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ORIGINAL PAPER

Redefining cardiac damage staging in aortic stenosis: the value of GLS and RVAc†

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See the editorial comment for this article 'Staging the severity of myocardial damage in aortic stenosis: a new addition to solving the puzzle', by L. Elif Sade and J. Gorcsan, https://doi.org/10.1093/ehjci/jead165.

Aims Cardiac damage staging has been postulated as a prognostic tool in patients undergoing transcatheter aortic valve replacement (TAVR). The aims of our study are (i) to validate cardiac damage staging systems previously described to stratify patients with aortic stenosis (AS), (ii) to identify independent risk factors for 1-year mortality in patients with severe AS undergoing TAVR, and (iii) to develop a novel staging model and compare its predictive performance to that of the above mentioned.

Methods and results Patients undergoing TAVR from 2017 to 2021 were included in a single-centre prospective registry. Transthoracic echocardiography was performed in all patients before TAVR. Logistic and Cox's regression analysis were used to identify predictors of 1-year all-cause mortality. In addition, patients were classified based on previously published cardiac damage staging systems, and the predictive performance of the different scores was measured.

Four hundred and ninety-six patients (mean age 82.1 ± 5.9 years, 53% female) were included. Mitral regurgitation (MR), left ventricle global longitudinal strain (LV-GLS) and right ventricular-arterial coupling (RVAc) were independent predictors of all-cause 1-year mortality. A new classification system with four different stages was developed using LV-GLS, MR, and RVAc. The area under the receiver operating characteristic curve was 0.66 (95% confidence interval 0.63–0.76), and its predictive performance was superior compared with the previously published systems ($P < 0.001$).

Conclusion Cardiac damage staging might have an important role in patients' selection and better timing for TAVR. A model that includes LV-GLS, MR, and RVAc may help to improve prognostic stratification and contribute to better selection of patients undergoing TAVR.

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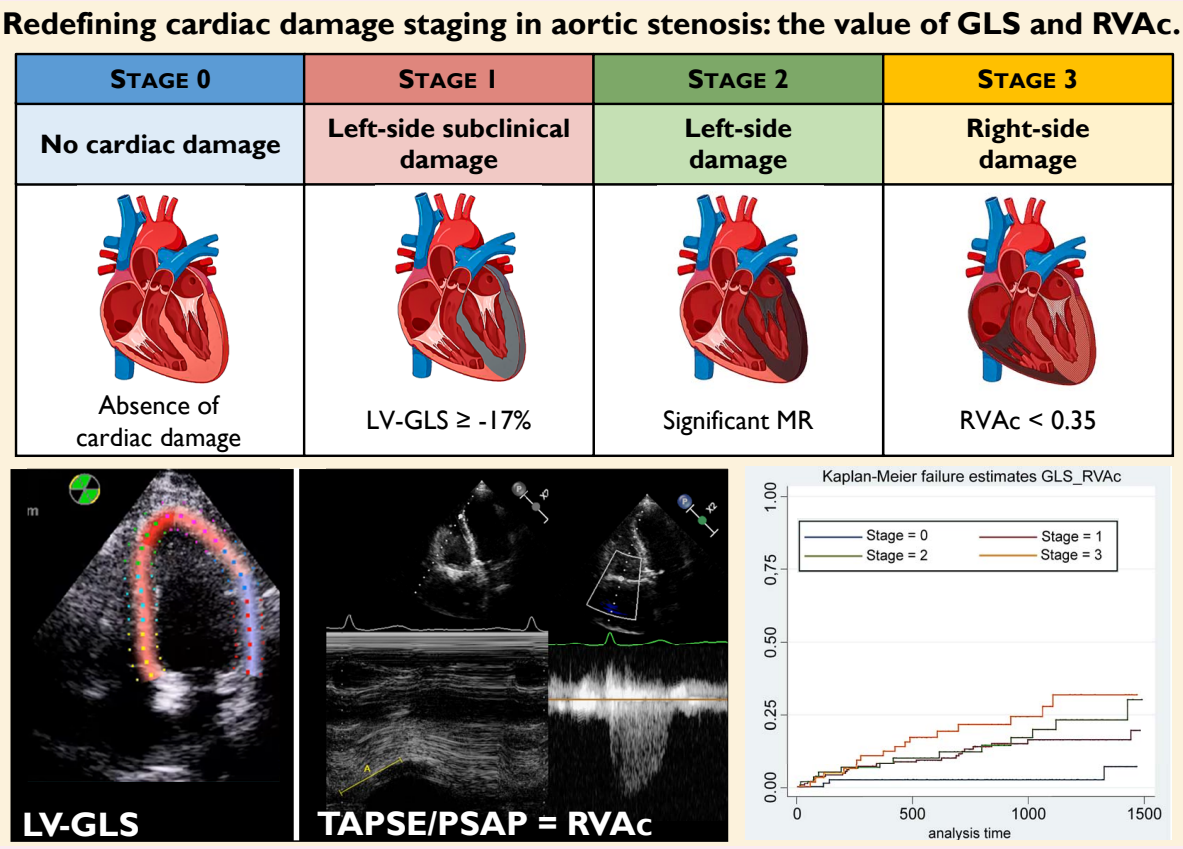
† All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Graphical Abstract



Keywords transcatheter aortic valve replacement • transcatheter aortic valve implantation • cardiac damage • staging • left ventricle global longitudinal strain • right ventricle arterial coupling

Introduction

Transcatheter aortic valve replacement (TAVR) has grown exponentially as a treatment for patients with severe aortic stenosis (AS) in different clinical scenarios.

Current guidelines base the indication for valve replacement on the presence of symptoms or impaired left ventricular ejection fraction (LVEF).[1] Although LVEF impairment has been claimed as the best established prognostic marker,[2–5] other cardiac parameters are related to outcomes. Previous authors have suggested that concomitant extra-aortic lesions could be a consequence of the overload caused by AS, which leads to progressive retrograde damage throughout the heart chambers.

Généreux *et al.* published in 2017 a prognostic staging system of cardiac damage with echocardiographic parameters that included LVEF, left atrial (LA) size, mitral regurgitation (MR), and right ventricular (RV) function, among others; they classified patients with severe AS into five different stages for risk stratification.[6] The aforementioned system has subsequently been validated in different cohorts[7–11] and thereafter modified by Okuno *et al.* who added sub-categories in an attempt to improve its predictive capacity.[12]

Regardless of the underlying mechanism, it is undeniable that extra-aortic injuries worsen the prognosis. Therefore, cardiac damage associated with severe AS continues to be a subject of research and controversy because of its implications for patient selection and for the optimal time to perform the intervention.[13–15]

The purposes of this study were (i) to validate cardiac damage staging systems previously described to stratify patients with AS, (ii) to identify independent risk factors for 1-year mortality in patients with severe AS undergoing TAVR, and (iii) to develop a novel staging model and compare its predictive performance to that of the above mentioned.

Methods

Study design and data collection

From January 2017 through January 2021, all consecutive patients with severe symptomatic AS, defined according to guidelines criteria,[1] who underwent TAVR at our hospital were included in a prospective registry.

Transthoracic echocardiograms (TTE) before the intervention were performed according to current guidelines[16] and were conducted and/or supervised by experts in cardiovascular imaging certified by the European Association of Cardiovascular Imaging.

Clinical data were obtained from patients' medical records. Four hundred and ninety-six patients were included in the analysis after excluding those with incomplete data and TAVR for indications other than AS.

The study protocol was approved by the institutional ethics committee at our hospital and all patients provided written informed consent for procedures.

Primary endpoint and follow-up

The primary endpoint was 1-year mortality. All patients had clinical follow-up and TTE at 1 year. Follow-up time was calculated as the difference between the date of the procedure and the date of death or last medical contact.

Statistical analysis

Data and events of patients were included in a prospective registry and subsequently analysed. Categorical data are presented as frequencies and percentages, and compared using the χ^2 test or Fisher's exact test. Continuous variables were expressed as mean ± SD and were compared using the Students' *t*-test and the Mann–Whitney *U* test as necessary. Assessment for the normality of data was performed using the Shapiro–Wilk test.

Logistic regression analysis was used to identify predictors of outcome. Comparison of cumulative event rates between groups was performed by Cox's regression. Kaplan–Meier method was used to calculate mortality distribution, and curves for cumulative incidence were generated.

Cardiac damage staging classification

First, patients were classified according to the cardiac damage systems previously proposed by Généreaux[6] and Okuno.[12]

To create a new staging system, variables clinically relevant and statistically significant in the univariable analysis were used for a subset regression procedure. The most suitable, parsimonious, and with the lowest Akaike information criterion multivariable model was selected.

Best cut-off values for continuous variables were obtained through receiver operating characteristic (ROC) curves. Quantitative variables were transformed into dichotomous variables to simplify their clinical application to our model.

The area under the ROC curve (AUC ROC) was used to measure the discriminatory capacity of different staging models to predict 1-year mortality. A comparison of the different staging systems AUC ROC was performed with De Long's algorithm. Predicted probabilities of 1-year mortality in each staging system sub-category were assessed by using marginal effects analyses.

All *P*-values were two-sided, and differences were considered statistically significant at $P < 0.05$. Statistical analyses were performed with Stata, version 16 (StataCorp, Lakeway Dr. College Station, TX, USA).

Results

Baseline characteristics and outcome

Four hundred and ninety-six consecutive patients that underwent TAVR were included. Mean age was 82.1 ± 5.9 years, 53.0% were female, and 81.5% were hypertensive. *Table 1* depicts baseline characteristics of patients. Baseline data stratified according to the staging systems of Généreux et al. and Okuno et al. are shown in the supplementary material. Overall, 1-year mortality in our population was 17.7% ($n = 88$). One-year cardiovascular mortality was 3.3% ($n = 16$). Mortality in our population was mostly due to non-cardiac causes, the most frequent being infections (36.4%, $n = 32$), oncological diseases (19.3%, $n = 17$), and COVID infection (12.5%, $n = 11$). The main cause of cardiovascular death was heart failure (87.5%, $n = 14$).

Clinical and echocardiographic predictors of 1-year mortality

Among clinical variables, chronic kidney disease (CKD), NYHA functional class III–IV, and EuroSCORE II showed significant differences between survivors and non-survivors.

Regarding echocardiographic variables, LVEF was significantly lower in patients who died at 1-year. We also observed statistically significant differences in the following variables: left ventricle global longitudinal strain (LV-GLS), MR, tricuspid annular plane systolic excursion (TAPSE), pulmonary artery systolic pressure (PASP), and right ventricular-arterial coupling (RVAc) (*Table 1*).

Among patients with significant MR (grades II–III), 88.6% ($n = 78$) were degenerative MR. Significant tricuspid regurgitation (TR) (grades II–III) was considered functional in all cases 100% ($n = 74$).

Table 2 shows the results of the univariable logistic and Cox regression analysis. CKD and EuroSCORE II, LVEF, LV-GLS, PASP, TAPSE, and RVAc had a significant association with mortality in both analyses.

The staging model derived from the subset regression procedure obtained among patients with LV-GLS available included LV-GLS, RVAc, defined as TAPSE to PASP ratio (TAPSE/PASP), and significant MR.

Multivariable logistic and Cox regression analyses for these three variables are shown in *Table 3*. To simplify the use of variables, both LV-GLS and RVAc were converted into binary variables. The best cut-off value to predict the primary endpoint for LV-GLS was −17% (Youden index of 0.23; HR 0.25, $P = <0.001$) and 0.35 for RVAc (Youden index of −0.34; HR 0.34, $P = <0.001$).

The new cardiac damage system was finally created as follows:

Stage 0, no cardiac damage: LV-GLS < −17%, RVAc ≥ 0.35, and absence of significant MR. Stage 1, left-sided subclinical damage: LV-GLS ≥ −17%. Stage 2, left-sided damage: significant MR. Stage 3, right-sided damage: RVAc < 0.35. Patients were hierarchically classified according to these stages (*Figure 1*).

Cardiac damage staging models

After classifying patients by Généreux staging system,[6] only six patients (1.26%) met the criteria for Stage 0; therefore, data for Stages 0 and 1 were merged in the same group (Stages 0–1). Thus, 11.9% of patients were classified as Stage 0–1, 50.2% as Stage 2, 11.7% as Stage 3, and 26.2% as Stage 4. As for the staging system from Okuno,[12] 8.5% patients were included in Stages 0 and 1, which were merged for the same reason; 27.0% in Stage 2, 15.3% in sub-categories 3a and 3b, and 49.2% in sub-categories 4a, 4b, and 4c.

In our staging system, Stage 0 included 24.5% of patients, Stage 1 included 42.8%, Stage 2 included 16.5%, and Stage 3 included 16.2% of patients. *Table 4* shows the results of Logistic and Cox regression analysis after applying the three different staging systems to our population.

For our proposed prognostic model, 1-year all-cause mortality increased progressively at each stage ($P = 0.004$). This same pattern was observed for 1-year non-cardiovascular (CV) death ($P = 0.019$) (*Table 5*). No significant differences between stages were observed when applying Généraux's and Okuno's systems.

The AUC ROC of our model (GLS-RVAc) was 0.70 (CI 0.619–0.781) and 0.657 (CI 0.627–0.763) when transforming the variables into dichotomous. Our model showed significantly better predictive performance than those proposed by Généreux [0.526 (CI 0.489–0.620)] and Okuno, [0.519 (CI 0. 460–0.586)]; $P < 0.001$ (*Figure 2*). Kaplan–Meier curves for each staging system show cumulative mortality (*Figure 3*).

Figure 4 shows marginal effects analysis for the predicted probability of 1-year mortality for each stage with the different scores. Applying Généreux's model,[6] the highest estimated probability of death is observed in Stage 3 (27.2%) followed by Stage 1 (19.3%). Okuno's model[12] showed the highest probability at Stage 2 (20.3%) followed by Stage 4 (17.6%). In our model, the probability of mortality increased progressively for each stage (5.8% for Stage 0, 18.1% for Stage 1, 25.8% for Stage 2, and 28.3% for Stage 3).

Discussion

The main findings of the present study can be summarized as follows:

(1) LV-GLS, MR, and RVAc were identified as independent predictors of 1-year all-cause mortality in patients with symptomatic severe AS.

Table 1 Epidemiological, clinical, and imaging characteristics of patients according to 1-year mortality

	Total population ($n = 496$)	Survivor ($n = 408$)	Not survivor ($n = 88$)	*P* value
Female (%)	263 (53.0)	215 (52.7)	48 (54.6)	0.753
Age, years	82.1 ± 5.9	82.0 ± 6.1	82.4 ± 4.9	0.559
BMI, kg/m^2	28.1 ± 5.7	27.9 ± 5.6	28.8 ± 6.2	0.187
Hypertension (%)	402 (81.5)	325 (79.7)	77 (87.5)	0.089
Dyslipidemia (%)	313 (63.1)	256 (62.8)	57 (64.8)	0.721
Diabetes (%)	178 (35.9)	146 (35.8)	32 (36.4)	0.918
Tobacco (%)	120 (24.2)	101 (24.8)	19 (21.6)	0.530
CKD (%)	131 (26.5)	90 (22.1)	41 (46.6)	**0.000**
Atrial Fibrillation (%)	138 (28.2)	108 (26.9)	30 (34.1)	0.172
CAD (%)	171 (34.8)	141 (34.8)	30 (34.5)	0.953
NYHA III–IV (%)	265 (64.2)	210 (62.0)	55 (74.3)	**0.044**
Logistic EuroSCORE	17.6 ± 12.7	17.1 ± 12.3	20.1 ± 14.3	**0.040**
Peak aortic velocity, m/s	4.3 ± 0.6	4.3 ± 0.6	4.2 ± 0.6	0.132
Peak aortic gradient, mmHg	75.0 ± 21.4	75.3 ± 22.0	73.6 ± 18.6	0.491
Mean aortic gradient, mmHg	45.2 ± 13.9	45.7 ± 14.3	43.2 ± 11.5	0.129
AVA, cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.166
LAVI, mL/m^2	50.0 ± 33.4	49.6 ± 35.8	51.8 ± 18.0	0.582
LVMI, g/m^2	126.3 ± 30.9	125.4 ± 30.4	130.6 ± 32.9	0.175
E/e′ ratio	15.3 ± 6.1	15.1 ± 6.1	16.7 ± 5.8	0.091
SVI, mL/m^2	39.2 ± 11.4	39.3 ± 11.4	38.5 ± 11.3	0.534
Low Flow	175 (37.1)	143 (36.9)	32 (38.1)	0.831
LVEF %	57.3 ± 10.2	57.8 ± 10.2	54.5 ± 9.8	**0.006**
LV-GLS, %	−14.6 ± 4.4	−15.0 ± 4.2	−13.0 ± 4.8	**0.001**
MR				
Trivial or absent	180 (36.6)	157 (38.8)	23 (26.7)	
I	223 (45.4)	184 (45.4)	39 (45.4)	**0.035**
II	67 (13.7)	49 (12.1)	18 (20.9)	
III	21 (4.3)	10 (3.7)	6 (7.0)	
TR				
Trivial or absent	222 (46.3)	189 (47.7)	33 (39.3)	
I	184 (38.3)	151 (38.1)	33 (39.3)	0.186
II	56 (11.7)	44 (11.1)	12 (14.3)	
III	18 (3.8)	12 (3.0)	6 (7.1)	
PASP, mmHg	36.5 ± 14.6	35.6 ± 13.8	40.8. ± 17.3	**0.007**
TAPSE, mm	20.4 ± 4.5	20.7 ± 4.5	19.1 ± 4.1	**0.005**
S-wave velocity, m/s	11.7 ± 3.1	11.7 ± 3.2	11.5 ± 2.9	0.661
RVAc	0.7 ± 0.3	0.7 ± 0.3	0.6 ± 0.2	**0.004**

Values are presented as mean ± SD and number and percentages. Bold values are significant.
AVA, aortic valve area; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; LAVI, left atrial volume index; LVEF, left ventricle ejection fraction; LV-GLS, left ventricle global longitudinal strain; LVMI, left ventricle mass index; MR, mitral regurgitation; NYHA, New York Heart Association classification; PASP, pulmonary artery systolic pressure; RVAc, right ventricular-arterial coupling; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

(2) A new cardiac damage staging model based on these echocardiographic parameters showed better predictive capacity for 1-year all-cause mortality compared with previous ones, with a gradual increase in risk for each stage.

Baseline extra-aortic valve cardiac damage parameters, which are significantly related to survival after the procedure, have been applied to design a stratification system in an attempt to improve TAVR candidates' selection and thus, the outcomes. These echocardiographic

Table 2 Univariable logistic and cox regression analyses for 1-year mortality

	Logistic regression	*P* value	Cox regression	*P* value
	Odds ratio (95% CI)		Hazard Ratio (95% CI)	
Sex	1.08 (0.68–1.71)	0.753	1.15 (0.72–1.81)	0.561
Age	1.01 (0.97–1.05)	0.558	1.00 (0.96–1.04)	0.966
BMI	1.02 (0.99–1.07)	0.189	1.03 (0.99–1.07)	0.109
Hypertension	1.79 (0.91–3.52)	0.092	2.07 (0.99–4.32)	0.052
Dyslipidemia	1.09 (0.67–1.77)	0.721	0.99 (0.62–1.59)	0.977
Diabetes	1.03 (0.64–1.66)	0.918	1.05 (0.66–1.67)	0.845
Tobacco	0.84 (0.48–1.46)	0.530	0.94 (0.55–1.62)	0.830
CKD	3.07 (1.90–4.96)	**0.000**	3.62 (2.28–5.73)	**0.000**
Atrial fibrillation	1.41 (0.86–2.30)	0.174	1.44 (0.90–2.31)	0.128
CAD	0.99 (0.61–1.60)	0.953	0.98 (0.61–1.59)	0.951
NYHA III–IV	1.78 (1.01–3.13)	**0.046**	1.56 (0.91–2.68)	0.109
Logistic EuroSCORE	1.02 (1.00–1.03)	**0.042**	1.02 (1.00–1.03)	**0.025**
AVA	2.34 (0.70–7.78)	0.167	2.00 (0.62–6.44)	0.246
LAVI	1.00 (1.00–1.01)	0.590	1.00 (1.00–1.01)	0.547
LVMI	1.01 (1.00–1.01)	0.176	1.00 (1.00–1.01)	0.270
E/e′	1.04 (0.99–1.09)	0.092	1.04 (0.99–1.09)	0.088
SVI	0.99 (0.97–1.01)	0.533	1.00 (0.98–1.02)	0.687
Low Flow	1.05 (0.65–1.71)	0.831	1.09 (0.68–1.76)	0.718
LVEF	0.97 (0.95–0.99)	**0.007**	0.98 (0.96–1.00)	**0.019**
LV-GLS	1.11 (1.04–1.18)	**0.001**	1.09 (1.03–1.16)	**0.003**
MR				
Trivial or absent				
I	1.45 (0.83–2.53)	0.194	1.28 (0.73–2.24)	0.385
II	2.51 (1.25–5.03)	**0.010**	1.63 (0.80–3.30)	0.178
III	2.73 (0.96–7.75)	0.059	2.65 (1.06–6.65)	**0.038**
TR				
Trivial or absent				
I	1.25 (0.74–2.12)	0.405	0.74 (0.43–1.27)	0.278
II	1.56 (0.75–3.27)	0.236	1.19 (0.60–2.39)	0.619
III	2.86 (1.00–8.16)	**0.049**	1.81 (0.70–4.68)	0.220
PASP	1.02 (1.01–1.04)	**0.008**	1.02 (1.01–1.04)	**0.003**
TAPSE	0.92 (0.87–0.97)	**0.005**	0.94 (0.88–0.99)	**0.025**
S wave velocity	0.98 (0.90–1.08)	0.660	0.99 (0.91–1.10)	0.891
RVAc	0.22 (0.08–0.62)	**0.004**	0.22 (0.08–0.63)	**0.005**

Bold values are significant.
AVA, aortic valve area; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; LAVI, left atrial volume index; LVEF, left ventricle ejection fraction; LV-GLS, left ventricle global longitudinal strain; LVMI, left ventricle mass index; MR, mitral regurgitation; NYHA, New York Heart Association classification; PASP, pulmonary artery systolic pressure; RVAc, right ventricular-arterial coupling; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

parameters associated with 1-year all-cause mortality in our cohort are consistent with previous evidence.

Impaired LV-GLS is a predictor of poor outcomes in patients undergoing TAVR. Recently, Lee *et al.*[17] reported that in patients with AS and preserved LVEF undergoing TAVR, reduced LV-GLS (>−16%) was independently associated with poor clinical outcomes. In the same vein, a meta-analysis by Wang *et al.*[18] concluded that impaired LV-GLS worsened the outcome in asymptomatic patients with AS regardless of LVEF. LV-GLS provides information about subclinical myocardial damage, which usually precedes the deterioration of LVEF.[19,20] Because of that, it was included in the first stage as an early and sensitive marker of subclinical myocardial left-sided damage.

Regarding MR, studies published by Chakravarty *et al.*[21] and Bedogni *et al.*[22] have already showed that significant MR was associated with higher all-cause mortality in patients undergoing TAVR. Given the low proportion of patients with reduced LVEF (8.9%), compared with the prevalence of significant MR (17.9%) in our cohort, the latter parameter was preferred as a marker for left-sided

Table 3 Multivariable logistic and Cox regression analysis for the selected model

	Multivariable logistic regression analysis		Multivariable Cox regression analysis	
	Odds ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
LV-GLS	2.46 (1.18–5.14)	0.016	1.97 (0.90–4.29)	0.089
MR	1.41 (1.00–1.98)	0.051	1.29 (0.91–1.83)	0.151
RVAc	2.23 (1.10–4.58)	0.027	2.40 (1.25–4.62)	0.009

LV-GLS, left ventricle global longitudinal strain; MR, mitral regurgitation; RVAc, right ventricular-arterial coupling.

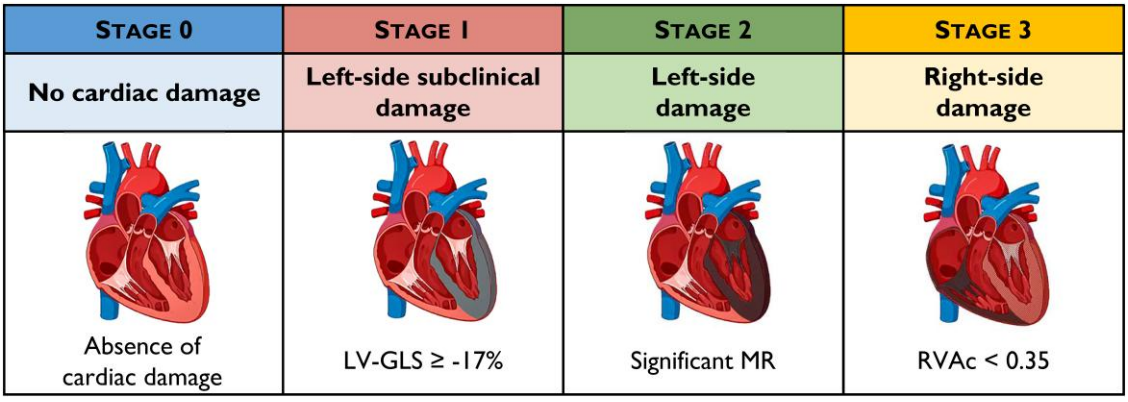


Figure 1 New cardiac damage classification system using LV-GLS, MR, and RVAc.

Table 4 Logistic regression and Cox analysis performance of the different staging systems in our cohort of patients who underwent TAVR

Stages	Logistic regression analysis		Cox regression analysis	
	Odds ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Généreux *et al.*				
Stages 0–1	Reference		Reference	
Stage 2	0.76 (0.36–1.61)	0.475	1.07 (0.49–2.32)	0.864
Stage 3	1.57 (0.65–3.80)	0.580	1.88 (0.78–4.54)	0.160
Stage 4	0.84 (0.38–1.89)	0.682	1.03 (0.452.40)	0.937
Okuno *et al.*				
Stages 0–1	Reference		Reference	
Stage 2	0.93 (0.36–2.37)	0.875	1.20 (0.44–3.22)	0.725
Stage 3	1.23 (0.46–3.33)	0.677	1,59 (0.57–4.47)	0.377
Stage 4	1.04 (0.43–2.49)	0.938	1.33 (0.52–3.39)	0.553
GLS-RVAC				
Stage 0	Reference		Reference	
Stage 1	3.31 (1.24–8.88)	**0.017**	5.11 (1.55–16.83)	**0.007**
Stage 2	5.71 (1.98–16.50)	**0.001**	5.85 (1.65–20.76)	**0.006**
Stage 3	6.32 (2.20–18.17)	**0.001**	8.53 (2.50–29.14)	**0.001**

Bold values are significant.

Table 5 Outcomes during follow-up after TAVR according to our staging classification of cardiac damage

	Stage 0 $n = 95$	Stage 1 $n = 166$	Stage 2 $n = 64$	Stage 3 $n = 63$	*P* value
30-day admission (%)	4 (4.2)	18 (10.8)	3 (4.7)	0 (0.0)	**0.013**
HF admission during 1 year (%)	17 (17.9)	30 (18.1)	8 (12.5)	7 (11.1)	0.477
1-year all-cause mortality (%)	8 (8.4)	29 (17.5)	17 (26.6)	18 (28.6)	**0.004**
1-year CV mortality (%)	1 (1.1)	5 (3.1)	3 (4.9)	4 (6.8)	0.273
1-year non-CV mortality (%)	3 (3.3)	16 (9.9)	10 (16.4)	10 (17.0)	**0.019**

Bold values are significant.
CV, cardiovascular; HF, heart failure.

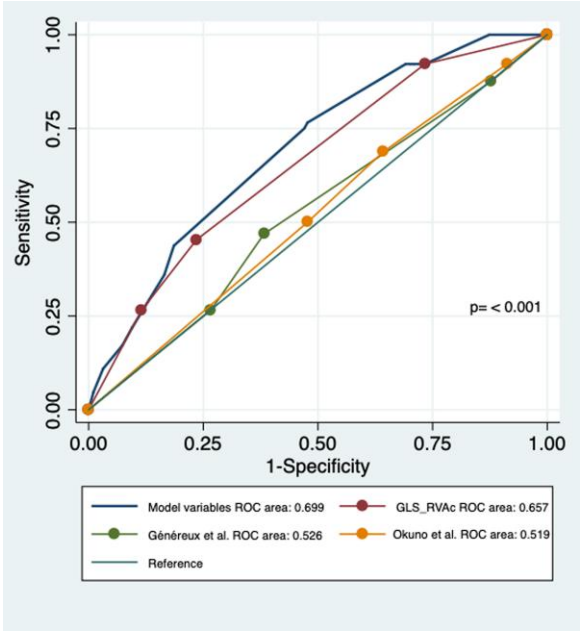


Figure 2 ROC curves comparison of the different staging models.

damage and was used for determining the presence of Stage 2 of cardiac damage.

Finally, the repercussion of severe AS on the right chambers and its prognostic implications have been previously described; the reduction in longitudinal function (TAPSE) and the presence of TR and elevated PASP have been independently associated with worse prognosis during follow-up.[23–25] Schwarz *et al.*[23] reported the impact of RV dysfunction on the outcomes of patients undergoing TAVR. A reduction in TAPSE values and Tei index were associated with worse outcomes. An increase in mortality has also been found in patients with significant TR undergoing TAVR. Omar *et al.*[26] showed that patients with significant TR had an increased risk of CV and all-cause mortality. Moreover, they reported worse long-term survival rates in patients without improvement in TR after TAVR.

The evaluation of RV function and pulmonary hypertension is therefore of utmost importance in terms of prognostic impact. Previously published stages of cardiac damage agree that patients with right-sided involvement have a marked increase in mortality. In fact, in the modification of the staging of damage published by Okuno *et al.*, it is remarkable how the subgroup of patients with severe pulmonary hypertension and RV dysfunction have a significantly worse prognosis.[12] Besides, in the three staging models analysed in this study, patients with higher mortality have in common the presence of elevated PSAP and/or RV systolic dysfunction.

Therefore, the assessment of right-sided dysfunction has been refined in our staging system by including RVAc. RV function is closely coupled with pulmonary circulation; as left overpressure increases, it eventually affects the right arterial circuit increasing the RV afterload and consequently causing RV to pulmonary artery uncoupling. Recent studies also reported an association between RVAc impairment and increased mortality in these patients.[27,28] Sultan *et al.* demonstrated that a TAPSE/PASP ratio <0.59 was associated with all-cause mortality in patients undergoing TAVR. This association was more striking in patients with a ratio <0.29.[29] Thus, the information on RV haemodynamic and myocardial efficiency provided by RVAc, with a prognostic impact, was incorporated to our final stage.

We created a new staging system with these predictor variables that intended to be simple and feasible to apply in real-life practice: no cardiac damage, subclinical left-sided damage, clinical left-sided damage, and right-sided damage. Like previous staging systems, our goal is to provide a tool that contributes to addressing the unmet need for improved patient selection and timing of TAVR.

When applying the staging systems proposed by Généreux and Okuno to our population, we found that they had limited discriminative performance for 1-year mortality, despite having similar baseline characteristics. This discrepancy could be related to the cut-off values used for some parameters included in their systems, namely, LAVI, LV mass, and E/e′ ratio. Most of our patients (both 1-year survivors and non-survivors) had significantly higher mean values for these variables compared with the proposed cut-off points, rendering them ineffective as risk discriminators. Another source of potential shortcomings is the complexity of the aforementioned models. The use of many predictor variables and the potential interaction between them could have led to poor risk discrimination in our population.

It is noteworthy that previous models assumed a retrograde pathophysiological cascade underlying cardiac damage. In fact, it is difficult to assume deterioration of LVEF as a first stage, despite its strong relationship with mortality described in previous literature.[2–5] On the other hand, when analysing the aetiology of significant MR in our cohort, we observed that most of them were of primary (degenerative) cause. Different studies have shown the association between significant MR and patients undergoing TAVR.[30–32] Nombela-Franco *et al.* already described that more than half of MR in these patients had an organic aetiology.[32] It is widely known that the risk factors predisposing to aortic valve degeneration are also common with those that contribute to mitral valve degeneration.[33,34] Although increased afterload secondary to AS may raise the severity of MR, the presence of both valve diseases

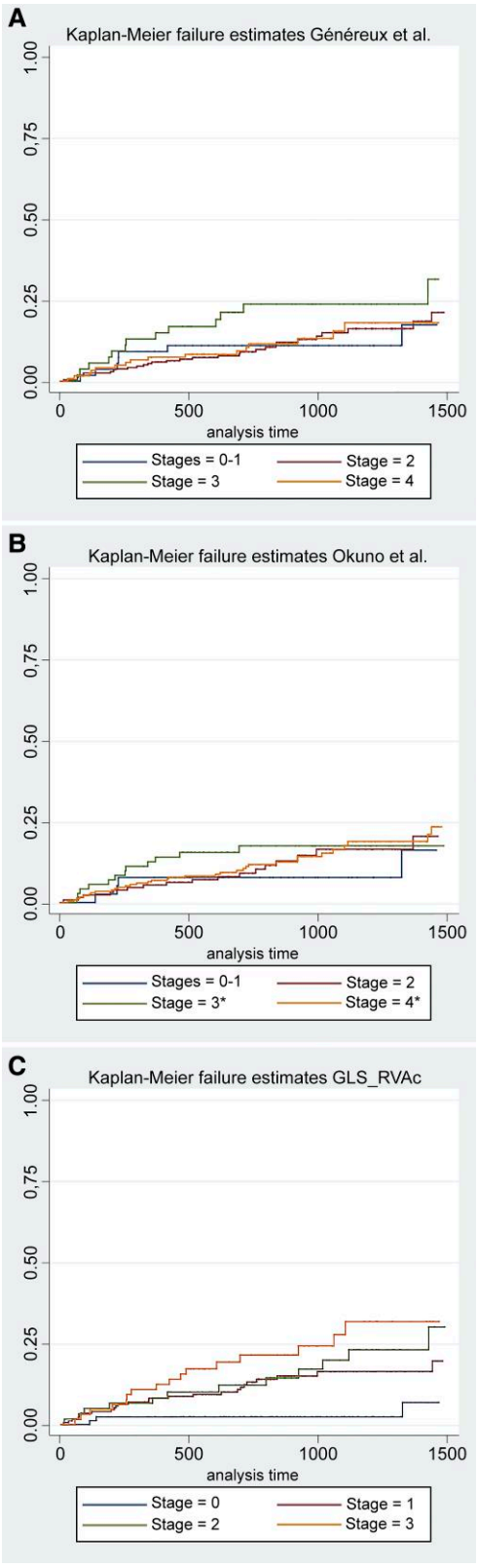


Figure 3 Kaplan–Meier mortality curves for three different staging systems *A*) Généreux *et al. B*) Okuno *et al. C*) GLS-RVAc model. (*): patients in sub-categories 3a and 3b, and 4a, 4b, and 4c were classified together as Stage 3 and 4, respectively.

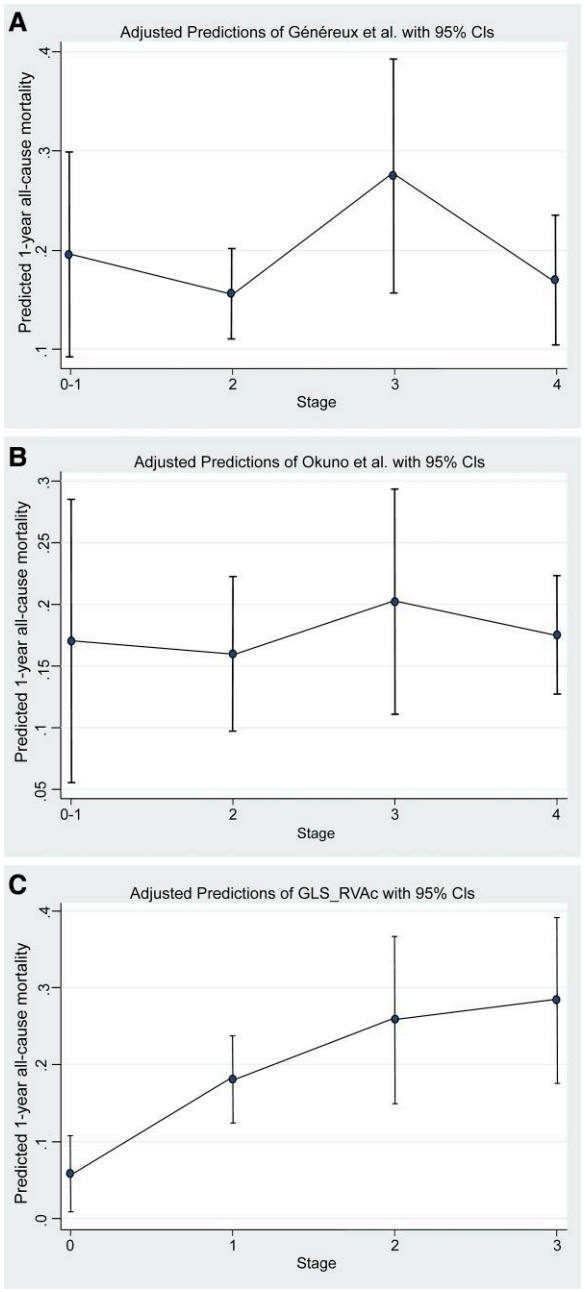


Figure 4 Margin effects analysis for the different cardiac damage staging models. *A*) Généreux *et al. B*) Okuno *et al. C*) GLS-RVAc model.

does not appear to imply, in most cases, a cause-and-effect relationship in which AS generates left ventricular damage and, secondarily, functional MR.

This consideration may lead to a paradigm shift in the interpretation of previous cardiac damage staging systems: while patients with worse prognosis tend to have more cardiac lesions, these lesions do not necessarily have to result from a retrograde pathophysiology, as initially proposed by Généreux *et al.*

Interestingly, in our model, a similar population distribution was observed as described in the two studies by Okuno *et al.* published in

2021.[11,12] A high percentage of patients met the criteria for advanced stages (Stages 3–4 in previous models and Stage 3 in ours). This raises the question of whether the optimal clinical time for intervention in patients with severe AS is when the presence of symptoms has been established or whether the presence of symptoms implies that a high percentage of patients already belong to an advanced stage of the disease.

The appropriate timing for TAVR remains an outstanding issue. Randomized clinical trials are needed to compare the different available staging systems for cardiac damage and propose a diagnostic and therapeutic algorithm that that will allow valve intervention to be indicated at the most clinically optimal time to improve patient prognosis.

Study limitations

This is a single-centre, observational study with the inherent limitations of this type of design. Despite the intended simplicity of our cardiac damage staging system, some parameters, particularly LV-GLS, may have some variability and may not necessarily be available in all patients. Although all echocardiogram studies were conducted and interpreted by experts in the field, no intra/inter observer variability was assessed. The analysis was developed to predict 1-year mortality only, which limits its long-term follow-up conclusions. The sample size is relatively small, so larger studies are needed to validate these results.

Conclusion

For the first time, a new and simplified staging system using LV-GLS and RVAc is proposed. It is feasible as it includes variables used in the daily routine and reliable because of its predictive capacity. Cardiac damage staging systems in severe AS should be applied in clinical practice for better selection and timing of TAVR in order to improve patients' outcomes.

Supplementary data

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

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Data availability

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

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