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Incremental Prognostic Utility of Myocardial Fibrosis Imaging By Speckle Tracking Echocardiography Post Transcatheter Aortic Valve Replacement

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Abstract

Background: Long-standing aortic stenosis (AS) results in fibrotic changes that often persist after TAVR. Fibrosis in AS preferentially affects the left ventricular (LV) basal segments and can lead to ventricular desynchrony.

Objective: Determine the prognostic utility of strain parameters as measured by speckle-tracking echocardiography in patients undergoing transcatheter aortic valve replacement (TAVR). We hypothesize that basal longitudinal strain (BLS) and mechanical dispersion (MD) measured after TAVR will predict all-cause mortality in severe AS

Methods: 159 patients (51% men, 81±9 years) with severe AS (aortic valve area 0.7±0.2 cm2, mean gradient 46±16mmHg) who underwent TAVR at our institution were retrospectively analyzed. 2D speckle-tracking echocardiography was used to assess myocardial deformation and MD (SD of time from Q/R on the ECG to peak strain in 16 LV segments) immediately after TAVR (median, 1 day). Images were analyzed offline using a vendor-independent software (TomTec).

Results: At 1-year post-TAVR, 28 (17.6%) patients died. Non-survivors demonstrated impaired global longitudinal strain (GLS, -11.2±3% vs -14.2±4%, p=0.001), impaired BLS (-10.9±2% vs -13.3±3%, p=0.001), and pronounced MD (86±33 ms vs 70±26 ms p=0.006) compared to survivors. Baseline multivariable Cox regression model (Figure) included age, STS, NYHA, renal disease, AV mean gradient, and post-TAVR paravalvular leak as significant univariates (model 1, p<0.001). An incremental prognostic value was achieved by adding BLS to model 1+ GLS (p=0.001). Addition of MD to the model 1 + GLS + BLS provided further incremental prognostic increase (p=0.008). For the measurement of GLS, the Interobserver Intraclass Correlation Coefficient was 0.87.

Conclusion: In severe AS, post-TAVR myocardial fibrosis assessed by strain imaging was significantly associated with cardiovascular events. This finding may provide incremental prognostic value in patients with AS.

Key Words

Transcatheter aortic valve replacement • Myocardial fibrosis • Speckle-tracking echocardiography • Basal longitudinal strain • Mechanical dispersion • Mortality

Introduction

Aortic stenosis (AS) is a common valvular heart disease that causes serious myocardial dysfunction [1]. Severe AS is often associated with the development of adverse cardiac symptoms and increased risk of mortality [2]. Untreated symptomatic patients

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have poor outcomes [3]. Transcatheter aortic valve replacement (TAVR) has proven to be an alternative to surgical aortic valve replacement for the treatment of symptomatic severe AS [4].

Randomized clinical trials comparing TAVR with standard-of-care therapies in selected patients with moderate to severe aortic stenosis who are at higher than normal risk for surgical aortic valve replacement have been completed and demonstrated one-year mortality rates for TAVR that were non-inferior and in some cases superior to standard surgical therapies [5-8].

To improve risk stratification in TAVR patients, several studies identified variables associated with poor outcomes. Age, Society of Thoracic Surgery (STS) score, New York Heart Association (NYHA) class, and renal disease were previously identified as prognostic predictors of mortality [9-12]. In addition, paravalvular leak (PVL) and post-procedural renal insufficiency were identified as important risk factors for post-TAVR mortality [13-15].

In long-standing AS, progressive valve narrowing triggers a hypertrophic response that preserves ventricular function for many years. Over time, the development of underlying myocardial fibrosis and myocyte injury leads to progression from hypertrophy to heart failure [16, 17]. Once myocardial fibrosis ensues, it provides a structural substrate for arrhythmogenicity, playing a major role in sudden cardiac death [18]. Moreover, histological studies demonstrated an association between myocardial fibrosis at the time of aortic valve replacement (AVR) and poor long-term outcomes post-valve replacement [19]. Myocardial biopsy is considered the gold standard for assessing myocardial fibrosis, however, it is an invasive procedure that could lead to several complications [20]. Therefore, a need for modern imaging techniques for noninvasive assessment of myocardial fibrosis has emerged.

In this context, two-dimensional speckle tracking echocardiography (2D-STE) is a promising imaging modality that allows the diagnosis of subclinical cardiac impairment including fibrotic changes not detected by conventional echocardiography [21]. 2D-STE provides an assessment of myocardial deformation and left ventricular torsion [22]. Of all the myocardial deformation parameters, global longitudinal strain (GLS) has been shown to be more clinically useful than circumferential or radial strains [23]. In recent studies, GLS had superior prognostic value to left ventricular ejection fraction (LVEF) in predicting cardiac death, urgent valve surgery or hospitalizations due to heart failure [24]. Additionally, GLS has been shown to be an independent predictor of outcomes in patients with severe asymptomatic AS [25].

More recently, regional or basal longitudinal strain (BLS) has been proven to be a superior predictor of future AVR in asymptomatic AS compared to GLS [26, 27]. Additionally, myocardial fibrosis related to long-standing AS can lead to desynchrony and pronounced mechanical dispersion (MD) which has been linked to poor outcomes in these patients [28].

In the early post-TAVR period, a dramatic reduction in the afterload and immediate offloading of the ventricle lead to improvement in strain parameters [29]. However, literature describing the prognostic utility of impaired BLS and MD immediately post-TAVR remains limited. We hypothesize that in addition to GLS, BLS and MD measured immediately post-TAVR will predict all-cause mortality in severe AS.

Methods

Study design and population

This retrospective study was conducted at Rush University Medical Center (RUMC), Chicago, USA. All patients underwent TAVR after evaluation by a multidisciplinary heart team. The study was reviewed and approved by the Institutional Review Board at RUMC. From a total of 187 patients with severe aortic stenosis (aortic valve area < 1 cm^2 , mean gradient > 40 mmHg) who underwent TAVR between January 2012 and March 2018 and had a follow-up echocardiogram performed immediately after TAVR, we excluded patients with incomplete data (n=11), concomitant significant valvular disease (n=10), and poor image quality or arrhythmia at the time of echocardiography (n=7). A total of 159 patients were included in the current study (Figure 1).

Two-dimensional strain imaging

In this study, myocardial strain parameters were measured by 2D-STE using a vendor-independent software (TomTec, Germany) immediately after TAVR

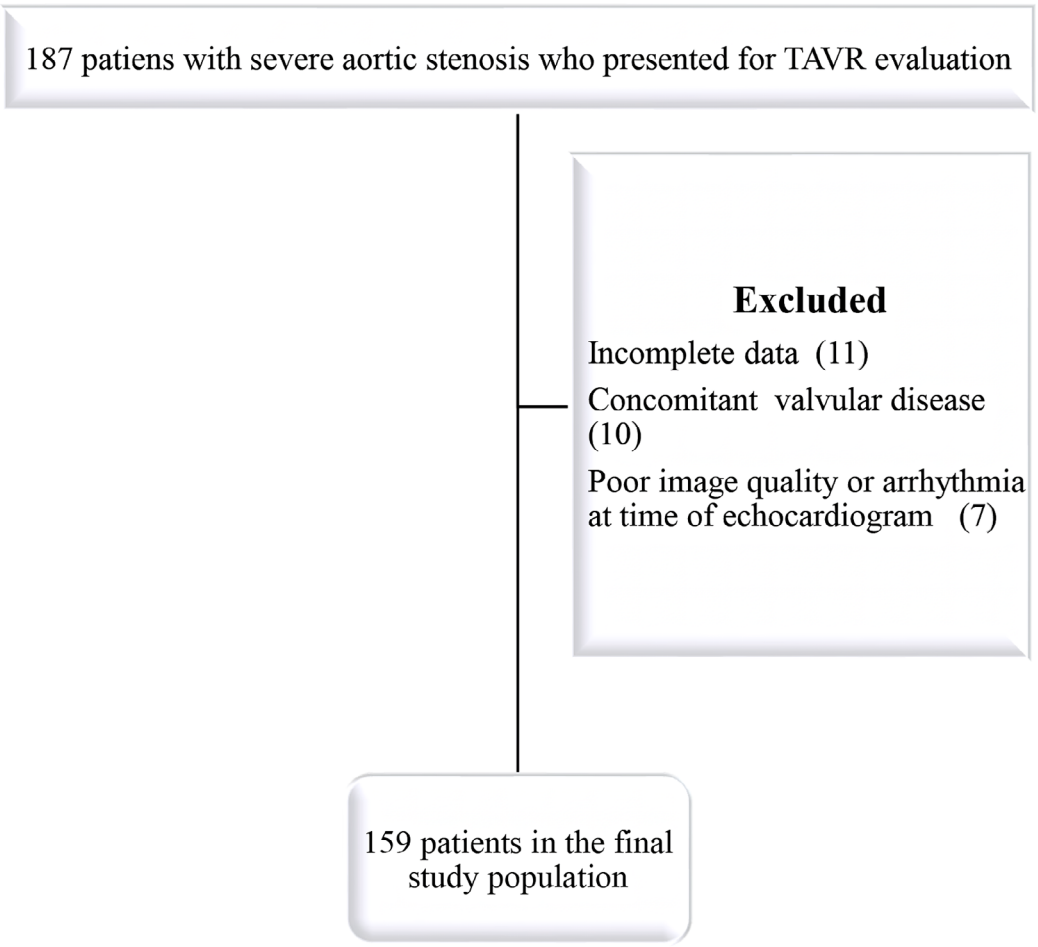

Figure 1. Patient Selection. Flow diagram of screening and exclusion criteria of patients with aortic stenosis.

(median, day 1). Two-dimensional strain analysis was performed on grey-scale images from the three apical views (longitudinal function) with frame rates of 70-90 frame/s and digitally stored for three cardiac cycles. Endocardial border tracking was achieved automatically using two points in the annular region and one point in the apical segments. Tracking quality was visually verified. Segments that failed initial tracking were manually adjusted. Segments that could not be tracked properly after manual adjustment were rejected. Peak systolic values from 16-segment model (6 basal, 6 mid and 4 apical segments) were averaged to obtain GLS (Figure 2). Six basal segments were averaged to obtain BLS. MD was defined as the standard deviation of time to peak strain (time of onset of Q/R wave in electrocardiogram to peak negative longitudinal strain during the cardiac cycle) in 16- segment model.

Statistical analyses

All calculations were performed using SPSS/PC statistical program (version 21, SPSS Inc., Chicago IL, USA). Continuous variables were reported as means ± SD while categorical variables were expressed as numbers or ratios. Comparisons between groups were achieved using unpaired Student's t-test for continuous variables while $\chi 2$ was used to evaluate dichotomous variables. A p-value of less than 0.05 was considered statistically significant. Cox proportionate hazard models were used to determine significant predictors of all-cause 1-year mortality. Multivariate regression analysis included all significant

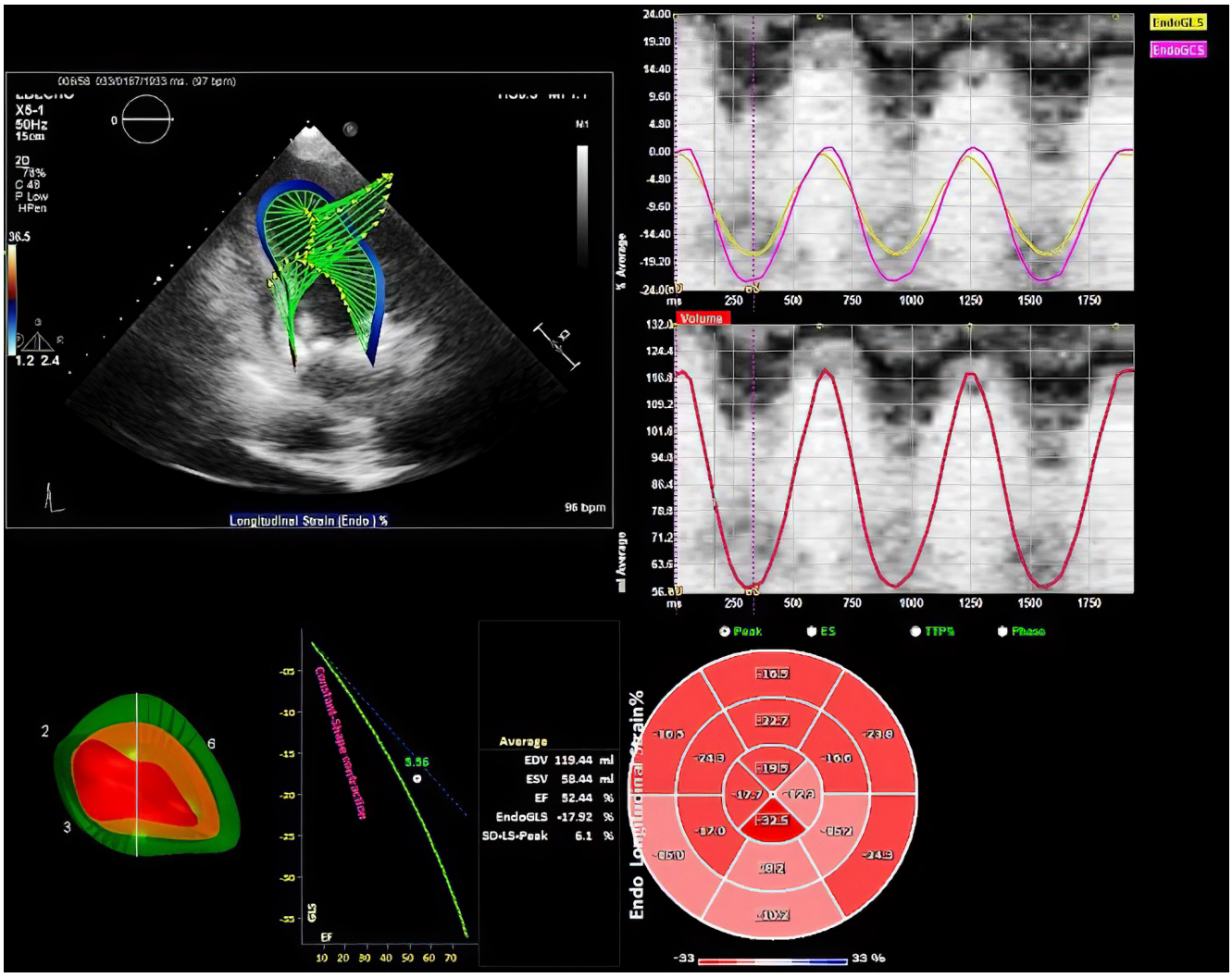

Figure 2. Two-dimensional speckle tracking echocardiography analysis. Strain curves and a color-coded 16-segment bull's eye plot are presented. Color lines indicate regional strain. Values of longitudinal strain are negative ***(sign -)***. Endocardial border tracking in apical four-chamber view can be achieved automatically. Global longitudinal strain can be calculated from 4 chamber views. Model 1 = Age, STS score, NYHA IV, Renal Disease (Cr >2 mg/dL), AV Mean Gradient, post-TAVR PVL.

univariates. To further illustrate the predictive value of strain parameters, cox models with separate addition of GLS, BLS, and MD to baseline model containing significant univariates were constructed. Model discrimination was further assessed using Harrell's C-statistic. Inter- and intra-observer were expressed by intra-class correlation coefficients.

Results

Study population selection is presented in Figure 1. Baseline characteristics stratified according to survival status and total cohort as summarized in Table 1. A total of 159 patients (mean age 80.7±9.1, 49% of women) were included in the study. A total of 28 (17.6%) patients expired one-year post-TAVR.

Cardiovascular risk factors including body mass index (BMI), hypertension, diabetes, hyperlipidemia, and kidney disease were not statistically significant between survivors and non-survivors (Table 1). Non-survivors had higher STS scores (8.1±5.4 vs 5.6±3.7, p=0.004) and more NYHA class IV (28.5% vs 10.6%, p=0.013) (Table 1).

Table 1. Baseline clinical characteristics of all patients.

	All Patients	Survivors	Non-survivors	P-value
N (%)	159	131 (82.4%)	28 (17.6%)	-
Age	80.7±9.1	80.1±9.7	83.5±4.9	0.073
Gender (Female %)	78 (49.0%)	64 (49%)	14 (50%)	0.913
BMI	29.2±7.4	29.7±7.6	27.2±5.7	0.103
NYHA Class IV	22 (13.8%)	14 (10.6%)	8 (28.5%)	0.013
STS score	6.1±4.1	5.6±3.7	8.1±5.4	0.004
Hyper-tension	141 (89%)	115 (88%)	26 (93%)	0.445
Hyper-lipidemia	98 (62%)	78 (60%)	20 (71%)	0.243
Diabetes	67 (42%)	50 (38%)	16 (57%)	0.065
CAD	111 (70%)	89 (68%)	22 (79%)	0.269
Creatinine	1.5±1.3	1.4±1.3	1.6±1.0	0.515
Baseline LVEF, %	55.3±15.4	55.9±15.0	52.2±17.2	0.224
Post-TAVR LVEF, % (Day1)	59±15	61 ±14.5	55±17	0.053
AV mean gradient	46.2±16.4	48.3±16.4	36.3±12.0	0.001
GLS, %	-13.7±4.1	-14.2±4.0	-11.2±3.1	0.001
BLS, %	-12.9±3.2	-13.3±3.2	-10.9±1.9	0.001
MD, msec	72.8±27.8	70.0±25.8	85.8±33.4	0.006

Data are expressed as mean ± SD or as number (percentage). Comparisons were performed using unpaired Student's T tests or $\chi 2$ tests. P-value refers to comparisons between survivors and nonsurvivors.

BMI: body mass index; NYHA: New York Heart Association; STS: Society of Thoracic Surgery; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; AV: aortic valve; GLS: global longitudinal strain; BLS: basal longitudinal strain; MD: mechanical dispersion.

GLS and BLS of non-survivors measured by 2D-STE as shown in Figure 2. Non-survivors demonstrated impaired GLS (-11.2±3% vs. -14.2±4%, p=0.001), impaired BLS (-10.9±2% vs -13.3±3%, p=0.001), and pronounced MD (86±33 ms vs 70±26 ms, p=0.006) compared to survivors.

Univariate analyses showed STS score, NYHA IV, renal disease (defined as baseline creatinine > 2 mg/dl), aortic valve (AV) mean gradient and post-TAVR PVL as significant univariates for 1-year mortality (Table 2). Baseline multivariate Cox regression model included age, STS, NYHA, renal disease, AV mean gradient, and post-TAVR PVL (model 1, p<0.001). Incremental prognostic information was achieved by adding strain parameters as shown in Figure 3. Addition of GLS to model 1 resulted in a significant C-statistic increase (40.6 vs. 34.3, p=0.032). A further incremental prognostic value was achieved by adding BLS to model 1 + GLS (47.5 vs. 40.6, p=0.001). Similarly, addition of MD to model 1 + GLS + BLS resulted in further incremental prognostic value (50.9 vs. 47.5, p=0.008). For the measurement of GLS, the Interobserver Intraclass Correlation Coefficient was 0.87.

Discussion

This retrospective clinical study provides evidence that myocardial strain parameters identified using 2D-STE immediately post-TAVR can be helpful in predicting poor outcomes in patients with AS. We demonstrated that both BLS and MD independently predict 1-year mortality in TAVR patients and provide incremental prognostic information in addition to known prognostic predictors of poor outcomes.

Myocardial fibrosis is an early morphologic change in patients with AS [18, 25, 26]. Two types of myocardial fibrosis were identified, interstitial fibrosis and replacement fibrosis. The interstitial fibrosis is reversible, and the latter is irreversible [27, 28]. Fibrosis affects myocardial diastolic and systolic function and provides a structural substrate for myocardial desynchrony [34]. Therefore, it plays a major role in sudden cardiac death and progression to heart failure [35]. Long-standing AS-related maladaptive myocardial changes resulting in fibrosis and ultimately impaired left ventricular (LV) function may persist after AVR and can affect clinical outcomes [31].

Previous studies developed a robust and definitive risk model to predict the outcomes of TAVR [36-38]. The basic model (model 1) included age, STS score, NYHA IV, renal disease, aortic valve mean-gradient, and post-TAVR PVL had a significant prognostic value in our patients. Various statistical metrics were employed to examine the incremental value of markers beyond model 1 [38-39]. Reviewing marker performances across the metrics, GLS, BLS, and MD emerged as the most promising markers.

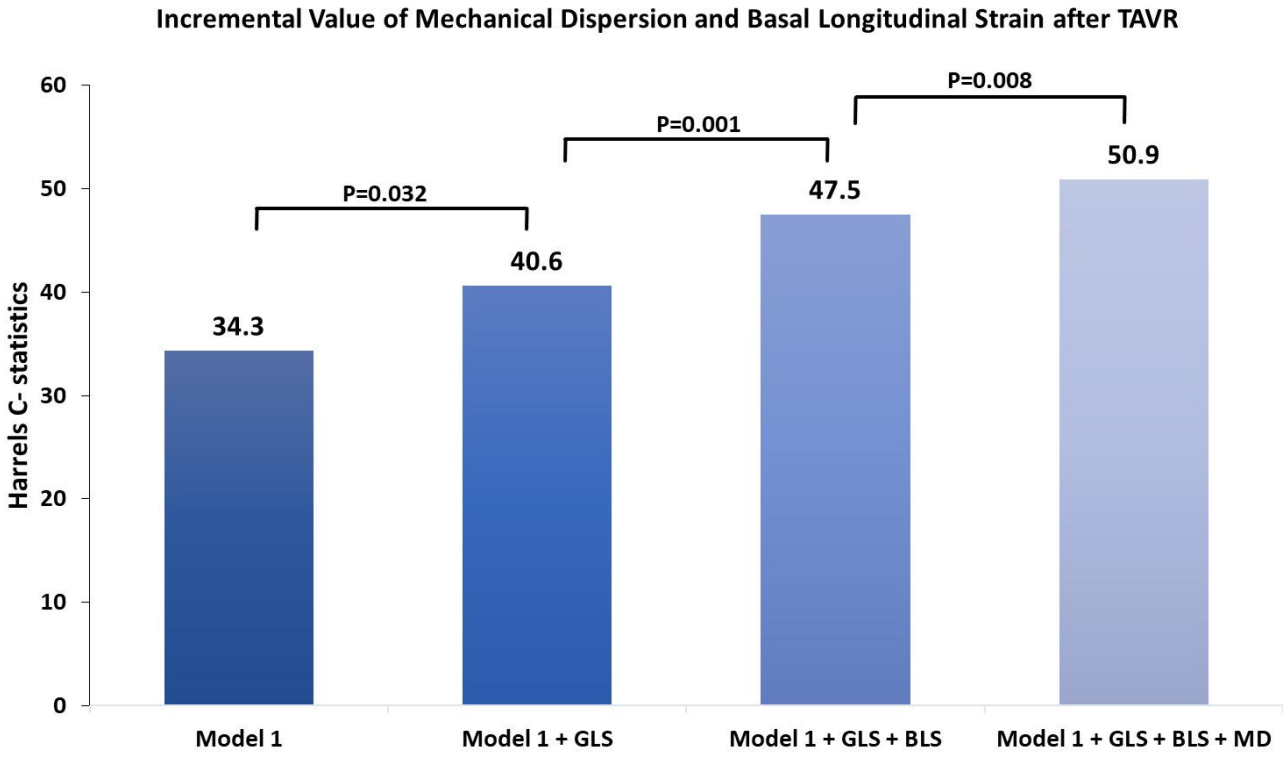

Figure 3. Incremental value of GLS, BLS, and MD post-TAVR. Incremental prognostic information by adding strain parameters. The C statistic values were obtained from the multivariable Cox proportional hazards regression models. Model 1 includes age, STS score, NYHA IV, renal disease (Cr > 2mg/dL), AV mean gradient and post-TAVR PVL as significant univariates. AV: aortic valve; BLS: basal longitudinal strain; Cr: creatinine; GLS: global longitudinal strain; MD: mechanical dispersion; NYHA: New York Heart Association; PVL: paravalvular leak; TAVR: transcatheter aortic valve replacement.

2D-STE is an emerging tool in detecting myocardial dysfunction prior to a clinically significant decrease in LVEF. When assessing for myocardial fibrosis, 2D-STE is cost-effective in comparison to cardiac MRI and less invasive than myocardial biopsy. Impaired pre-TAVR myocardial strain parameters have been linked to adverse outcomes in patients with AS [17]. In this study, we sought to determine if these strain parameters hold a prognostic value even post-TAVR.

Reduction of left ventricular afterload immediately post-TAVR results in improved myocardial strain parameters. In a study done by Delgado et al., a 19% reduction in GLS was noted immediately post-TAVR compared to baseline parameters [40]. In our study, GLS remained an important prognostic variable in multivariate analysis when adjusting for variables in model 1. However, addition of BLS to model 1 + GLS showed a further improvement in incremental prognostic value. This may be explained by the fact that fibrotic changes in AS primarily affect the basal segments and later progress to mid and apical segments [30]. In addition to BLS, MD has also been associated with myocardial fibrosis and heterogeneous myocardial contraction in AS [39]. Studies have shown a moderate correlation between the prevalence of myocardial fibrosis as detected on cardiac MR, and MD measured with 2D-STE [41]. In our study, MD was a significant predictor of all cause 1-year mortality in univariate analyses and remained a significant predictor in multivariate analysis. Additionally, MD resulted in a significant incremental prognostic value when added to model 1 in combination with BLS and GLS. To our knowledge, this is the first study that describes BLS and MD as important prognostic variables immediately post-TAVR. This emphasizes the potential use of 2D-STE in guiding the management of post-TAVR patients.

Table 2. Univariable and multivariate cox regression analysis for predictors of all-cause 1-year mortality.

	Univariate		Multivariate	
Variables	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Age	1.039 (0.99-1.09)	0.094		
Gender (Male)	1.038 (0.49-2.17)	0.922		
BMI	0.954 (0.90-1.01)	0.108		
HTN	0.553 (0.13-2.32)	0.419		
CAD	1.63 (0.67-4.10)	0.269		
Diabetes	2.03 (0.96-4.30)	0.062		
STS score	1.110 (1.04-1.19)	0.003		
NYHA IV	2.92 (1.28-6.63)	0.011		
Renal Disease (Cr>2)	2.31 (1.02-5.24)	0.046		
Baseline LVEF	0.987 (0.96-1.01)	0.260		
Post-TAVR LVEF, % (Day1)	0.978 (0.95-1.01)	0.056		
AV Mean Gradient	0.949 (0.92-0.97)	0.001		
Post-TAVR PVL	2.339 (1.45-3.75)	0.001		
GLS, %	1.21 (1.08-1.34)	0.001	1.12 (1.01-1.24)	0.045
BLS, %	1.29 (1.12-1.47)	0.001	1.21 (1.05-1.40)	0.008
MD, msec	1.02 (1.01-1.03)	0.003	1.02 (1.01-1.04)	0.001
Adjust for: age, STS score, NYHA IV, renal disease, AV mean gradient, post-TAVR PVL				

HR: Hazard ratio; BMI: body mass index; Cr: creatinine; NYHA: New York Heart Association; STS: Society of Thoracic Surgery; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; AV: aortic valve; TAVR: trans-catheter aortic valve replacement; PVL: paravalvular leak; GLS: global longitudinal strain; BLS: basal longitudinal strain; MD: mechanical dispersion.

Conclusion

We demonstrated that post-TAVR BLS and MD are independent predictors of 1-year mortality in patients with severe AS. Our study further demonstrates the incremental prognostic utility of these parameters to known markers of poor out. Early assessment of myocardial strain and mechanical dispersion should be considered as new indices for identifying patients at risk for poor outcomes post-TAVR.

Limitations

Baseline myocardial strain data was not available before TAVR. Therefore, it was not possible to determine whether pre- and post-TAVR strain parameters provide similar or different prognostic information. Another important limitation of our study is the lack of enough data to calculate the delta change in myocardial strain post-TAVR which could be an additional prognostic variable in TAVR patients. Further studies are needed to determine the prognostic implication of this factor. Although internal validation confirmed our results, the differential performance of the markers investigated here needs to be reexamined in larger study populations. More studies are needed to assess whether post-TAVR index-enhanced risk stratification can guide management decisions of post-TAVR patients, alongside with previous models.

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All co-authors have contributed to the development of this research project and the writing of this manuscript.

Conflict of Interest

The authors have no conflict of interest relevant to this publication.

Comment on this Article or Ask a Question

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