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Staging Cardiac Damage in Patients With Symptomatic Aortic Valve Stenosis

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ABSTRACT

BACKGROUND In severe aortic stenosis (AS), patients often show extra-aortic valvular injury. Recently, a new staging system for severe AS has been proposed on the basis of the extent of cardiac damage.

OBJECTIVES The present study evaluated the prevalence and prognostic impact of these different stages of cardiac damage in a large, real-world, multicenter cohort of symptomatic severe AS patients.

METHODS From the ongoing registries from 2 academic institutions, a total of 1,189 symptomatic severe AS patients were selected and retrospectively analyzed. According to the extent of cardiac damage on echocardiography, patients were classified as Stage 0 (no cardiac damage), Stage 1 (left ventricular damage), Stage 2 (mitral valve or left atrial damage), Stage 3 (tricuspid valve or pulmonary artery vasculature damage), or Stage 4 (right ventricular damage). Patients were followed for all-cause mortality and combined endpoint (all-cause mortality, stroke, and cardiac-related hospitalization).

RESULTS On the basis of the proposed classification, 8% of patients were classified as Stage 0, 24% as Stage 1, 49% as Stage 2, 7% as Stage 3, and 12% as Stage 4. On multivariable analysis, cardiac damage was independently associated with all-cause mortality and combined outcome, although this was mainly determined by Stages 3 and 4.

CONCLUSIONS In this large multicenter cohort of symptomatic severe AS patients, stage of cardiac injury as classified by a novel staging system was independently associated with all-cause mortality and combined endpoint, although this seemed to be predominantly driven by tricuspid valve or pulmonary artery vasculature damage (Stage 3) and right ventricular dysfunction (Stage 4). (J Am Coll Cardiol 2019;74:538–49) © 2019 by the American College of Cardiology Foundation.

In aortic stenosis (AS), referral for aortic valve replacement (AVR) is currently driven by the severity of AS and by the presence of AS-related symptoms or signs of left ventricular (LV) systolic dysfunction (defined as an LV ejection fraction <50%) (1,2). Severity of AS is primarily quantified on echocardiography using hemodynamic parameters of the aortic valve specifically, that is, mean

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transvalvular pressure gradient, peak aortic jet velocity, and aortic valve area (3). However, the clinical outcomes of patients with severe AS are not influenced by the stenotic aortic valve only. Changes in the LV structure and function as well as hemodynamic consequences beyond the LV such as significant mitral (4,5) and tricuspid regurgitation (5,6), and right ventricular (RV) dysfunction (7,8) have been associated with poor outcomes in patients with severe AS undergoing AVR. Recently, a new staging system for severe AS has been proposed on the basis of the extent of anatomic and functional cardiac damage (9). Généreux et al. (9) demonstrated the strong predictive value of a proposed model to stage patients with severe AS who were included for the PARTNER II (Placement of AoRTic TraNscathetER Valves) trial. The generalization of this staging model to an unselected, symptomatic, severe AS population has not been tested. Therefore, the present study aimed at evaluating the prevalence of the different stages of extra-aortic valvular cardiac damage and its impact on prognosis in a large, real-world, multicenter cohort of symptomatic severe AS patients.

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METHODS

PATIENT POPULATION AND DATA COLLECTION. From the ongoing registries of patients with aortic valve disease from 2 academic institutions (Leiden University Medical Center, Leiden, the Netherlands, and National Heart Centre, Singapore, Singapore) between 1999 and 2017, a total of 1,189 patients with symptomatic severe AS were selected upon available echocardiographic data at baseline (defined as the first available echocardiogram with symptomatic severe AS). Severe AS was defined according to current guidelines as a mean aortic valve gradient ≥40 mm Hg and/or aortic valve area <1.0 cm^2 (or an indexed aortic valve area <0.6 cm^2/m^2) and/or a peak aortic jet velocity ≥4 m/s (1-3). At each participating center, echocardiographic measurements were performed by experienced observers. Patients with previous AVR were excluded. Baseline demographic and clinical data, including cardiovascular risk factors and medication use, and clinical follow-up data were collected using the hospital records and departmental patient information systems, and analyzed retrospectively. This retrospective analysis of clinically acquired data was approved by the respective institutional review boards of each participating center, and the need for patient written informed consent was waived due to the retrospective nature of the study.

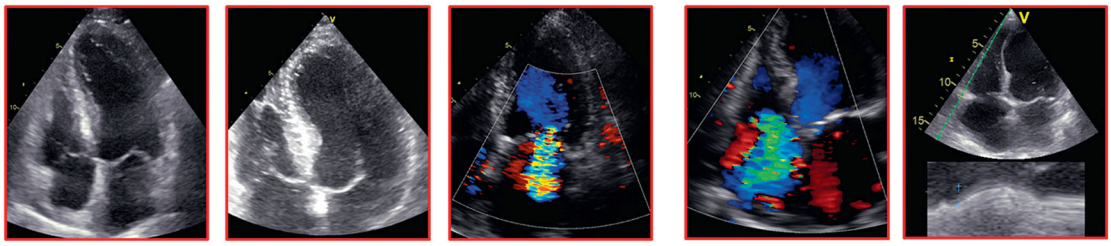
TRANSTHORACIC ECHOCARDIOGRAPHY. Using commercially available ultrasound systems, 2-dimensional, color, pulsed, and continuous wave Doppler images were obtained from the apical and parasternal views according to current recommendations with the patient at rest in a left lateral decubitus position (10). From the apical 3- or 5-chamber views, continuous wave Doppler recordings were obtained to estimate peak aortic jet velocity (3). Mean and peak transvalvular pressure gradients were calculated using the Bernoulli equation (3). Aortic valve area (AVA) was calculated according to the continuity equation using velocity time integrals of the LV outflow tract and aortic valve, and indexed for body surface area (indexed AVA) (3). In the parasternal long-axis view, LV dimensions were assessed, and LV mass was calculated by Devereux's formula and indexed for body surface area (LV mass index) (10). LV end-diastolic and end-systolic volumes were evaluated in the apical 2- and 4-chamber views, and the LV ejection fraction was calculated according to the Simpson's biplane method (10). Using the biplane method of disks, left atrial volumes were measured at end-systole in the apical 2- and 4-chamber views and indexed for body surface area (left atrial [LA] volume index) (10). Pulsed-wave Doppler recordings of the transmitral flow were used to obtain peak early (E) and late (A) diastolic velocities to assess LV diastolic function (11). Using tissue Doppler imaging of the mitral annulus on the apical 4-chamber view, the e′ was measured at both the lateral and septal side, and averaged to calculate the E/e′ ratio for estimation of LV filling pressures (11). Severity of mitral and tricuspid regurgitation was graded according to a multiparametric approach, as recommended (12). The RV pressure was calculated from the peak velocity of the tricuspid regurgitant jet according to the Bernoulli equation, adding the right atrial pressure determined by the inspiratory collapse and diameter of the inferior vena cava to estimate the systolic arterial pulmonary pressure (10,13). For the evaluation of RV systolic function, anatomical M-mode was applied on the focused apical 4-chamber view of the RV to measure tricuspid annular plane systolic excursion (TAPSE) (10).

DEFINITIONS STAGING CLASSIFICATION. The presence and extent of extra-aortic valvular cardiac damage was evaluated on baseline transthoracic echocardiography (i.e., the first available echocardiogram with symptomatic severe AS) and accordingly,

ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis
AVA = aortic valve area
AVR = aortic valve replacement
CI = confidence interval
HR = hazard ratio
IQR = interquartile range
LA = left atrial
LV = left ventricular
MR = mitral regurgitation
RV = right ventricular
TAPSE = tricuspid annular plane systolic excursion
TR = tricuspid regurgitation

FIGURE 1 Stages of Cardiac Damage in Severe AS



	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No cardiac damage	**Left ventricular damage**	**Left atrial or mitral damage**	**Pulmonary vasculature or tricuspid damage**	**Right ventricular damage**
Echocardiographic criteria		LV mass index ♂ >115 g/m^2 ♀ >95 g/m^2 LV ejection fraction <50% E/e' ratio >14	Left atrial volume index >34 ml/m^2 Presence of atrial fibrillation Moderate/severe mitral regurgitation	Systolic pulmonary arterial pressure ≥60 mm Hg Moderate/severe tricuspid regurgitation	TAPSE <16 mm

Proposed staging classification based on the extent of echocardiographic signs of extra-aortic valvular cardiac damage. AS = aortic stenosis; LA = left atrial; LV = left ventricular; TAPSE = tricuspid annular plane systolic excursion.

patients were classified into 5 independent stages as proposed by Généreux et al. (9) (**Figure 1**): Stage 0—no signs of cardiac damage; Stage 1—LV damage (LV ejection fraction <50%, LV mass index >95 g/m^2 for women or >115 g/m^2 for men, or E/e′ >14) (10,11), Stage 2—mitral valve or LA damage (LA volume index >34 ml/m^2 or mitral regurgitation [MR] ≥grade 3 or presence of atrial fibrillation at the moment of echocardiography) (10,12), Stage 3—tricuspid valve or pulmonary artery vasculature damage (systolic pulmonary artery pressure ≥60 mm Hg or tricuspid regurgitation [TR] ≥grade 3) (12), or Stage 4—RV damage (TAPSE <16 mm) (13). Patients were classified according to the criteria of the worst (i.e., highest) stage present.

CLINICAL ENDPOINTS AND FOLLOW-UP. All patients were followed-up for the occurrence of surgical or transcatheter AVR, all-cause mortality, stroke, and hospitalization for cardiac cause. The primary outcome was all-cause mortality, as ascertained by review of hospital records linked to the governmental death registry database. The secondary outcome was a composite of all-cause mortality, stroke (major or minor), and cardiac-related hospitalization, occurring between baseline echocardiography and last follow-up.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD or median (interquartile range [IQR]), as appropriate. Categorical data are presented as frequencies and percentages. Patients were divided according to stage of cardiac damage. For comparison of continuous variables between groups, the analysis of variance test with Bonferroni's post hoc analysis or the Kruskal-Wallis test was used for normally and non-normally distributed variables, respectively. Categorical variables were compared using the chi-square test. The Kaplan-Meier method was used to calculate survival and event rates for the different stages of cardiac damage; comparison of cumulative event rates between these groups was performed by log-rank test. For the secondary outcome, patients were censored at the occurrence of the first event. To evaluate the association of the staging classification and other clinical and echocardiographic parameters with the primary and secondary endpoints, univariable Cox proportional hazards analyses were performed. From this analysis, statistically significant ($p \leq 0.05$) or clinically relevant variables were selected and introduced as covariates in multivariable Cox proportional hazards models. The occurrence of surgical or transcatheter AVR was entered as a time-dependent covariate. For both uni- and multivariable analyses, hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. SPSS software version 23.0 (IBM, Armonk, New York) was used for statistical analyses. A 2-sided p value <0.05 was considered statistically significant.

TABLE 1 Clinical Characteristics of Total Patient Population and According to Stage of Cardiac Damage

	Total population (N = 1,189)	Stage 0 (n = 97)	Stage 1 (n = 282)	Stage 2 (n = 588)	Stage 3 (n = 82)	Stage 4 (n = 140)	p Value*
Age, yrs	73.4 ± 10.8	72.7 ± 9.9	71.6 ± 11.4	73.8 ± 10.7	75.0 ± 10.3	75.3 ± 10.2†	0.004
Male	624 (53)	65 (67)	139 (49)	301 (51)	34 (42)	85 (61)	0.002
Body mass index, kg/m^2	25.5 ± 4.6	26.1 ± 4.7	25.5 ± 4.2	25.6 ± 4.9	24.6 ± 4.6‡	24.8 ± 4.4	0.098
Body surface area, m^2	1.74 ± 0.24	1.79 ± 0.24	1.76 ± 0.23	1.74 ± 0.25	1.68 ± 0.24	1.75 ± 0.25	0.048
Hypertension	857 (72)	67 (69)	210 (75)	430 (73)	56 (68)	94 (67)	0.429
Hypercholesterolemia	790 (66)	67 (69)	185 (66)	397 (68)	49 (60)	92 (66)	0.668
Diabetes mellitus	317 (27)	30 (31)	80 (28)	144 (25)	18 (22)	45 (32)	0.069
Coronary artery disease	563 (47)	42 (43)	131 (47)	267 (45)	30 (37)	93 (66)	<0.001
Previous myocardial infarction	189 (16)	12 (12)	36 (13)	85 (15)	14 (17)	42 (30)	<0.001
History of smoking	330 (28)	36 (37)	82 (29)	158 (27)	20 (24)	34 (24)	0.198
Chronic obstructive pulmonary disease	129 (11)	11 (11)	31 (11)	49 (8)	17 (21)	21 (15)	0.005
History of atrial fibrillation	354 (30)	8 (8)	35 (12)	184 (31)	45 (55)	82 (59)	<0.001
NYHA functional class ≥III	393 (33)	27 (31)	67 (26)	189 (35)	44 (55)	66 (49)	<0.001
Symptoms							
Angina	358 (30)	33 (34)	98 (35)	175 (30)	18 (22)	34 (24)	0.072
Dyspnea	956 (81)	72 (74)	207 (74)	473 (81)	77 (94)	127 (91)	<0.001
Syncope	103 (9)	9 (9)	37 (13)	53 (9)	0 (0)	4 (3)	<0.001
Estimated glomerular filtration rate, ml/min/1.73 m^2	61.8 ± 24.9	69.1 ± 22.0	64.7 ± 24.5	62.8 ± 24.7	49.3 ± 24.3†‡§	53.9 ± 25.5†‡§	<0.001
Systolic blood pressure, mm Hg	135.6 ± 24.0	139.6 ± 21.9	137.1 ± 24.3	136.9 ± 23.8	129.6 ± 26.5	128.1 ± 22.1†‡§	<0.001
Diastolic blood pressure, mm Hg	71.0 ± 13.0	73.4 ± 13.3	73.0 ± 12.5	70.0 ± 12.8†	70.1 ± 13.7	70.2 ± 13.5	0.007
Medication							
Beta-blocker	644 (54)	41 (42)	152 (54)	325 (55)	42 (51)	84 (60)	0.090
ACE inhibitor/ARB	548 (46)	45 (46)	128 (45)	275 (47)	37 (45)	63 (45)	0.992
Aspirin/thienopyridines	556 (47)	46 (47)	144 (51)	262 (45)	37 (45)	67 (48)	0.491
Oral anticoagulant	263 (22)	12 (12)	26 (9)	127 (22)	33 (40)	65 (46)	<0.001
Statin	757 (64)	67 (69)	186 (66)	367 (62)	46 (56)	91 (65)	0.354
Calcium-channel blocker	359 (30)	27 (29)	89 (32)	190 (32)	20 (24)	33 (24)	0.200
Diuretic agents	515 (43)	25 (26)	100 (36)	252 (43)	59 (72)	79 (56)	<0.001

Values are mean ± SD or n (%). *p Values depict differences between stages of cardiac damage and are calculated by analysis of variance and Kruskal-Wallis H test for continuous data (with normal and non-normal distribution, respectively), and by chi-square test for categorical data. †p < 0.05 versus Stage 1 with Bonferroni's post hoc analysis. ‡p < 0.05 versus Stage 0 with Bonferroni's post hoc analysis. §p < 0.05 vs. Stage 2 with Bonferroni's post hoc analysis.

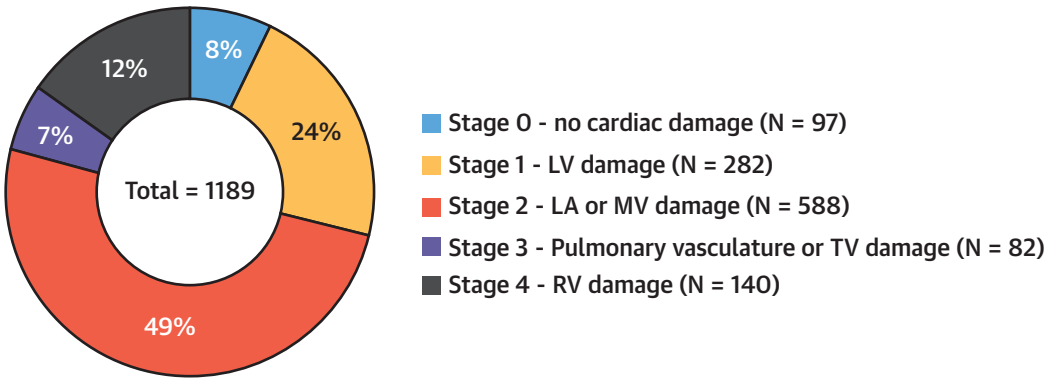
ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; NYHA = New York Heart Association.

RESULTS

PATIENT CHARACTERISTICS. Baseline clinical characteristics for the overall study population (mean age 73 ± 11 years, 53% male) are listed in Table 1. The majority of patients had cardiovascular risk factors: hypertension and hypercholesterolemia were present in 72% and 66% of the population, respectively, and almost one-half of the patients (47%) had coronary artery disease. As per design of the study, all patients were symptomatic, and one-third (33%) had New York Heart Association (NYHA) functional class III or IV symptoms. Patients were divided by the presence and extent of extra-aortic valvular cardiac damage seen on echocardiography (Figure 1): 8% (97) of patients were classified as Stage 0 (no cardiac damage), 24% (282) as Stage 1 (LV damage), 49% (588) as Stage 2 (mitral valve or LA damage), 7% (82) as Stage 3 (tricuspid valve or pulmonary artery vasculature damage), and 12% (140) as Stage 4 (RV damage) (Figure 2). Compared with patients in less advanced stages, the patients in the higher stages were older, had more severe symptoms (NYHA functional class ≥3), worse kidney function, and more frequently had a history of coronary artery disease, previous myocardial infarction, and atrial fibrillation. In addition, these patients more often used oral anticoagulation and diuretic agents.

Baseline echocardiographic parameters for the overall study population and per separate stage of cardiac damage are presented in Table 2. The mean LV ejection fraction was 54 ± 14%, LV mass index 133 ± 40 g/m^2, mean aortic valve gradient 43 ± 16 mm Hg, peak aortic jet velocity 4.1 ± 0.7 m/s, and AVA 0.78 ± 0.18 cm^2. Interestingly, patients in Stages 3 and 4 showed a lower mean aortic valve gradient and peak

FIGURE 2 Distribution of Stages of Cardiac Damage in Total Population



LA = left atrial; LV = left ventricular; MV = mitral valve; RV = right ventricular; TV = tricuspid valve.

aortic jet velocity, corresponding with a higher percentage of low-flow low-gradient severe AS (29% in Stage 3 and 46% in Stage 4 compared with ≤16% in less advanced stages; $p < 0.001$). Patients in more advanced stages had lower LV ejection fraction and more often had an LV ejection fraction <50%, higher E/e′ ratios and LA volume indices, and more often had significant mitral and tricuspid regurgitation compared with patients in lower stages. The incidences of the individual staging components of cardiac damage in the total study population are presented in Table 3.

LONG-TERM OUTCOMES. During follow-up, 917 patients (77%) underwent AVR within a median time of 67 (IQR: 5 to 197) days, of whom 47% received a transcatheter AVR and 53% a surgical AVR. During a median follow-up of 42 (IQR: 20 to 77) months, 472 patients (40%) died, and over a median time of 35 (IQR: 14 to 67) months, 617 patients (52%) reached the combined endpoint (all-cause mortality, stroke, and cardiac-related hospitalization). The clinical outcomes during follow-up per stage of cardiac damage are presented in Table 4.

SURVIVAL ANALYSIS. Kaplan-Meier curve analysis showed that patients with more advanced stages of cardiac damage had significantly higher 5-year cumulative event rates (Figure 3A) (log-rank chi-square 93.4; $p < 0.001$). Particularly for Stage ≥2, significantly higher 5-year cumulative event rates were noted compared with Stage 0 ($p < 0.02$ for all) and Stage 1 ($p < 0.01$ for all). Similarly, for the combined outcome, the more advanced stages showed significantly higher cumulative 5-year event rates (Figure 3B) (log-rank chi-square 70.1; $p < 0.001$), specifically for Stage ≥2 compared with Stage 0 ($p < 0.02$ for all) and Stage 1 ($p < 0.01$ for all). For the subgroup of patients treated with surgical or transcatheter AVR, patients with more advanced cardiac damage showed higher cumulative events rates for both total and postoperative-only all-cause mortality and combined outcome (Online Figures 1 and 2, respectively).

PROGNOSTIC VALUE OF PROPOSED STAGING CLASSIFICATION. The correlates of all-cause mortality and the combined endpoint on univariable and multivariable Cox regression analyses are shown in Table 5. On multivariable analysis, age, previous myocardial infarction, renal function, surgical or transcatheter AVR, and stage of cardiac damage were independently associated with all-cause mortality. For each increase in stage, a 28% higher risk for all-cause mortality was observed (95% CI: 1.158 to 1.422; $p < 0.001$). When evaluating each separate stage of cardiac damage, only Stage 3 (HR: 1.975; 95% CI: 1.125 to 3.469; $p = 0.018$) and Stage 4 (HR: 2.472; 95% CI: 1.471 to 4.155; $p = 0.001$) were independently associated with all-cause mortality. For the combined endpoint, age, previous myocardial infarction, renal function, surgical or transcatheter AVR, and stage of cardiac damage were independent predictors on multivariable analysis. A 19% increase in risk for the combined outcome was observed for each increasing stage (95% CI: 1.091 to 1.299; $p < 0.001$). However, only Stage 2 (HR: 1.456; 95% CI: 1.002 to 2.118; $p = 0.049$), Stage 3 (HR: 1.764; 95% CI: 1.104 to 2.819; $p = 0.018$), and Stage 4 (HR: 1.947; 95% CI: 1.268 to 2.988; $p = 0.002$) were independently

TABLE 2 Echocardiographic Characteristics of Total Patient Population and According to Stage of Cardiac Damage

	Total Population (N = 1,189)	Stage 0 (n = 97)	Stage 1 (n = 282)	Stage 2 (n = 588)	Stage 3 (n = 82)	Stage 4 (n = 140)	p Value*
Heart rate at moment of TTE, beats/min	74.7 ± 14.8	76.4 ± 13.2	72.2 ± 12.5	73.6 ± 14.4	81.0 ± 18.7†‡	79.6 ± 16.9†‡	<0.001
Valve morphology							<0.001
Tricuspid	1,049 (88)	76 (78)	228 (81)	535 (91)	77 (94)	133 (95)	
Bicuspid	140 (12)	21 (22)	54 (19)	53 (9)	5 (6)	7 (5)	
Atrial fibrillation at moment of TTE	165 (14)	0 (0)	0 (0)	81 (14)	28 (34)	56 (40)	<0.001
LV end-diastolic diameter, mm	48.2 ± 8.0	41.4 ± 5.3	47.4 ± 6.9§	48.8 ± 8.1§	50.2 ± 8.0†§	50.9 ± 8.2†‡§	<0.001
LV end-systolic diameter, mm	33.4 ± 9.6	26.8 ± 6.0	32.1 ± 8.2§	33.2 ± 9.4§	36.4 ± 10.2†‡§	39.4 ± 10.8†‡§	<0.001
Septal wall thickness, mm	12.5 ± 2.4	11.4 ± 1.5	12.3 ± 1.9§	12.9 ± 2.6†§	12.2 ± 2.3	12.3 ± 2.5‡§	<0.001
Posterior wall thickness, mm	11.9 ± 2.2	10.9 ± 1.4	11.7 ± 1.8§	12.2 ± 2.3§	11.8 ± 2.0§	11.5 ± 2.3‡	<0.001
LV mass index, g/m^2	132.6 ± 39.7	87.7 ± 14.5	124.5 ± 30.0§	140.7 ± 42.4†§	142.3 ± 36.6†§	138.2 ± 34.9†§	<0.001
LV end-diastolic volume, ml	107.3 ± 46.8	79.4 ± 25.2	97.4 ± 41.8§	111.9 ± 49.3†§	113.1 ± 45.5§	123.6 ± 46.1†§	<0.001
LV end-systolic volume, ml	54.7 ± 40.0	31.1 ± 14.1	46.5 ± 34.1§	55.6 ± 40.9†§	64.9 ± 40.3†§	77.5 ± 45.3†‡§	<0.001
LV ejection fraction, %	54.2 ± 14.3	62.9 ± 7.0	57.8 ± 12.0§	55.1 ± 13.4†§	46.9 ± 14.9†‡§	41.6 ± 16.1†‡§‖	<0.001
LV ejection fraction <50%	339 (29)	0 (0)	52 (18)	156 (27)	39 (48)	92 (66)	<0.001
Peak E-wave velocity, cm/s	96.2 ± 43.0	68.5 ± 16.7	78.0 ± 27.8	100.2 ± 42.1†§	132.5 ± 51.3†‡§	115.0 ± 51.5†‡§‖	<0.001
E′, cm/s	5.3 ± 2.0	6.5 ± 2.3	4.7 ± 1.5§	5.4 ± 2.0†§	5.7 ± 1.9†	5.3 ± 2.1§	<0.001
E/e′, ratio	19.3 ± 10.2	10.8 ± 2.2	18.0 ± 8.0§	19.8 ± 10.3§	24.2 ± 11.4†‡§	23.3 ± 12.7†‡§	<0.001
Left atrial volume index, ml/m^2	44.5 ± 23.1	24.8 ± 5.9	26.1 ± 6.1	50.8 ± 19.1†§	60.4 ± 34.3†‡§	57.9 ± 28.2†‡§	<0.001
Significant mitral regurgitation	68 (6)	0 (0)	0 (0)	35 (6)	14 (17)	19 (14)	<0.001
Systolic pulmonary arterial pressure, mm Hg	36.5 ± 14.0	26.9 ± 8.7	30.4 ± 8.5	34.9 ± 10.0†§	61.4 ± 14.6†‡§	42.8 ± 16.6†‡§‖	<0.001
Significant tricuspid regurgitation	65 (6)	0 (0)	0 (0)	0 (0)	39 (48)	26 (19)	<0.001
Tricuspid annular plane systolic excursion, mm	20.8 ± 4.4	22.2 ± 3.3	21.9 ± 3.5	21.8 ± 3.6	20.1 ± 3.6†‡§	13.3 ± 1.9†‡§‖	<0.001
Mean aortic valve gradient, mm Hg	43.1 ± 15.5	41.9 ± 12.5	43.9 ± 14.4	46.0 ± 16.0	38.2 ± 14.1†‡	33.5 ± 14.3†‡§	<0.001
Peak aortic jet velocity, m/s	4.1 ± 0.7	4.1 ± 0.6	4.1 ± 0.6	4.2 ± 0.7	3.9 ± 0.7†‡	3.6 ± 0.7†‡§‖	<0.001
Aortic valve area, cm^2	0.78 ± 0.18	0.84 ± 0.19	0.78 ± 0.17§	0.78 ± 0.18	0.75 ± 0.20§	0.73 ± 0.17‡§	<0.001
Indexed aortic valve area, cm^2/m^2	0.45 ± 0.11	0.47 ± 0.11	0.45 ± 0.10	0.46 ± 0.12	0.45 ± 0.12	0.43 ± 0.12§	0.021
Low-flow low-gradient AS	224 (19)	15 (16)	39 (14)	81 (14)	24 (29)	65 (46)	<0.001

Values are mean ± SD or n (%). *p values depict differences between stages of cardiac damage and are calculated by analysis of variance and Kruskal-Wallis H test for continuous data (with normal and non-normal distribution, respectively), and by chi-square test for categorical data. †p < 0.05 versus Stage 1 with Bonferroni's post hoc analysis. ‡p < 0.05 versus Stage 2 with Bonferroni's post hoc analysis. §p < 0.05 versus Stage 0 with Bonferroni's post hoc analysis. ‖p < 0.05 versus Stage 3 with Bonferroni's post hoc analysis.

AS = aortic stenosis; LV = left ventricular; TTE = transthoracic echocardiogram.

associated with all-cause mortality, stroke, and cardiac-related hospitalization. In patients treated with surgical or transcatheter AVR, stage of cardiac damage was significantly associated with both total and post-operative all-cause mortality and combined outcome, respectively, although only Stage 4 was independently associated with these outcomes when considering separate stages of cardiac damage (Online Tables 1 and 2).

DISCUSSION

The present study demonstrated that, in a large real-world and multicenter cohort of symptomatic severe AS patients, extra-aortic valvular cardiac injury such as LA dilation, MR, and RV dysfunction is highly prevalent (**Central Illustration**). Classified according to a newly proposed staging system, extra-aortic valvular cardiac damage is independently associated with all-cause mortality and a combined outcome of all-cause mortality, stroke, and cardiac-related hospitalization, although this effect seems to be primarily driven by Stages 3 (tricuspid valve or pulmonary artery vasculature damage) and 4 (RV damage).

PREVALENCE OF CARDIAC DAMAGE IN SEVERE AS.

In severe AS, chronic pressure overload imposed on the LV by progressive calcification and narrowing of the aortic valve induces a compensatory concentric hypertrophic response of the LV myocardium. After this initial adaptive response to normalize LV wall pressure and maintain cardiac output, ongoing development of LV hypertrophy will negatively influence both LV systolic and diastolic function, and will eventually result in the formation of myocardial fibrosis (14). At this time, most patients will be symptomatic (14). Currently, AVR is indicated in patients with severe AS who are symptomatic or have reduced LV systolic function (i.e., LV ejection fraction <50%) (1,2). However, the hemodynamic

TABLE 3 Incidence of the Individual Staging Components of Cardiac Damage in Total Population

Stage 0—no damage	97/1,189
Stage 1—LV damage	282/1,189
Increased LV mass index, >95 g/m^2 for women or >115 g/m^2 for men	882 (74)
LV ejection fraction <50%	339 (29)
E/e′ ratio >14	625 (53)
Stage 2—left atrial or mitral valve damage	588/1,189
Indexed left atrial volume >34 ml/m^2	757 (64)
Moderate or severe mitral regurgitation	68 (6)
Presence of atrial fibrillation at time echocardiography	165 (14)
Stage 3—pulmonary vasculature or tricuspid valve damage	82/1,189
Systolic pulmonary artery pressure ≥60 mm Hg	74 (6)
Moderate or severe tricuspid regurgitation	65 (6)
Stage 4—right ventricular damage	140/1,189
Tricuspid annular plane systolic excursion <16 mm	140 (12)

Values are n/N or n (%).
LV = left ventricular.

effects of chronic pressure overload in severe AS are not limited to the LV only. Elevated LV filling pressures may lead to LA dilation, and this LA remodeling together with changes in LV geometry have been associated with an increased risk for the development of atrial fibrillation and MR (4,15). Rising LA pressure gradients will then contribute to an increase in pulmonary artery pressure, which may eventually lead to right atrial and ventricular remodeling, inducing TR and, ultimately, RV dysfunction (16).

Multiple studies have demonstrated a high prevalence of extra-aortic valvular cardiac damage in severe AS patients. Atrial fibrillation has been reported in 8% to 13% of patients undergoing surgical AVR and in up to 51% of transcatheter AVR patients (15). Both significant MR and TR are frequently observed, with reported rates ranging from 13% to 20% for MR (4,17) and 11% to 27% for TR (6,18–20). Severe pulmonary hypertension has been reported in 10% of surgical AVR and in up to 36% of transcatheter AVR patients (21,22). For RV dysfunction, prevalence rates of 24% to 29% have been observed (7,8,23).

These percentages are largely consistent with the reported prevalence of cardiac damage by Généreux et al. (9) and by the present study. Interestingly, higher rates of low-flow low-gradient severe AS were seen in Stage 3 (tricuspid valve or pulmonary artery vasculature damage) and Stage 4 (RV damage) (29% and 46% vs. 14% to 16% in the less advanced stages, respectively), consistent with previous studies (7,20,24).

TABLE 4 Clinical Outcomes During Follow-Up per Stage of Cardiac Damage

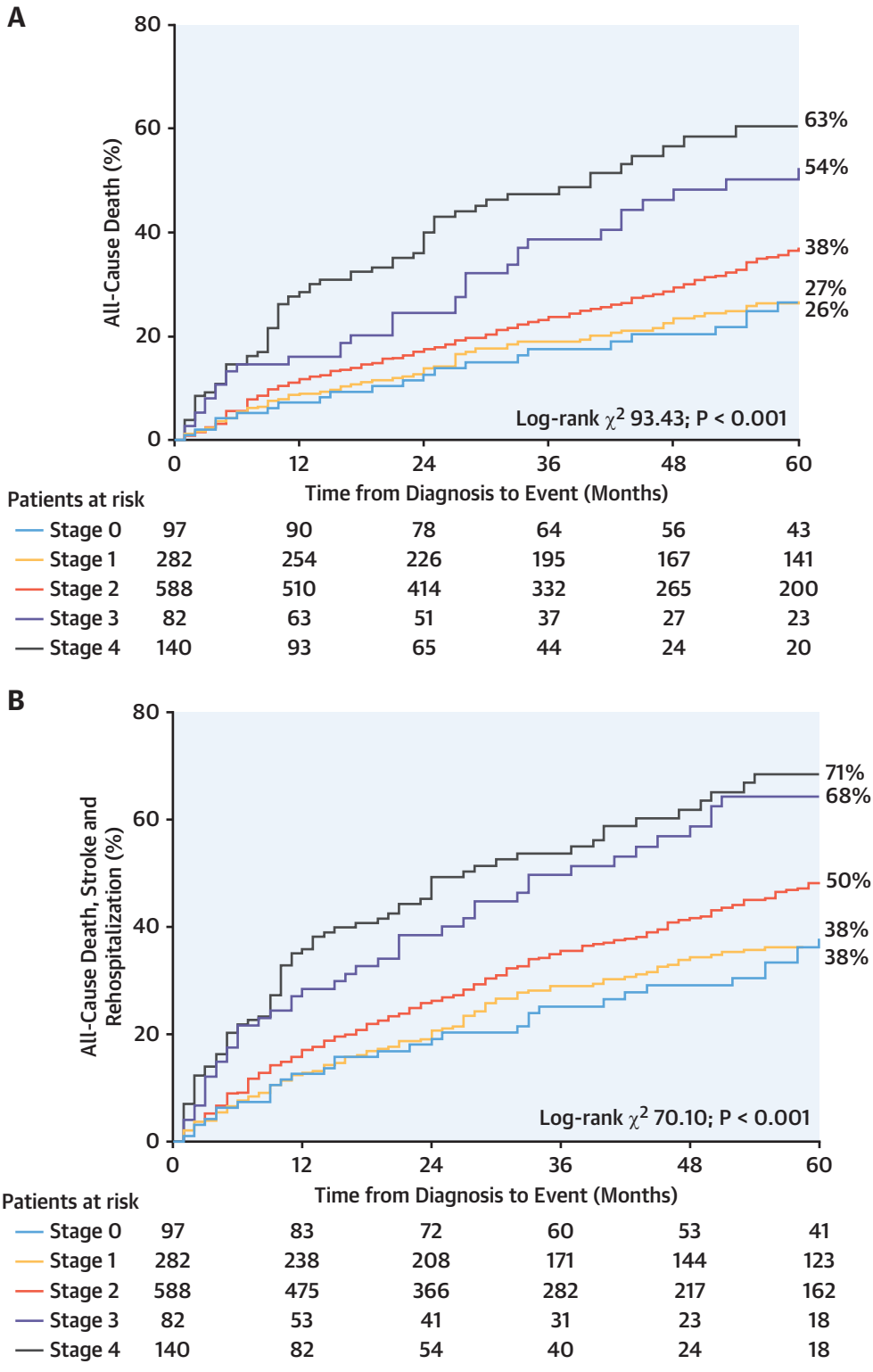
	Stage 0 (n = 97)	Stage 1 (n = 282)	Stage 2 (n = 588)	Stage 3 (n = 82)	Stage 4 (n = 140)	p Value*
Surgical or transcatheter AVR	80 (78)	84 (238)	77 (452)	66 (54)	68 (95)	<0.001
All-cause death	27 (26)	32 (90)	39 (229)	55 (45)	59 (82)	<0.001
1 yr	7 (7)	10 (28)	13 (78)	23 (19)	34 (47)	
Any stroke	12 (11)	9 (25)	10 (58)	12 (10)	17 (24)	0.104
Major stroke	6	11	37	5	11	
Minor stroke	5	14	21	5	13	
Cardiac-related hospitalization	12 (12)	16 (46)	22 (131)	24 (20)	18 (25)	0.055
Combined endpoint, all-cause death, any stroke, and cardiac-related rehospitalization	40 (39)	46 (128)	52 (303)	66 (54)	66 (93)	<0.001

Values are % (n) or n. *p values are calculated by chi-square test.
AVR = aortic valve replacement.

PROGNOSTIC RELEVANCE OF CARDIAC DAMAGE IN AS. Multiple studies have reported a negative prognostic impact of the individual cardiac damage components in severe AS patients, irrespective of the underlying etiology (either severe AS itself or concomitant comorbidities). Although the presence of LV damage (i.e., LV systolic or diastolic dysfunction or LV hypertrophy [Stage 1]) (25,26) and of LA and mitral valve damage (i.e., significant MR, atrial fibrillation, or left atrial enlargement [Stage 2]) (5,15,17,27) have independently been associated with an increased risk for mortality, this effect was not observed in the present study when taking into account the whole extent of cardiac injury. This discrepancy may be attributed to the high prevalence of Stage 1 and Stage 2 in the current population and the stronger association between more advanced stages and clinical outcomes. Importantly, pulmonary artery vasculature or tricuspid valve damage (i.e., severe pulmonary hypertension or significant TR [Stage 3]) and RV dysfunction (Stage 4) were shown to be the strongest predictors for all-cause mortality in the present study, as shown previously in studies focusing on the effects of pulmonary hypertension (21), significant TR (6,20), and RV dysfunction in severe AS patients (7,8,19).

Studies considering the collective prognostic effect of the different expressions of extra-aortic valvular cardiac injury are limited. In a cohort of 432 severe AS patients undergoing surgical AVR, Tan et al. (28) assessed the incremental predictive value of multiple pre-operatively assessed echocardiographic variables, including LV ejection fraction, E/e′, LV mass index, LA volume index, MR and TR grade, systolic pulmonary artery pressure, and several right atrial and ventricular functional parameters. After correcting for operative risk, only LV mass index, right atrial area index, mean

FIGURE 3 Survival Analyses According to Stage of Cardiac Damage for Total Population



Kaplan-Meier estimates for the cumulative event rates of all-cause mortality **(A)** and the combined endpoint **(B)** according to stage of cardiac damage.

TABLE 5 Univariable and Multivariable Cox Proportional Hazard Analyses in the Total Study Population

	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
All-cause mortality				
Age, per 1 yr increase	1.033 (1.024–1.043)	<0.001	1.020 (1.009–1.031)	<0.001
Male, yes/no	0.926 (0.773–1.110)	0.406	1.027 (0.837–1.261)	0.802
Coronary artery disease, yes/no	1.386 (1.157–1.662)	<0.001	0.933 (0.741–1.173)	0.551
Previous myocardial infarction, yes/no	2.092 (1.684–2.597)	<0.001	1.698 (1.285–2.244)	<0.001
Chronic obstructive pulmonary disease, yes/no	1.134 (0.841–1.529)	0.409		
History of atrial fibrillation, yes/no	1.531 (1.264–1.854)	<0.001	1.016 (0.812–1.270)	0.892
NYHA functional class ≥III, yes/no	1.541 (1.267–1.874)	<0.001	1.205 (0.976–1.487)	0.083
eGFR per 1 ml/min/1.73 m^2 increase	0.976 (0.972–0.979)	<0.001	0.981 (0.977–0.985)	<0.001
Systolic blood pressure, per 1 mm Hg increase	0.995 (0.991–0.999)	0.012	0.996 (0.992–1.000)	0.059
Diuretics, yes/no	1.332 (1.111–1.596)	0.002	1.041 (0.844–1.284)	0.709
Peak aortic jet velocity, per 1 m/s increase	0.678 (0.595–0.772)	<0.001	0.952 (0.817–1.110)	0.531
Indexed AVA, per 0.01 cm^2/m^2 increase	1.005 (0.997–1.014)	0.197	2.001 (0.793–5.046)	0.142
Surgical or transcatheter AVR, yes/no	0.395 (0.323–0.483)	<0.001	0.498 (0.397–0.625)	<0.001
Stage of cardiac damage, per 1 stage increase	1.481 (1.358–1.616)	<0.001	1.283 (0.158–1.422)	<0.001
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.111 (0.718–1.720)	0.635	1.126 (0.682–1.858)	0.644
Stage 0 vs. Stage 2	1.611 (1.074–2.417)	0.021	1.486 (0.930–2.374)	0.098
Stage 0 vs. Stage 3	2.736 (1.688–4.435)	<0.001	1.975 (1.125–3.469)	0.018
Stage 0 vs. Stage 4	3.847 (2.470–5.991)	<0.001	2.472 (1.471–4.155)	0.001
Combined endpoint				
Age, per 1 yr increase	1.026 (1.018–1.034)	<0.001	1.013 (1.004–1.022)	0.007
Male, yes/no	0.991 (0.845–1.161)	0.911	1.013 (0.850–1.207)	0.887
Coronary artery disease, yes/no	1.419 (1.210–1.663)	<0.001	1.000 (0.822–1.217)	1.000
Previous myocardial infarction, yes/no	1.862 (1.531–2.266)	<0.001	1.474 (1.156–1.880)	0.002
Chronic obstructive pulmonary disease, yes/no	1.116 (0.859–1.448)	0.411		
History of atrial fibrillation, yes/no	1.447 (1.221–1.714)	<0.001	1.095 (0.899–1.333)	0.368
NYHA functional class ≥III, yes/no	1.379 (1.162–1.638)	<0.001	1.110 (0.923–1.335)	0.268
eGFR, per 1 ml/min/1.73 m^2 increase	0.982 (0.979–0.985)	<0.001	0.986 (0.983–0.990)	<0.001
Systolic blood pressure, per 1 mm Hg increase	0.996 (0.993–0.999)	0.018	0.997 (0.944–1.001)	0.165
Diuretics, yes/no	1.420 (1.211–1.664)	<0.001	1.124 (0.938–1.346)	0.206
Peak aortic jet velocity, per 1 m/s increase	0.729 (0.650–0.817)	<0.001	0.937 (0.821–1.069)	0.333
Indexed AVA, per 0.01 cm^2/m^2 increase	1.000 (0.993–1.007)	0.938	1.664 (0.743–3.726)	0.216
Surgical or transcatheter AVR, yes/no	0.677 (0.564–0.813)	<0.001	0.798 (0.651–0.979)	0.031
Stage of cardiac damage, per 1 stage increase	1.355 (1.256–1.462)	<0.001	1.191 (1.091–1.299)	<0.001
Stages according to cardiac damage				
Stage 0 vs. Stage 1	1.117 (0.780–1.598)	0.547	1.157 (0.777–1.724)	0.474
Stage 0 vs. Stage 2	1.508 (1.080–2.106)	0.016	1.456 (1.002–2.118)	0.049
Stage 0 vs. Stage 3	2.356 (1.560–3.559)	<0.001	1.764 (1.104–2.819)	0.018
Stage 0 vs. Stage 4	2.901 (1.993–4.223)	<0.001	1.947 (1.268–2.988)	0.002

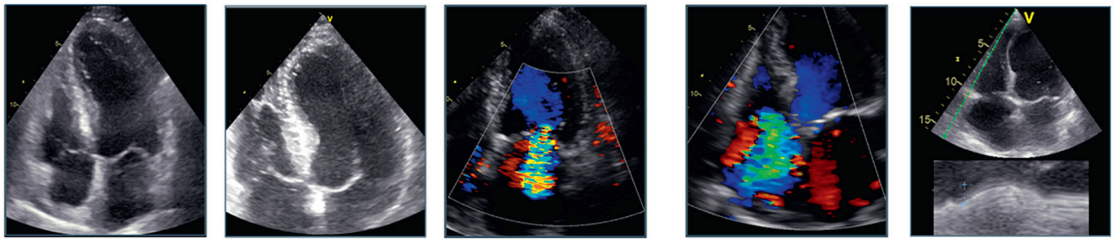
Univariable and multivariable Cox proportional hazard analyses for the identification of independent associates of all-cause mortality and the combined endpoint of all-cause mortality, stroke, and cardiac-related hospitalization were performed in the total study population.

AVA = aortic valve area; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; other abbreviations as in Tables 1 and 4.

gradient <40 mm Hg, MR grade, and LV end-diastolic volume index were independently predictive for 2-year all-cause mortality (28). In the more recently proposed staging classification based on the anatomic and functional extent of cardiac damage, stages of cardiac injury were independently associated with an increased risk of 1-year mortality and adverse events in intermediate-risk severe AS patients undergoing either transcatheter or surgical AVR (9). To our knowledge, the present study is the first to confirm the prognostic impact of this staging model in a large unselected real-world and multicenter cohort of symptomatic severe AS patients over longer-term follow-up (median follow-up time 42 [IQR: 20 to 77] months) and to extend the earlier findings by demonstrating that the prognostic impact of this classification is mainly determined by the presence of significant TR or pulmonary artery

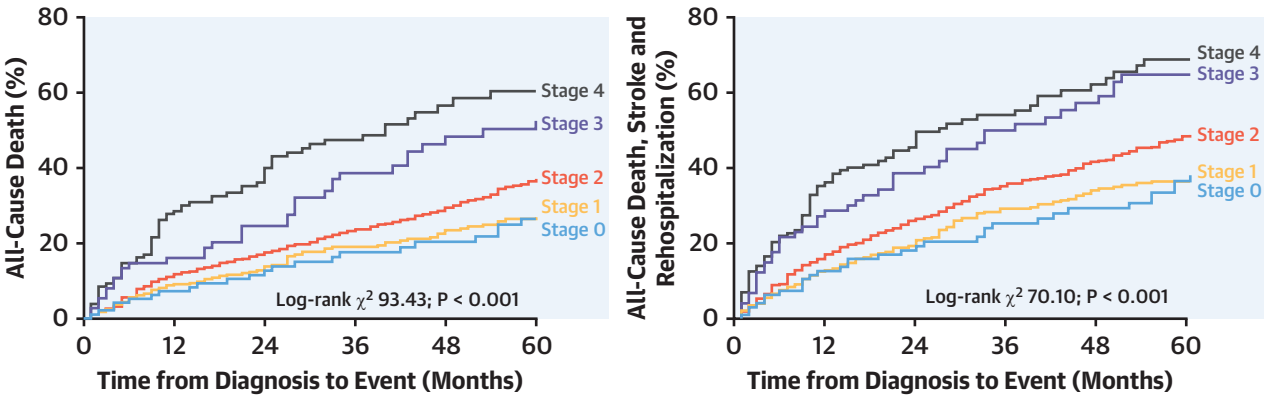
CENTRAL ILLUSTRATION **Clinical Outcomes of Stages of Cardiac Damage in a Real-World Multicenter Severe Symptomatic Aortic Stenosis Cohort**

Staging Classification According to Extent of Cardiac Damage



	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No cardiac damage	Left ventricular damage	Left atrial or mitral valve damage	Pulmonary vasculature or tricuspid valve damage	Right ventricular damage
Prevalence in cohort	8% (N = 97)	24% (N = 282)	49% (N = 588)	7% (N = 82)	12% (N = 140)

Outcomes According to Stages of Cardiac Damage



Vollema, E.M. et al. J Am Coll Cardiol. 2019;74(4):538-49.

(Top) After classification of patients with symptomatic severe AS according to the recently proposed staging system based on the presence and extent of extra-aortic valvular cardiac injury on echocardiography, a high prevalence of cardiac damage (e.g., left atrial enlargement and right ventricular dysfunction) was seen in the study population. **(Bottom)** For both all-cause mortality **(left)** and the combined outcome of all-cause mortality, stroke, and cardiac rehospitalization **(right)**, the more advanced stages (i.e., Stage ≥2) showed significantly higher cumulative 5-year event rates.

hypertension (Stage 3) and RV dysfunction (Stage 4). Our results suggest that incorporation of the proposed staging system in future risk models, in particular the components of these advanced stages, could potentially aid in the risk stratification of severe AS patients, because these aspects are generally not included in current risk prediction models. Future prospective studies are needed to confirm the prognostic value of this staging classification and to determine its additional incremental value in the risk assessment of specific AS subpopulations.

STUDY LIMITATIONS. The present study has limitations inherent to its retrospective nature. The participating centers were referral centers for cardiac surgery and the decision for AVR was made at the discretion of the respective heart teams (as recommended by current guidelines [1,2]); therefore, selection and referral bias may be present. However, in

this real world, multicenter cohort, patients were included regardless of treatment or operative risk category. In the proposed staging classification, reduced LV ejection fraction (<50%) was included as a criterion for Stage 1 (**Figure 1**) (9). However, low LV ejection fraction is associated with a worse prognosis than atrial fibrillation (i.e., Stage 2) (29), potentially resulting in an underestimation of prognosis of patients in Stage 1. In the present study, subanalyses excluding Stage 1 patients with an LV ejection fraction <50% (Online Figure 3, Online Table 3) showed similar results as the analyses using the proposed staging classification (**Figure 3, Table 5**). The modest impact on prognosis of LV ejection fraction <50% in Stage 1 may be explained by the low prevalence of reduced LV ejection fraction in this stage versus increasing stages of cardiac damage (**Table 2**). Distinction between subtypes of significant TR (i.e., due to pulmonary hypertension or due to atrial fibrillation only) was beyond the scope of this paper; future studies will need to elucidate the role of different underlying pathophysiological mechanisms of TR on prognosis in severe AS patients. In the present study, only TAPSE was used to estimate RV systolic dysfunction. Consideration of other RV systolic function parameters could have resulted in a more accurate assessment of RV function, because TAPSE only takes into account the tricuspid lateral annulus displacement. However, TAPSE is easy to obtain, less dependent on image quality, and has been validated in large patient cohorts (13,19). Furthermore, TAPSE as a measure of RV dysfunction has been demonstrated to have prognostic implications in severe AS patients (7,8,19). Future studies incorporating 3-dimensional imaging techniques or RV free wall longitudinal strain for the assessment of RV systolic function in the proposed staging system might provide a more accurate evaluation of RV damage (30,31).

CONCLUSIONS

In this large multicenter cohort of symptomatic severe AS patients, extra-aortic valvular cardiac injury was present in the majority of patients. Stage of cardiac damage as classified by a novel proposed staging system (9) was independently associated with all-cause mortality, although pulmonary artery hypertension and TR (Stage 3) and RV dysfunction (Stage 4) seemed to be the main determinants of this association. Incorporation of this proposed staging system into current risk stratification models, in particular the components of these advanced stages, may aid in the risk assessment of severe AS patients and their different subpopulations.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Echocardiographic staging of cardiac damage in patients with symptomatic severe AS is independently associated with risk of all-cause mortality, and most apparent in those with Stage 3 (pulmonary artery hypertension and/or tricuspid regurgitation) or Stage 4 (right ventricular dysfunction).

TRANSLATIONAL OUTLOOK: Prospective studies are needed to confirm the prognostic value of this staging scheme and assess its incremental value in the assessment of specific subpopulations.

REFERENCES

1. Nishimura RA, Otto CM, Bonow RO, 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.

2. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.

3. Baumgartner HC, Hung JC-C, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Eur Heart J Cardiovasc Imaging 2017;18:254–75.

4. Unger P, Dedobbeleer C, Van Camp G, Plein D, Cosyns B, Lancellotti P. Mitral regurgitation in patients with aortic stenosis undergoing valve replacement. Heart 2010;96:9–14.

5. Zilberszac R, Gleiss A, Binder T, et al. Prognostic relevance of mitral and tricuspid regurgitation in patients with severe aortic stenosis. Eur Heart J Cardiovasc Imaging 2018;19:985–92.

6. Lindman BR, Maniar HS, Jaber WA, et al. Effect of tricuspid regurgitation and the right heart on survival after transcatheter aortic valve replacement: insights from the Placement of Aortic Transcatheter Valves II inoperable cohort. Circ Cardiovasc Interv 2015;8:e002073.

7. Galli E, Guirette Y, Feneon D, et al. Prevalence and prognostic value of right ventricular dysfunction in severe aortic stenosis. Eur Heart J Cardiovasc Imaging 2015;16:531–8.

8. Asami M, Stortecky S, Praz F, et al. Prognostic value of right ventricular dysfunction on clinical outcomes after transcatheter aortic valve replacement. J Am Coll Cardiol Img 2019;12:577–87.

9. Genereux P, Pibarot P, Redfors B, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. Eur Heart J 2017;38:3351–8.

10. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–70.

11. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016;17:1321–60.

12. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2013;14:611–44.

13. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713.

14. Carabello BA, Paulus WJ. Aortic stenosis. Lancet 2009;373:956–66.

15. Tarantini G, Mojoli M, Urena M, Vahanian A. Atrial fibrillation in patients undergoing transcatheter aortic valve implantation: epidemiology, timing, predictors, and outcome. Eur Heart J 2017;38:1285–93.

16. Kammerlander AA, Marzluf BA, Graf A, et al. Right ventricular dysfunction, but not tricuspid regurgitation, is associated with outcome late after left heart valve procedure. J Am Coll Cardiol 2014;64:2633–42.

17. Barbanti M, Webb JG, Hahn RT, et al. Impact of preoperative moderate/severe mitral regurgitation on 2-year outcome after transcatheter and surgical aortic valve replacement: insight from the Placement of Aortic Transcatheter Valve (PARTNER) Trial Cohort A. Circulation 2013;128:2776–84.

18. Barbanti M, Binder RK, Dvir D, et al. Prevalence and impact of preoperative moderate/severe tricuspid regurgitation on patients undergoing transcatheter aortic valve replacement. Catheter Cardiovasc Interv 2015;85:677–84.

19. Schwartz LA, Rozenbaum Z, Ghantous E, et al. Impact of right ventricular dysfunction and tricuspid regurgitation on outcomes in patients undergoing transcatheter aortic valve replacement. J Am Soc Echocardiogr 2017;30:36–46.

20. Amano M, Izumi C, Taniguchi T, et al. Impact of concomitant tricuspid regurgitation on long-term outcomes in severe aortic stenosis. Eur Heart J Cardiovasc Imaging 2019;20:353–60.

21. Zlotnick DM, Ouellette ML, Malenka DJ, et al. Effect of preoperative pulmonary hypertension on outcomes in patients with severe aortic stenosis following surgical aortic valve replacement. Am J Cardiol 2013;112:1635–40.

22. Alushi B, Beckhoff F, Leistner D, et al. Pulmonary hypertension in patients with severe aortic stenosis: prognostic impact after transcatheter aortic valve replacement: pulmonary hypertension in patients undergoing TAVR. J Am Coll Cardiol Img 2019;12:591–601.

23. Koifman E, Didier R, Patel N, et al. Impact of right ventricular function on outcome of severe aortic stenosis patients undergoing transcatheter aortic valve replacement. Am Heart J 2017;184:141–7.

24. Cavalcante JL, Rijal S, Althouse AD, et al. Right ventricular function and prognosis in patients with low-flow, low-gradient severe aortic stenosis. J Am Soc Echocardiogr 2016;29:325–33.

25. Asami M, Lanz J, Stortecky S, et al. The impact of left ventricular diastolic dysfunction on clinical outcomes after transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2018;11:593–601.

26. Minamino-Muta E, Kato T, Morimoto T, et al. Impact of the left ventricular mass index on the outcomes of severe aortic stenosis. Heart 2017;103:1992–9.

27. Beach JM, Mihaljevic T, Rajeswaran J, et al. Ventricular hypertrophy and left atrial dilatation persist and are associated with reduced survival after valve replacement for aortic stenosis. J Thorac Cardiovasc Surg 2014;147:362–9.e8.

28. Tan TC, Flynn AW, Chen-Tournoux A, et al. Risk prediction in aortic valve replacement: incremental value of the preoperative echocardiogram. J Am Heart Assoc 2015;4:e002129.

29. Ito S, Miranda WR, Nkomo VT, et al. Reduced left ventricular ejection fraction in patients with aortic stenosis. J Am Coll Cardiol 2018;71:1313–21.

30. Dahou A, Clavel MA, Capoulade R, et al. Right ventricular longitudinal strain for risk stratification in low-flow, low-gradient aortic stenosis with low ejection fraction. Heart 2016;102:548–54.

31. Carluccio E, Biagioli P, Alunni G, et al. Prognostic value of right ventricular dysfunction in heart failure with reduced ejection fraction: superiority of longitudinal strain over tricuspid annular plane systolic excursion. Circ Cardiovasc Imaging 2018;11:e006894.

KEY WORDS aortic stenosis, cardiac damage, classification, prognosis, staging

APPENDIX For supplemental figures and tables, please see the online version of this paper.