Cardiac Damage Staging Classification Predicts Prognosis in All the Major Subtypes of Severe Aortic Stenosis: Insights from the National Echo Database Australia

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Background: There are currently no established prognostic models for "low-gradient" severe aortic stenosis (AS), including those with low-flow, low-gradient (LFLG) or normal-flow, low-gradient (NFLG) severe AS. The "cardiac damage staging classification" has been validated as a clinically useful prognostic tool for high-gradient severe AS but not yet for these other common subtypes of severe AS, LFLG and NFLG.

Methods: The authors analyzed data from the National Echo Database of Australia, a large national, multicenter registry with individual data linkage to mortality. Of 192,060 adults (mean age, 62.8 ± 17.8 years) with comprehensive ultrasound profiling of the native aortic valve studied between 2000 and 2019, 12,013 (6.3%) had severe AS. On the basis of standard echocardiographic parameters, 5,601 patients with high-gradient, 611 with classical and 959 with paradoxical LFLG, and 911 with NFLG severe AS were identified. Mean follow-up was 88 ± 45 months. All-cause and cardiovascular-related mortality were assessed for each group on an adjusted basis (age and sex) and analyzed by cardiac damage stage.

Results: Patients with LFLG AS had greater associated cardiac damage at diagnosis (stages 3 and 4 in 34% of those with classical LFLG, 22.5% of those with paradoxical LFLG, 15.5% of those with NFLG, and 14% of those with high-gradient AS; $P < .001$). For all four major subtypes of severe AS, there was a progressive increase in 1- and 5-year mortality with increasing cardiac damage score. For example, for paradoxical LFLG severe AS, compared with stage 0 patients, adjusted 1-year all-cause mortality was 22% higher in stage 1 patients, 55% higher in stage 2 patients ($P = .095$), and 155% higher in stage 3 and 4 patients ($P < .001$). Among patients with classical LFLG severe AS, compared with stage 1 patients, adjusted 1-year all-cause mortality was 55% higher in stage 2 patients ($P = .018$) and 100% higher in stage 3 and 4 patients ($P < .001$).

Conclusions: Regardless of severe AS subtype, increasing severity denoted by the cardiac damage staging classification is strongly associated with increasing mortality risk. (J Am Soc Echocardiogr 2021;34:1137-47.)

Keywords: LFLG aortic stenosis, Cardiac damage staging classification, Aortic stenosis prognosis

A substantial subset of patients with evidence of severe aortic stenosis (AS) on echocardiography (aortic valve area [AVA] <1 cm^2) do not have high-pressure gradients across their aortic valves (AVs; i.e., mean gradient ≥ 40 mm Hg and/or peak velocity ≥ 4 m/sec). This phenomenon is commonly termed "low-gradient" severe AS.[1] Where this occurs because of reduced left ventricular (LV) stroke volume, patients are said to have "low-flow, low-gradient" (LFLG) severe AS. These cases can be further delineated according to concurrent reduced (classical LFLG severe AS) versus preserved (paradoxical LFLG severe AS) LV ejection fraction (LVEF). Patients with normal stroke volumes are considered to have "normal-flow, low-gradient" (NFLG); while current guidelines generally regard these patients as

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Abbreviations

AS = Aortic stenosis

AV = Aortic valve

AVA = Aortic valve area

AVR = Aortic valve replacement

LA = Left atrial

LFLG = Low-flow, low-gradient

LV = Left ventricular

LVEF = Left ventricular ejection fraction

NEDA = National Echo Database of Australia

NFLG = Normal-flow, low-gradient

RV = Right ventricular

SVI = Stroke volume index

having only moderate AS, it has been argued that up to 50% have severe stenosis, with evidence backing the case for early intervention.[1] Currently, however, there are no established prognostic models specific to patients with "low-gradient" AS to help guide management decisions.

Predominantly among patients with high-flow, high-gradient severe AS scheduled for intervention, Généreux *et al.*[2] recently described a novel prognostic model, using a staging classification system based on the extent of extra AV anatomic and functional cardiac damage on echocardiography. This cardiac damage staging classification has been more recently validated in larger cohorts of patients with both symptomatic and asymptomatic severe AS,[3,4] but only a small minority of patients in these studies had LFLG severe AS (<20%).

In this context, the aim of our study was to explore the prognostic utility of this cardiac damage classification, specifically in patients with "low-gradient" AS, by analyzing data from the National Echo Database of Australia (NEDA).[5] NEDA is a large clinical registry currently containing >1 million echocardiograms, from >600,000 unique individuals, and has already generated clinically important insights into the prevalence and outcomes of AS.[6,7]

METHODS

Study Design and Data

The purpose and overall design of NEDA have been previously described.[5] In brief, NEDA is an ongoing observational registry containing detailed echocardiographic and basic demographic data from adults from >25 participating centers around Australia. At the time of study census, NEDA contained >1 million echocardiographic reports from >600,000 individual patients. Survival status and date of death (when relevant) for each patient in the database were obtained at the study census date (May 2019) using enhanced probability matching linkage with the well-validated Australian National Death Index.[8] Causes of death were categorized according to ICD-10 coding.[9] Events with ICD-10 chapter codes in the range of I00 to I99 were considered cardiovascular-related mortality; these included valvular heart disease, ischemic heart disease, heart failure, cerebrovascular disease, and peripheral vascular disease.

Study Cohort

From the entire NEDA at time of the study census (May 2019), only patients ≥18 years of age with echocardiographic investigations performed since 2000 and containing parameters necessary for the appropriate diagnosis of severe AS were included in this analysis. Hence, only echocardiographic investigations with available AVA, AV peak velocity, and AV mean gradient data were included. Additionally, for patients with multiple available serial echocardiographic studies, only the first chronologic investigation was included. This resulted in an analysis cohort of 199,543 patients that was then further assessed to specifically identify patients with severe native valve AS (Figure 1).

Patients were classified into the different subtypes of severe AS using criteria based on current expert recommendations.[1,10] High-gradient severe AS was defined as AV mean gradient ≥ 40 mm Hg and/or peak velocity ≥ 4 m/sec (regardless of AVA). Classical LFLG severe AS was defined as AVA ≤ 1 cm^2 with AV mean gradient < 40 mm Hg, AV peak velocity < 4 m/sec, stroke volume index (SVI) ≤ 35 mL/m^2, and LVEF < 50%. Paradoxical LFLG severe AS was defined as AVA ≤ 1 cm^2 with AV mean gradient < 40 mm Hg, AV peak velocity < 4 m/sec, SVI ≤35 mL/m^2, and LVEF ≥ 50%. NFLG severe AS was defined as AVA ≤ 1 cm^2 with AV mean gradient < 40 mm Hg, AV peak velocity < 4 m/sec, and SVI >35 mL/m^2.

AVA for all included echocardiograms was calculated using the continuity equation with either the velocity-time integral and/or peak velocity ratio,[11] with the minimum value used for the aforementioned diagnostic criteria. Reported LVEF was obtained by following hierarchal methods: physician reported, volumetric apical biplane (Simpson), volumetric apical four-chamber, volumetric apical two-chamber, and the Teichholz formula. LV mass was calculated using the American Society of Echocardiography two-dimensional linear formula.[12] Patients were recorded to have undergone AV replacement (AVR) during follow-up if any of their subsequent available echocardiograms in the database reported evidence of a replaced or implanted AV. The follow-up period for each patient was from the time of the diagnostic echocardiographic examination to the time of study census (May 2019). Mean follow-up duration was 95 ± 45 months for patients with high-gradient AS, 76 ± 43 months for those with classical LFLG AS, 66 ± 39 months for those with paradoxical LFLG AS, and 83 ± 45 months for those with NFLG AS ($P < .001$).

Cardiac Damage Staging Classification

Patients were categorized into five independent stages on the basis of the degree of cardiac damage reported during index echocardiography (i.e., the first diagnostic transthoracic echocardiographic examination for severe AS), as previously defined[2,4]:

Stage 0: no significant extra AV damage detected.
Stage 1: evidence of LV damage, including hypertrophy (LV mass index > 95 g/m^2 for women and >115 g/m^2 for men), systolic dysfunction (LVEF < 50%), and/or severe diastolic dysfunction (E/e′ ratio > 14).
Stage 2: evidence of left atrial (LA) or mitral valve damage, including LA dilatation (>34 mL/m^2), atrial fibrillation (recorded at the time of echocardiography), and/or moderate to severe mitral regurgitation.
Stage 3: evidence of systolic pulmonary hypertension (right ventricular [RV] systolic pressure ≥60 mm Hg) and/or moderate to severe tricuspid regurgitation.
Stage 4: evidence of moderate to severe RV systolic dysfunction.

Statistical Analysis

Statistical calculations were performed using SPSS (IBM, Armonk, NY), and significance was inferred at a two-sided P value of <.05. Comparisons between severe AS groups were assessed using analysis

HIGHLIGHTS

- Prognosis in low-gradient severe AS is worse with greater cardiac damage score.
- Cardiac damage staging score is useful for prognosis in low-gradient severe AS.
- Low- versus high-gradient severe AS patients can have higher cardiac damage scores.

of variance, Student's *t* test, or the χ^2 test, as appropriate. Differences in all-cause and cardiovascular-related 1- and 5-year mortality among cardiac damage stages for each severe AS subgroup were plotted (Kaplan-Meir survival curves) and further assessed using Cox multivariable regression analyses, adjusting for patient age and sex. Patients with stages 3 and 4 were grouped together in mortality curves and regression analyses (because of the small number of stage 4 patients). For all-cause mortality analyses, patients were included only if follow-up was ≥1 year or 5 years for each relevant analysis. Additionally, for cardiovascular-related mortality analyses, patients were included only if the cause of death was available. We also

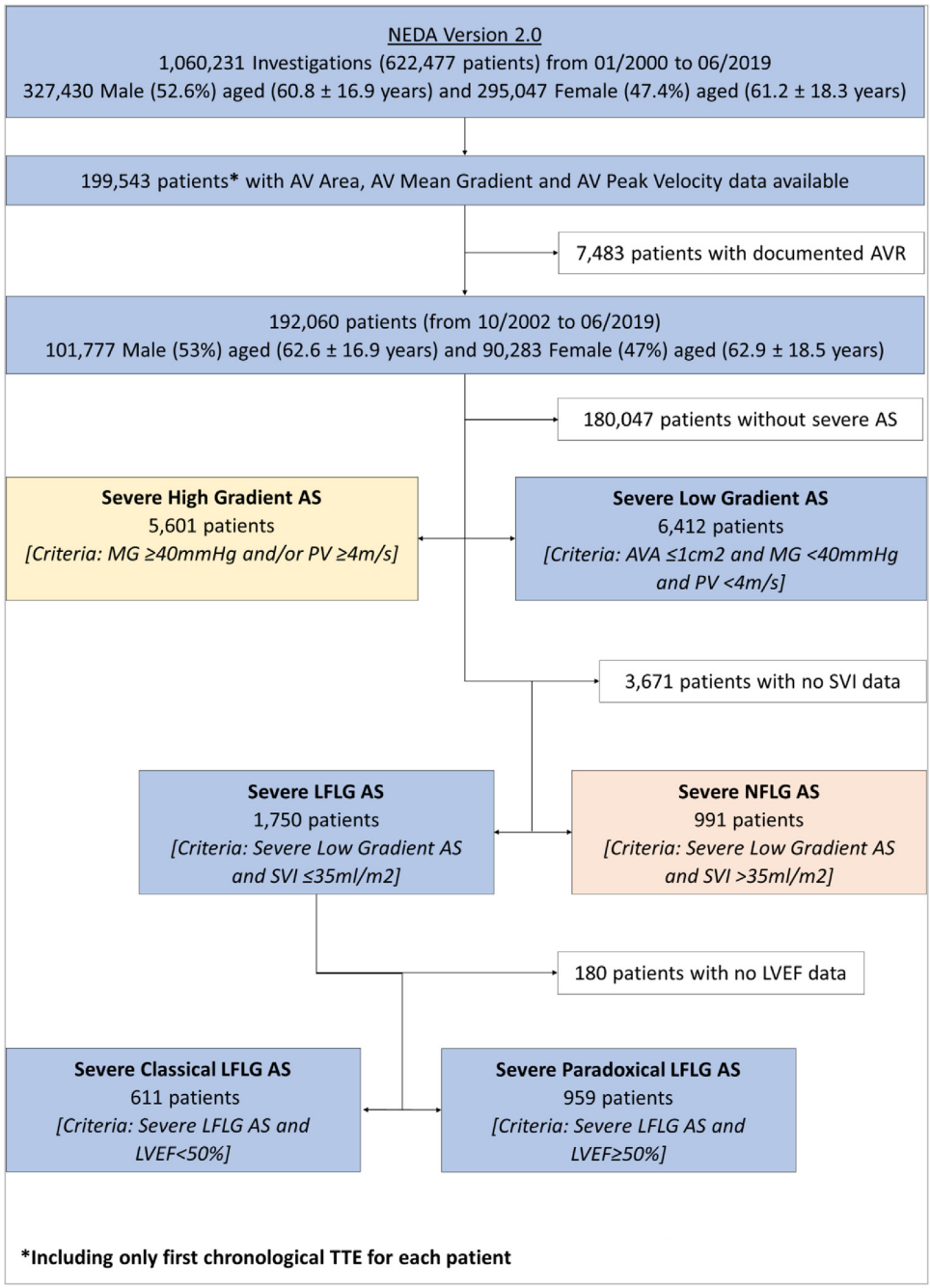

Figure 1 Study flowchart.

Table 1 Baseline group characteristics and cardiac damage stage parameters

Variable	High gradient (n = 5,601)	Classical LFLG (n = 611)	Paradoxical LFLG (n = 959)	NFLG (n = 991)	P value
Age, y	75.0 ± 13.0	76.2 ± 12.2	74.3 ± 14.4	77.2 ± 12.0	<.001
Sex, female	2,392 (42.7)	222 (36.3)	602 (62.8)	578 (58.3)	<.001
BMI, kg/m^2	27.8 ± 6.1	26.9 ± 5.7	28.6 ± 6.9	26.2 ± 5.2	<.001
AVR during follow-up	2,300 (41.1)	119 (19.5)	126 (13.2)	273 (27.5)	<.001
AV characteristics					
AVA (VTI), cm^2	0.80 ± 0.28	0.83 ± 0.28	0.87 ± 0.26	0.94 ± 0.17	<.001
Indexed AVA (VTI), cm^2/m^2	0.43 ± 0.15	0.45 ± 0.16	0.48 ± 0.15	0.54 ± 0.12	<.001
Mean gradient, mm Hg	49.8 ± 12.4	19.2 ± 9.7	18.0 ± 9.6	27.6 ± 7.1	<.001
Peak velocity, m/sec	4.6 ± 0.5	2.8 ± 0.7	2.7 ± 0.7	3.4 ± 0.4	<.001
Cardiac damage stage					
Stage 0	1,695 (30.3)	0 (0)	328 (34.2)	259 (26.1)	<.001
Stage 1	975 (17.4)	148 (24.2)	161 (16.8)	171 (17.3)	<.001
High LV mass	1,763 (31.5)	287 (47.0)	254 (26.5)	316 (31.9)	
LVEF < 50%	835 (14.9)	611 (100)	0 (0)	163 (16.5)	
E/e′ ratio > 14	1,286 (25.4)	133 (21.8)	178 (18.6)	264 (26.6)	
Stage 2	2,134 (38.1)	256 (41.9)	256 (26.7)	406 (41.0)	<.001
LA dilatation (>34 mL/m^2)	2,233 (39.9)	283 (46.3)	285 (29.7)	419 (42.3)	
Moderate to severe MR	763 (13.6)	200 (32.7)	111 (11.6)	178 (18.0)	
Atrial fibrillation	524 (9.4)	125 (20.5)	183 (19.1)	96 (9.7)	
Stages 3 and 4	797 (14.2)	207 (33.9)	214 (22.3)	155 (15.6)	<.001
Moderate to severe TR	447 (8.0)	161 (26.4)	174 (18.1)	110 (11.1)	
RVSP ≥ 60 mm Hg	473 (8.4)	77 (12.6)	75 (7.8)	70 (7.1)	
RV systolic impairment	113 (2.0)	25 (4.1)	11 (1.1)	8 (0.8)	

Data are expressed as mean ± SD or as number (percentage). Patients were classified into the highest hierarchical stage (i.e., worst stage) if at least one of the criteria was met within that stage.
BMI, Body mass index; *MR*, mitral regurgitation; *TR*, tricuspid regurgitation; *VTI*, velocity-time integral.

performed a "sensitivity" analysis, repeating the above calculations only in patients without recorded AVR during follow-up (see Supplemental Table 1).

RESULTS

Of 199,543 patients with comprehensive echocardiographic assessment of their aortic valves (Figure 1), 192,060 had a native aortic valve (mean age, 62.8 ± 17.8 years; 53% men). Severe AS was identified in 12,013 patients (6.3%; 95% CI, 6.2%–6.4%). Of these, 5,601 patients had high-gradient severe AS and 6,412 patients had low-gradient severe AS, 2,741 of whom had SVI data available. The final studied cohort included 5,601 patients with high-gradient severe AS, 611 patients with confirmed classical LFLG severe AS, 959 patients with confirmed paradoxical LFLG severe AS, and 991 patients with confirmed NFLG severe AS (Table 1).

The distribution of cardiac damage stage among the different subtypes of severe AS is shown in Figure 2. Patients with classical LFLG severe AS presented with higher cardiac damage scores (mean score, 2.1 ± 0.8) compared with those with other severe AS subtypes; the mean score was 1.4 ± 1.2 in patients with paradoxical LFLG severe AS, 1.5 ± 1.1 in those with NFLG severe AS, and 1.4 ± 1.1 in those with high-gradient severe AS ($P < .001$).

Survival data for all four major subtypes of severe AS, by cardiac damage score, are shown in Table 2 and Figures 3 to 6. Outcomes for the specific AS subtypes are summarized in the following.

Cardiac Damage Stage and Outcomes in Patients with LFLG Severe AS

No patients with classical LFLG were classified as stage 0 because of the presence of LV systolic impairment. For classical LFLG severe AS (Figure 3, Supplemental Figure 1), compared with patients with stage 1, those with stages 3 and 4 had significantly higher all-cause and cardiovascular adjusted mortality at both 1 and 5 years ($P < .001$). Patients with stage 2 had significantly higher all-cause adjusted mortality at both 1 and 5 years ($P = .018$ and $P = .036$) but nonsignificantly higher cardiovascular adjusted mortality ($P = .075$ and $P = .155$).

For paradoxical LFLG severe AS (Figure 4, Supplemental Figure 2), compared with patients with stage 0, those with stages 3 and 4 had significantly higher all-cause and cardiovascular adjusted mortality at both 1 and 5 years ($P < .003$), while those with stage 2 had significantly higher cardiovascular 1-year adjusted mortality ($P = .028$) and both all-cause and cardiovascular 5-year adjusted mortality ($P = .002$ and $P = .001$) but only nonsignificantly higher all-cause 1-year adjusted mortality ($P = .095$). There was no significant difference in any adjusted mortality rate between patients with stage 0 and stage 1.

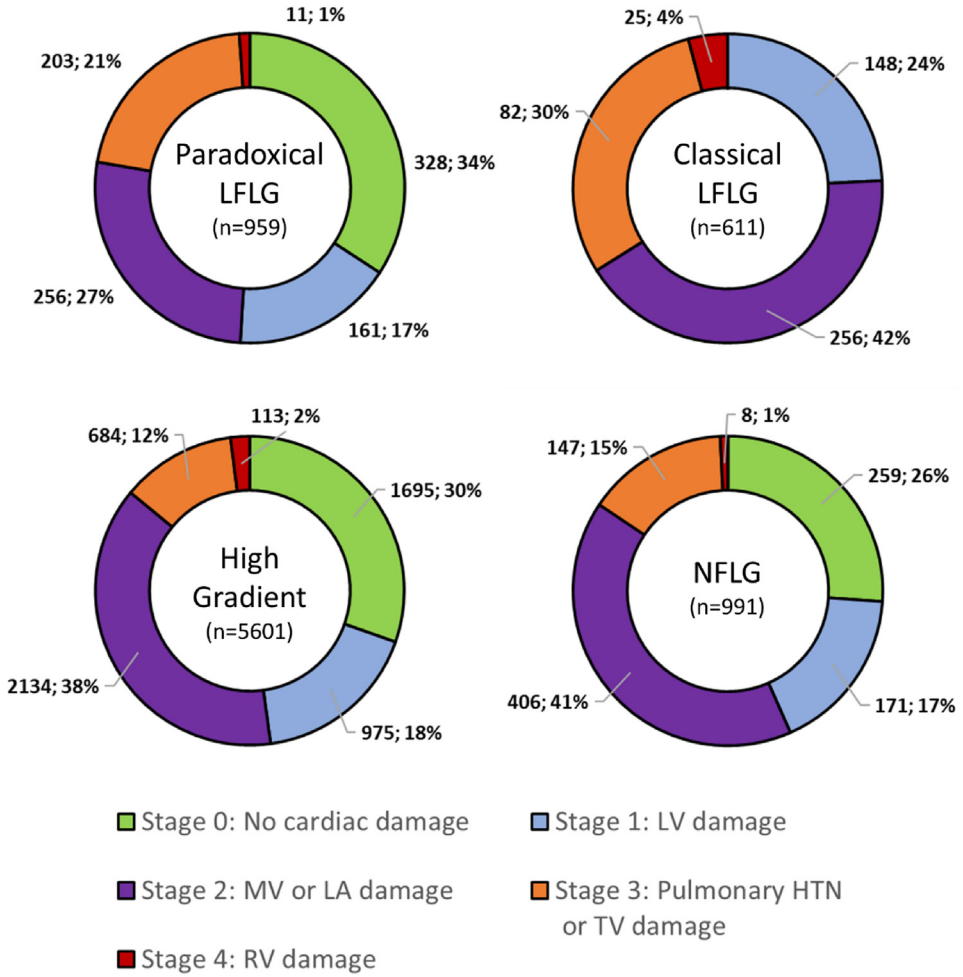

Figure 2 Cardiac damage stage distribution, showing the observed distribution of cardiac damage stages among the different subtypes of severe AS.

Cardiac Damage Stage and Outcomes in Patients with NFLG Severe AS

For NFLG severe AS (Figure 5, Supplemental Figure 3), compared with stage 0 patients, those with stages 3 and 4 had significantly higher all-cause and cardiovascular adjusted mortality at both 1 and 5 years ($P < .013$ and $P < .001$), while in stage 2 patients, only adjusted cardiovascular mortality was significantly higher at both 1 and 5 years ($P = .033$ and $P = .001$). Five-year adjusted cardiovascular mortality was significantly higher in stage 1 than stage 0 patients ($P = .009$). Both adjusted all-cause and cardiovascular mortality were similar between stage 1 and stage 2 patients.

Cardiac Damage Stage and Outcomes in Patients with High-Gradient Severe AS

Patients with high-gradient severe AS with stages 3 and 4 had substantially higher mortality ($P < .006$) at both 1 and 5 years compared with those with stage 0 (Figure 6, Supplemental Figure 4). For stage 2 patients, 5-year all-cause and cardiovascular mortality was also significant higher ($P < .005$). Unexpectedly, 1-year outcomes were significantly higher in stage 1 ($P = .014$ and $P = .026$) but not in stage 2 ($P = .117$ and $P = .061$) patients. There was no significant separation between those with stages 1 and 2 for any of the foregoing analyses.

Cardiac Damage Stage and Outcomes in Patients without Recorded AVR

Repeating the above analyses including only patients without recorded AVR during the follow-up period (see Supplemental Figures 5-12) revealed similar results. In patients with classical LFLG severe AS, there was stronger statistical separation between stage groups; the previously nonsignificant higher cardiovascular mortality rates between stage 2 and stage 1 patients were significant in this analysis ($P = .017$ and $P = .031$, at 1 and 5 years, respectively). Likewise, in high-gradient patients, the greater adjusted 5-year mortality in stage 1 patients and 1-year mortality in stage 2 patients became statistically significant ($P < .001$).

DISCUSSION

In this study of a large contemporary "real-world" cohort of >2,500 patients with severe "low-gradient" AS and detailed

Table 2 One- and 5-year mortality according to severe AS subtype and cardiac damage stage

1-y all-cause mortality	High gradient (*n* = 5,542)	Classical LFLG (*n* = 590)	Paradoxical LFLG (*n* = 900)	NFLG (*n* = 969)
Stage 0	10.7% (reference)	NA	8.2% (reference)	7.9% (reference)
Stage 1	14.3% (1.32 ± 1.06–1.65)	19.2% (ref)	13.5% (1.27 ± 0.71–2.28)	5.3% (0.56 ± 0.26–1.24)
Stage 2	14.8% (1.16 ± 0.96–1.40)	31.1% (1.69 ± 1.09–2.61)	18.1% (1.54 ± 0.93–2.55)	12.3% (1.16 ± 0.65–1.95)
Stages 3 and 4	31.4% (2.35 ± 1.93–2.87)	38.0% (2.22 ± 1.44–3.43)	31.5% (2.79 ± 1.72–4.54)	22.8% (2.07 ± 1.18–3.62)
1-y cardiovascular mortality	**High gradient (*n* = 5,201)**	**Classical LFLG (*n* = 550)**	**Paradoxical LFLG (*n* = 834)**	**NFLG (*n* = 893)**
Stage 0	6.4% (reference)	NA	2.0% (reference)	1.7% (reference)
Stage 1	9.2% (1.39 ± 1.04–1.85)	12.4% (ref)	3.5% (1.21 ± 0.37–4.00)	2.5% (1.22 ± 0.31–4.89)
Stage 2	9.9% (1.26 ± 0.99–1.60)	19.9% (1.66 ± 0.95–2.90)	9.5% (2.82 ± 1.12–7.11)	7.7% (3.13 ± 1.09–8.96)
Stages 3 and 4	23.4% (2.71 ± 2.11–3.48)	28.3% (2.48 ± 1.43–4.28)	14.7% (4.23 ± 1.68–10.6)	12.9% (5.07 ± 1.60–15.3)
5-y all-cause mortality	**High gradient (*n* = 4,579)**	**Classical LFLG (*n* = 465)**	**Paradoxical LFLG (*n* = 631)**	**NFLG (*n* = 746)**
Stage 0	38.8% (reference)	NA	39.6% (reference)	39.6% (reference)
Stage 1	44.0% (1.13 ± 0.99–1.29)	62.1% (ref)	53.2% (1.09 ± 0.77–1.54)	49.6% (1.19 ± 0.86–1.66)
Stage 2	51.0% (1.17 ± 1.05–1.30)	71.7% (1.37 ± 1.03–1.82)	67.1% (1.63 ± 1.21–2.19)	56.1% (1.27 ± 0.97–1.67)
Stages 3 and 4	72.6% (1.85 ± 1.64–2.10)	82.3% (1.97 ± 1.47–2.63)	76.7% (2.21 ± 1.64–2.98)	72.9% (1.94 ± 1.43–2.64)
5-y cardiovascular mortality	**High gradient (*n* = 4,112)**	**Classical LFLG (*n* = 394)**	**Paradoxical LFLG (*n* = 512)**	**NFLG (*n* = 630)**
Stage 0	20.1% (reference)	NA	13.1% (reference)	12.4% (reference)
Stage 1	26.8% (1.30 ± 1.08–1.57)	38.0% (ref)	23.8% (1.21 ± 0.65–2.23)	28.6% (2.09 ± 1.20–3.62)
Stage 2	29.6% (1.27 ± 1.09–1.48)	44.8% (1.35 ± 0.91–1.99)	37.4% (2.42 ± 1.46–4.02)	33.9% (2.24 ± 1.39–3.62)
Stages 3 and 4	50.3% (2.25 ± 1.90–2.66)	54.5% (1.87 ± 1.26–2.78)	44.6% (3.18 ± 1.90–5.34)	37.8% (2.84 ± 1.65–4.87)

The table shows the unadjusted 1- and 5-year all-cause and cardiovascular mortality rates and also the fully adjusted hazard ratio ± 95% CI.
n denotes number at risk at the start of each analysis.
NA, Not applicable.

echocardiographic assessment, we present for the first time the prognostic implications of the extent of cardiac damage at the time of diagnosis in this relatively poorly characterized subpopulation of severe AS patients. We found a significant and strong association between cardiac damage stage and medium- to long-term survival in patients with classical LFLG, paradoxical LFLG, and NFLG severe AS. Our results further contribute to the evolving understanding of low-gradient severe AS and validate the recently described cardiac damage staging classification as a clinically relevant prognostic tool to help guide management decisions in such patients.

LFLG AS is characterized by evidence of severe stenosis (AVA ≤ 1 cm^2) with reduced flow across the AV (SVI ≤ 35 mL/m^2). This heterogenous group is then often further subdivided according the underlying cause of the reduced cardiac output as distinguished by ventricular contractility; patients with reduced LV systolic function are said to have classical LFLG severe AS and patients with preserved systolic function are deemed to have "paradoxical" LFLG severe AS. In the latter group, the associated reduced flow state is due to restrictive LV pathophysiology and/or small ventricular volumes, and this situation is often compared with heart failure with preserved ejection fraction.[1]

Généreux *et al.*[2] first suggested a cardiac damage–related staging classification and demonstrated a strong prognostic association between the extent of extra-AV cardiac damage and 1-year outcomes

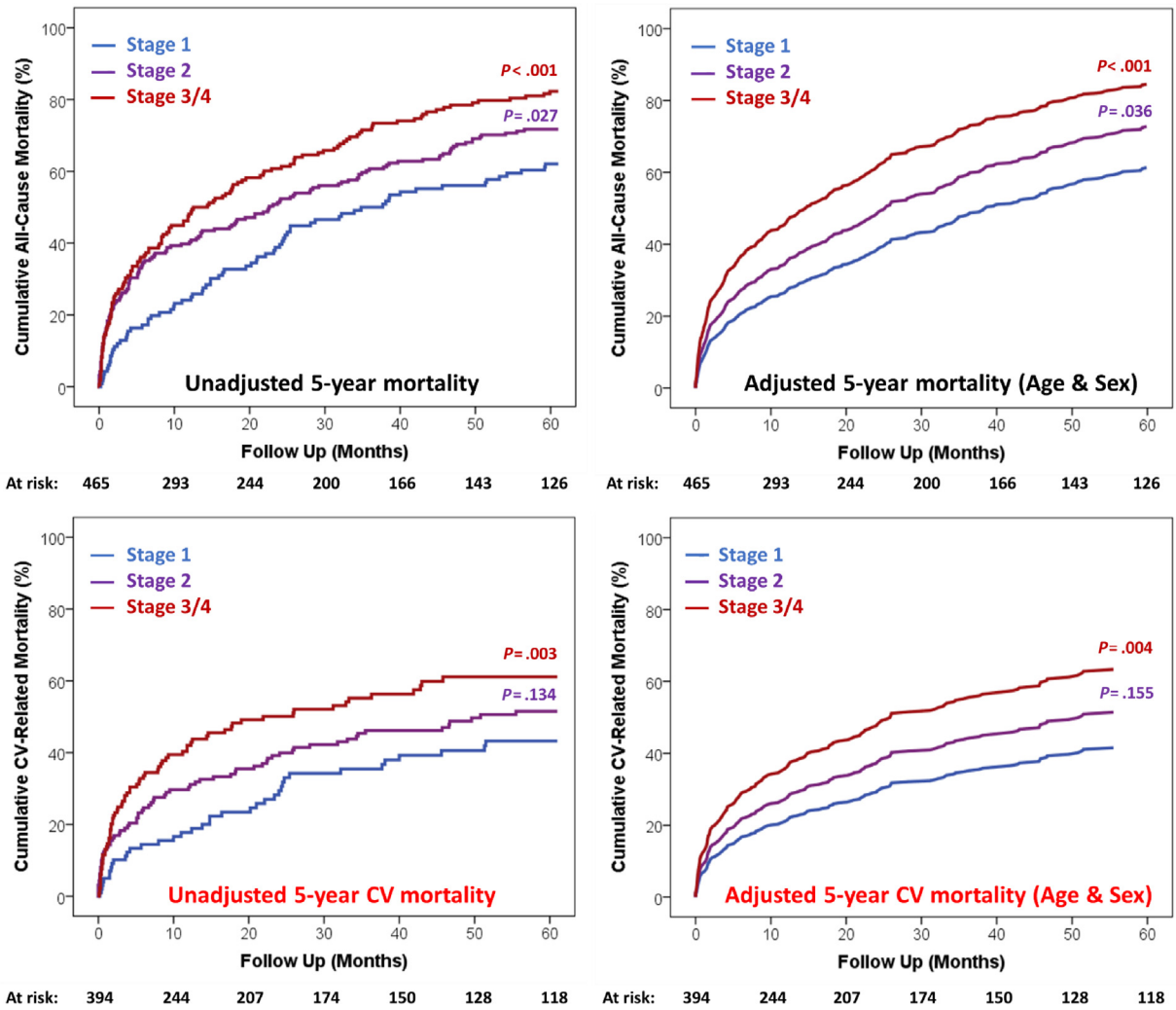

Figure 3 Five-year mortality in classical LFLG severe AS, showing 5-year all-cause and cardiovascular-related mortality rates in patients with classical LFLG severe AS, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 1 group).

in 1,611 patients with severe AS undergoing AVR. More recently, this prognostic association was also demonstrated for long-term outcomes in a nonselected severe AS cohort.[4] However, in this series the majority of patients (77%) underwent AVR, and only a minority (19% [224 patients]) had LFLG AS. Considering that patients with LFLG severe AS are known to have poorer outcomes,[1] both in general and after AVR, compared with those with high-gradient severe AS, it is clearly important to investigate and identify valid and reliable prognostic markers in patients with LFLG AS, as we have done here.

Subjects with classical LFLG AS have evidence of associated LV systolic dysfunction and thus, by definition, cannot be classified as stage 0. We observed a significant incremental mortality increase with each cardiac damage stage in patients with classical LFLG severe AS, including following adjustment for age and sex. Adjusted 1 and 5 year mortality was 56% and 20% higher, respectively, in those with evidence of significant LA and/or mitral valve disease (stage 2) at diagnosis and 100% (i.e., twofold) and 38% higher, respectively, in those with evidence of significant pulmonary hypertension, tricuspid valve, and/or RV disease (stages 3 and 4) at diagnosis. This observed prognostic association between cardiac damage staging and medium- to long-term outcomes became even more pronounced when including only patients with classical LFLG severe AS with no known AVR during follow-up (Supplemental Figures 5 and 6).

Compared with patients with classical LFLG severe AS, those with paradoxical LFLG severe AS had less cardiac damage at diagnosis, manifested by significantly lower rates of stages 2 to 4. In patients with paradoxical LFLG severe AS, after adjustment, there was no significant difference in outcomes for those with the previously specified criteria for LV hypertrophy or diastolic failure (i.e., in stage 1 vs stage 0 patients). This is not surprising, as the presence of low SVI despite the "normal" LV systolic function in this population implies an underlying element of LV "insufficiency." On the other hand, as with classical LFLG severe AS, we observed an incremental mortality increase with higher cardiac damage stages in patients with paradoxical LFLG severe AS. Adjusted mortality at 1 and 5 years was 56% and 38% higher, respectively, in those with evidence of significant LA and/or mitral valve disease (stage 2) at diagnosis and 156% and

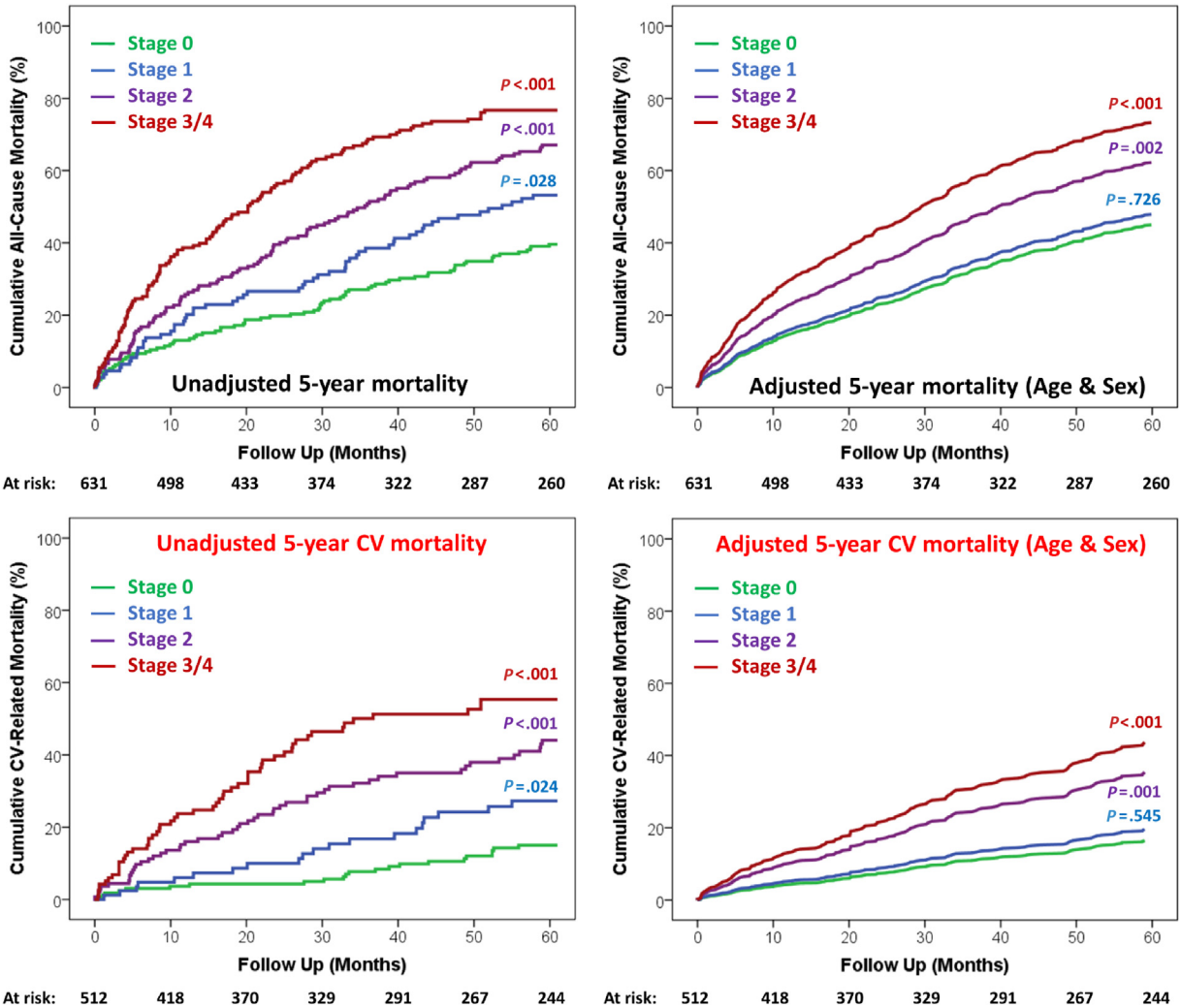

Figure 4 Five-year mortality in paradoxical LFLG severe AS, showing 5-year all-cause and cardiovascular-related mortality rates in patients with paradoxical LFLG severe AS, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 0 group).

64% higher, respectively, in those with evidence of significant pulmonary hypertension, tricuspid valve, and/or RV disease (stages 3 and 4) at diagnosis. Again, these associations remained significant when considering only patients with paradoxical LFLG severe AS with no known AVR during follow-up (Supplemental Figures 7 and 8).

The management of patients with NFLG severe AS can often be challenging; although current guidelines[10,13] regard these patients as having only moderate AS, evidence suggests that intervention is indicated in at least some.[14] In this context, it is pertinent to highlight that the accepted AVA cutoff for severe stenosis of 1 cm^2 corresponds in many patients to a mean gradient of only 30 to 35 mm Hg[15] and that this AVA threshold (1 cm^2) has been independently associated with improved outcomes following intervention.[16] As with patients with LFLG severe AS, we observed a significant association between cardiac damage stage and survival in patients with NFLG severe AS. However, this correlation was more prominent with cardiovascular-specific mortality; adjusted all-cause mortality in stage 1 and stage 2 patients with NFLG severe AS was not significantly higher, but 5-year adjusted cardiovascular mortality was 96% and 107% higher, respectively. The relative prognosis of NFLG severe AS patients with stages 3 and 4 (vs stage 0) was substantially worse, with 275% and 55% higher 1- and 5-year adjusted all-cause mortality, respectively.

Only a minority of low-gradient patients had documented AVR (either surgical or transcatheter) during the follow-up period: 19.5% of those with classical LFLG, 13.2% of those with paradoxical LFLG, and 27.5% of those with NFLG severe AS. These figures must be interpreted with caution, however, as they would likely underestimate the true incidence of AVR performed by not accounting for patients without postprocedural transthoracic echocardiography recorded in the database (because of early postoperative mortality or loss to follow-up, for example). Nevertheless, our supplemental analysis demonstrates, for the first time, the prognostic power of this echocardiographic cardiac damage staging classification in a severe AS cohort undergoing mainly conservative management.

Consistent with previously reported data,[4] patients with LFLG severe AS in our cohort presented with more advanced cardiac damage staging compared with high-gradient patients; overall, the relative

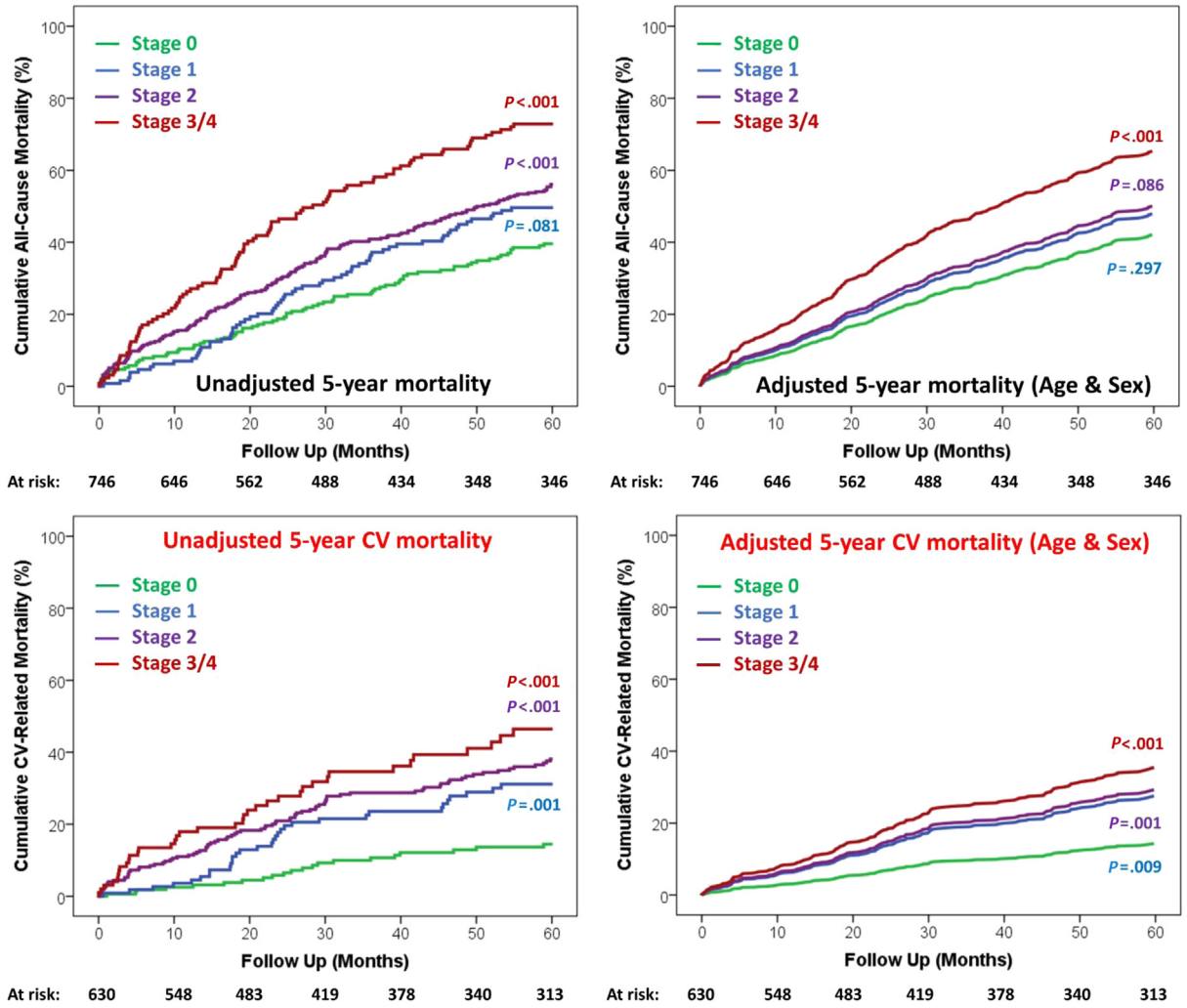

Figure 5 Five-year mortality in NFLG severe AS, showing 5-year all-cause and cardiovascular-related mortality rates in patients with NFLG severe AS, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 0 group).

percentage of stages 3 and 4 in patients with LFLG severe AS was 27% compared with 14% in those with high-gradient severe AS. Our results again confirm the prognostic utility of the cardiac damage staging classification in a large cohort of 5,601 unselected patients with high-gradient severe AS, including specifically a subcohort of >3,000 patients with no recorded valvular intervention (see Appendix). Compared with patients with no evidence of extra-AV cardiac damage, adjusted all-cause mortality was significantly higher in patients with stages 1 and 2 and higher still in those with stages 3 and 4 in the classification. Interestingly, there was only a negligible difference in adjusted outcomes between stage 1 and 2 patients (i.e., no adverse prognostic association seen with the presence of severe mitral regurgitation or LA disease in those with evidence of LV diastolic or systolic dysfunction).

Limitations

NEDA represents a national network of >25 participating centers with both inpatient and outpatient services across all the states of Australia. Therefore, it represents the heterogeneity of cases seen in "real-world" clinical cardiology practice across an advanced health care system servicing a multiracial population. Inherently, NEDA contains a certain selection bias by drawing on results only from those adults undergoing cardiac ultrasound. Nevertheless, Australia's universal health care system minimizes the chance of important referral bias on the basis of subjects' ability to pay for this test (or for subsequent interventions). NEDA does not contain routine clinical data, and we acknowledge the importance of symptomatic status and comorbidities in the prognostication and appropriate management of patients with severe AS. Nonetheless, we believe that overreliance on symptomatology in the natural history of severe AS may be detrimental, considering that many patients do not present with overt symptoms because they progressively adopt a more sedentary lifestyle and especially with recent evidence showing benefit of early intervention compared with an initial conservative approach in patients with asymptomatic severe AS.[17,18] Indeed, current guidelines highlight the diagnostic and prognostic benefit of exercise testing and other imaging modalities in presumed asymptomatic patients with severe AS.[13]

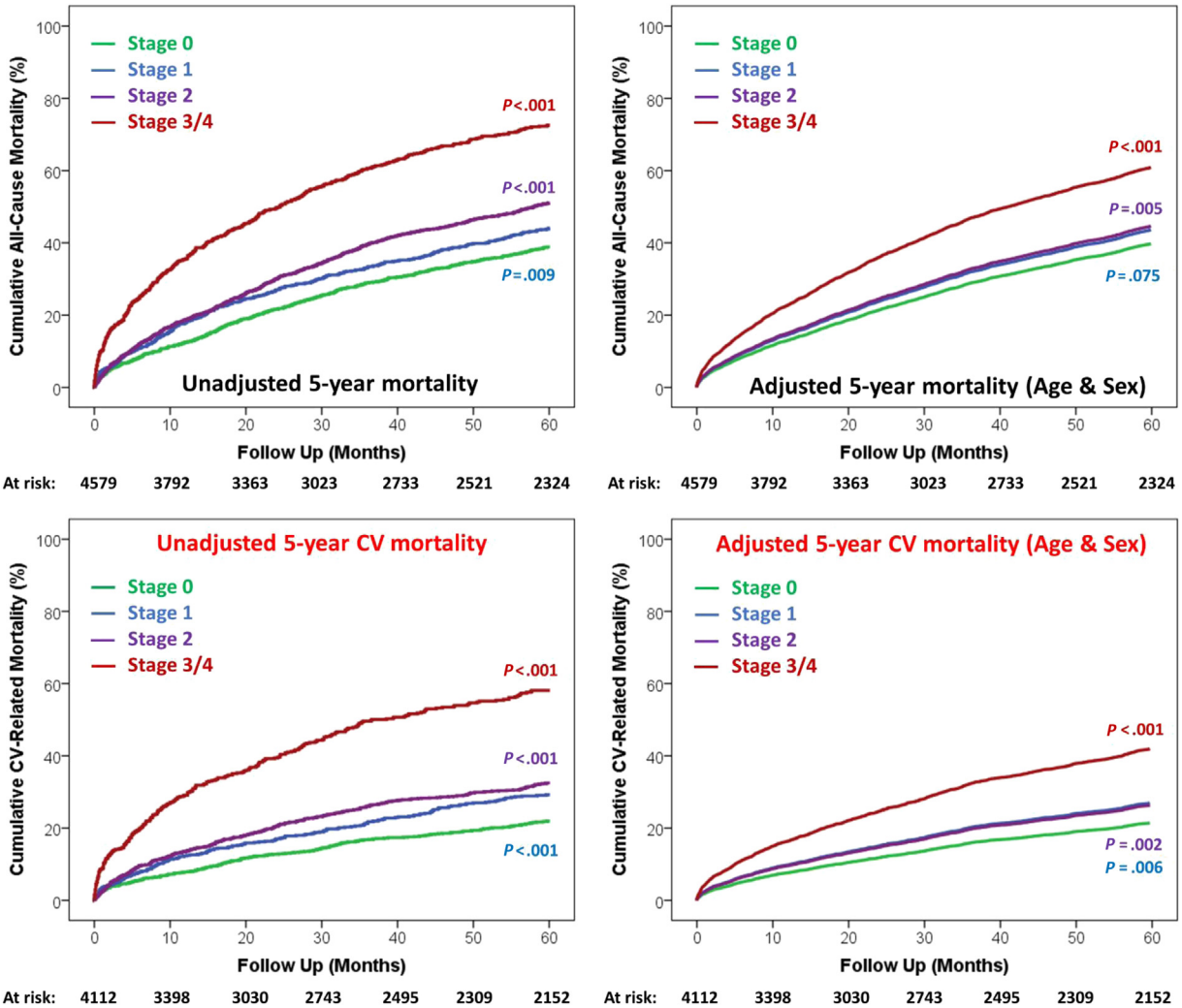

Figure 6 Five-year mortality in high-gradient severe AS, showing 5-year all-cause and cardiovascular-related mortality rates in patients with high-gradient severe AS, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with Stage 0 group).

SVI measurement was available in slightly fewer than half the patients in the database with a low-gradient severe AS profile, which may have introduced a selection bias into the final analyzed cohort. The frequency of SVI measurement in the low-gradient group increased from 43% overall to 73% considering only patients diagnosed from 2015 (data not shown in results), suggesting that awareness in routine clinical practice for the different hemodynamic profiles of severe AS may have improved over the study period.

Several echocardiographic parameters used for the staging classification, such as mitral regurgitation and tricuspid regurgitation severity or estimated pulmonary systolic pressure, are known to be dynamic and depend on each patient's fluid status (for example) at time of index transthoracic echocardiography. This limitation (in context of the cardiac damage classification) has not been described previously and should be considered when assessing patients with severe congestive cardiac failure. There were no available objective raw data for RV systolic function (i.e., tricuspid annular plane systolic excursion or RV S′) in the database, and the presence or absence of RV dysfunction was therefore determined on the basis of the reporting cardiologist's qualitative assessment. This may account for the smaller proportion of stage 4 patients in our cohort, compared with previous reports[2,4] (1.8% vs 9%–12%). Also, we acknowledge sources of echocardiography-related measurement error, especially those related to LV outflow tract diameter assessment[19]; this may be particularly relevant to subjects diagnosed with low-gradient severe AS.

CONCLUSION

The extent of echocardiographic extra-AV cardiac damage at diagnosis, as described by the cardiac damage stage classification, is significantly and independently associated with medium- and long-term outcomes in low-gradient severe AS subpopulations. We believe that our novel data support the use of this simple yet powerful prognostic tool and will assist clinicians with management decisions in patients with the major recognized subtypes of severe AS.

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We thank all the NEDA centers and their patients for contributing to these data.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2021.05.017.

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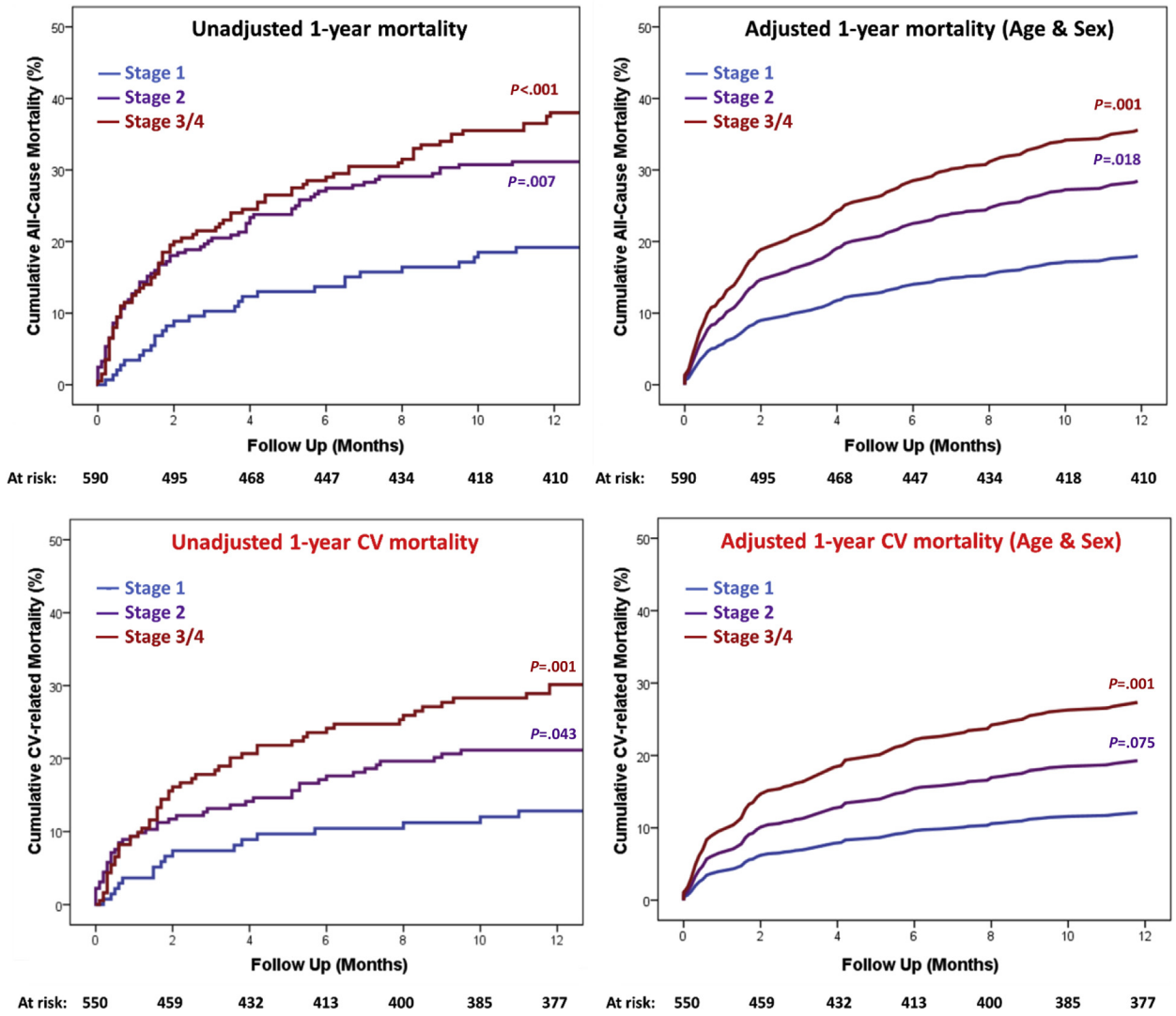
SUPPLEMENTAL MATERIALS

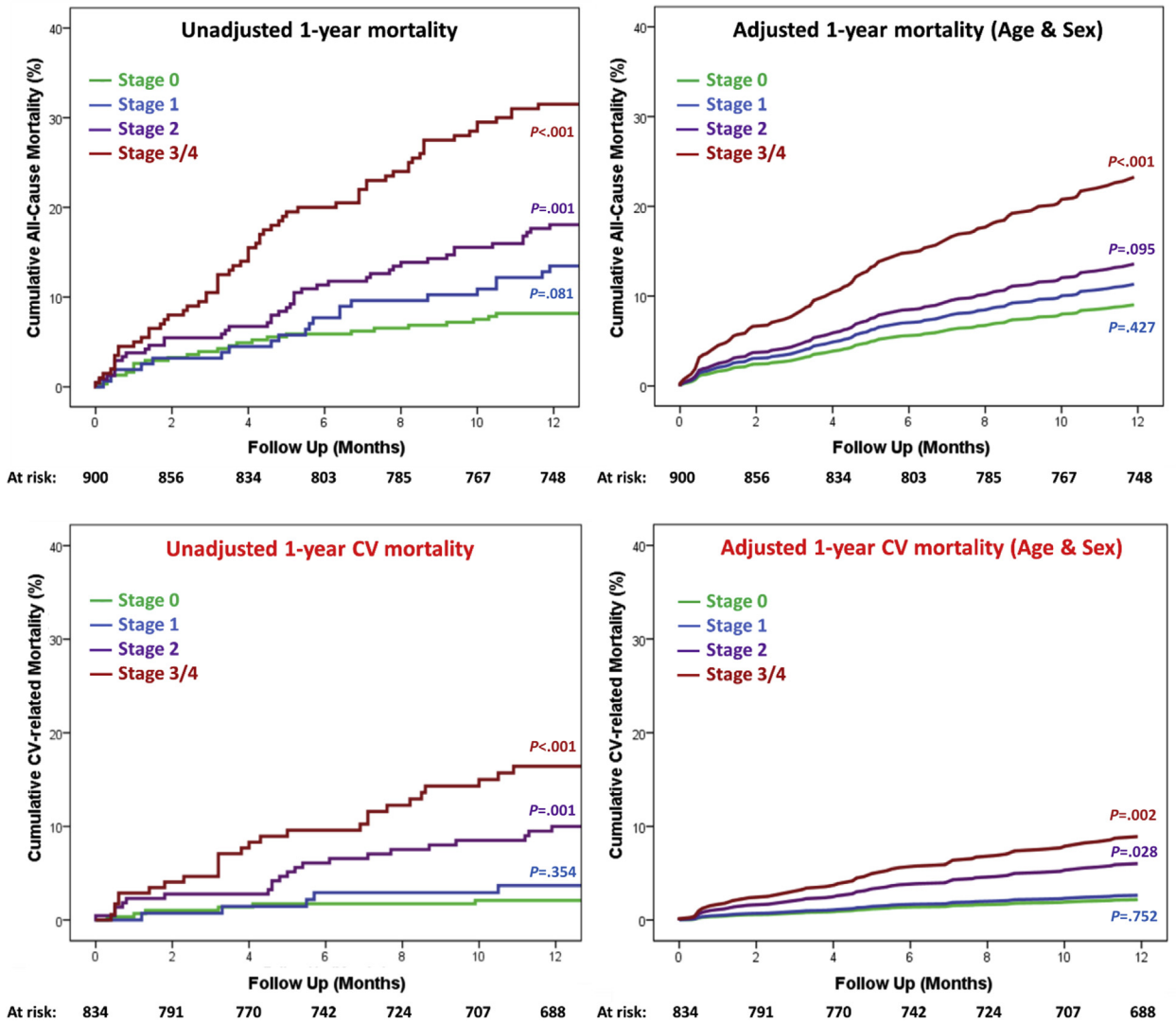
Supplemental Analysis: Repeating the main analysis, including only patients without recorded AVR during follow-up.

Supplemental Table 1 Baseline group characteristics

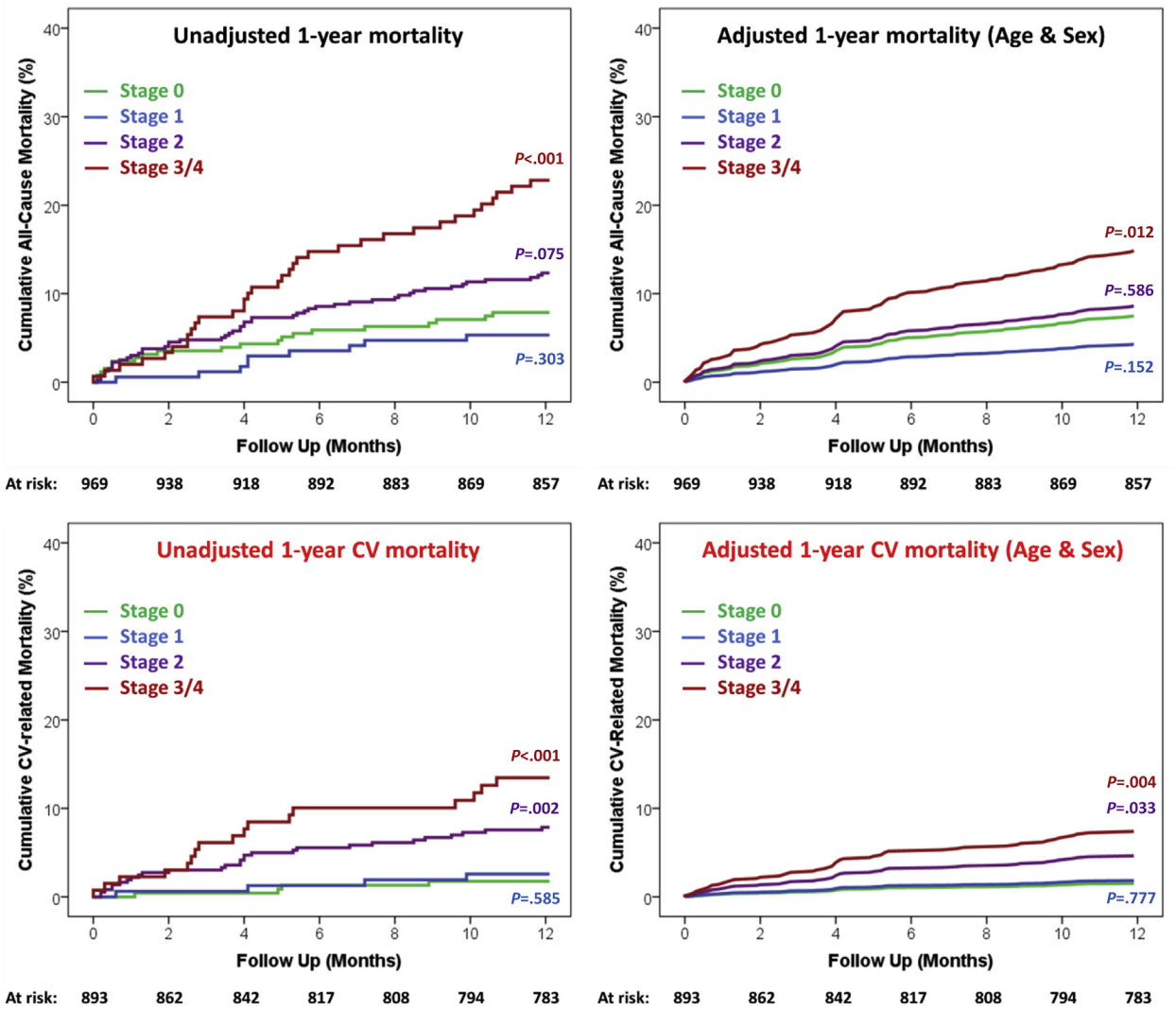
Variable	High gradient (*n* = 3,298)	Classical LFLG (*n* = 491)	Paradoxical LFLG (*n* = 829)	NFLG (*n* = 718)
Age, y	77.2 ± 12.8	77.7 ± 11.5	74.5 ± 14.8	78.1 ± 12.4
Sex, female	1,483 (45.0)	192 (39.1)	535 (64.5)	445 (62.0)
BMI, kg/m^2	27.0 ± 6.0	26.6 ± 5.6	28.4 ± 6.8	25.8 ± 5.4
AV characteristics				
AVA from VTI, cm^2	0.79 ± 0.32	0.85 ± 0.30	0.87 ± 0.27	0.94 ± 0.18
Mean gradient, mm Hg	48.5 ± 12.1	17.5 ± 9.5	16.9 ± 9.3	26.4 ± 7.3
Peak velocity, m/sec	4.5 ± 0.5	2.7 ± 0.7	2.6 ± 0.7	3.3 ± 0.5
Cardiac damage stage				
Stage 0	1,079 (32.7)	0 (0)	290 (35.0)	189 (26.3)
Stage 1	549 (16.6)	120 (24.4)	146 (17.6)	129 (18.0)
High LV mass	1,018 (30.9)	244 (49.7)	223 (26.9)	235 (32.7)
LVEF < 50%	495 (15.0)	491 (100)	0 (0)	112 (15.6)
E/e′ > 14	674 (20.4)	103 (21.0)	149 (18.0)	186 (25.9)
Stage 2	1,118 (33.9)	195 (39.7)	208 (25.1)	268 (37.3)
LA dilatation (>34 mL/m^2)	1,214 (36.8)	219 (44.6)	230 (27.7)	290 (40.4)
Moderate to severe MR	415 (12.6)	166 (33.8)	91 (11.0)	121 (16.9)
Atrial fibrillation	345 (10.5)	108 (22.0)	155 (18.7)	75 (10.4)
Stages 3 and 4	552 (16.7)	176 (35.8)	185 (22.3)	132 (18.4)
Moderate to severe TR	303 (9.2)	140 (28.5)	149 (18.0)	93 (13.0)
RVSP ≥ 60, mm Hg	344 (10.4)	64 (13.0)	68 (8.2)	62 (8.6)
RV systolic impairment	89 (2.7)	20 (4.1)	7 (0.8)	6 (0.8)



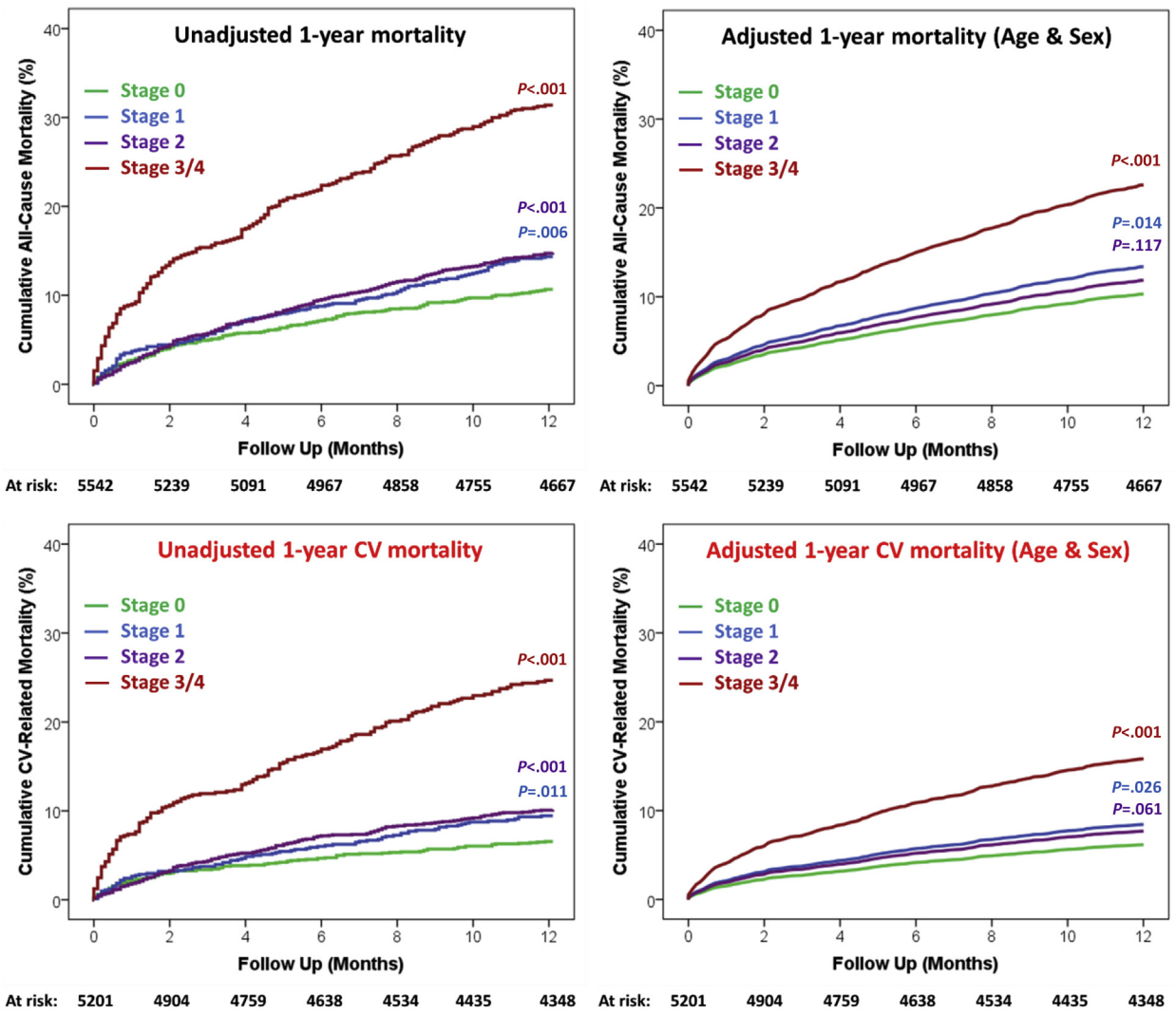
Supplemental Figure 1 One-year survival in classical LFLG severe AS, showing 1-year mortality rates in patients with classical LFLG severe AS, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 1 group).



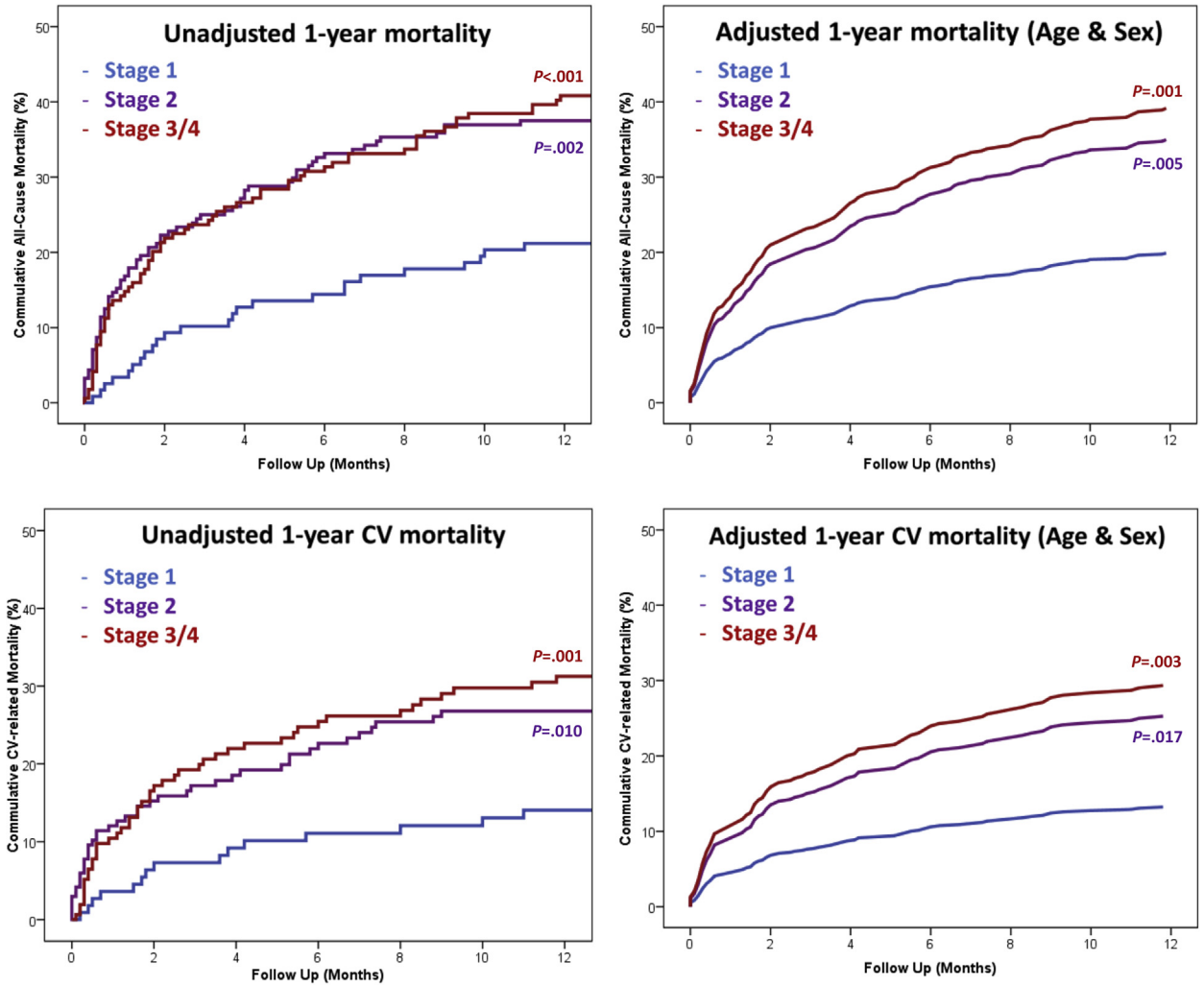
Supplemental Figure 2 One-year survival in paradoxical LFLG severe AS, showing 1-year mortality rates in patients with paradoxical LFLG severe AS, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 0 group).



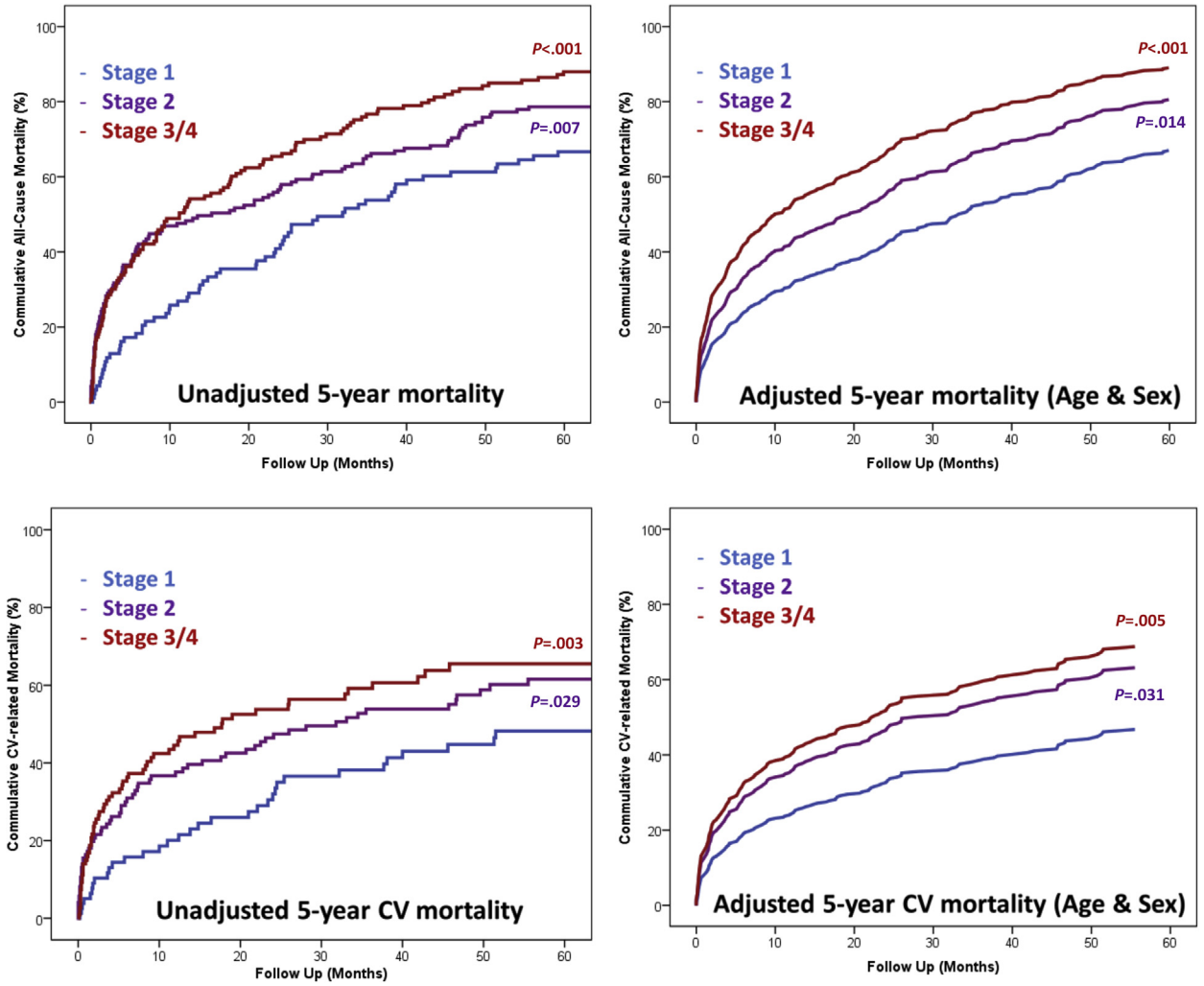
Supplemental Figure 3 One-year survival in NFLG severe AS, showing 1-year mortality rates in patients with NFLG severe AS, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 0 group).



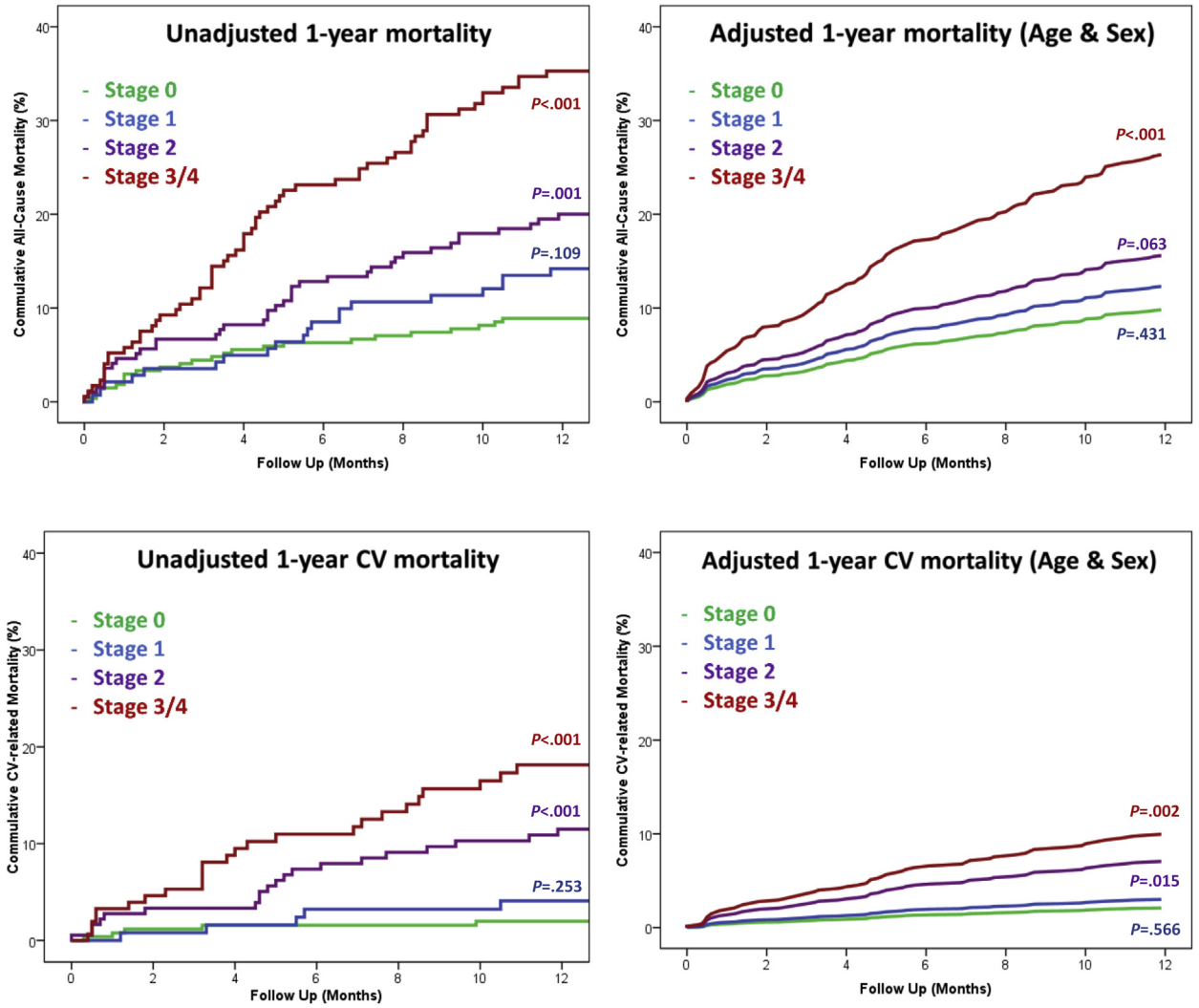
Supplemental Figure 4 One-year survival in high-gradient severe AS, showing 1-year mortality rates in patients with high-gradient severe AS, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 0 group).



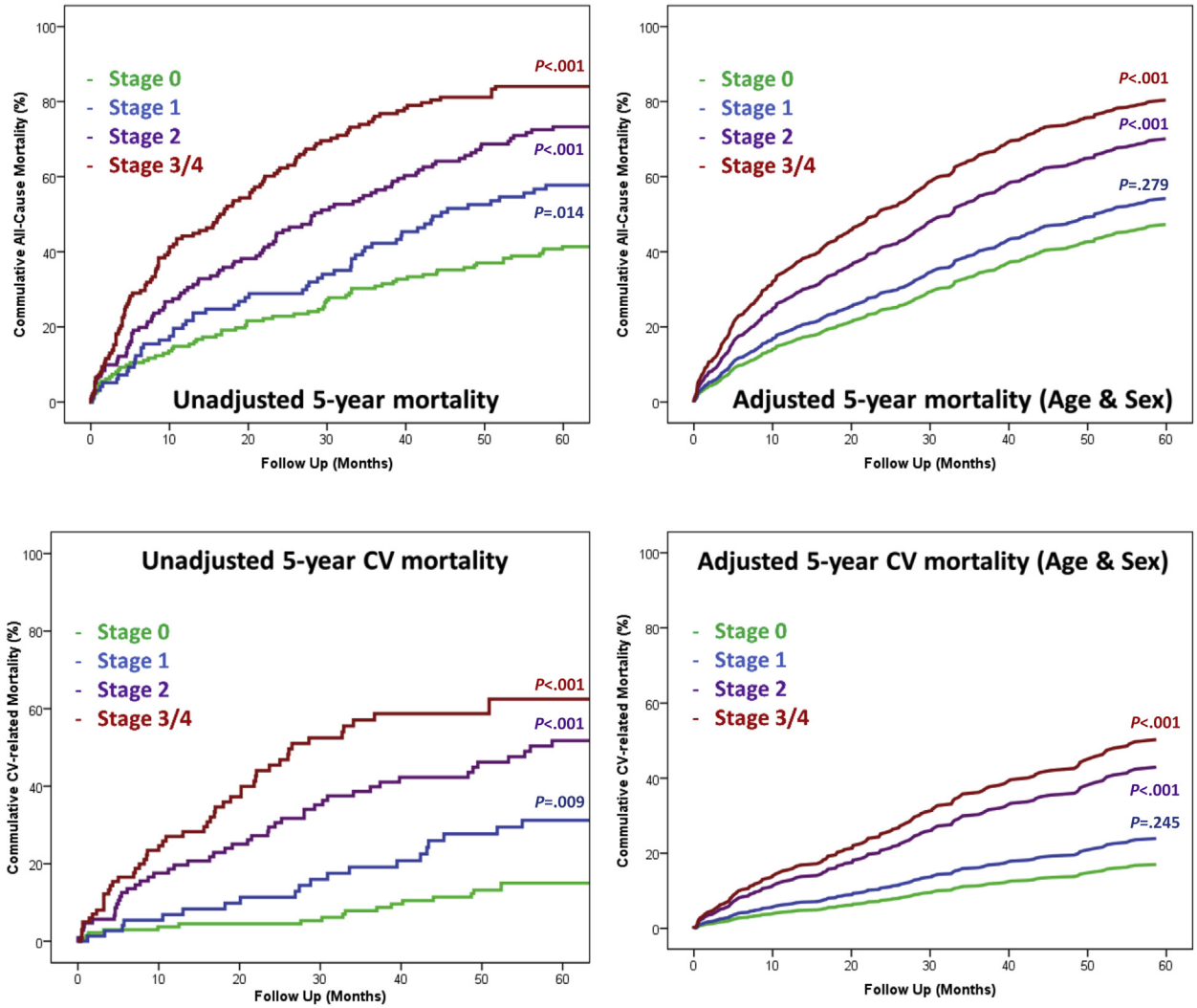
Supplemental Figure 5 One-year survival in classical LFLG severe AS without recorded AVR, showing 1-year mortality rates in patients with classical LFLG severe AS without recorded AVR, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 1 group).



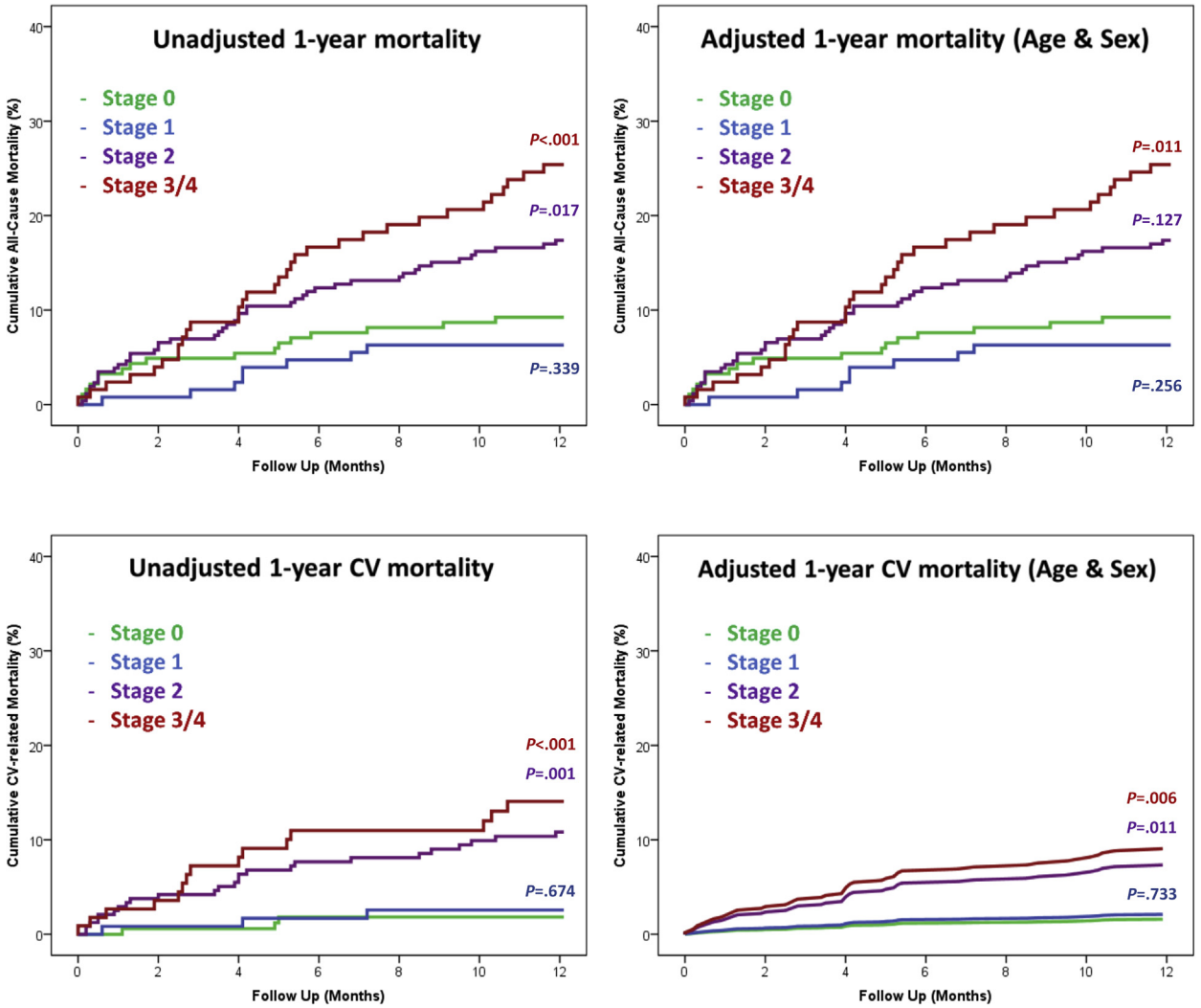
Supplemental Figure 6 Five-year survival in classical LFLG without recorded AVR, showing 5-year mortality rates in patients with classical LFLG severe AS without recorded AVR, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 1 group).



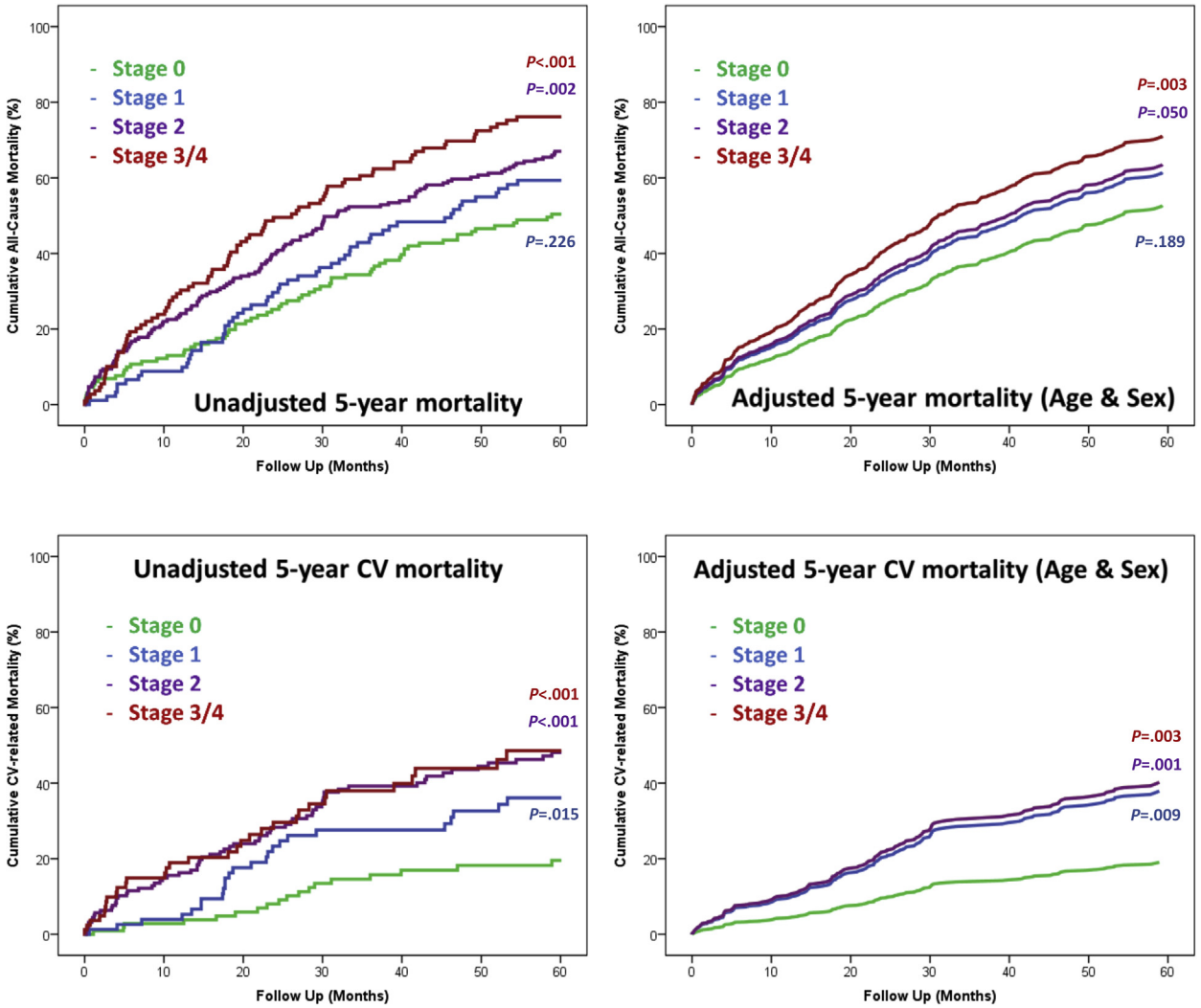
Supplemental Figure 7 One-year survival in paradoxical LFLG severe AS without recorded AVR, showing 1-year mortality rates in patients with paradoxical LFLG severe AS without recorded AVR, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 0 group).



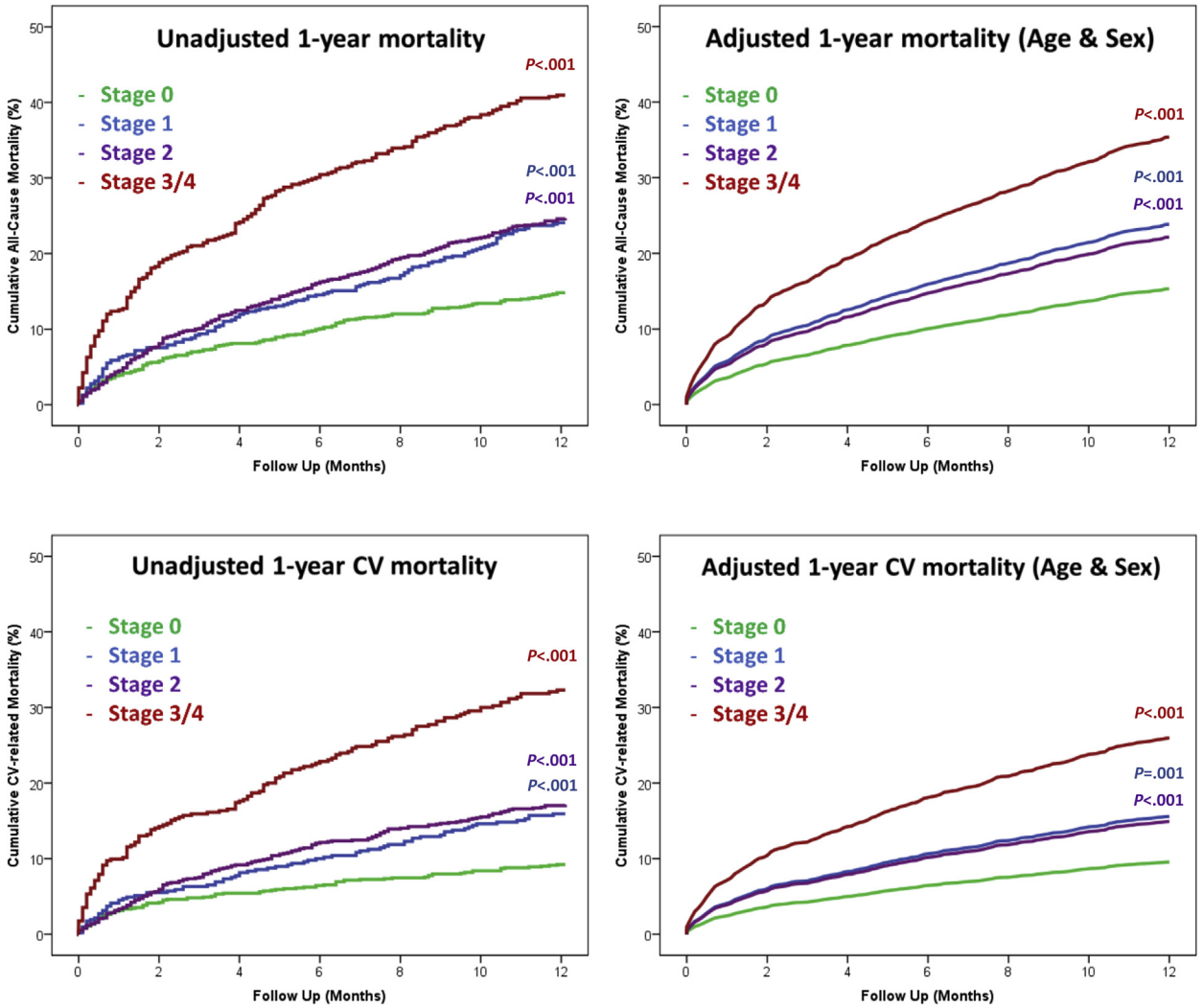
Supplemental Figure 8 Five-year survival in paradoxical LFLG without recorded AVR, showing 5-year mortality rates in patients with paradoxical LFLG severe AS without recorded AVR, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 0 group).



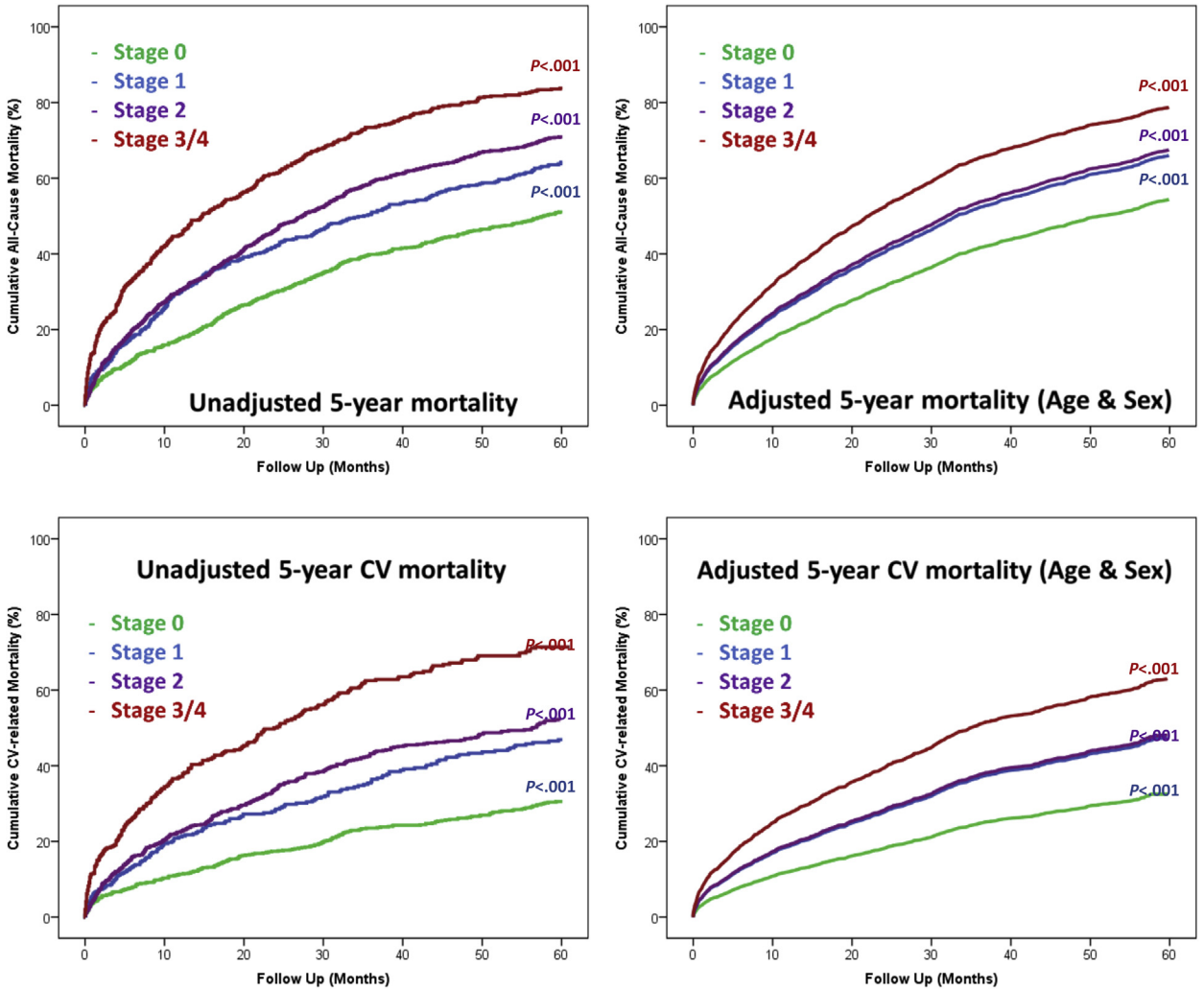
Supplemental Figure 9 One-year survival in NFLG severe AS without recorded AVR, showing 1-year mortality rates in patients with NFLG severe AS without recorded AVR, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 0 group).



Supplemental Figure 10 Five-year survival in NFLG severe AS without recorded AVR, showing 5-year mortality rates in patients with NFLG severe AS without recorded AVR, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 0 group).



Supplemental Figure 11 One-year survival in high-gradient severe AS without recorded AVR, showing 1-year mortality rates in patients with high-gradient severe AS without recorded AVR, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 0 group).



Supplemental Figure 12 Five-year survival in high-gradient severe AS without recorded AVR, showing 5-year mortality rates in patients with high-gradient severe AS without recorded AVR, both unadjusted *(left)* and adjusted for patient age and sex *(right)*, according to cardiac damage stage (*P* values comparing with stage 0 group).