ESC European Society of Cardiology

European Heart Journal Open (2022) **2**, 1–11
https://doi.org/10.1093/ehjopen/oeac074

**ORIGINAL ARTICLE**
*Valvular heart disease*

# Characterization of myocardial mechanics and its prognostic significance in patients with severe aortic stenosis undergoing aortic valve replacement

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*Received 28 June 2022; revised 25 October 2022; accepted 2 November 2022; online publish-ahead-of-print 5 November 2022*

Handling Editor: Frank A. Flachskampf

**Aims** Aortic stenosis (AS) induces characteristic changes in left ventricular (LV) mechanics that can be reversed after aortic valve replacement (AVR). We aimed to comprehensively characterize LV mechanics before and after AVR in patients with severe AS and identify predictors of short-term functional recovery and long-term survival.

**Methods and results** We prospectively performed comprehensive strain analysis by 2D speckle-tracking echocardiography in 88 patients with severe AS and LV ejection fraction ≥50% (mean age 71 ± 12 years, 42% female) prior to and within 7 days after AVR. Patients were followed for up to 5.2 years until death from any cause or last encounter. Within days after AVR, we observed an absolute increase in global longitudinal strain (GLS) (−16.0 ± 2.0% vs. −18.5 ± 2.1%, $P<0.0001$) and a decrease in apical rotation (10.5 ± 4.0° vs. 8.3 ± 2.8°, $P=0.0002$) and peak systolic twist (18.2 ± 5.0° vs. 15.5 ± 3.8°, $P=0.0008$). A baseline GLS is less negative than −16.2% was 90% sensitive and 67% specific in predicting a ≥ 20% relative increase in GLS. During a median follow-up of 3.8 years, a global circumferential systolic strain rate (GCSRs) less negative than −1.9% independently predicted lower survival.

**Conclusion** In patients with severe AS, a reversal in GLS, apical rotation, and peak systolic twist abnormalities towards normal occurs within days of AVR. Baseline GLS is the strongest predictor of GLS recovery but neither was associated with long-term survival. In contrast, abnormal baseline GCSRs are associated with worse outcomes.

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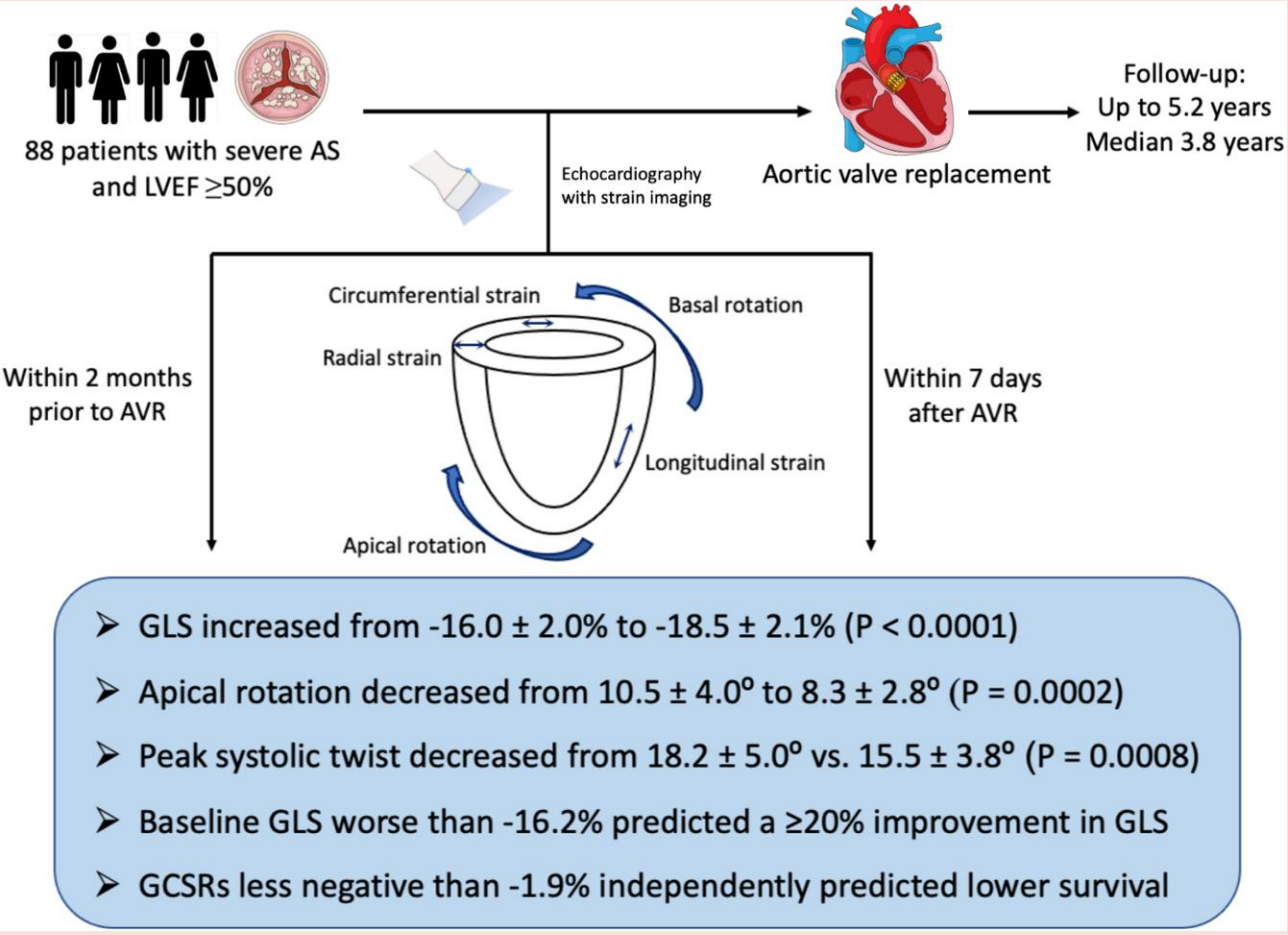
## Graphical Abstract




**Keywords** Aortic stenosis • Aortic valve replacement • Echocardiography • Strain

# Introduction

Progressive aortic stenosis (AS) leads to adverse left ventricular (LV) remodelling and fibrosis as a result of chronic pressure overload.[1] Patients with severe AS who experience a reduction in LV ejection fraction (EF) demonstrate worse outcomes than those whose LVEF remains preserved.[2] As such, current guidelines recommend aortic valve replacement in patients with an LVEF <50% whether or not they are symptomatic.[3] However, even patients with severe AS and preserved LVEF exhibit evidence of systolic impairment that may have negative prognostic consequences.[1,4–5] Therefore, identifying patients with subclinical LV systolic dysfunction is important as an earlier intervention in these patients could potentially improve outcomes.

Strain analysis with speckle-tracking echocardiography (STE) can be used to detect subclinical LV systolic dysfunction that occurs before overt changes in LVEF.[6] Patients with severe AS in particular exhibit characteristic changes in myocardial mechanics, which include reductions in global longitudinal strain (GLS) and global radial strain (GRS), as well as compensatory increases in global circumferential strain (GCS), basal rotation, and peak systolic twist.[7] Previous studies have demonstrated the effect of AVR on some but not all of these parameters within the same cohort of patients with severe AS.[8–17] Furthermore, whether there are any preoperative characteristics that can predict significant short-term recovery of systolic function after AVR is unknown.

The objectives of this study were: (1) to characterize the short-term changes in myocardial mechanics after AVR for severe AS; (2) to examine the relationship between changes in LV loading conditions and changes in myocardial mechanics post-AVR; and (3) to identify baseline characteristics in myocardial mechanics that predict recovery of GLS in the short term and survival in the long term after AVR.

# Methods

## Study population

We prospectively screened 98 patients with severe AS (defined by a mean gradient ≥40 mm Hg and an aortic valve area ≤1.0 $cm^2$) and a preserved EF (defined as an LVEF ≥50%) on transthoracic echocardiography performed at the Mayo Clinic, Rochester, Minnesota, between 1 November 2014 and 31 August 2015, who were deemed to be candidates for AVR. Exclusion criteria included: (1) age <18 years; (2) irregular rhythm; (3) inadequate image quality; (4) moderate or greater aortic

or mitral regurgitation pre- or post-AVR. After excluding 10 patients due to inadequate image quality, a total of 88 patients were enrolled. All patients underwent surgical or transcatheter AVR within two months of their baseline echocardiogram.

The study was approved by the Mayo Clinic Institutional Review Board and all patients provided written informed consent to participate in the study.

## Clinical data at baseline and in follow-up

Electronic health records of patients in the cohort were reviewed for demographic information, symptoms, functional status, medical history, laboratory investigations, coronary angiography results, and AVR procedural notes. Relevant medical history extracted from the medical record included traditional cardiovascular risk factors (i.e. diabetes, hypertension, dyslipidemia, current tobacco use) and coronary artery disease, defined as ≥50% luminal stenosis in ≥1 epicardial artery or prior surgical or percutaneous coronary revascularization.

The primary clinical outcome examined was all-cause mortality. Patients were followed for up to 5.2 years until death from any cause or last clinical encounter.

## Image acquisition and analysis

Each patient underwent transthoracic echocardiography within two months prior to and within 7 days after AVR. Blood pressure, heart rate, height, and weight were recorded immediately before the echocardiographic studies. A single echocardiographer performed all of the studies and was blinded to the clinical data. Images were acquired using standard commercially available equipment (IE33 or EPIQ7, Philips Medical Systems, Andover, Massachusetts) with a fully sampled matrix-array transducer (X5-1). Image settings were adjusted to optimize endocardial border definition. Acquired images were analyzed offline with TomTec 4D LV-Analysis speckle-tracking software (TomTec Imaging Systems, Image-Arena version 4.6, Unterschleissheim, Germany).

Standard M-mode, 2D, and Doppler measurements were performed based on current American Society of Echocardiography guidelines. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF were determined using the biplane method of disks (modified Simpson's rule).

Peak global longitudinal strain (GLS) and global longitudinal strain rate (GLSRs) were determined by averaging the segmental longitudinal strain and strain rate values from all segments measured in the three standard apical views (4-chamber, long-axis, and 2-chamber). Peak global circumferential strain (GCS), global circumferential systolic strain rate (GCSRs), global radial strain (GRS), and global radial systolic strain rate (GRSRs) were determined by averaging the segmental circumferential and radial strain and strain rate values measured in the three parasternal short-axis views (basal, mid, and apical levels). Peak systolic basal and apical rotations were measured from the parasternal short-axis basal and apical views, respectively, along the mid-wall of the myocardium. Peak systolic twist was defined as the difference between the peak systolic apical rotation and peak systolic basal rotation.

We used LVEDV as a measure of LV preload and valvulo-arterial impedance ($Z_{va}$) as a measure of LV afterload. $Z_{va}$ was determined by the formula $Z_{va} = (SAP + MG)/SVI$, where SAP is the systolic arterial pressure, MG is the mean gradient across the aortic valve, and SVI is the stroke volume index.[18–19]

Patients who demonstrated ≥20% increase in baseline GLS post-AVR were classified as responders while those who did not were considered non-responders. We chose a cut-off of 20% to emulate the definition of contractile reserve, which has traditionally been defined as an increase in stroke volume by 20%, and since differences in GLS values by ≥20% would be unlikely to result from intra- and inter-observer variability alone.

## Reproducibility analysis

To determine the reproducibility of measurements of strain and rotation, 20 randomly selected patients were re-analyzed by the same investigator to assess intra-observer variability and by a second experienced echocardiographer to assess inter-observer variability.

## Statistical analysis

Data are expressed as mean ± standard deviation for continuous variables and number (percentages) for categorical variables. Continuous variables with normal distributions from different patients were compared using the Student's *t*-test and those from the same patients at two different time points were compared with the matched-paired *t*-test. The Mann–Whitney U test was used to compare non-normally distributed continuous variables. Categorical variables were compared with the chi-square or Fisher exact tests. Associations between two continuous variables were measured using the Pearson correlation coefficient (r). Intra- and inter-observer variability was reported as the mean difference ± standard deviation along with the accompanying intra-class correlation coefficient (ICC). Receiver operating characteristic (ROC) curves were used to identify optimal cutoff values to predict GLS recovery or survival. Survival was assessed using Kaplan–Meier curves, which were compared with log-rank tests. Cox proportional hazards analyses were performed to determine whether identified predictors of survival remained significant after adjustment for demographic variables. Statistics were performed using JMP 10.0 software (SAS Institute Inc., Cary, North Carolina).

# Results

## Baseline clinical characteristics

A total of 88 patients with severe AS and LVEF ≥50% were included in the study, of whom 28% were classified as having a bicuspid aortic valve while the remaining patients were noted to have trileaflet morphology. *Table 1* lists their baseline clinical characteristics prior to AVR. Female patients accounted for 42% of the cohort and the mean age was 71 ± 12 years. Coronary artery disease and systemic hypertension were present in 47 and 77% of patients, respectively. The majority of the patients were symptomatic (65% endorsed symptoms of angina, syncope, or dyspnea) or demonstrated reduced functional status (76% were New York Heart Association functional class II or greater). Transcatheter AVR was performed in 31% of patients.

## Conventional echocardiographic parameters pre- and post-AVR

*Table 2* lists the echocardiographic characteristics of patients with severe AS and LVEF ≥50% within the study cohort at baseline (within two months of AVR) and during short-term follow-up (within 7 days post-AVR). The mean interval between AVR and echocardiographic follow-up was 4.1 ± 1.6 days. Post-AVR, the average mean gradient decreased from 51 ± 13 mm Hg to 12 ± 6 mm Hg, the mean aortic valve area increased from 0.9 ± 0.2 $cm^2$ to 2.5 ± 0.8 $cm^2$, and the valvulo-arterial impedance, $Z_{va}$, decreased from 3.8 ± 0.8 mmHg/mL/$m^2$ to 2.9 ± 0.7 mmHg/mL/$m^2$ ($P < 0.0001$ for all).

## Myocardial mechanics pre- and post-AVR

Myocardial mechanics of patients with severe AS and LVEF ≥50% before and after AVR are also shown in *Table 2*. There was a significant increase in GLS from −16.0 ± 2.0% to −18.5 ± 2.1% post-AVR ($P <$

**Table 1 Baseline clinical characteristics in survivors vs. non-survivors prior to AVR**

| Variable | Overall ($n = 88$) | Survivors ($n = 73$) | Non-survivors ($n = 15$) | *P* value |
|---|---|---|---|---|
| Demographics | | | | |
| Age | 71 ± 12 | 70 ± 11 | 79 ± 11 | 0.01 |
| Female | 37 (42) | 43 (59) | 8 (53) | 0.69 |
| Body surface area ($m^2$) | 1.94 ± 0.25 | 1.96 ± 0.23 | 1.87 ± 0.31 | 0.31 |
| Functional status | | | | |
| New York Heart Association I/II/III/IV | 20/34/32/2 | 19/30/23/1 | 1/4/9/1 | 0.07 |
| Medical history | | | | |
| Coronary artery disease | 39 (44) | 32 (44) | 7 (47) | 0.84 |
| Diabetes mellitus | 31 (35) | 24 (33) | 7 (47) | 0.31 |
| Hypertension | 68 (77) | 55 (75) | 13 (87) | 0.34 |
| Dyslipidemia | 63 (72) | 54 (74) | 9 (60) | 0.27 |
| Current tobacco use | 10 (11) | 7 (10) | 3 (20) | 0.25 |
| Physical examination | | | | |
| Heart rate (beats/min) | 69 ± 12 | 69 ± 12 | 65 ± 9 | 0.13 |
| Systolic blood pressure (mm Hg) | 129 ± 19 | 128 ± 18 | 135 ± 21 | 0.25 |
| Diastolic blood pressure (mm Hg) | 69 ± 11 | 70 ± 11 | 65 ± 11 | 0.13 |
| Laboratory investigations | | | | |
| NT-proBNP (pg/mL) | 428 (199–1321) | 301 (186–931) | 1935 (1075–3339) | 0.0009 |
| Aortic valve replacement | | | | |
| Transcatheter | 27 (31) | 16 (22) | 11 (73) | 0.0002 |

Normally distributed continuous variables expressed as mean ± standard deviation. Non-normally distributed continuous variables expressed as median (interquartile range). Categorical variables expressed as *n* (%).
*Abbreviations*: AVR, Aortic valve replacement.

0.0001). There were also modest but significant increases in GLSRs (from $-0.96 \pm 0.15\ s^{-1}$ to $-1.27 \pm 0.19\ s^{-1}$, $P < 0.0001$) and GCSRs (from $-1.83 \pm 0.48\ s^{-1}$ to $-2.08 \pm 0.55\ s^{-1}$, $P = 0.003$). Peak systolic apical rotation decreased from 10.5 ± 4.0 to 8.3 ± 2.8° ($P < 0.0002$) and peak systolic twist decreased from 18.2 ± 5.0° to 15.5 ± 3.8° ($P<0.0008$). There were no significant differences in GCS, GRS, GRSRs, and peak systolic basal rotation detected within the short interval between AVR and follow-up.

## Relationship between loading conditions and myocardial mechanics

The relationship between changes in loading conditions (LVEDV as a measure of preload, aortic valve area, and $Z_{va}$ as a measure of afterload) and changes in myocardial mechanics (GLS, GCS, GRS, basal rotation, apical rotation, and twist) was evaluated by linear regression analysis (*Table 3*). There was a significant association between the reduction in $Z_{va}$ and the absolute increase in GLS post-AVR ($r = 0.31$ $P = 0.003$).

## Predictors of GLS recovery

The clinical and echocardiographic characteristics of patients who demonstrated ≥20% increase in GLS post-AVR (responders) compared to those who did not (non-responders) are outlined in Supplementary material online, *Tables S1 and S2*. A total of 39 (44%) patients demonstrated a ≥ 20% increase in baseline GLS. Responders and non-responders demonstrated significant differences in baseline GLS (−14.8 ± 1.8 vs. −16.9 ± 1.6%, $P < 0.0001$), GLSRs ($-0.9 \pm 0.2\ s^{-1}$ vs. $-1.0 \pm 0.1\ s^{-1}$, $P = 0.02$) and $Z_{va}$ ($4.0 \pm 0.9$ vs. $3.6 \pm 0.6$ mmHg/mL/$m^2$, $P = 0.004$). On ROC analysis, baseline GLS was found to have the highest area-under-curve (AUC = 0.82) compared with GLSRs (AUC = 0.64) and $Z_{va}$ (AUC = 0.65) to identify responders. A baseline GLS ≤ −16.2% was 90% sensitive and 67% specific in predicting a ≥ 20% increase in GLS post-AVR (*Figure 1*).

## Survival according to baseline myocardial mechanics

During a median follow-up of 3.8 years, 15 (17%) patients in the cohort died. Clinical and echocardiographic characteristics in surviving patients were compared to non-survivors (*Tables 1 and 4*). Patients who died during follow-up were more likely to be older (79 ± 11 years vs. 70 ± 11 years, $P = 0.01$), have higher levels of NT-proBNP [1935 (1075, 3339) pg/mL vs. 301 (186, 931) pg/mL, $P = 0.0009$] and septal E/e' values (24.8 ± 9.8 vs. 15.8 ± 7.4, $P = 0.01$), and were more likely to undergo transcatheter rather than surgical AVR (73 vs. 22%, $P = 0.0002$).

With respect to baseline myocardial mechanics, non-survivors had lower absolute (i.e. less negative) GCS (−24.6 ± 3.9 vs. −28.1 ± 5.4%, $P = 0.007$), GCSRs ($-1.62 \pm 0.24\ s^{-1}$ vs. $-1.87 \pm 0.50\ s^{-1}$, $P = 0.005$), and basal rotation (−6.7 ± 1.9° vs. −7.9 ± 2.4°, $P = 0.04$) than surviving patients (*Table 5*).

Survival in patients who demonstrated ≥20% increase in GLS post-AVR (responders) was similar to non-responders (*Figure 2A*). There was a trend towards higher all-cause mortality in patients with a baseline GCS less negative than −26% ($P = 0.09$) (*Figure 2B*). Survival was lower among patients with a GCSRs less negative than $-1.9\ s^{-1}$ (*Figure 2C*) and a basal rotation less negative than −5.4° (*Figure 2D*), including after adjustment for age and gender. The baseline GCS, GCSRs, and basal rotation cutoffs were determined by ROC analysis (see Supplementary material online, *Figure S1*).

**Table 2 Echocardiographic parameters pre- and post-AVR**

| Variable | Overall ($n = 88$) | | $P$ value |
|---|---|---|---|
| | Pre-AVR | Post-AVR | |
| LV linear and volumetric measurements | | | |
| LV mass index (g/m$^2$) | 110.3 ± 34.2 | 108.8 ± 35.1 | 0.37 |
| LV end-diastolic volume index (mL/m$^2$) | 65.8 ± 23.5 | 62.2 ± 20.3 | 0.003 |
| LV end-systolic volume index (mL/m$^2$) | 24.7 ± 14.1 | 24.0 ± 11.7 | 0.33 |
| Stroke volume index (mL/m$^2$) | 41.1 ± 11.3 | 38.1 ± 10.7 | 0.002 |
| LV ejection fraction (%) | 60.6 ± 6.0 | 62.3 ± 6.9 | 0.04 |
| LV diastolic function parameters | | | |
| E velocity (m/s) | 0.97 ± 0.46 | 1.03 ± 0.37 | 0.003 |
| A velocity (m/s) | 1.08 ± 0.41 | 0.95 ± 0.34 | 0.006 |
| E/A ratio | 0.93 ± 0.38 | 1.12 ± 0.45 | 0.0002 |
| Septal e' velocity (cm/s) | 0.06 ± 0.02 | 0.06 ± 0.02 | 0.68 |
| Septal E/e' ratio | 17.2 ± 8.4 | 19.1 ± 9.4 | 0.006 |
| Measures of aortic stenosis severity | | | |
| Aortic valve mean gradient (mmHg) | 51 ± 13 | 12 ± 6 | <0.0001 |
| Aortic valve area (cm$^2$) | 0.9 ± 0.2 | 2.3 ± 0.8 | <0.0001 |
| Measures of LV afterload | | | |
| Valvulo-arterial impedance ($Z_{va}$) (mmHg/mL/m$^2$) | 3.8 ± 0.8 | 2.9 ± 0.7 | <0.0001 |
| Myocardial mechanics | | | |
| Longitudinal strain | | | |
| GLS (%) | −16.0 ± 2.0 | −18.5 ± 2.1 | <0.0001 |
| GLSRs (/s) | −0.96 ± 0.15 | −1.27 ± 0.19 | <0.0001 |
| Circumferential strain | | | |
| GCS (%) | −27.5 ± 5.3 | −27.0 ± 5.9 | 0.50 |
| GCSRs (/s) | −1.83 ± 0.48 | −2.08 ± 0.55 | 0.0003 |
| Radial strain | | | |
| GRS (%) | 36.5 ± 7.0 | 34.9 ± 8.5 | 0.13 |
| GRSRs (/s) | 1.98 ± 0.36 | 2.09 ± 0.36 | 0.06 |
| Rotation (°) | | | |
| Basal rotation | −7.7 ± 2.4 | −7.2 ± 2.2 | 0.29 |
| Apical rotation | 10.5 ± 4.0 | 8.3 ± 2.8 | 0.0002 |
| Twist | 18.2 ± 5.0 | 15.5 ± 3.8 | 0.0008 |

Data expressed as mean ± standard deviation.
*Abbreviations*: AVR, Aortic valve replacement; GCS, Global circumferential strain; GCSRs, Global circumferential systolic strain rate; GLS, Global longitudinal strain; GLSRs, Global longitudinal systolic strain rate; GRS, Global radial strain; GRSRs, Global radial systolic strain rate; LV, Left ventricular.

## Comparison between surgical and transcatheter AVR

Compared with patients undergoing surgical AVR, patients who underwent transcatheter AVR were on average older (80 ± 8 years vs. 68 ± 11 years, $P < 0.0001$) and had a worse functional class distribution (NYHA I/II/III/IV 1/8/16/2 vs. 19/26/16/0, $P = 0.0004$), higher NT-proBNP level [median 1159 (interquartile range 516–3157) pg/mL vs. 243 (153 to 753) pg/mL, $P = 0.0001$], higher septal E/e' ratio (22.9 ± 9.3 vs. 14.6 ± 6.5, $P = 0.0004$), and higher mortality (41 vs. 7%, $P = 0.0002$) (see Supplementary material online, *Table S3*). Patients undergoing transcatheter AVR also demonstrated lower absolute values of GLSRs (−0.91 ± 0.13 s$^{-1}$ vs. −0.98 ± 0.15 s$^{-1}$, $P = 0.03$), GCSRs (−1.67 ± 0.49 s$^{-1}$ vs. −1.90 ± 0.46 s$^{-1}$, $P = 0.045$), basal rotation (−6.9 ± 1.7° vs. −8.0 ± 2.5°, $P = 0.02$), apical rotation (−9.1 ± 4.0° vs. 11.1 ± 3.9°, $P = 0.04$), and twist (16.0 ± 4.8° vs. 19.2 ± 4.8°, $P = 0.007$).

Regardless of type of AVR, there was a significant decrease in mean gradient, increase in aortic valve area, decrease in $Z_{va}$, and increase in absolute value of GLS, GLSRs, and GCSRs similar to the overall cohort (see Supplementary material online, *Table S4*). In contrast, a significant decrease in the absolute value of peak systolic apical rotation and peak systolic twist was only observed in the surgical AVR subgroup.

In a subgroup analysis excluding the smaller subgroup of patients who underwent transcatheter AVR, there remained a significant association between the reduction in $Z_{va}$ and the absolute increase in GLS following surgical AVR ($r = 0.26$ $P = 0.047$) (see Supplementary material online, *Table S5*).

Similar to the overall cohort, responders (who showed ≥20% increase in GLS post-AVR) had a lower absolute mean GLS at baseline compared with non-responders in both the surgical (−15.0 ± 1.8 vs. −16.8 ± 1.6%, $P = 0.0003$) and transcatheter (−14.6 ± 1.8 vs. −17.2 ± 1.6%, $P = 0.0007$) subgroups (see Supplementary material online, *Table S6*).

Trends in baseline myocardial mechanics were similar in patients who underwent surgical or transcatheter AVR with non-survivors demonstrating lower absolute GCS, GCSRs, and basal rotation compared with surviving patients, although these did not reach statistical significance in the subgroup analysis (see Supplementary material online, *Table S7*).

## Intra-observer and inter-observer variability

Reproducibility analysis demonstrated good intra- and inter-observer agreement with an ICC ≥ 0.85 for all measures of myocardial mechanics (see Supplementary material online, *Table S8*).

# Discussion

This is to our knowledge the most comprehensive study of myocardial mechanics and its prognostic significance in patients with severe AS undergoing AVR. Within 7 days after AVR, there were significant absolute increases in GLS, GLSRs, and GCSRs, significant decreases in apical rotation and twist, and no significant change in GCS, GRS, GRSRs, and basal rotation. The improvement in GLS correlated with the reduction in $Z_{va}$. A lower absolute GLS value at baseline was the strongest predictor of GLS recovery after AVR. However, significant short-term improvement in GLS was not associated with improved survival. All-cause mortality was higher in patients with lower absolute baseline GCS, GCSRs, and basal rotation values, with the latter two parameters remaining statistically significant after adjustment for age and gender.

Prior studies have consistently demonstrated a reduction in GLS in response to chronic pressure overload from severe AS.[7,20–26] GLS may be affected before GCS or GRS since it reflects contraction of longitudinally arranged endocardial fibers, which are most vulnerable to increased wall stress and ischaemia.[27–28] The reduction in afterload following AVR significantly reduces wall stress and subendocardial ischaemia, which may increase longitudinal motion. In the current study, GLS significantly increased while GCS and GRS showed no significant

**Table 3 Relationship between changes in loading conditions and LV mechanics pre- and post-AVR**

| Variable | Δ LVEDVI (mL/m$^2$) | | Δ Aortic valve area (cm$^2$) | | Δ $Z_{va}$ (mmHg/mL/m$^2$) | |
|---|---|---|---|---|---|---|
| | r | *P* value | r | *P* value | r | *P* value |
| Longitudinal strain | | | | | | |
| Δ GLS (%) | −0.11 | 0.32 | −0.12 | 0.25 | 0.31 | 0.003 |
| Δ GLSRs ($s^{-1}$) | 0.15 | 0.16 | −0.14 | 0.21 | 0.0006 | 0.995 |
| Circumferential strain | | | | | | |
| Δ GCS (%) | −0.08 | 0.44 | −0.16 | 0.15 | −0.03 | 0.78 |
| Δ GCSRs ($s^{-1}$) | 0.004 | 0.97 | −0.21 | 0.06 | −0.007 | 0.95 |
| Radial strain | | | | | | |
| Δ GRS (%) | −0.03 | 0.79 | −0.14 | 0.21 | 0.02 | 0.88 |
| Δ GRSRs ($s^{-1}$) | −0.29 | 0.008 | −0.07 | 0.54 | 0.08 | 0.46 |
| Rotation (°) | | | | | | |
| Δ Basal rotation | −0.14 | 0.23 | −0.11 | 0.33 | 0.10 | 0.39 |
| Δ Apical rotation | −0.06 | 0.61 | 0.15 | 0.17 | −0.10 | 0.37 |
| Δ Twist | 0.004 | 0.97 | 0.17 | 0.15 | −0.09 | 0.45 |

Data presented are Pearson correlation coefficients (r) with associated *P* value.
*Abbreviations*: Δ Change in; GCS, Global circumferential strain; GCSRs, Global circumferential systolic strain rate; GLS, Global longitudinal strain; GLSRs, Global longitudinal systolic strain rate; GRS, Global radial strain; GRSRs, global radial systolic strain rate; LVEDVI, Left ventricular end-diastolic volume index; $Z_{va,}$ Valvulo-arterial impedance.

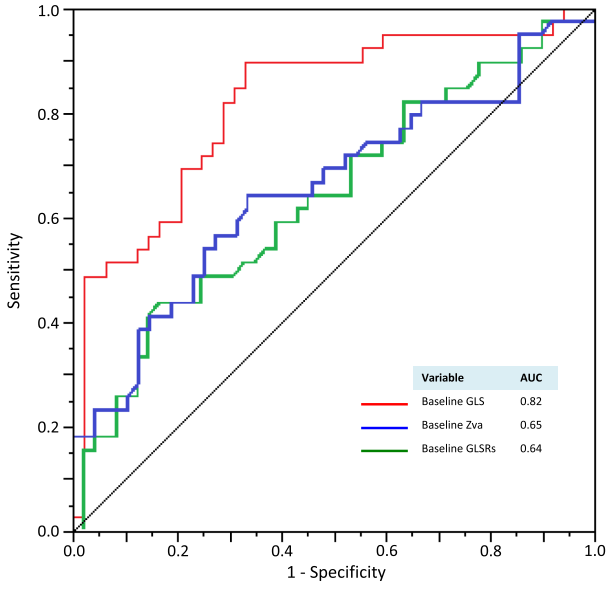



**Figure 1** Receiver operating characteristic (ROC) analysis comparing baseline global longitudinal strain (GLS), global longitudinal systolic strain rate (GLSRs), and valvulo-arterial impedance ($Z_{va}$) to accurately identify patients who will experience a gain in GLS of ≥20% after aortic valve replacement (AVR). A baseline GLS more negative than −16.2% had a sensitivity of 90% and a specificity of 67% to predict short-term recovery of GLS of ≥20% post-AVR.

change during short-term follow up, consistent with prior studies that uniformly demonstrate increases in GLS with or without accompanying changes in GCS and GRS after AVR.[8–9,11–14,16,29–30]

Apical rotation and twist have been shown to increase in response to the reduction in GLS from progressive AS, which is thought to be part of a compensatory mechanism to maintain LVEF.[7,16,31–34] In our study, we observed a significant decrease in apical rotation and twist that accompanied the increase in GLS post-AVR, consistent with most prior studies.[12,15–17,35] Our findings provide further evidence of the characteristic changes in myocardial mechanics that are expected to occur with progressive AS, which can be at least partially reversed after AVR.

**Table 4 Baseline echocardiographic characteristics in survivors vs. non-survivors prior to AVR**

| Variable | Survivors ($n = 73$) | Non-survivors ($n = 15$) | *P* value |
|---|---|---|---|
| LV linear and volumetric measurements | | | |
| LV mass index (g/m$^2$) | 110.2 ± 35.4 | 110.7 ± 27.5 | 0.95 |
| LV end-diastolic volume index (mL/m$^2$) | 66.2 ± 24.8 | 64.0 ± 14.0 | 0.66 |
| LV end-systolic volume index (mL/m$^2$) | 24.7 ± 15.0 | 25.0 ± 8.7 | 0.92 |
| LV stroke volume index (mL/m$^2$) | 41.5 ± 11.7 | 39.0 ± 8.8 | 0.38 |
| LV ejection fraction (%) | 60.4 ± 6.2 | 61.0 ± 5.6 | 0.72 |
| LV diastolic function parameters | | | |
| E velocity (m/s) | 0.93 ± 0.43 | 1.18 ± 0.56 | 0.14 |
| A velocity (m/s) | 1.08 ± 0.41 | 1.12 ± 0.40 | 0.76 |
| E/A ratio | 0.88 ± 0.30 | 1.18 ± 0.67 | 0.16 |
| Septal e' velocity (cm/s) | 0.06 ± 0.02 | 0.05 ± 0.02 | 0.24 |
| Septal E/e' ratio | 16 ± 7 | 25 ± 10 | 0.01 |
| Aortic stenosis severity | | | |
| Aortic valve mean gradient (mm Hg) | 52 ± 13 | 49 ± 7 | 0.26 |
| Aortic valve area (cm$^2$) | 0.9 ± 0.2 | 0.8 ± 0.2 | 0.31 |
| Measures of LV afterload | | | |
| $Z_{va}$ (mm Hg/mL/m$^2$) | 3.8 ± 0.8 | 3.8 ± 0.9 | 0.89 |
| LV myocardial mechanics | | | |
| Longitudinal strain | | | |
| GLS (%) | −16.0 ± 2.0 | −16.2 ± 2.2 | 0.72 |
| GLSRs (/s) | −0.96 ± 0.15 | −0.95 ± 0.14 | 0.79 |
| Circumferential strain | | | |
| GCS (%) | −28.1 ± 5.4 | −24.6 ± 3.9 | 0.007 |
| GCSRs (/s) | −1.87 ± 0.50 | −1.62 ± 0.24 | 0.005 |
| Radial strain | | | |
| GRS (%) | 36.6 ± 6.7 | 36.2 ± 8.4 | 0.88 |
| GRSRs (/s) | 1.94 ± 0.34 | 2.14 ± 0.44 | 0.13 |
| Rotation (°) | | | |
| Basal rotation | −7.9 ± 2.4 | −6.7 ± 1.9 | 0.04 |
| Apical rotation | 10.5 ± 3.9 | 10.6 ± 4.5 | 0.94 |
| Twist | 18.4 ± 4.9 | 17.3 ± 5.3 | 0.45 |

Normally distributed continuous variables expressed as mean ± standard deviation.
*Abbreviations*: AVR, Aortic valve replacement; GCS, Global circumferential strain; GCSRs, Global circumferential systolic strain rate; GLS, Global longitudinal strain; GLSRs, Global longitudinal systolic strain rate; GRS, Global radial strain; GRSRs, Global radial systolic strain rate.

**Table 5 Measures of myocardial mechanics to predict all-cause mortality**

| Variable | HR (95% CI) | *P* value |
|---|---|---|
| Model 1 GCS | | |
| \| GCS \| < 26 vs. ≥ 26% | 1.83 (0.66–5.12) | 0.25 |
| Age | 1.07 (1.01–1.14) | 0.02 |
| Female | 1.15 (0.41–3.21) | 0.79 |
| Model 2 GCSRs | | |
| \| GCSRs \| < 1.9 vs. ≥ 1.9% | 8.36 (1.06–66.1) | 0.008 |
| Age | 1.05 (0.99–1.12) | 0.06 |
| Female | 0.95 (0.34–2.68) | 0.93 |
| Model 3 Basal rotation | | |
| \| Basal rotation \| < 5.4° vs. ≥ 5.4° | 4.59 (1.28–16.5) | 0.02 |
| Age | 1.05 (0.99–1.12) | 0.05 |
| Female | 2.08 (0.63–6.79) | 0.22 |

Data expressed as hazard ratio (95% confidence interval).
*Abbreviations*: CI, confidence interval; GCS, Global circumferential strain; GCSRs, Global circumferential systolic strain rate; HR, Hazard ratio.

In contrast, we did not observe a significant change in GCS or GRS, which could be due to a number of reasons. First, GCS has been reported to either increase[7,12,32] or decrease[16,29,32] in response to progressive AS. GCS might initially increase to compensate for the decline in GLS but later decrease in advanced stages once myocardial reserve is exhausted. In addition, unlike GLS, which appears to be more sensitive to changes in afterload, GCS and GRS might require more time to adapt to changes in loading conditions. Significant increases in GLS have been detected as early as intra-operatively to within 24 to 72 h[8,14,36] while the earliest changes in GCS and GRS have been shown to occur within 7 days after AVR.[10,12–13,29] Finally, GCS could represent a component of myocardial deformation that is less amenable to recovery once a certain threshold of remodeling has occurred. One prior study demonstrated no significant change in circumferential strain following AVR despite long-term follow-up of up to six years.[17]

As expected, the changes in myocardial mechanics post-AVR appears to be predominantly mediated by a reduction in afterload. $Z_{va}$ has been used as a measure of afterload imposed on the LV from the cumulative effects of valvular obstruction and systemic arterial resistance.[18] A higher $Z_{va}$ has been shown to be associated with a lower absolute GLS regardless of LVEF.[7,19,29,37] Similarly, our study demonstrated that a reduction in $Z_{va}$ after AVR was associated with an increase in GLS.

Baseline GLS impairment was the strongest predictor of short-term GLS recovery. A baseline GLS more abnormal than −16.2% was 90% sensitive and 67% specific in identifying patients with ≥20% improvement in GLS following AVR. Prior studies have similarly identified baseline GLS impairment as an important factor in predicting response but with important differences.[36,38] In contrast to our study, Kempny et al. reported a pre-interventional GLS more negative than −13.3% to have a 66.7% sensitivity and an 86.3% specificity in predicting an improvement to at least −15% during a median follow-up of 70 days.[38] On the other hand, Ando et al suggested that a pre-AVR GLS is less negative than −13.7% was 82% sensitive, and 82% specific for a > 25% relative improvement in GLS post-AVR.[36] Differences in cohort composition, the definition of GLS recovery, and timing of follow-up could have accounted for these differences in findings.

While increases in GLS post-AVR have been associated with improvement in functional status and short-term post-operative outcomes,[38–39] we found no difference in all-cause mortality between responders and non-responders. Several reasons could have accounted for this. First, we only measured short-term changes in GLS detected within 7 days even though full GLS recovery could take much longer. In addition, non-responders might represent a widely heterogeneous group of patients whose baseline GLS values range from near normal to irreversibly impaired. Finally, outcomes could depend less on the

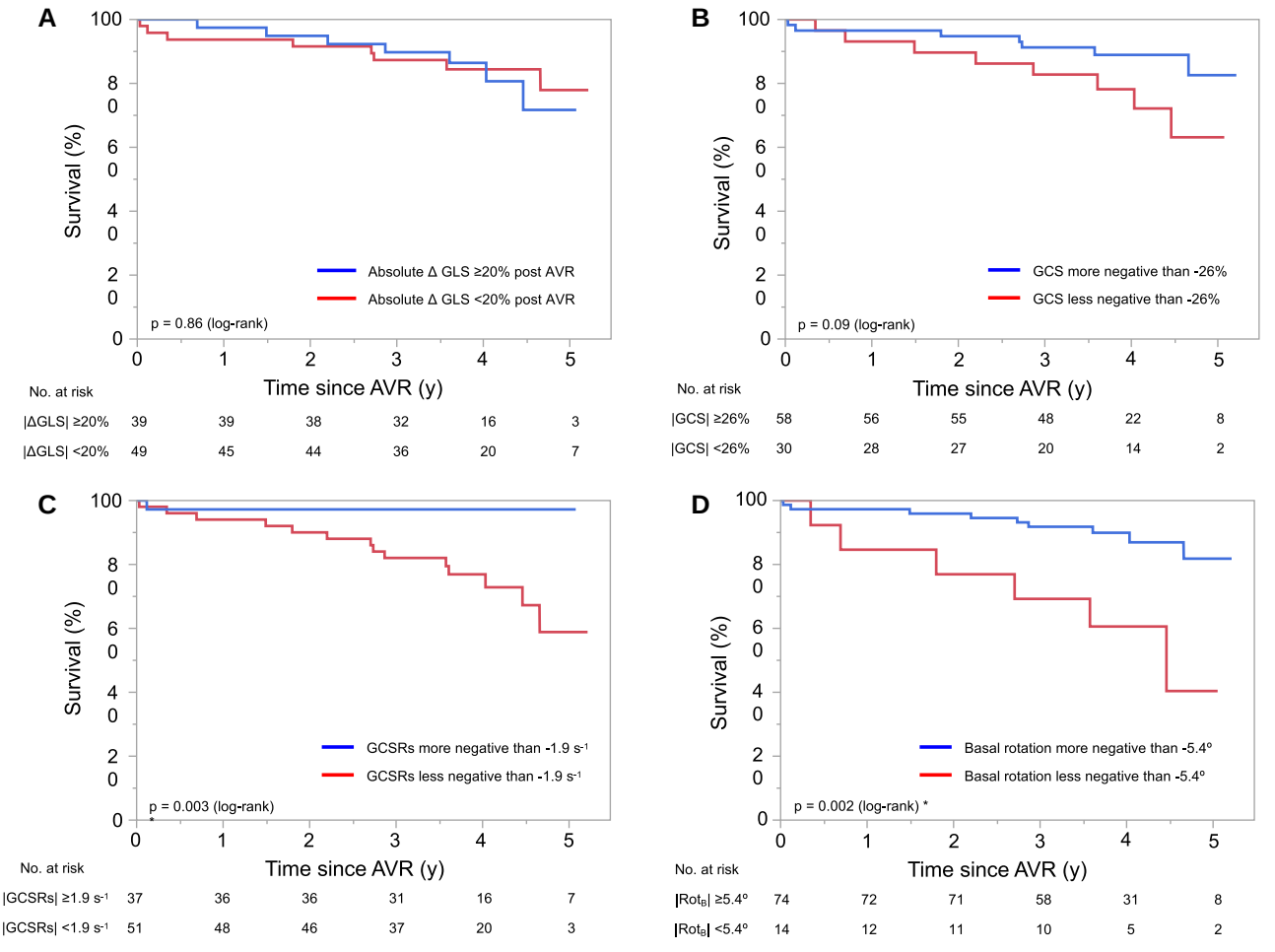



**Figure 2** Survival analysis in patients with severe aortic stenosis post aortic valve replacement (AVR) according to: (*A*) global longitudinal strain (GLS) response to AVR; (*B*) baseline global circumferential strain (GCS); (*C*) baseline global circumferential systolic strain rate (GCSRs); and (*D*) baseline basal rotation. Cutoff values for GCS, GCSRs, and basal rotation were determined from receiver operating characteristic (ROC) analyses. There was a trend towards increased all-cause mortality when the baseline GCS was less negative than −26%. A GCSRs less negative than −1.9% and a basal rotation less negative than −5.4% predicted lower survival. *GCSRs and basal rotation remained statistically significant after adjusting for age and gender.

relative changes of a single parameter alone and more on the interaction of multiple components of myocardial deformation to preserve myocardial function.

Similarly, we did not find an association between baseline GLS and all-cause mortality in our study. In contrast, a recent meta-analysis[40] that included 10 studies with 1067 patients suggested that a baseline GLS less negative than −14.7% was independently associated with an increased risk of death among asymptomatic patients with severe aortic stenosis, although its sensitivity and specificity was modest at 60 and 70% respectively. Instead, we found a trend towards increased all-cause mortality in patients with severe aortic stenosis who had a GCS less negative than −26%. Basal rotation is less negative than −5.4% and GCSRs less negative than −1.9% prior to AVR independently predicted increased risk of death after adjustment for age and gender. Carasso et al similarly showed that compensatory changes in circumferential strain and apical rotation were blunted in symptomatic compared to asymptomatic patients with severe AS.[41] Lee et al reported an increased risk of heart failure readmission or all-cause death in symptomatic patients with severe AS who had a GCS less negative than −22.2%.[42] Taken together, these findings once again support a model in which the ability of circumferential and rotational mechanics to compensate for an impaired longitudinal function could have prognostic value in patients with severe AS (*Figure 3*).

## Limitations

We performed a single-centre, observational study with a relatively small cohort of patients with severe AS and acknowledge the many prior studies documenting improved LV strain after AVR. However, our study adds value to the existing body of literature by providing a more comprehensive characterization of myocardial mechanics and its short- and long-term prognostic value in patients with severe AS undergoing AVR. In addition, there is a lack of standardized methodology for measuring circumferential and radial strain, strain rate, and rotation, and validation of our strain measurements using reference standards such as tagged magnetic resonance imaging or sonomicrometry was not performed as it was beyond the scope of our study. Nevertheless, intra- and inter-observer variability analysis demonstrated good reproducibility. Furthermore, we included patients who underwent both surgical and transcatheter AVR, which may have

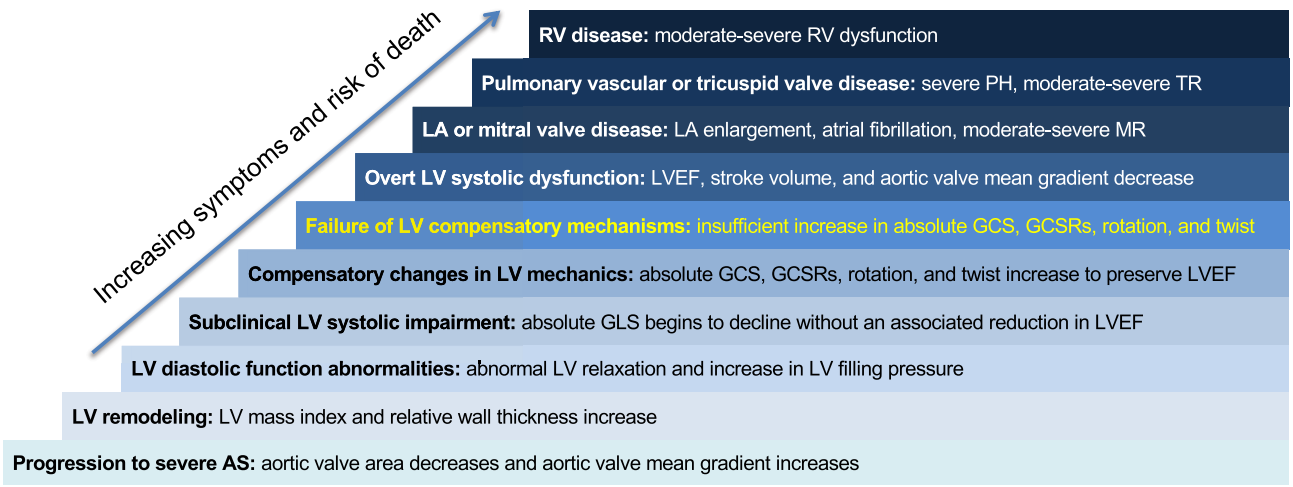



**Figure 3** Combined model of aortic stenosis progression that incorporates the earlier subclinical changes in myocardial mechanics with the later stage changes proposed by Généreux et al.[43] Decompensation appears to be heralded by a failure of compensatory mechanisms to preserve left ventricular ejection fraction, which occurs when there is an insufficient increase or decline in global circumferential strain, apical rotation, and peak systolic twist. *Abbreviations*: AS, aortic stenosis; GLS, global longitudinal strain; GCS, global circumferential strain; GCSRs, global circumferential systolic strain rate; LA, left atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PH, pulmonary hypertension; RV, right ventricular; TR, tricuspid regurgitation.

introduced an additional confounding element to the echocardiographic measures and survival analysis. Reassuringly, overall trends were maintained in the subgroup analysis by type of AVR. Finally, age- and gender-adjusted GCSRs and basal rotation were the only baseline parameters in our study that independently predicted increased all-cause mortality but are not routinely measured in clinical practice. Further studies are needed to determine the relative prognostic value of these parameters compared to GLS in patients with severe AS.

# Conclusions

In patients with severe AS and preserved LVEF, GLS improved and apical rotation and twist decreased from supranormal levels post-AVR. The improvement in GLS correlated with the reduction in $Z_{va}$, providing further mechanistic evidence that such improvement is predominantly mediated by afterload reduction. Greater baseline GLS impairment was the strongest predictor of short-term GLS recovery after AVR. However, neither baseline GLS nor GLS response post-AVR was associated with long-term outcomes. Instead, there was a trend towards increased all-cause mortality in patients with relatively lower GCS, with age- and gender-adjusted GCSRs and basal rotation being the only parameters that independently predicted worse outcomes.

# Author contributions

Conception and design of the study: X.B., V.T.N., H.R.V., D.F.Y.; acquisition of data or analysis and interpretation of data: X.B., K.L.G., L.F.N., A.P., H.V.S., J.J.T., D.F.Y.; drafting the article or revising it critically for important intellectual content: X.B., P.A.P., S.V.P., H.R.V., D.F.Y. All authors read and approved the final manuscript.

## Ethics approval

This study was approved by the Mayo Clinic Institutional Review Board.

## Consent to participate

All patients gave informed consent to participate.

# Lead author biography

Dr Hector R. Villarraga is a cardiologist at Mayo Clinic in Rochester, Minnesota, and an Associate Professor of Medicine at the College of Medicine His research interests include the evaluation of myocardial mechanical function by speckle tracking echocardiography (strain) in cardiomyopathies with normal ejection fraction and in cardio-oncology, as well as the applicability of echocardiography in-day-to day patient care.

## Data Availability

Data are available from the corresponding author on reasonable request.

# Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

## Acknowledgements

Not applicable.

## Funding

This research did not receive any grants from funding agencies in the public, commercial, or not-for-profit sectors.

**Conflict of interest:** None declared.

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