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ORIGINAL RESEARCH

A Cardiac Computed Tomography–Based Score to Categorize Mitral Annular Calcification Severity and Predict Valve Embolization

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ABSTRACT

OBJECTIVES This study aims to establish a computed tomography (CT)-based scoring system for grading mitral annular calcification (MAC) severity and potentially aid in predicting valve embolization during transcatheter mitral valve (MV) replacement using balloon-expandable aortic transcatheter heart valves.

BACKGROUND Transcatheter MV replacement is emerging as an alternative treatment for patients with severe MAC who are not surgical candidates. Although cardiac CT is the imaging modality of choice in the evaluation of candidates for valve-in-MAC (ViMAC), a standardized grading system to quantify MAC severity has not been established.

METHODS We performed a multicenter retrospective review of cardiac CT and clinical outcomes of patients undergoing ViMAC. A CT-based MAC score was created using the following features: average calcium thickness (mm), degrees of annulus circumference involved, calcification at one or both fibrous trigones, and calcification of one or both leaflets. Features were assigned points according to severity (total maximum score = 10) and severity grade was assigned based on total points (mild ≤3, moderate 4 to 6, and severe ≥7 points). The association between MAC score and device migration/embolization was evaluated.

RESULTS Of 117 patients in the TMVR in MAC registry, 87 had baseline cardiac CT of adequate quality. Of these, 15 were treated with transatrial access and were not included. The total cohort included 72 (trans-septal = 37, transapical = 35). Mean patient age was 74 ± 12 years, 66.7% were female, and the mean Society of Thoracic Surgery risk score was 15.4% ± 10.5. The mean MAC score was 7.7 ± 1.4. Embolization/migration rates were lower in higher scores: Patients with a MAC score of 7 had valve embolization/migration rate of 12.5%, MAC score ≥8 had a rate of 8.7%, and a MAC score of ≥9 had zero ($p = 0.023$). Patients with a MAC score of ≤6 had 60% embolization/migration rate versus 9.7% in patients with a MAC score ≥7 ($p < 0.001$). In multivariable analysis, a MAC score ≤6 was in independent predictor of valve embolization/migration (odds ratio [OR]: 5.86 [95% CI: 1.00 to 34.26]; $p = 0.049$).

CONCLUSIONS This cardiac CT-based score provides a systematic method to grade MAC severity which may assist in predicting valve embolization/migration during trans-septal or transapical ViMAC procedures.
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ABBREVIATIONS AND ACRONYMS

CT = computed tomography

MAC = mitral annular calcification

MR = mitral regurgitation

MS = mitral stenosis

MV = mitral valve

MVA = mitral valve area

NYHA = New York Heart Association functional classification

TAVR = transcatheter aortic valve replacement

THV = Transcatheter heart valve

TMVR = transcatheter mitral valve replacement

ViMAC = valve-in mitral annular calcification

Mitral annular calcification (MAC) is a degenerative process of the mitral annulus that more commonly affects the posterior aspect of the annulus fibrosa but often extends to the anterior aspect, may involve the entire annular circumference, and may also involve the myocardium and mitral leaflets causing mitral valve (MV) dysfunction (1,2). The true prevalence of MAC is poorly understood ranging from 4.3% to 15%, increasing with age as well as other cardiovascular risk factors including chronic kidney disease (3-7). MAC has been found to be as in high as 49.3% of patients undergoing transcatheter aortic valve replacement (TAVR) (8), and is associated with higher cardiovascular death and all-cause mortality (7,9,10). The main challenge to understanding true prevalence and the clinical impact of MAC is the lack of a universally accepted definition and grading classification of severity. Although echocardiography has historically been the primary imaging modality for detection and quantification of MAC (11), studies have used different definitions of MAC severity, making comparisons challenging (Supplemental Table 1) (3,9,12,13). Computed tomography (CT) is complimentary to echocardiography due to its excellent spatial resolution as well as the high x-ray attenuation of calcium and has been the imaging modality of choice to evaluate candidates for transcatheter MV replacement (TMVR) (14). However, a standard method to categorize MAC severity on CT has not been established.

TMVR using balloon-expandable aortic transcatheter heart valves (THVs) is emerging as an

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.

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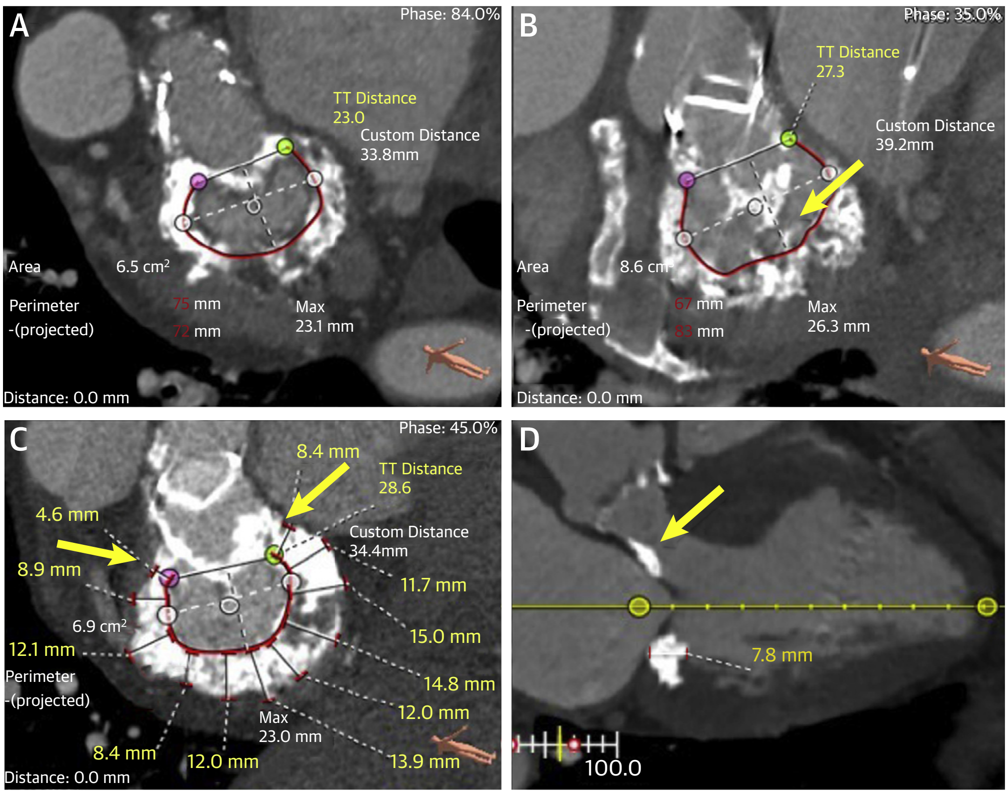
FIGURE 1 Mitral Annulus Area, Calcium Thickness, and Calcium Distribution Evaluation Using Cardiac Computed Tomography



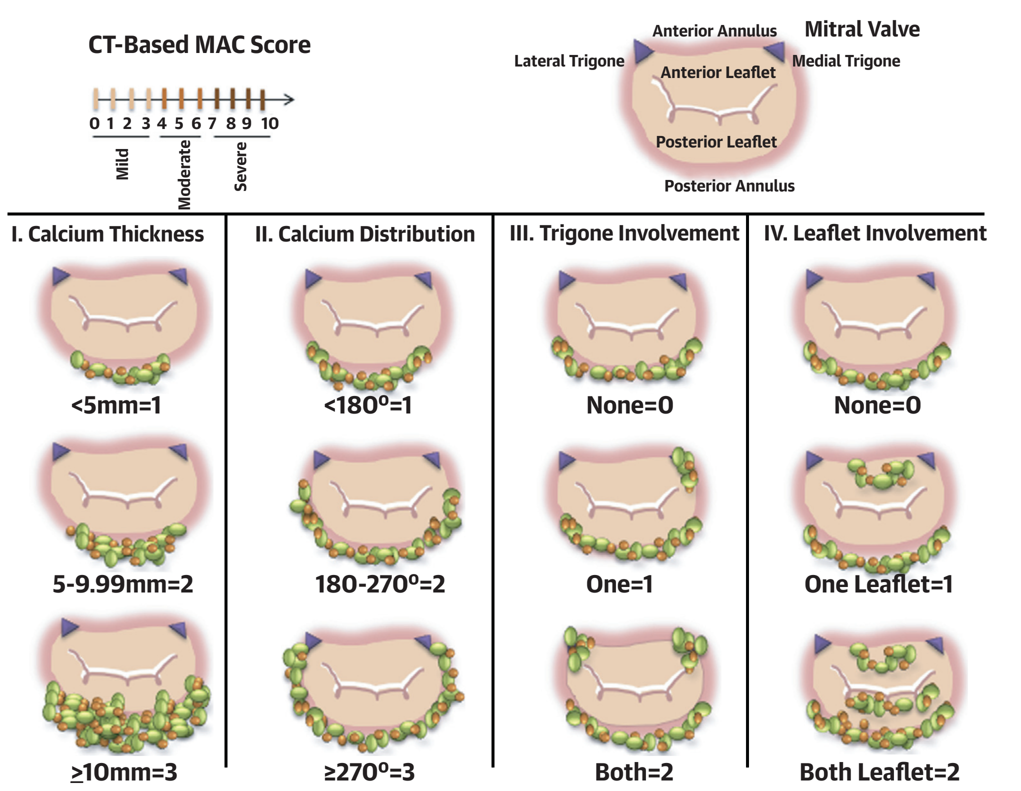
Cardiac computed tomography-based measurements of the calcified mitral annulus using 3Mensio Structural Heart Mitral Workflow version 8.1 (Pie Medical Imaging, Maastricht, the Netherlands). **(A)** Mitral "neo-annulus" area measurement made in surgeon's short-axis view using D-shape method. **(B)** When spicules of calcium were present, tracing the contour of neo-annulus was performed by cutting through spicules of calcium **(yellow arrow). (C)** Calcium thickness measurement made in surgeon's short-axis view. The calcium distribution involves most of the circumference near 360°. Both trigones are calcified **(arrows). (D)** The left ventricular outflow tract view shows calcium involvement of the anterior leaflet **(arrow).** This view is helpful to evaluate degree of leaflet calcification and length of the anterior leaflet.

alternative treatment option for patients with severe MAC and MV dysfunction who are not candidates for conventional MV surgery. The initial experience of TMVR in MAC was valve-in-MAC (ViMAC) with the off-label use of aortic THV devices in MAC (15-19). However, there are now ongoing prospective early feasibility clinical trials evaluating the safety and feasibility of ViMAC with the SAPIEN 3 valve (20,21), and dedicated transcatheter mitral prostheses (22). In the era of TMVR, there is a need for a standardized classification of MAC severity specific to TMVR to better evaluate anatomic feasibility for device implantation. The purpose of this study was to develop a CT-based MAC score to systematically grade MAC severity and estimate valve embolization risk in trans-septal or transapical ViMAC procedures using balloon-expandable aortic THVs.

METHODS

Cardiac CT scans from the TMVR in the MAC Global Registry consisting of 117 patients from 52 centers in 11 countries from North America, Europe, and South America who underwent TMVR with compassionate use of balloon-expandable THV between September 2012 and March 2017 were evaluated. Methods of data collection, including baseline clinical and echocardiographic characteristics, procedural outcomes, 30-day and 1-year outcomes data, were described in the original publication of clinical outcomes (19). Of 117 patients, 30 did not have a baseline CT or had a CT which was not sent to the core lab (n = 19), or the CT was of insufficient quality for meaningful analysis, such as non-gated or non-contrast CT (n = 11). The remaining 87 had baseline cardiac CT scans of

FIGURE 2 Elements Used of the MAC Score and Their Corresponding Points



Average annulus calcium thickness (<5 mm = 1 point, 5 to 9.9 mm = 2 points, ≥10 mm = 3 points); calcium distribution in annulus circumference (<180° = 1 point, 180° to 270° = 2, ≥270° = 3); trigone calcification (none = 0, anterolateral = 1, posteromedial = 1); and mitral leaflet calcification (none = 0, anterior = 1, posterior = 1). A severity grade is assigned based on total points accumulated as follows: mild MAC = 3 points or less, moderate MAC = 4 to 6 points, and severe MAC ≥7 points. CT = computed tomography; MAC = mitral annular calcification.

adequate quality for evaluation of MV anatomy and were included in this substudy focusing on CT analysis of anatomic characteristics. Of these, 15 were treated with transatrial access and were not included in the prediction of embolization analysis to avoid introducing bias as surgeons can place anchoring sutures during open transatrial procedure to decrease risk of embolization. The remaining 72 cases were treated with trans-septal (n = 37) or transapical (n = 35) access and were included in this analysis. CT acquisition protocols varied among institutions with slice thickness between 0.5 mm and 1 mm in most cases (range 0.4 to 1.3 mm; mean, 0.68 ± 0.19 mm). Cardiac CT images were analyzed using 3Mensio Structural Heart Mitral Workflow version 8.1 (Pie Medical Imaging, Maastricht, the Netherlands). The default window level used was 1,300/300 with minor adjustments for visual optimization. Mitral annular dimensions were obtained in best systolic and diastolic phase using 3Mensio mitral workflow, tracing annular area at leaflet insertion point in long- and short-axis multiplanar reconstruction images, and using the D-shaped method to decrease variability at aorto-mitral curtain level as previously described (23). In some cases with very severe calcification of the annulus, it was not possible to delineate leaflet insertion point to trace the true annulus. In those cases, the “neo-annulus” formed by the inner contour of calcium was traced. To account for blooming artifact, the neo-annulus contour was traced approximately 1 mm inside from the boundary of blood pool and calcium interface (Figure 1A). When spicules of calcium protruded into the left ventricular (LV) cavity, the neo-annulus contour was followed by cutting through the spicule of calcium (Figure 1B). Calcium thickness and distribution were evaluated in diastole using the short-axis view (Figure 1C). Longitudinal calcium thickness was measured in long axis

TABLE 1 CT-Based MAC Severity Score*

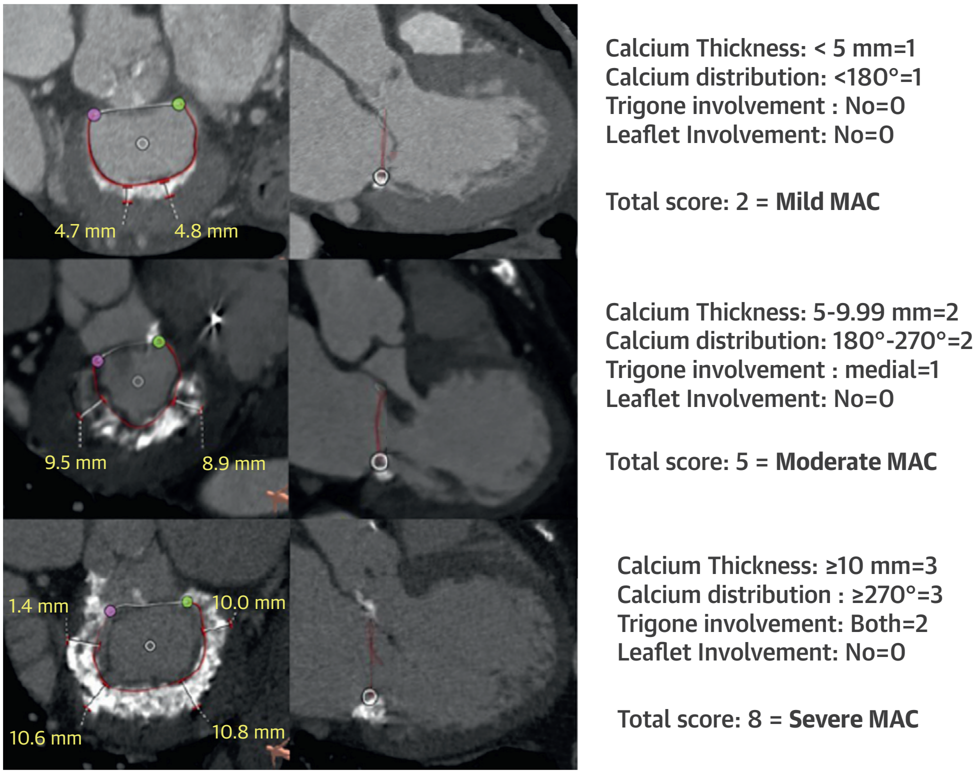
CT Findings	Points
Calcium thickness, mm	
<5	1
5-9.99	2
≥10	3
Calcium distribution	
<180°	1
180°-270°	2
≥270 °	3
Trigone involvement	
None	0
Anterolateral	1
Posteromedial	1
Leaflet involvement	
None	0
Anterior	1
Posterior	1
Total points	10

*MAC grade severity: mild: ≤3 points; moderate: 4 to 6 points; severe: ≥7 points.
CT = computed tomography; MAC = mitral annular calcification.

(Figure 1D). When images in diastole were not available (n = 13), calcium thickness and related measurements were obtained in systole. Anterior and posterior leaflet calcification were also evaluated in the LV outflow tract (LVOT) view (Figure 1D).The degree of THV oversizing was determined using the nominal area of the THV size implanted in relation to mitral annulus area using standard TAVR sizing method with balloon-expandable valves and expressed in percentage of oversize (nominal area of THV/annular area, $-1 \times 100\%$). Sizing was considered adequate if the THV nominal area was between -5% and 20% oversizing compared with mitral annulus area. Undersizing was defined as THV nominal area more than 5% smaller than the native mitral annulus area ($>-5\%$ oversizing compared to the mitral annulus area). This analysis was approved by the Mayo Clinic Institutional Review Board and patient consent was waived.

The proposed MAC score and its individual elements were evaluated searching for correlation with

FIGURE 3 Case Examples



Case examples of MAC severity grade using the CT-based score system. **(Left)** Calcium distribution thickness evaluated in the short axis mitral annulus view. **(Center)** Evaluation of the anterior leaflet calcium involvement in the 3-chamber long-axis view. **(Right)** MAC severity grade according to the CT-based MAC score. Abbreviations as in Figure 2.

TABLE 2 Baseline Patient Characteristics (N = 72)

Age, yrs	74 ± 12
Female	48/72 (66.7)
Diabetes	29/63 (46.0)
Atrial fibrillation	27/61 (44.3)
Peripheral arterial disease	10/63 (15.9)
Chronic obstructive pulmonary disease	25/63 (39.7)
On home oxygen	13/60 (21.7)
Chronic renal failure	37/66 (56.1)
Prior TIA or stroke	14/63 (22.2)
Hospitalization due to heart failure during prior 12 months	47/60 (78.3)
Prior CABG	25/66 (37.9)
Prior AVR	38/69 (55.1)
TAVR	9/38 (23.7)
SAVR	29/38 (76.3)
Mechanical	12/29 (41.4)
Bioprosthetic	17/29 (58.6)
Receiving long-term anticoagulation	28/55 (50.9)
STS score (n = 52)	15.4 ± 10.5
NYHA functional class	
II	6/68 (8.8)
III	30/68 (44.1)
IV	32/68 (47.1)
Echocardiography	
Ejection fraction, % (n = 58)	61.6 ± 9.5
Mean MVG, mm Hg (n = 61)	12.3 ± 4.7
MVA, cm^2 (n = 53)	1.2 ± 0.5
Systolic PAP, mm Hg (n = 57)	58.6 ± 19.6
LVOT gradient, mm Hg (n = 37)	3.1 ± 8.6
0 to 1 (+) MR	18/64 (28.2)
2 (+) MR	23/64 (35.9)
3(+) MR	13/64 (20.3)
4(+) MR	10/64 (15.6)

Values are mean ± SD or n/N (%).

AVR = aortic valve replacement; CABG = coronary artery bypass graft; LVOT = left ventricular outflow tract; MVA = mitral valve area; MVG = mitral valve gradient; MR = mitral regurgitation; NYHA = New York Heart Association functional class; PAP = pulmonary artery pressure; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack

TABLE 3 Cardiac CT Measurements (N = 72)

Diastole (missing 13)	
Cardiac phase for measurements in diastole, %	73.5 (7.4)
Mitral annulus area, mm^2	587.5 (141.7)
Septolateral diameter, mm	21.8 (3.3)
Intercommisural diameter, mm	31.4 (4.2)
Trigone to trigone distance, mm	23.3 (3.8)
Thickness MAC min diastole, mm	4.7 (1.5)
Thickness MAC max diastole, mm	12.8 (5.2)
Average MAC thickness short axis, mm	8.3 (2.3)
MAC thickness ≤5 mm	5 (7.1)
MAC thickness 5 to 10 mm	49 (70.0)
MAC thickness ≥10 mm	16 (22.9)
Average MAC thickness longitudinal axis, mm	11.6 (3.85)
MAC thickness ≤5 mm	1 (1.4)
MAC thickness 5 to 10 mm	24 (34.3)
MAC thickness ≥10 mm	45 (64.3)
Caseous* MAC? (no = 0, yes = 1)	20 (27.8)
MAC continuity (not continuous = 0, 1 single piece = 1)	45 (62.5)
MAC distribution	
<180°	6 (8.3)
180° to 270°	20 (27.8)
≥270°	46 (63.9)
Trigone involvement	
None	4 (5.6)
Anterolateral only	3 (4.2)
Posteromedial only	3 (4.2)
Both	62 (86.1)
Mitral valve leaflet calcified	
None	5 (6.9)
Anterior only	47 (65.3)
Posterior only	2 (2.8)
Both	18 (25.0)
Systole	
Cardiac phase for measurements in systole, %	35.3 (6.2)
Mitral annulus area, mm^2	582.5 (124.9)
Septolateral diameter, mm	22.0 (3.0)
Intercommisural diameter, mm	32.3 (4.2)
Trigone to trigone distance, mm	23.7 (4.4)
MAC score	7.7 (1.4)

Values are n (%). *Caseous MAC: calcified mitral annulus containing central areas that are noncalficied resembling liquefaction necrosis.

Abbreviations as in Table 1.

valve migration or embolization. For this analysis, valve migration was defined as any device migration noted on fluoroscopy or echocardiography immediately after valve deployment during the index procedure, resulting in severe mitral paravalvular regurgitation and/or requiring treatment with a second THV (valve-in-valve). For correlation with migration and embolization test, only the patients treated with transseptal and transapical access were included.

ELEMENTS OF THE CT-BASED MAC SCORE. The following features observed on cardiac CT scans were included in the MAC score: average annulus calcium thickness in short axis in mm, distribution of calcium in the annulus circumference (expressed in degrees of circumference involved), presence of calcification in one or both fibrous trigones, and presence of calcification in one or both mitral leaflets extending ≥5 mm from leaflet insertion point at annulus level (Figure 1D). We divided each of these categories into subcategories and assigned points according to severity (Figure 2). A total score was derived from the sum of points in each category and maximum score was 10. Scoring was as follows: average annulus calcium thickness (<5 mm = 1 point, 5 to 9.99 mm = 2 points, ≥10 mm = 3 points); calcium distribution in annular circumference (<180° = 1 point, 180° to

TABLE 4 Procedural Results (N = 72)

Device type	
Edwards	
SAPIEN	5/72 (6.9)
SAPIEN XT	33/72 (45.8)
SAPIEN 3	33/72 (45.8)
Inovare	1/72 (1.4)
Device size, mm	
23	7/72 (9.7)
26	30/72 (41.7)
29	34/72 (47.2)
30 (Inovare)	1/72 (1.4)
Access	
Transapical	35/72 (48.6)
Transseptal	37/72 (51.4)
Traditional (wire free in LV)	32/37
Modified (wire externalized through percutaneous sheath in LV)	5/37
Predilation	14/61 (23.0)
AVR during same procedure	5/70 (7.1)
TAVR	5/5 (100)
SAVR	0/5 (0)
Procedural results	
Technical success*	50/72 (69.4)
LVOT obstruction with hemodynamic compromise	10/72 (13.9)
Valve embolization	5/72 (6.9)
Device migration	7/72 (9.7)
Need for a second valve	13/72 (18.1)
Due to MR	9/13 (69.2)
Due to migration	4/13 (30.8)
LV perforation	2/72 (2.8)
Conversion to open heart surgery	4/72 (5.6)
Embolization	3/4 (75)
LVOT obstruction	1/4 (25)
Ejection fraction (n = 36)	57.9 ± 11.7
Mean MVG (mm Hg) (n = 60)	4.23 ± 2.3
MVA, cm^2 (n = 29)	2.74 ± 0.79
Residual MR at end of procedure	
Trace or none	30/50 (60)
Mild	18/50 (36)
≥3(+)†	2/50 (4)

Values are n/N (%) or mean ± SD. *According to Mitral Valve Academic Research Consortium definition. †All paravalvular except for 1 moderate central MR.
LV = left ventricular; other abbreviations as in Table 2.

TABLE 5 Valve Embolization/Migration Events in Relation to MAC Score

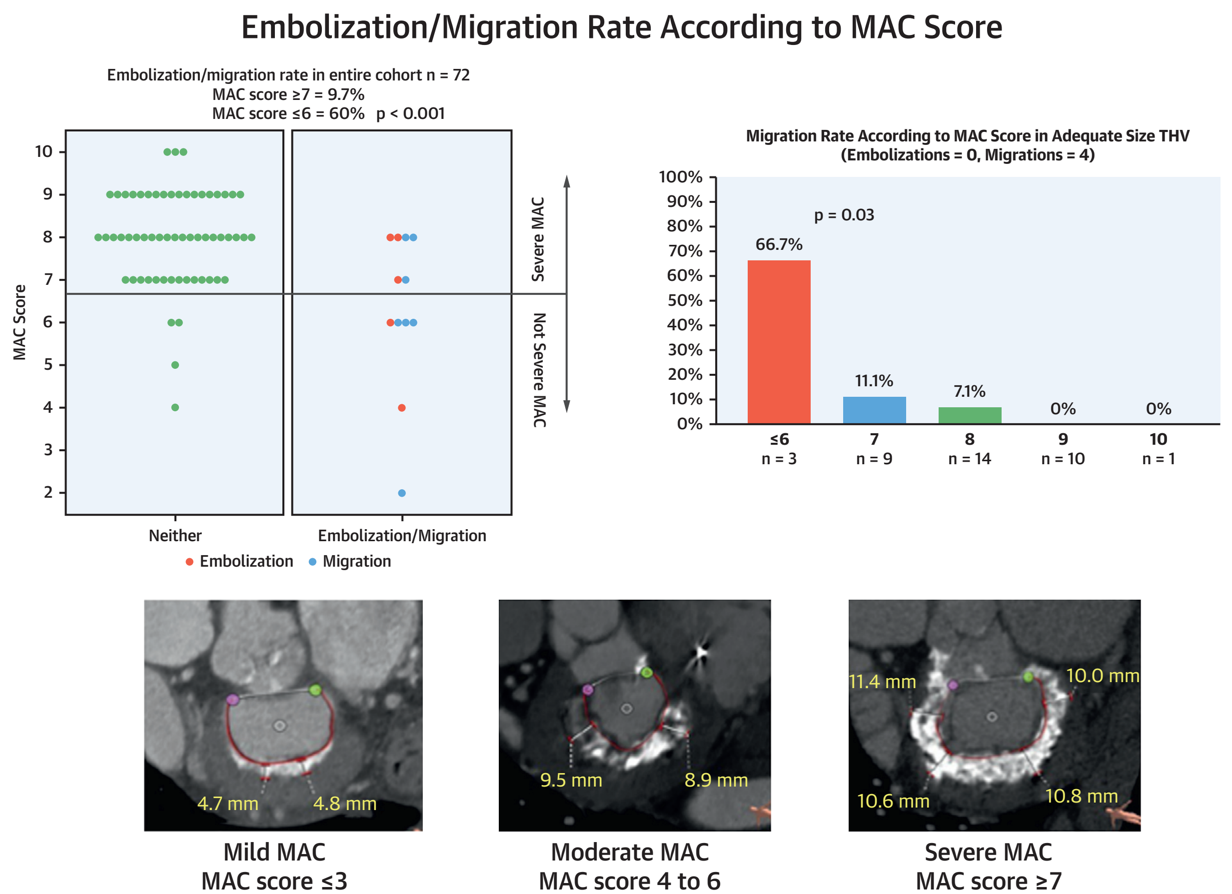
MAC Score	All (%)	p Value	THV Undersized (%)	p Value	THV Adequate Size (%)	p Value
≤6	60	<0.001	57.1	0.033	66.7	0.026
≥7	9.7		14.9		5.9	
7	12.5		14.3		11	
≤7	30.8	0.023	35.7	0.221	25	0.09
≥8	8.7		14.3		4	
≥9	0		0		0	
10	0		0		0	

THV = transcatheter heart valve; other abbreviation as in Table 1.

270° = 2, ≥270° = 3); trigone calcification (none = 0, anterolateral = 1, posteromedial = 1); and mitral leaflet calcification (none = 0, anterior = 1, posterior = 1). A severity grade is assigned based on total points accumulated as follows: mild MAC = 3 points or less, moderate MAC = 4 to 6 points, and severe MAC ≥7 points (Table 1). The longitudinal calcium thickness from the atrial to ventricular side of the mitral annulus was not included in the score because it is often not homogeneous (usually greater in posterior aspect of annulus) and has not been found to add incremental value to predict valve embolization. Examples of the use of this grading system are shown in Figure 3.

STATISTICAL ANALYSIS. Continuous variables were summarized as mean and standard deviation. Categorical variables were presented as frequency and percentage. Comparisons between discrete groups were made using the Fisher exact test. Comparisons of continuous variables between groups were made using one-way analysis of variance. To test the reproducibility of the proposed MAC score, 3 independent readers (M.G., O.K., and H.M.C.) reviewed 20 studies, and inter-rater reliability of MAC score was evaluated by calculating the two-way intraclass correlation coefficient (ICC) and its 95% confidence interval (CI). A univariate logistic regression was used to model the association between embolization/migration with MAC score (≤6 and ≤7). Univariate logistic regressions were also fit to the MAC score components: short-axis calcium thickness, long-axis calcium thickness calcium distribution, anterolateral and posteromedial trigone involvement, and anterior and posterior leaflet involvement. Since a major risk factor for valve embolization when using a balloon expandable THV is valve undersizing, we further analyzed patients in 2 groups, undersized versus non-undersized. Multivariable logistic regression analysis was performed for MAC score ≤6 adjusting for undersizing and calcification of anterior leaflet. The odds ratio (OR), 95% CIs, and the Wald test's p values were reported. The multivariable model was compared to the MAC score univariate model using their respective Akaike information criterion scores resulting in a difference of 0.016 (p = 0.99). For the purposes of this paper, all p values were two-sided and values of >0.05 were considered significant. All analyses were conducted using R (Version 3.4.2, R Foundation for Statistical Computing, Vienna Austria).

CENTRAL ILLUSTRATION Valve Embolization/Migration Rates in Relation to MAC Score



Guerrero, M. et al. J Am Coll Cardiol Img. 2020;■(■):■-■.

(Left) Valve embolization or migration events in relation to MAC score in entire cohort of patients (treated with undersized and adequate size valves). **(Right)** Valve migration rates according to MAC score in patients treated with adequate size THV. Only migration rates are shown, there were no valve embolizations in this group. **(Bottom)** Examples of MAC severity grades based on MAC score. MAC = mitral annular calcification; THV = transcatheter heart valve.

RESULTS

PATIENT CHARACTERISTICS. Baseline clinical characteristics are listed in Table 2. Mean age was 74 ± 12 years, and 66.7% were female. Multiple comorbidities were present. The mean Society of Thoracic Surgeons predicted risk of mortality score was 15.4 ± 10.5%. The LV systolic function was preserved and the primary pathology was mitral stenosis in most patients. Mean MV diastolic gradient was 12.3 ± 4.7 mm Hg and mean MV area was 1.2 ± 0.5 cm^2. Most patients (91.2%) were in New York Heart Association functional class III-IV.

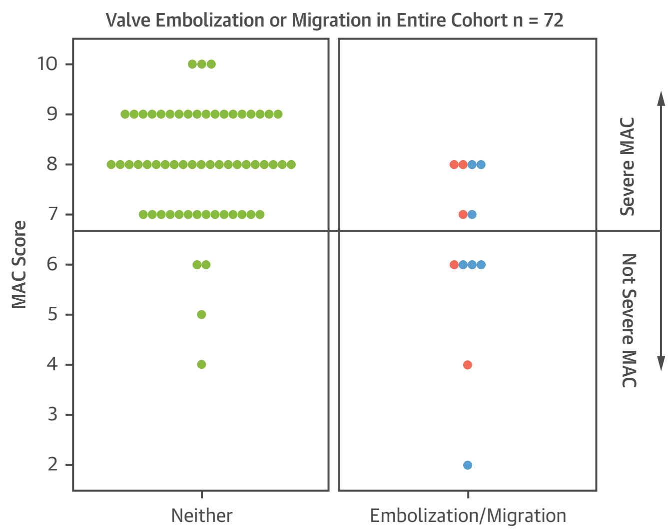
CARDIAC CT MEASUREMENTS AND REPRODUCIBILITY TEST. Baseline cardiac CT measurements are summarized in Table 3. Mean MAC score in the cohort of 72 patients was 7.7 ± 1.4. The ICC between MAC scores from an advanced cardiac imaging cardiologist (O.K.) and an interventional cardiologist (M.G.) was 0.88 (95% CI: 0.73 to 0.95; $p < 0.001$), indicating good correlation between independent readers. When measurements from a noncardiologist member were included performed by a pre-medical school student research volunteer (H.M.C.) as a third blind reader, the reliability remained good with an ICC of 0.751 (95% CI: 0.556 to 0.882; $p < 0.001$).

PROCEDURAL RESULTS. Table 4 summarizes procedural results. Delivery access was trans-septal in 37 patients (51.4%) and transapical in 35 (48.6 %). Clinical outcomes have been previously reported. There were no annular ruptures reported in this cohort (19).

Of the 72 cases included in the embolization/migration analysis, 37 patients (51.4%) received a THV within the recommended margins of degree of size (−5% to 20% oversize) and were considered sized adequately for purpose of this analysis; with average oversizing of 11.95 ± 15.65%. The remaining 35 patients (48.6%) were considered undersized; and were treated with a THV smaller than the recommended size by the manufacturer for the aortic position. The mean degree of undersizing in these subjects was −15.86 ± 8.59%. The mean MAC score was similar in both groups, 7.6 ± 1.47 in the undersized group and 7.8 ± 1.34 in the non-undersized group ($p = 0.55$).

EMBOLIZATION/MIGRATION. There were 5 valve embolizations during the index procedure in the 72 patients (6.9%) and 7 valve migrations (9.7%). The combined incidence of migration and embolization was 12 (16.7%). Most valve migrations were treated percutaneously with a second valve during index procedure. Four valve embolizations were treated surgically and 1 percutaneously by placing the SAPIEN XT valve in the interatrial septum with a 30-mm Amplatzer Septal Occluder device. Three of 5 patients (60%) who had embolization, died within 30 days post-procedure (2 treated surgically and 1 percutaneously). Examples of a good valve implant and a valve embolization are shown in Videos 1 and 2. Embolization/migration rates in relation to MAC score are summarized in Table 5. A MAC score of ≤6 ($n = 10$) was associated with higher likelihood of valve embolization or migration (6 of 10, 60%) compared to patients with a MAC score of ≥7 (6 of 62, 9.7%) ($p < 0.001$) (Central Illustration). The sensitivity of a MAC score of ≤6 to predict valve embolization or migration was 50% (95% CI: 0.21 to 0.79) and the specificity was 93% (95% CI: 0.84 to 0.98), with a positive predictive value of 60% (95% CI: 0.80 to 0.96) and negative predictive value of 90% (95% CI: 0.80 to 0.96) (Figure 4).

FIGURE 4 **Valve Embolization or Migration in Relation to MAC Score**



	≤6 (N = 10)	≥7 (N = 62)	p Value
Embolization or Migration			< 0.001
N	10	62	
No	4 (40.0%)	56 (90.3%)	
Yes	6 (60.0%)	6 (9.7%)	

● Neither ● Embolization ● Migration

Green dots represent patients who had a valve-in-MAC procedure without valve embolization or migration. **Blue dots** represent valve migration. **Red dots** represent valve embolization. Abbreviation as in Figure 2.

UNDERSIZED GROUP. All 5 valve embolizations occurred in the undersized group (5 of 35, 14.3%). The mean undersize percentage in the valve embolization group was -18.45 ± 16.19%. The MAC score was ≤6 in 2 patients (1 patient had a MAC score of 4, 1 patient had a MAC score of 6), and ≥7 in 3 (1 patient had a MAC score of 7, 2 patients had a MAC score of 8). There were 3 valve migrations among the 35 undersized valves (3 of 35, 8.6%). The remaining 27 of 35 undersized valves (77.1%) did not migrate or embolize despite being undersized. Patients in the undersized group who had a MAC score of ≤6 (4 of 7) had embolization/migration rate of 57.1% versus 14.3% (4 of 28) in patients with MAC score ≥7 ($p = 0.033$). No patient with a MAC score of 9 ($n = 8$) or 10 ($n = 2$) had valve migration or embolization despite being treated with an undersized valve. The sensitivity of the MAC score ≤6 in this group was 50% (95% CI: 0.16 to 0.84) with specificity of 89% (95% CI: 0.71 to 0.98), positive predictive value of 57% (95% CI: 0.18 to 0.90), and negative predictive value of 86% (95% CI: 0.67 to 0.96) (Figure 5).

NON-UNDERSIZED GROUP (TREATED WITH ADEQUATE SIZE THV). Of the 37 patients in the non-undersized group, there were 4 valve migrations (10.8%) and no embolizations. Thirty-four (91.9%) of these patients had a MAC score of ≥7 and 3 (8.1%) had a score of ≤6. The migration rate in this group was 66.7% in patients with MAC score ≤6 (2 of 3, 66.7%) and 5.9% in patients with MAC score ≥7 (2 of 34, 5.9%) ($p = 0.026$). The sensitivity of the MAC score ≤6 in this group was 50% (95% CI: 0.07 to 0.93) with specificity of 97% (95% CI: 0.84 to 1.00) and a positive predictive value of 67% (95% CI: 0.09 to 0.99) and negative predictive value of 94% (95% CI: 0.80 to 0.99) (Figure 6). The only valve migration event in

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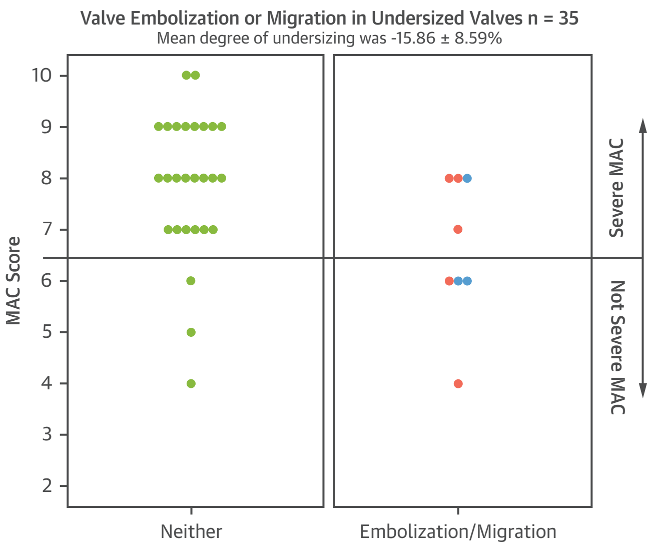
FIGURE 5 Valve Embolization or Migration in Relation to MAC Score in Patients Treated With Undersized Transcatheter Heart Valves



	≤6 (N = 7)	≥7 (N = 28)	p Value
Embolization or Migration			0.033
N	7	28	
No	3 (42.9%)	24 (85.7%)	
Yes	4 (57.1%)	4 (14.3%)	

● Neither ● Embolization ● Migration

Green dots represent patients who had a valve-in-MAC procedure without valve embolization or migration. Only subjects treated with an undersized sized valve are included. **Blue dots** represent valve migration events and **red dots** represent valve embolization events. Abbreviation as in Figure 2.

a patient with a MAC score of 8 in this cohort of patients treated with adequate size THV occurred in the setting of LVOT obstruction which could have contributed to migration. The embolization/migration rates in relation to MAC score in patients treated with adequate size THVs are summarized in Figure 7.

PREDICTORS OF VALVE EMBOLIZATION OR MIGRATION. In univariate analysis, factors associated with higher risk of valve migration or embolization included a MAC score ≤7 and mitral regurgitation as the primary pathology. Factors associated with a lower risk of embolization included a calcium thickness of ≥5 mm, calcium distribution of >270° of annular circumference, anterolateral trigone and anterior leaflet calcified. On multivariable analysis, a MAC score of ≤6 was an independent predictor of valve migration or embolization with OR of 5.86 (95% CI: 1.00 to 34.26) ($p = 0.049$) (Table 6).

PARAVALVULAR LEAK. There was no correlation between MAC score and presence of mild or greater paravalvular leak.

DISCUSSION

The proposed cardiac CT-based MAC score provides a systematic and reproducible method to grade the severity of MAC. This score requires basic software features capable of TAVR CT analysis that can identify multiplanar phasic reconstruction and contrast CT segmentation analysis. The interobserver correlation between independent readers was good. This grading tool may facilitate communication among physicians when evaluating treatment options for patients undergoing evaluation for TMVR in MAC. Importantly, the score was independently associated with risk of valve embolization or migration during trans-septal and transapical TMVR in MAC when using balloon-expandable aortic THVs.

The evaluation of patients with MAC is complex and must consider the clinical need for TMVR based on symptoms refractory to medical treatment, surgical risk, absence of futility, severity of MV dysfunction, and absence of contraindications such as high risk of LVOT obstruction. The proposed score does not address those factors but may help predict embolization of a balloon-expandable aortic THV.

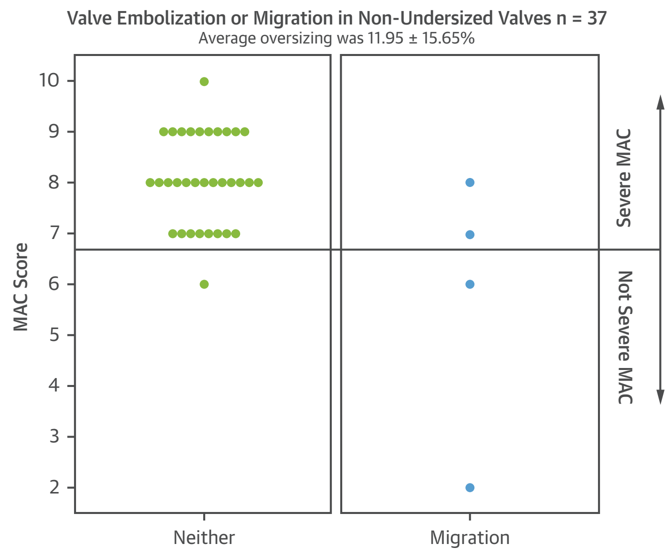
The MITRAL (Mitral Implantation of Transcatheter Valves) trial was the first prospective multicenter clinical trial evaluating TMVR in MAC using balloon expandable aortic THVs (NCT02370511) (20). Traditionally, MAC has been an exclusion criterion for new TMVR device early-feasibility clinical trials. However, there is already a clinical trial evaluating a THV designed for the MV that allows inclusion of patients with MAC under a MAC arm in the main pivotal study (22,24). In the absence of a standardized MAC definition and terminology for TMVR device implantation, subjective MAC severity grading may confound TMVR clinical trial inclusion and exclusion criteria and may limit clinical evaluation of patients with MAC.

One of the important complications of TMVR in MAC using balloon-expandable aortic THVs is valve embolization or migration (18). The amount and distribution of calcium play an important role in anchoring of a THV in the mitral position. Valve anchoring during a trans-septal ViMAC using a balloon-expandable aortic THV requires the presence of calcification at the base of A2 and P2 mitral annulus or involvement of either or both trigones and the P2 segment of the mitral annulus. The greater the distribution and thickness of MAC among these segments the better TMVR device anchoring and less risk of device embolization. The proposed CT MAC score puts into consideration the individual components that contribute to TMVR device anchoring (calcium thickness, amount of annular circumference involved, trigone calcification, and mitral anterior leaflet calcification). The proposed score may help predict valve anchoring when using the correct size balloon-expandable aortic THVs in trans-septal and transapical ViMAC procedures.

This study found that patients with a MAC score of ≤6 (mild or moderate MAC) have very high risk of embolization when treated with a balloon-expandable THV whereas patients with a MAC score of ≥7 (severe MAC) have a lower risk of valve embolization or migration when treated with a properly sized valve. The number of valve embolization/migration events was small. Therefore, these data are hypothesis generating and should be taken with caution. However, these findings suggest that patients with MAC score ≤6 should not be treated with transseptal or transapical ViMAC using a balloon-expandable aortic THV. These patients may be better served with a surgical transatrial approach, whereby placing anchoring sutures may decrease the risk of embolization or migration, or a TMVR procedure using a THV designed for the MV which possesses an anchoring mechanism to prevent embolization.

STUDY LIMITATIONS. The total number of patients is small. Therefore, the use of this score to predict valve embolization must be further validated in larger studies and cannot be recommended as the only screening tool at this time. However, this is the largest registry of patients with MAC that includes early experience and its associated complications such as valve embolization which is rarely seen in current practice. Not all CT scans were available for analysis, 30 of 117 were not sent to us (n = 19) or had poor quality (n = 11) and were not included in analysis. This could have introduced bias as patients who could not have CT scan due to renal failure might have also had more severe MAC. This paper does not address other important complications such a LVOT obstruction or paravalvular leak as the main focus of this analysis was prediction of valve embolization. This is a retrospective review of self-reported data. Valve migration was not evaluated by an imaging core lab nor adjudicated by an independent team. This analysis is device specific and applies only to balloon-expandable aortic THVs. The findings cannot be extrapolated to other valve technologies. It is possible that not all valve migrations were detected or

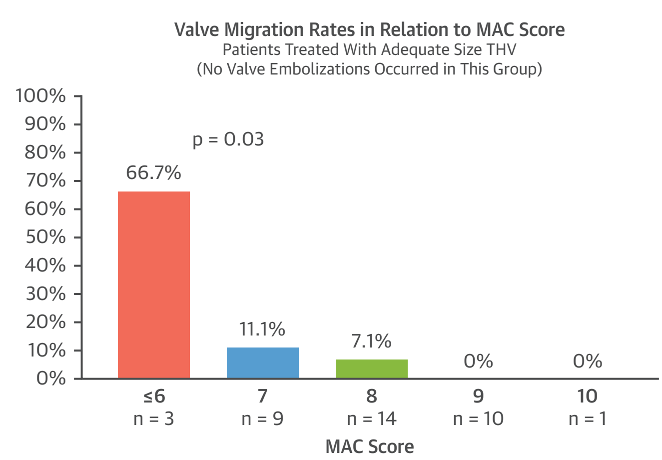
FIGURE 6 **Valve Embolization or Migration in Relation to MAC Score in Patients Treated With Adequately Sized Transcatheter Heart Valves**



	≤6 (N = 3)	≥7 (N = 34)	p Value
Embolization or Migration			0.026
N	3	34	
No	1 (33.3%)	32 (94.1%)	
Yes	2 (66.7%)	2 (5.9%)	

Green dots represent patients who had a valve-in-MAC procedure without valve migration or embolization. Only subjects treated with valve sized correctly are included. **Blue dots** represent valve migration events. Abbreviation as in Figure 2.

FIGURE 7 **Valve Migration Percentage Rates in Relation to MAC Score in Patients Treated With Adequately Sized Transcatheter Heart Valves**



Percentage of valve migration events in relation to MAC score in patients treated with a valve sized correctly. MAC = mitral annular calcification; THV = transcatheter heart valve.

TABLE 6 Predictors of Valve Embolization or Migration

	Univariate		Multivariate	
Age (1 Yr Increase)	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
MAC score ≤6*	14 (3.18-70.36)	<0.001	5.86 (1.00-34.26)	0.049
MAC score ≤7	4.67 (1.3-19.38)	0.022		
Valve undersized	2.44 (0.69-9.98)	0.179	1.77 (0.38-8.21)	0.467
Anterior leaflet calcified	0.05 (0.01-0.27)	0.001	0.13 (0.01-1.03)	0.053
Posterior leaflet calcified	0.84 (0.17-3.23)	0.814		
Calcium thickness short axis 5-9.99 mm	0.12 (0.01-0.86)	0.035		
Calcium thickness short axis ≥10 mm	0.04 (0.0-0.52)	0.023		
Calcium thickness long axis ≥10 mm	0.21 (0.05-0.75)	0.020		
Calcium distribution 180-270°	0.12 (0.01-0.98)	0.053		
Calcium distribution ≥270°	0.10 (0.01-0.70)	0.021		
Anterolateral trigone calcified	0.11 (0.02-0.56)	0.008		
Posteromedial trigone calcified	0.21 (0.04-1.23)	0.068		
Caseous MAC	0.20 (0.01-1.12)	0.131		
Transseptal vs. transapical	0.77 (0.24-2.27)	0.646		
Regurgitation vs. stenosis	3.85 (1.08-14.73)	0.039		

*Adjusted for undersized valve and anterior leaflet calcified.
CI = confidence interval; OR = odds ratio; other abbreviation as in Table 1.

reported. Although the participating sites were encouraged to submit all cases, it is possible that not all consecutive cases during that time frame were submitted. Data were not collected on additional factors that may contribute to improved anchoring of an aortic balloon-expandable valve in the mitral annulus such as radiation-induced valvular disease.

In addition, there are technical factors that may affect the risk of valve embolization during ViMAC procedures using an aortic THV such as depth of implantation in relation to annulus and flare of the THV frame in the left ventricle. In general, a more ventricular implantation is preferred to decrease risk of embolization into the left atrium (i.e., 80% ventricular/20% atrial) (25). Strategies such as deploying the THV with additional contrast volume than the nominal volume recommended (i.e., 2 ml of additional contrast for the 23-mm SAPIEN 3, 3 ml for the 26-mm, and 4 ml for the 29-mm valve size) or balloon post-dilatation can be used to flare the ventricular edge of THV stent frame to decrease risk of embolization (25). Details of contrast volume used during valve deployment or depth of implantation in relation to annulus were not available. Therefore, it is possible that those factors during valve deployment could have influenced the results of this study and not have been accounted for.

CONCLUSIONS

The proposed cardiac CT-based MAC score provides a systematic and reproducible method to grade MAC severity to facilitate communication among health care providers in the evaluation of patients being considered for TMVR in MAC. It may also assist in predicting valve embolization/migration during trans-septal or transapical ViMAC procedures using balloon-expandable aortic THV devices; therefore, it may improve patient selection process for the various treatment options.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: A CT-based score can provide a systematic method for grading the severity of MAC and potentially identify patients at risk of valve embolization during trans-septal or transapical ViMAC procedures using balloon-expandable aortic THVs.

TRANSLATIONAL OUTLOOK: Imaging tools are needed to refine the screening process to improve patient selection and procedural outcomes of TMVR in patients with MAC.

REFERENCES

1. Korn D, Desanctis RW, Sell S. Massive calcification of the mitral annulus. A clinicopathological study of fourteen cases. N Engl J Med 1962;267:900–9.

2. Dewitzky WI. About the construction and the emergence of a different form of chronic changes in the heart valves. Virchows Archiv I pahtol Anat 1910:273–377.

3. Kanjanauthai SNK, Katz R, et al. Relationships of mitral annular calcification to cardiovascular risk factors: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 2010;213:558–62.

4. Allison MA, Cheung P, Criqui MH, Langer RD, Wright CM. Mitral and aortic annular calcification are highly associated with systemic calcified atherosclerosis. Circulation 2006;113:861–6.

5. Asselbergs FW, Mozaffarian D, Katz R, et al. Association of renal function with cardiac calcifications in older adults: the cardiovascular health study. Nephrol Dial Transplant 2009;24:834–40.

6. Foley PW, Hamaad A, El-Gendi H, Leyva F. Incidental cardiac findings on computed tomography imaging of the thorax. BMC Res Notes 2010;3:326.

7. Fox CS, Larson MG, Vasan RS, et al. Cross-sectional association of kidney function with valvular and annular calcification: the Framingham heart study. J Am Soc Nephrol 2006;17:521–7.

8. Abramowitz Y, Kazuno Y, Chakravarty T, et al. Concomitant mitral annular calcification and severe aortic stenosis: prevalence, characteristics and outcome following transcatheter aortic valve replacement. Eur Heart J 2017;38:1194–203.

9. Fox CS, Vasan RS, Parise H, et al. Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study. Circulation 2003;107:1492–6.

10. Benjamin EJ, Plehn JF, D'Agostino RB, et al. Mitral annular calcification and the risk of stroke in an elderly cohort. N Engl J Med 1992;327:374–9.

11. Movva R, Murthy K, Romero-Corral A, Seetha Rammohan HR, Fumo P, Pressman GS. Calcification of the mitral valve and annulus: systematic evaluation of effects on valve anatomy and function. J Am Soc Echocardiogr 2013;26:1135–42.

12. Kohsaka S, Zhezhen J, Rundek T, et al. Impact of mitral annular calcification on cardiovascular events in a multiethnic community. J Am Coll Cardiol Img 2008;1:617–23.

13. Barasch E, Gottdiener JS, Marino Larson EK, Chaves PHM, Newman AB, Manolio TA. Clinical significance of calcification of the fibrous skeleton of the heart and aortosclerosis in community dwelling elderly. The Cardiovascular Health Study (CHS). Am Heart J 2006;151:39–47.

14. Narang A, Guerrero M, Feldman T, Pursnani A. Computed tomography assessment for transcatheter mitral valve interventions. J Cardiovasc Surg 2016;57:360–71.

15. Guerrero M, Greenbaum A, O'Neill W. First in human percutaneous implantation of a balloon expandable transcatheter heart valve in a severely stenosed native mitral valve. Catheter Cardiovasc Interv 2014;83:E287–91.

16. Mellert F, Sinning JM, Werner N, et al. First-in-man transapical mitral valve replacement using the Direct Flow Medical aortic valve prosthesis. Eur Heart J 2015;36:2119.

17. Lim ZY, Boix R, Prendergast B, et al. First reported case of transcatheter mitral valve implantation in mitral annular calcification with a fully repositionable and self-expanding valve. Circ Cardiovasc Interv 2015;8:e003031.

18. Guerrero M, Dvir D, Himbert D, et al. Transcatheter mitral valve replacement in native mitral valve disease with severe mitral annular calcification: results from the first multicenter global registry. J Am Coll Cardiol Intv 2016;9:1361–71.

19. Guerrero M, Urena M, Himbert D, et al. 1-year outcomes of transcatheter mitral valve replacement in patients with severe mitral annular calcification. J Am Coll Cardiol 2018;71:1841–53.

20. Guerrero M. MITRAL Trial (Mitral Implantation of TRAnscatheter vaLves). ClinicalTrials.gov Identifier NCT02370511. Available at: https://clinicaltrials.gov/ct2/show/NCT02370511. Accessed May 2, 2020.

21. Smith R. Surgical Implantation of TRAnscatheter vaLve in Native Mitral Annular Calcification (SITRAL) Study. Available at: https://clinicaltrials.gov/ct2/show/NCT02830204?term=surgical+implantation+of+transcatheter+valves&rank=1. Accessed May 2, 2020.

22. Sorajja P. Feasibility Study of the Tendyne Mitral Valve System for Use in Subjects With Mitral Annular Calcification. Available at: https://clinicaltrials.gov NCT 03539458. Accessed May 2, 2020.

23. Blanke P, Dvir D, Cheung A, et al. Mitral annular evaluation with CT in the context of transcatheter mitral valve replacement. J Am Coll Cardiol Img 2015;8:612–5.

24. Clinical trial to evaluate the Safety en Effectiveness of Using the Tendyne Mitral Valve System for the Treatment of Symptomatic Mitral Regurgitation. Available at: https://clinicaltrials.gov/ct2/show/NCT03433274?term=summit+tendyne&draw=2&rank=1. Accessed May 2, 2020.

25. Guerrero M, Salinger M, Pursnani A, et al. Transseptal transcatheter mitral valve-in-valve: a step by step guide from preprocedural planning to postprocedural care. Catheter Cardiovasc Interv 2018;92:E185–96.

KEY WORDS mitral annular calcification, mitral valve replacement, transcatheter mitral valve replacement, valve embolization, valve migration

APPENDIX For a supplemental table and videos, please see online version of this paper.