Prognostic implications of cardiac damage classification based on computed tomography in severe aortic stenosis

Hirasawa, K.; VanRosendael, P.J.; Fortuni, F.; Singh, G.K.; Kuneman, J.H.; Vollema, E.M.; ... ; Delgado, V.

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2022) **23**, 578–585
doi:10.1093/ehjci/jeab071

Prognostic implications of cardiac damage classification based on computed tomography in severe aortic stenosis

Kensuke Hirasawa[1], Philippe J. vanRosendael[1], Federico Fortuni[1,2], Gurpreet K. Singh[1], Jurrien H. Kuneman[1], E. Mara Vollema[1], Nina Ajmone Marsan[1], Juhani Knuuti [1,3], Jeroen J. Bax[1,3]*, and Victoria Delgado [1]

[1]Department of Cardiology, Heart Lung Centre, Leiden University Medical Centre, Albinusdreef 2, 2300 RC Leiden, The Netherlands; [2]Division of Cardiology, Department of Medical Sciences, AOU Città della Salute e della Scienza, University of Turin, Turin, Italy; and [3]Turku PET Centre, Turku University Hospital, University of Turku, Turku, Finland

Received 30 January 2021; editorial decision 25 March 2021; accepted 29 March 2021; online publish-ahead-of-print 14 April 2021

Aims An echocardiographic staging system of severe aortic stenosis (AS) based on additional extra-valvular cardiac damage has been associated with prognosis after transcatheter aortic valve implantation (TAVI). Multidetector row computed tomography (MDCT) is key in the evaluation of AS patients undergoing TAVI and can potentially detect extra-valvular cardiac damage. This study aimed at evaluating the prognostic implications of an MDCT staging system of severe AS in patients undergoing TAVI.

Methods and results A total of 405 patients (80 ± 7 years, 52% men) who underwent full-beat MDCT prior to TAVI were included. The extent of cardiac damage was assessed by MDCT and classified in five categories; Stage 0 (no cardiac damage), Stage 1 (left ventricular damage), Stage 2 (left atrium and mitral valve damage), Stage 3 (right atrial damage), and Stage 4 (right ventricular damage). Twenty-seven (7%) patients were stratified as Stage 0, 96 (24%) as Stage 1, 152 (38%) as Stage 2, 78 (19%) as Stage 3, and 52 (13%) as Stage 4. During a median follow-up of 3.7 (IQR 1.7–5.5) years, 150 (37%) died. On multivariable Cox regression analysis, cardiac damage Stage 3 (HR vs. Stage 0: 4.496, $P = 0.039$) and Stage 4 (HR vs. Stage 0: 5.565, $P = 0.020$) were independently associated with all-cause mortality.

Conclusion The MDCT-based staging system of cardiac damage in severe AS effectively identifies the patients who are at higher risk of death after TAVI.

Keywords aortic stenosis • extra-aortic valvular cardiac damage • multidetector computed tomography

Introduction

Aortic stenosis (AS) is one of the most prevalent valvular heart diseases and is predicted to increase in prevalence along with the ageing of the population. In the current recommendations of the European Society of Cardiology and American College of Cardiology/American Heart Association guidelines,[1,2] aortic valve intervention is recommended in patients with symptomatic severe AS and/or left ventricular (LV) systolic dysfunction, defined as LV ejection fraction (EF) <50%. However, recent studies demonstrated the association between extra-aortic valvular cardiac damage and the prognosis of patients with severe AS.[3–5] Généreux *et al.*[4] proposed the new staging system of extra-aortic valvular cardiac damage using 2D transthoracic echocardiography (TTE) and showed the prognostic value in patients included in the PARTNER II (Placement of AoRTic TraNscathetER Valves) trial treated with transcatheter aortic valve implantation (TAVI). Patients treated with TAVI undergo multidetector row computed tomography (MDCT) to select the prosthesis size and evaluate the feasibility of transfemoral access. MDCT data acquired along the cardiac cycle permit assessment of 3D LV and right ventricular (RV) systolic function and quantification of cardiac chamber volumes.[6] We hypothesized that the staging of extra-

* Corresponding author. Tel: +31 (7) 15 262 020; Fax: +31 (7) 15 266 809. E-mail: j.j.bax@lumc.nl

aortic valvular cardiac damage based on MDCT evaluation can be used as an alternative of the proposed staging system based on TTE.[4] The purpose of this study is to evaluate the impact of an MDCT-derived staging system of severe AS on the outcomes of patients undergoing TAVI.

Methods

Study population and data collection

A total of 445 patients who had undergone a full-beat MDCT scan prior to TAVI at the Leiden University Medical Centre in the Netherlands, were included in this retrospective analysis. Patients were enrolled from November 2007 to August 2019. Patients with intracardiac devices ($n = 22$), prior valvular procedures ($n = 5$), insufficient quality of the MDCT images ($n = 7$), or patients who died due to complications related to the TAVI procedure ($n = 6$) were excluded (*Figure 1*). The baseline demographic, clinical and procedural data were collected from the medical record system of the cardiology department (EPD-Vision version 12.5.4, Leiden, The Netherlands). Due to the retrospective design of current analysis, the institutional review board approved this retrospective analysis of clinically acquired data without the need for patient's written informed consent. The data that supports the findings of this study are available on reasonable request to the corresponding author.

Clinical and echocardiographic parameters

Demographic, clinical data including New York Heart Association (NYHA) functional class symptoms, comorbidities, renal function, heart rhythm, and medications as well as procedural variables were collected from the departmental cardiology information system (EPD-Vision 11.8.4.0). TTE was performed within 1 month prior to the TAVI procedure using commercially available ultrasound systems. Aortic valve area (AVA) was calculated according to the continuous equation and indexed for body surface area (BSA).

MDCT data acquisition and analysis

Clinically indicated MDCT scans were performed for the planning of the TAVI procedure with an helical 64-slice detector scanner (Aquilion 64; Toshiba Medical Systems, Otawara, Japan); or a volumetric 320-slice detector scanner (AquilionOne, Toshiba Medical Systems, Tochigi-ken, Japan) using dedicated protocols, as described in detail before.[7,8] The median time period between the date of MDCT and the date of TAVI was 28 days [interquartile range (IQR): 5–88 days]. The entire cardiac cycle was imaged and prospective electrocardiographic-triggered dose modulation was applied. The estimated mean radiation dose for 64-slice scanner ($n = 18$) was 20.7 ± 6.9 mSv. The estimated mean radiation dose for the full-beat acquired, dynamic 320-slice scanner ($n = 387$) was 11.3 ± 6.7 mSv, and ranged from 2.5 to 40.1 mSv, dependent on body size composition and heart rate. Reconstructions were made at each 10% of the RR interval which were subsequently transferred to a remote work station for offline analysis.

The MDCT images were analysed using 3mensio software (version 10.0, Pie Medical Imaging, Bilthoven, The Netherlands). For volumetric chamber quantification, the entire cardiac cycle was visually analysed to define the reconstructions with the end-systolic and end-diastolic phases. Subsequently, the endocardial borders of the right and left atria and ventricles were manually traced at the end-systolic and end-diastolic phases on 4-mm slices enabling the calculation of volumes (*Figure 2*). Next, the LV and RV end-diastolic volumes (EDV) and end-systolic volumes (ESV)

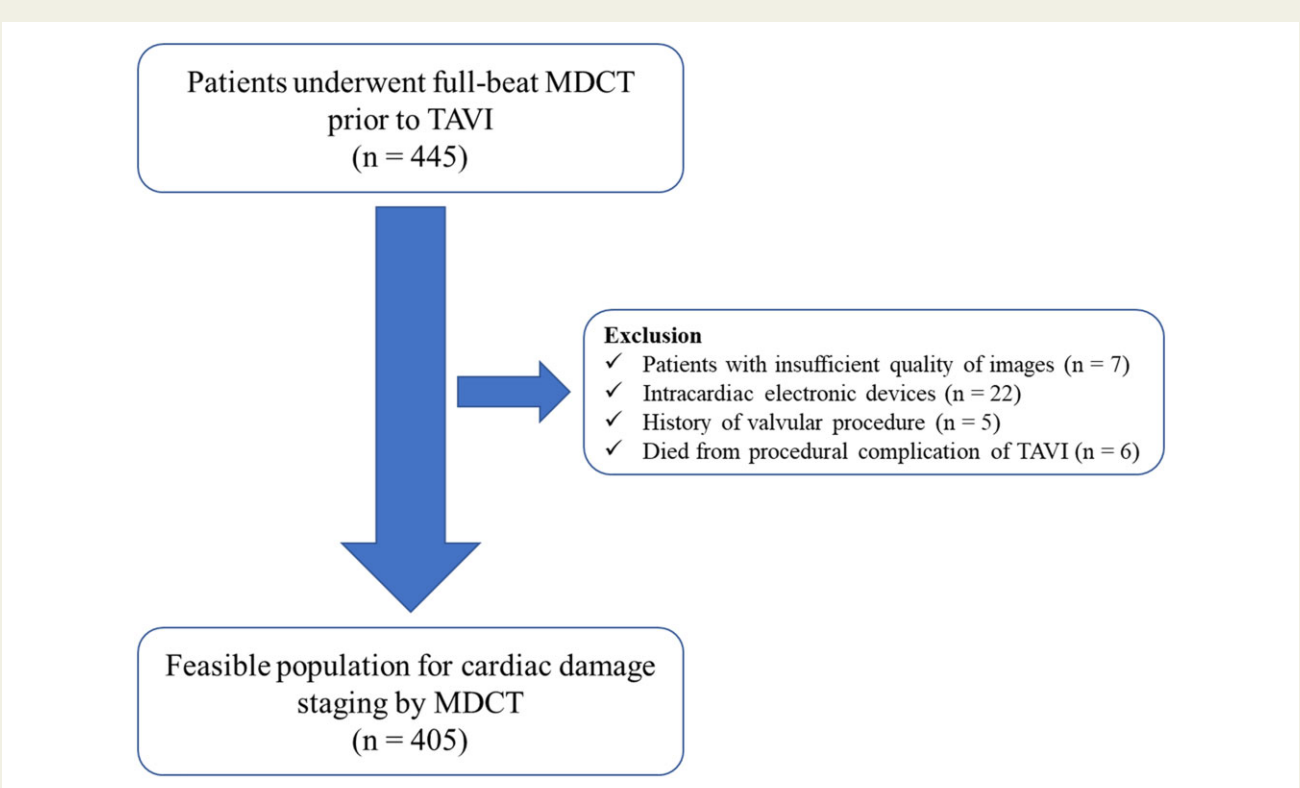
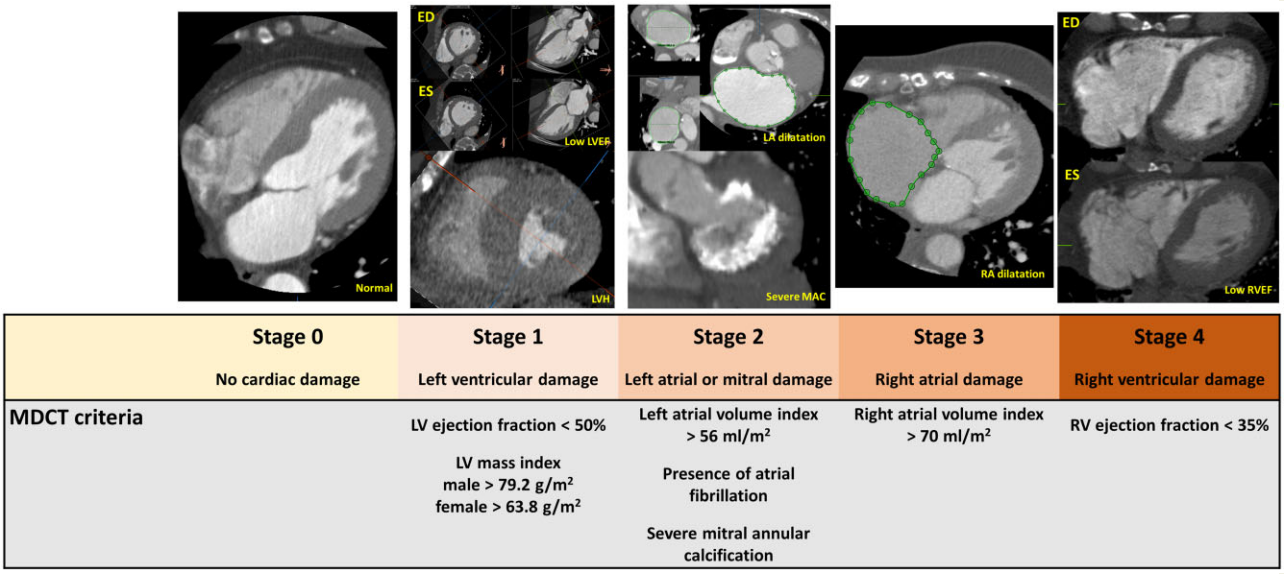


Figure 1 Study flowchart. MDCT, multidetector computed tomography; TAVI, transcatheter aortic valve implantation.



	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No cardiac damage	Left ventricular damage	Left atrial or mitral damage	Right atrial damage	Right ventricular damage
MDCT criteria		LV ejection fraction < 50% LV mass index male > 79.2 g/m^2 female > 63.8 g/m^2	Left atrial volume index > 56 ml/m^2 Presence of atrial fibrillation Severe mitral annular calcification	Right atrial volume index > 70 ml/m^2	RV ejection fraction < 35%

Figure 2 Definition of staging classification using MDCT in AS. Staging classification of AS based on the extent of extra-aortic cardiac damage evaluated using MDCT. ED, end-diastole; ES, end-systole; MAC, mitral annular calcification; MDCT, multidetector computed tomography; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; RA, right atrium; RV, right ventricle; RVEF, right ventricular ejection fraction.

were assessed and indexed for BSA. RVEF and LVEF were calculated using the following formula: EF (%) = [(EDV - ESV)/EDV] × 100. Left atrial (LA) and right atrial (RA) volumes were measured (*Figure 2*) at end-systole and were indexed for BSA (LAVI and RAVI). To estimate the degree of LV hypertrophy, the epicardial LV border was manually traced at the end-diastolic phase as previously described (*Figure 2*).[9,10] Subsequently, LV mass index was calculated with the following formula: LV mass index = [(LV epicardial volume - EDV) × 1.05]/BSA.[9,10] The severity of mitral annular calcification (MAC) was qualitatively assessed and categorized into a 0–3 graded scale according to the degree of circumferential involvement of the mitral ring as previously described (*Figure 2*)[11]: Grade 0 or normal mitral annulus when there was no MAC, Grade 1, or mild MAC when <1/3 of the annulus was involved, Grade 2 or moderate MAC when 1/3 to 1/2 of the annulus was involved, and Grade 3 when there was severe MAC on more than half of the mitral annular circumference.

Definitions of cardiac damage staging classification

Similar to previous staging algorithms that classified with echocardiography the extent of extra-aortic valve cardiac damage in patients with severe AS,[3–5] the following clinical and MDCT characteristics were used for MDCT-based staging classification. Stage 0 includes patients in whom no cardiac damage was observed. Stage 1 is defined by the presence of LV damage due to LV hypertrophy[12,13] (LV mass index > 79.2 g/m^2 for men, > 63.8 g/m^2 for women) or LV systolic dysfunction (LVEF < 50%). Stage 2 is defined by the presence of LA dilation (LAVI> 56 mL/m^2),[14] mitral valve damage (Grade 3 MAC), or atrial fibrillation. In the absence of MDCT-defined cut-off values that define significant RA dilatation or RV dysfunction, a spline curve analysis was used to evaluate the change in the risk of all-cause mortality over a range of RAVI and RVEF in this study population (Supplementary data online, *Figure S1*). For RAVI, the spline curve revealed an excess risk of all-cause mortality for volumes >70 mL/m^2. For RVEF, the spline curve revealed an excess risk of all-cause mortality for values <35%. Because these values provided prognostic implications in this specific population, RA dilatation reflected by a RAVI >70 mL/m^2 was chosen to define Stage 3 of cardiac damage and RV dysfunction defined as RVEF <35% was chosen to define Stage 4 of cardiac damage. Patients were classified according to the cardiac anomaly defining the most advanced stage of cardiac damage.

Follow-up

The primary endpoint was overall mortality after TAVI. Mortality data were collected by review of the individual medical patient records which are linked to the governmental death registry.

Statistical analysis

Continuous data are presented as mean ± standard deviation or median and interquartile range, as appropriate, and compared between the groups using the analysis of variance test and Bonferroni's correction for multiple comparisons. Categorical variables were expressed as frequency (percentage) and compared with the χ^2 or Fisher's exact test as appropriate. Kaplan–Meier analyses and log-rank tests were used to analyse the cumulative events of all-cause mortality and compared them across the stages of cardiac damage. In addition, a Kaplan–Meier landmark analysis including patients who survived the first 30 days after the procedure was performed. Univariable Cox proportional hazards analyses were used to identify the clinical factors that were associated with all-cause mortality. Subsequently, parameters that were statistically significant in the univariate model were included in the multivariate Cox proportional hazard model. The hazard ratio (HR) and the 95% confidence interval (CI) are presented. Two-sided *P*-values of <0.05 were used to define statistical significance. The statistical analyses were performed using SPSS software

version 25 (SPSS, Inc., Chicago, IL, USA) and in R environment (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

Demographic and clinical characteristics for the overall population ($n = 405$, mean age 80 ± 7 years, 52% male) and MDCT-derived cardiac damage stages are shown in *Table 1*. Overall, the majority of the patients had hypertension (76%), 61% of the patients had coronary artery disease, and 20% had atrial fibrillation. A significant proportion of patients presented with NYHA functional class III or IV heart failure symptoms. The TAVI procedure was performed using a transapical approach in 31% of the patients. The results of the MDCT analysis of the overall population and of the subgroups stratified according to the cardiac damage stage are shown in *Table 2*. In the overall population, the mean MDCT-derived LVEF was 54 ± 15%, the RVEF 48 ± 12%, and the LV mass index was 90 ± 22 g/m^2. The mean LAVI was 62 ± 19 mL/m^2 and the mean RAVI 60 ± 22 mL/m^2.

Staging cardiac damage

According to the MDCT-derived cardiac damage staging algorithm, 27 patients (6.7%) were in Stage 0 (no cardiac damage), 96 patients (23.7%) in Stage 1 (LV damage), 152 patients (37.5%) in Stage 2 (atrial fibrillation or LA or mitral damage), 78 patients (19.3%) in Stage 3 (RA damage), and 52 patients (12.8%) in Stage 4 (RV damage) (*Figure 3*). The distribution of the specific components of MDCT-assessed cardiac damage is shown in *Table 3*. LV hypertrophy was present in 82% of the patients, RA dilation in 26%, whereas RV dysfunction was present in 13% of the patients. The proportion of men was higher in Stages 3 and 4 (67% and 54%, respectively). Based on the definition of staging, atrial fibrillation was more frequently present in the more advanced stages of cardiac damage. The use of diuretic medication increased along with the stage of cardiac damage.

Compared to previously published staging classification based on TTE,[3] MDCT-derived cardiac damage staging algorithm led to larger proportion of patients classified as Stage 1 and less patients in Stage 4 [TTE-derived staging algorithm: 20 patients (5%) were in Stage 0, 55 (14%) in Stage 1, 154 (38%) in Stage 2, 74 (18%) in Stage 3, 102 (25%) in Stage 4].

Table 1 Baseline demographic and clinical characteristics of total patients and according to the cardiac damage staging

	All ($n = 405$)	Stage 0 ($n = 27$)	Stage 1 ($n = 96$)	Stage 2 ($n = 152$)	Stage 3 ($n = 78$)	Stage 4 ($n = 52$)	*P*-value
Age, years	80 ± 7	80 ± 6	78 ± 9	81 ± 6	81 ± 6	80 ± 8	0.063
Male, %	212 (52%)	12 (44%)	54 (56%)	66 (43%)	52 (67%)	28 (54%)	0.014
BSA, m^2	1.85 ± 0.21	1.85 ± 0.22	1.85 ± 0.19	1.82 ± 0.19	1.90 ± 0.19	1.86 ± 0.28	0.089
Hypertension, (%)	309 (76%)	23 (85%)	76 (79%)	116 (76%)	53 (68%)	41 (79%)	0.307
Dyslipidaemia, (%)	264 (65%)	19 (70%)	69 (72%)	95 (63%)	52 (67%)	29 (56%)	0.308
Diabetes, (%)	115 (28%)	8 (30%)	34 (35%)	38 (25%)	21 (27%)	14 (27%)	0.501
Coronary artery disease, (%)	246 (61%)	19 (70%)	59 (62%)	96 (63%)	47 (60%)	25 (48%)	0.293
Chronic obstructive pulmonary disease, (%)	90 (22%)	1 (4%)	24 (25%)	32 (21%)	20 (26%)	13 (25%)	0.155
Atrial fibrillation, (%)	80 (20%)	0 (0%)	0 (0%)	22 (15%)	39 (50%)	19 (37%)	<0.001
eGFR, mL/min/1.73 m^2	67 ± 24	70 ± 21	70 ± 25	67 ± 24	69 ± 24	60 ± 22	0.152
Medication							
ACE inhibitor or ARB (%)	216 (53%)	16 (59%)	46 (48%)	58 (56%)	74 (54%)	24 (44%)	0.414
Diuretics (%)	223 (54%)	10 (37%)	42 (47%)	56 (54%)	73 (54%)	42 (78%)	<0.001
Beta blockers (%)	256 (62%)	15 (56%)	62 (65%)	59 (57%)	91 (67%)	34 (63%)	0.930
NYHA functional classification							
I	30 (7%)	2 (7%)	7 (7%)	16 (11%)	2 (3%)	3 (6%)	0.481
II	140 (35%)	9 (33%)	32 (33%)	54 (36%)	30 (39%)	15 (29%)	
III	198 (49%)	14 (52%)	51 (53%)	68 (45%)	40 (51%)	25 (49%)	
IV	37 (9%)	2 (7%)	6 (6%)	14 (9%)	6 (8%)	9 (17%)	
Transapical approach, (%)	125 (31%)	4 (14%)	22 (23%)	55 (36%)	27 (35%)	17 (33%)	0.064

Values are expressed as mean ± SD or *n* (%).
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BSA, body surface area; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.
P-values depict difference between cardiac damage stages are calculated by analysis of variance for continuous values with normal distribution, Kruskal–Walls *H* test for continuous values with non-normal distribution, and chi-square test for categorical data, respectively.

Table 2 Baseline MDCT parameter of total patients and according to the cardiac damage staging

	All ($n = 405$)	Stage 0 ($n = 27$)	Stage 1 ($n = 96$)	Stage 2 ($n = 152$)	Stage 3 ($n = 78$)	Stage 4 ($n = 52$)	*P*-value[a]
LVEDV, mL	161 ± 53	132 ± 30	149 ± 45	159 ± 45	167 ± 47[b]	196 ± 83[b,c,d,e]	<0.001
LVESV, mL	79 ± 50	51 ± 18	68 ± 40	73 ± 39	82 ± 40[b]	128 ± 80[b,c,d,e]	<0.001
Indexed LVEDV, mL/m^2	87 ± 26	71 ± 12	81 ± 23	87 ± 22[b]	88 ± 22[b]	105 ± 40[b,c,d,e]	<0.001
Indexed LVESV, mL/m^2	42 ± 26	27 ± 8	37 ± 22	40 ± 21	43 ± 20[b]	68 ± 41[b,c,d,e]	<0.001
LVEF, %	54 ± 15	62 ± 7	57 ± 15	57 ± 14	53 ± 13[b]	39 ± 18[b,c,d,e]	<0.001
LV mass index, g/m^2	90 ± 22	65 ± 14	90 ± 18[b]	92 ± 22[b]	92 ± 23[b]	96 ± 26[b]	<0.001
LA volume, mL	114 ± 37	84 ± 13	86 ± 15	118 ± 22[b,c]	142 ± 51[b,c,d]	130 ± 35[b,c]	<0.001
LAVI, mL/m^2	62 ± 19	45 ± 6	47 ± 7	65 ± 11[b,c]	75 ± 27[b,c,d]	71 ± 20[b,c]	<0.001
RA volume, mL	112 ± 45	83 ± 20	84 ± 20	97 ± 23[c]	170 ± 43[b,c,d]	132 ± 52[b,c,d,e]	<0.001
RAVI, mL/m^2	60 ± 22	45 ± 10	46 ± 10	53 ± 11[b,c]	89 ± 19[b,c,d]	72 ± 27[b,c,d,e]	<0.001
RVEDV, mL	145 ± 40	130 ± 25	131 ± 31	136 ± 31	173 ± 42[b,c,d]	163 ± 52[b,c,d]	<0.001
RVESV, mL	76 ± 30	65 ± 17	62 ± 21	66 ± 20	88 ± 24[b,c,d]	119 ± 37[b,c,d,e]	<0.001
Indexed RVEDV, mL/m^2	78 ± 20	70 ± 12	71 ± 14	75 ± 14	91 ± 19[b,c,d]	89 ± 31[b,c,d]	<0.001
Indexed RVESV, mL/m^2	41 ± 16	35 ± 8	33 ± 10	36 ± 10	46 ± 11[b,c,d]	64 ± 22[b,c,d,e]	<0.001
RVEF, %	48 ± 12	50 ± 7	53 ± 9	52 ± 9	49 ± 8[c]	27 ± 6[b,c,d,e]	<0.001

Values are expressed as mean ± SD.
LA, left atrium; LAVI, indexed left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; RA, right atrium; RAVI, indexed right atrial volume; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume.
[a]*P*-values depict difference between cardiac damage stages are calculated by analysis of variance for continuous values with normal distribution, Kruskal–Walls *H* test for continuous values with non-normal distribution, respectively.
[b]$P < 0.05$ vs. stage 0 with Bonferroni's *post hoc* analysis.
[c]$P < 0.05$ vs. stage 1 with Bonferroni's *post hoc* analysis.
[d]$P < 0.05$ vs. stage 2 with Bonferroni's *post hoc* analysis.
[e]$P < 0.05$ vs. stage 3 with Bonferroni's *post hoc* analysis.

Survival analysis

During a median follow-up of 3.7 years (IQR: 1.7–5.5 years), 150 patients (37%) died. The Kaplan–Meier analysis revealed a significantly higher 5-year mortality rate in patients with more advanced stages of cardiac damage (log-rank χ^2 23.4; $P < 0.001$, *Figure 4A*). The Kaplan–Meier landmark analysis, including only patients who survived the first 30 days after TAVI, showed significantly higher event rates in Stages 3 and 4 (log-rank χ^2 14.1: $P = 0.007$, *Figure 4B*).

In univariate Cox proportional hazards analysis, the stage of cardiac damage was associated with all-cause mortality (HR: 1.406; 95% CI: 1.210–1.634, $P < 0.001$). Compared to cardiac damage Stage 0, Stage 3 (HR: 5.500; 95% CI: 1.324–22.85, $P = 0.019$) and Stage 4 (HR: 7.562; 95% CI: 1.809–32.51, $P = 0.006$) were significantly associated with a higher risk of all-cause mortality (*Table 4*). Furthermore, NYHA functional class ≥III, lower estimated glomerular filtration rate (eGFR), use of diuretics, the presence of chronic obstructive pulmonary disease and transapical TAVI were significantly associated with increased mortality. On multivariate analysis, the presence of chronic obstructive pulmonary disease, lower eGFR, transapical TAVI, and MDCT-derived stage of cardiac damage remained independently associated with all-cause mortality. Compared to cardiac damage Stage 0, the adjusted HR for all-cause mortality of Stages 3 and 4 were 4.496 (95% CI: 1.318–18.80, $P = 0.039$) and 5.565 (95% CI: 1.172–23.51, $P = 0.020$), respectively (*Table 4*).

The Kaplan–Meier survival curves using the TTE-derived cardiac damage staging classification showed similar results to those of MDCT-derived algorithm (Supplementary data online, *Figure S1*). The uni- and multivariate Cox regression analyses, each increase in stage was associated with increased risk of all-cause mortality (Supplementary data online, *Table S1*).

Discussion

This study demonstrates that the degree of extra-aortic valvular damage using an MDCT-based staging system is associated with all-cause mortality in patients with severe AS treated with TAVI. The presence of significant cardiac damage, represented by RA dilation (Stage 3) and RV dysfunction (Stage 4), may reflect irreversible damage secondary to pressure overload, and these stages were independently associated with increased risk of all-cause mortality. The present study suggests that the MDCT staging may fulfil an important role in the risk stratification of patients who are evaluated for TAVI and that this technique could be a complementary to the TTE-based staging system.

The relevance of MDCT-derived cardiac damage staging

Previous studies have shown the additional prognostic value of the assessment and staging of extra-aortic valve cardiac damage staging in

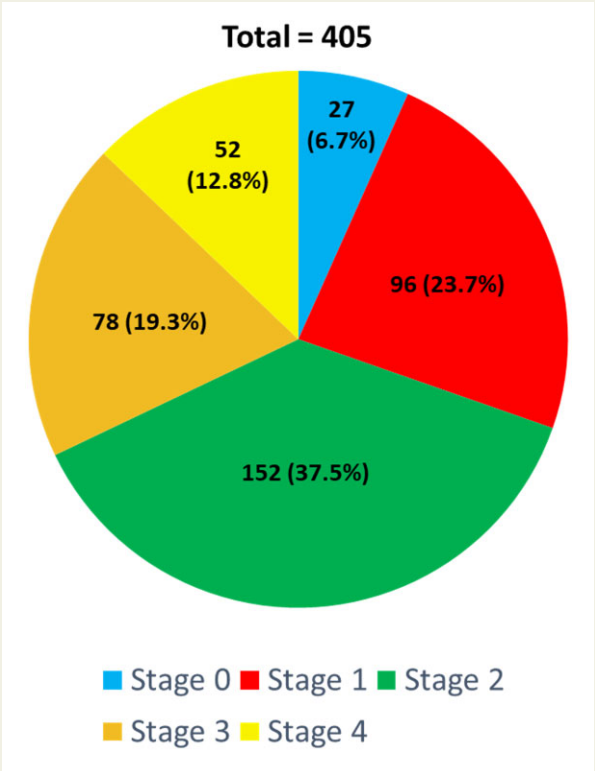


Figure 3 Distribution of cardiac damage stages using MDCT in total population.

Table 3 The individual components according to cardiac damage staging using MDCT

Stage 0: no damage	27/405
Stage 1: LV damage	96/405
Increased LV mass index	
>79.2 g/m^2 for men or	331/405 (82%)
>63.8 g/m^2 for women	
LV ejection fraction < 50%	144/405 (36%)
Stage 2: LA or mitral valve damage	152/405
Indexed LA volume > 56 mL/m^2	236/405 (58%)
Presence of severe MAC	52/405 (13%)
Presence of AF at time of MDCT	80/405 (20%)
Stage 3: RA damage	78/405
Indexed RA volume > 70 mL/m^2	106/405 (26%)
Stage 4: RV damage	52/405
RV ejection fraction < 35%	52/405 (13%)

Values are expressed as *n*/*N* or *n* (%).
AF, atrial fibrillation; LA, left atrial; LV, left ventricular; MAC, mitral annular calcification; RA, right atrial; RV, right ventricular.

patients with AS who are evaluated for TAVI using TTE.[3–5] One important advantage of the use of MDCT over TTE for the assessment of extra-aortic valvular damage is that MDCT enables high spatial resolution images in 3D over all four cardiac chambers enabling more accurate assessment of wall thickness, valvular calcifications, and chamber dilation.[6,15–17]

The proposed MDCT-derived staging system partly incorporates parameters that are based on the 2D TTE-derived staging characteristics and, additionally, other parameters that are better assessed with 3D imaging. The relevance and reference values of left-sided measurements including LVEF,[15] LV mass index,[10,12,18] and LAVI[14,16] as analysed by MDCT have been shown before. The severity of MAC was also included for defining mitral damage (Stage 2), since it was previously shown to be associated with increasing mortality.[11,19] However, in contrast to the TTE-based staging system in which the severity of tricuspid regurgitation (TR) is assessed, current MDCT study assessed the severity of RA volume for the definition of Stage 3, as RA volume is strongly associated with significant TR,[20] and can be also a marker of RV diastolic dysfunction. In addition, 3D assessed RVEF is considered as a reference method for RV systolic function and this parameter was used to define Stage 4.[21,22] Since prognostic values for RAVI and RVEF have not yet been defined in patients with severe AS undergoing TAVI, spline curve analyses were performed which demonstrated relevant cut-off values of >70 mL/m^2 for RAVI and of <35% for RVEF (Supplementary data online, *Figure S2*).

The clinical implication of MDCT-derived staging

In this study, the prevalence of the different stages of cardiac damage was fairly similar to the TTE-based studies.[3–5] After correcting for several important clinical factors, MDCT-assessed right heart damage (Stages 3 and 4) was independently associated with all-cause mortality in patients undergoing TAVI. This study confirms the hypothesis that significant RA dilation indicates longstanding pressure overload reflecting a marker of late, and potentially irreversible damage.[3–5]

Asami *et al.*[23] have shown in 1116 patients undergoing TAVI that RV dysfunction (as assessed with echocardiographic tricuspid annular plane systolic excursion and systolic movement of the RV lateral wall by tissue Doppler imaging) was associated with 1-year cardiovascular mortality [HR 2.94 (95% CI 2.02–4.27), $P < 0.001$]. In the present cohort, RV function was assessed by 3 D RVEF and the landmark analysis of 30-days after TAVI (to minimize procedure-related death) showed that patients with RV failure had a higher mortality risk (*Figure 4B*). Consequently, MDCT may identify those patients who require more accurate post-procedural and outpatient clinic monitoring.

The majority of patients undergoing TAVI are evaluated with a preprocedural MDCT for prosthesis sizing and determining the feasibility of transfemoral access. Therefore, the current MDCT staging system of cardiac damage could be easily implemented in the preprocedural MDCT analysis.

Study limitations

First, the current study is single-centre retrospective observational study and had limitations inherent to the study design. Second, this study included a relatively old cohort with a significant proportion (31%) of patients who were treated with a transapical TAVI. Third, the cut-off values of RVEF and RAVI for the MDCT-derived staging were defined from spline curve analysis using the same cohort of patients. Therefore, the optimal cut-off values of RVEF and RAVI for risk stratification should be confirmed in other populations.

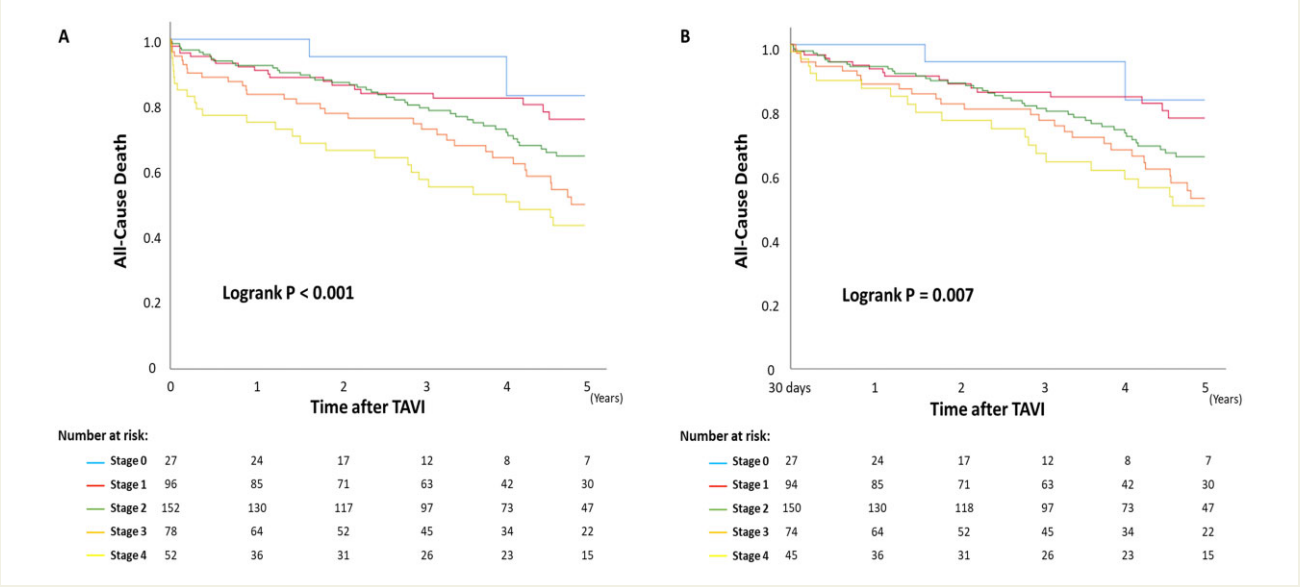


Figure 4 Survival analysis according to the extent of cardiac damage using MDCT staging system. (*A*) Kaplan–Meier analysis for mortality including all patients and (*B*) Landmark Kaplan–Meier analysis for mortality after 30 days. TAVI, transcatheter aortic valve implantation.

Table 4 Univariable and multivariable Cox regression for all-cause mortality after TAVI

	Univariable			Multivariable		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Stage of cardiac damage, per 1 stage increase	1.406	1.210–1.634	<0.001			
Stages according to cardiac damage						
Stage 1 vs. Stage 0	3.162	0.752–13.302	0.116	2.637	0.623–11.163	0.188
Stage 2 vs. Stage 0	3.755	0.915–15.408	0.066	2.929	0.709–12.104	0.138
Stage 3 vs. Stage 0	5.500	1.324–22.850	0.019	4.496	1.318–18.797	0.039
Stage 4 vs. Stage 0	7.562	1.809–32.511	0.006	5.565	1.172–23.506	0.020
Age, per 1 year increase	0.982	0.962–1.002	0.082	—	—	—
Male, yes/no	1.259	0.912–1.738	0.162	—	—	—
Coronary artery disease, yes/no	1.306	0.931–1.831	0.122	—	—	—
COPD, yes/no	1.785	1.258–2.532	0.001	1.674	1.172–2.390	0.005
NYHA functional class ≥ III, yes/no	1.482	1.059–2.073	0.022	1.387	0.986–1.951	0.060
eGFR, per 1 mL/min/1.73m^2 increase	0.987	0.980–0.995	0.001	0.991	0.983–0.999	0.024
SBP, 1 mmHg increase	0.994	0.987–1.001	0.091			
Diuretic, yes/no	1.705	1.210–2.404	0.002	1.158	0.799–1.680	0.438
Indexed AVA, per 0.01 cm^2/m^2 increase	0.995	0.980–1.009	0.461			
Transapical approach, yes/no	1.623	1.177–2.239	0.003	1.498	1.076–2.084	0.017

AVA, aortic valve area; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NYHA, New York Heart Association; SBP, systolic blood pressure.

Conclusions

In patients with severe AS who are evaluated for TAVI, the assessment of extra-aortic valve cardiac damage using MDCT may help to identify those patients with the highest long-term risk for mortality after TAVI. In particular, the presence of RA (Stage 3) and RV damage (Stage 4) were independently associated with a high risk for all-cause mortality.

Supplementary data

Supplementary data are available at *European Heart Journal–Cardiovascular Imaging* online.

Funding

K.H. was financially supported by an ESC research grant [R-2018-18122].

Conflict of interest: The Department of Cardiology of the Leiden University Medical Centre received research grants from Abbott Vascular, Bayer, Bioventrix, Medtronic, Biotronik, Boston Scientific, GE Healthcare, and Edwards Lifesciences. N.A.M. and J.J.B. received speaker fees from Abbott Vascular. V.D. received speaker fees from Abbott Vascular, Edwards Lifesciences, GE Healthcare, MSD, Novartis, and Medtronic. J.K. received consultancy fees from GE Healthcare and AstraZeneca and speaker fees from GE Healthcare, Bayer, Lundbeck and Merck, outside of the submitted work. The remaining authors have nothing to disclose.

References

1. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ *et al.*; ESC Scientific Document Group. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–91.
2. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA *et al.* 2014 aha/acc guideline for the management of patients with valvular heart disease: a report of the American college of cardiology/American heart association task force on practice guidelines. *J Am Coll Cardiol* 2014;**63**:e57–185.
3. Vollema EM, Amanullah MR, Ng ACT, van der Bijl P, Prevedello F, Sin YK *et al.* Staging cardiac damage in patients with symptomatic aortic valve stenosis. *J Am Coll Cardiol* 2019;**74**:538–49.
4. Genereux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA *et al.* Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J* 2017;**38**:3351–8.
5. Tastet L, Tribouilloy C, Marechaux S, Vollema EM, Delgado V, Salaun E *et al.* Staging cardiac damage in patients with asymptomatic aortic valve stenosis. *J Am Coll Cardiol* 2019;**74**:550–63.
6. Greupner J, Zimmermann E, Grohmann A, Dubel HP, Althoff TF, Borges AC *et al.* Head-to-head comparison of left ventricular function assessment with 64-row computed tomography, biplane left cineventriculography, and both 2- and 3-dimensional transthoracic echocardiography: comparison with magnetic resonance imaging as the reference standard. *J Am Coll Cardiol* 2012;**59**:1897–907.
7. van Velzen JE, Schuijf JD, de Graaf FR, Boersma E, Pundziute G, Spano F *et al.* Diagnostic performance of non-invasive multidetector computed tomography coronary angiography to detect coronary artery disease using different endpoints: detection of significant stenosis vs. detection of atherosclerosis. *Eur Heart J* 2011;**32**:637–45.
8. van Rosendael PJ, Joyce E, Katsanos S, Debonnaire P, Kamperidis V, van der Kley F *et al.* Tricuspid valve remodelling in functional tricuspid regurgitation: multidetector row computed tomography insights. *Eur Heart J Cardiovasc Imaging* 2016;**17**:96–105.
9. Raman SV, Shah M, McCarthy B, Garcia A, Ferketich AK. Multi-detector row cardiac computed tomography accurately quantifies right and left ventricular size and function compared with cardiac magnetic resonance. *Am Heart J* 2006;**151**:736–44.
10. Budoff MJ, Ahmadi N, Sarraf G, Gao Y, Chow D, Flores F *et al.* Determination of left ventricular mass on cardiac computed tomographic angiography. *Acad Radiol* 2009;**16**:726–32.
11. Abramowitz Y, Kazuno Y, Chakravarty T, Kawamori H, Maeno Y, Anderson D *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.
12. Mao SS, Li D, Rosenthal DG, Cerilles M, Zeb I, Wu H *et al.* Dual-standard reference values of left ventricular volumetric parameters by multidetector ct angiography. *J Cardiovasc Comput Tomogr* 2013;**7**:234–40.
13. Klein R, Ametepe ES, Yam Y, Dwivedi G, Chow BJ. Cardiac CT assessment of left ventricular mass in mid-diastasis and its prognostic value. *Eur Heart J Cardiovasc Imaging* 2017;**18**:95–102.
14. Truong QA, Charipar EM, Ptaszek LM, Taylor C, Fontes JD, Kriegel M *et al.* Usefulness of electrocardiographic parameters as compared with computed tomography measures of left atrial volume enlargement: from the romicat trial. *J Electrocardiol* 2011;**44**:257–64.
15. Asferg C, Usinger L, Kristensen TS, Abdulla J. Accuracy of multi-slice computed tomography for measurement of left ventricular ejection fraction compared with cardiac magnetic resonance imaging and two-dimensional transthoracic echocardiography: a systematic review and meta-analysis. *Eur J Radiol* 2012;**81**:e757–62.
16. Arsanjani R, Flint N, Beigel R, Khachatryan T, Shalev A, Shturman A *et al.* Comparison of accuracy of left atrial area and volume by two-dimensional transthoracic echocardiography versus computed tomography. *Am J Cardiol* 2019;**123**:1180–4.
17. Takahashi A, Funabashi N, Kataoka A, Yajima R, Takahashi M, Uehara M *et al.* Quantitative evaluation of right atrial volume and right atrial emptying fraction by 320-slice computed tomography compared with three-dimensional echocardiography. *Int J Cardiol* 2011;**146**:96–9.
18. Juneau D, Erthal F, Clarkin O, Alzahrani A, Alenazy A, Hossain A *et al.* Mid-diastolic left ventricular volume and mass: normal values for coronary computed tomography angiography. *J Cardiovasc Comput Tomogr* 2017;**11**:135–40.
19. Okuno T, Asami M, Khan F, Praz F, Heg D, Lanz J *et al.* Does isolated mitral annular calcification in the absence of mitral valve disease affect clinical outcomes after transcatheter aortic valve replacement? *Eur Heart J Cardiovasc Imaging* 2020;**21**:522–32.
20. Nemoto N, Schwartz JG, Lesser JR, Pedersen WD, Sorajja P, Garberich R *et al.* The right atrium and tricuspid annulus are cardinal structures in tricuspid regurgitation with or without pulmonary hypertension. *Int J Cardiol* 2017;**230**:171–4.
21. Surkova E, Muraru D, Iliceto S, Badano LP. The use of multimodality cardiovascular imaging to assess right ventricular size and function. *Int J Cardiol* 2016;**214**:54–69.
22. Valsangiacomo Buechel ER, Mertens LL. Imaging the right heart: the use of integrated multimodality imaging. *Eur Heart J* 2012;**33**:949–60.
23. Asami M, Stortecky S, Praz F, Lanz J, Raber L, Franzone A *et al.* Prognostic value of right ventricular dysfunction on clinical outcomes after transcatheter aortic valve replacement. *JACC Cardiovasc Imaging* 2019;**12**:577–87.