, although patients with prior MV surgery were excluded from the study, patients with organic MV disease such as rheumatic or prolapse without any intervention may lead to inconsistency in the study results. Finally, the use of only TTE for postoperative PVAR grading, without recourse to more detailed modalities can be considered another limitation of the study.

Conclusions

In patients undergoing TAVI for severe AS, MAC affecting at least one-third of the posterior MV annulus was detected in 45.4% of the population when preoperative TTE was combined with CT. MAC, which is more commonly observed in older patients, females, and those with AF, does not directly affect in-hospital and long-term mortality. However, its association with increased need for post-TAVI PPI and PVAR may adversely impact long-term prognosis.

Ethics approval statement: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Medipol University (Approval Date: 12.10.2023, No:2023/841).

Conflict of interest: None of the authors have conflicting financial interests to report.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contributions: Study design, conception and writing (A.H.), data collection and processing (A.Y.), literatüre review and analysis (F.E.O., B.G.S.), materials (S.K.).

Availability of data and materials: The authors confirm that the data supporting the findings of this study are available within the article.

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