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Feature-Tracking Global Longitudinal Strain Predicts Death in a Multicenter Population of Patients with Ischemic and Nonischemic Dilated Cardiomyopathy Incremental to Ejection Fraction and Late Gadolinium Enhancement

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the prognostic value of cardiac magnetic resonance (CMR) feature-tracking–derived global longitudinal strain (GLS) in a large multicenter population of patients with ischemic and nonischemic dilated cardiomyopathy.

BACKGROUND Direct assessment of myocardial fiber deformation with GLS using echocardiography or CMR feature tracking has shown promise in providing prognostic information incremental to ejection fraction (EF) in single-center studies. Given the growing use of CMR for assessing persons with left ventricular (LV) dysfunction, we hypothesized that feature-tracking–derived GLS may provide independent prognostic information in a multicenter population of patients with ischemic and nonischemic dilated cardiomyopathy.

METHODS Consecutive patients at 4 U.S. medical centers undergoing CMR with EF <50% and ischemic or nonischemic dilated cardiomyopathy were included in this study. Feature-tracking GLS was calculated from 3 long-axis cine-views. The primary endpoint was all-cause death. Cox proportional hazards regression modeling was used to examine the association between GLS and death. Incremental prognostic value of GLS was assessed in nested models.

RESULTS Of the 1,012 patients in this study, 133 died during median follow-up of 4.4 years. By Kaplan-Meier analysis, the risk of death increased significantly with worsening GLS tertiles (log-rank $p < 0.0001$). Each 1% worsening in GLS was associated with an 89.1% increased risk of death after adjustment for clinical and imaging risk factors including EF and late gadolinium enhancement (LGE) (hazard ratio [HR]:1.891 per %; $p < 0.001$). Addition of GLS in this model resulted in significant improvement in the C-statistic (0.628 to 0.867; $p < 0.0001$). Continuous net reclassification improvement (NRI) was 1.148 (95% confidence interval: 0.996 to 1.318). GLS was independently associated with death after adjustment for clinical and imaging risk factors (including EF and late gadolinium enhancement) in both ischemic (HR: 1.942 per %; $p < 0.001$) and nonischemic dilated cardiomyopathy subgroups (HR: 2.101 per %; $p < 0.001$).

CONCLUSIONS CMR feature-tracking–derived GLS is a powerful independent predictor of mortality in a multicenter population of patients with ischemic or nonischemic dilated cardiomyopathy, incremental to common clinical and CMR risk factors including EF and LGE. (J Am Coll Cardiol Img 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

EF = ejection fraction

GLS = global longitudinal strain

ICD = implantable cardioverter defibrillator

LGE = late gadolinium enhancement

LV = left ventricular

NRI = net reclassification improvement

Ejection fraction (EF) is the principal measure used in clinical practice to assess cardiac mechanics. It provides significant prognostic information and is used widely for many clinical and therapeutic decisions, particularly in patients with left ventricular (LV) dysfunction. More recently, direct assessment of myocardial fiber deformation with echocardiographic global longitudinal strain (GLS) imaging has shown promise in providing diagnostic and prognostic information that is incremental to EF (1,2).

Cardiac magnetic resonance (CMR) imaging has evolved into a major tool for assessment of patients with LV dysfunction, providing precise measurements of EF and tissue characterization with late gadolinium enhancement (LGE) (3). LGE can help establish the underlying cause of LV dysfunction and is a powerful predictor of adverse cardiovascular outcomes (3). Recent developments in CMR feature-tracking techniques now allow assessment of GLS from standard cine-CMR images (4).

We have recently reported the prognostic association of GLS with mortality in a small population of mixed cardiomyopathy patients from a single center (5). However, the prognostic value of GLS in patients with ischemic versus nonischemic cardiomyopathy is unknown. Moreover, the robustness of these associations, as well as the variability of feature-tracking GLS measurements in a multicenter setting, remains unclear. The aim of this study was to evaluate the prognostic value of CMR feature-tracking-derived GLS in a large multicenter population of patients with ischemic and nonischemic cardiomyopathy undergoing CMR at several centers in the United States.

METHODS

STUDY DESIGN. Four geographically diverse medical centers in the United States participated in this observational multicenter study. The University of Illinois in Chicago served as the data-coordinating center, using a cloud-based database (CloudCMR, HeartIT, Durham, North Carolina) containing de-identified searchable data from consecutive patients with full DICOM datasets from the participating centers. Institutional review board approval was obtained at each center.

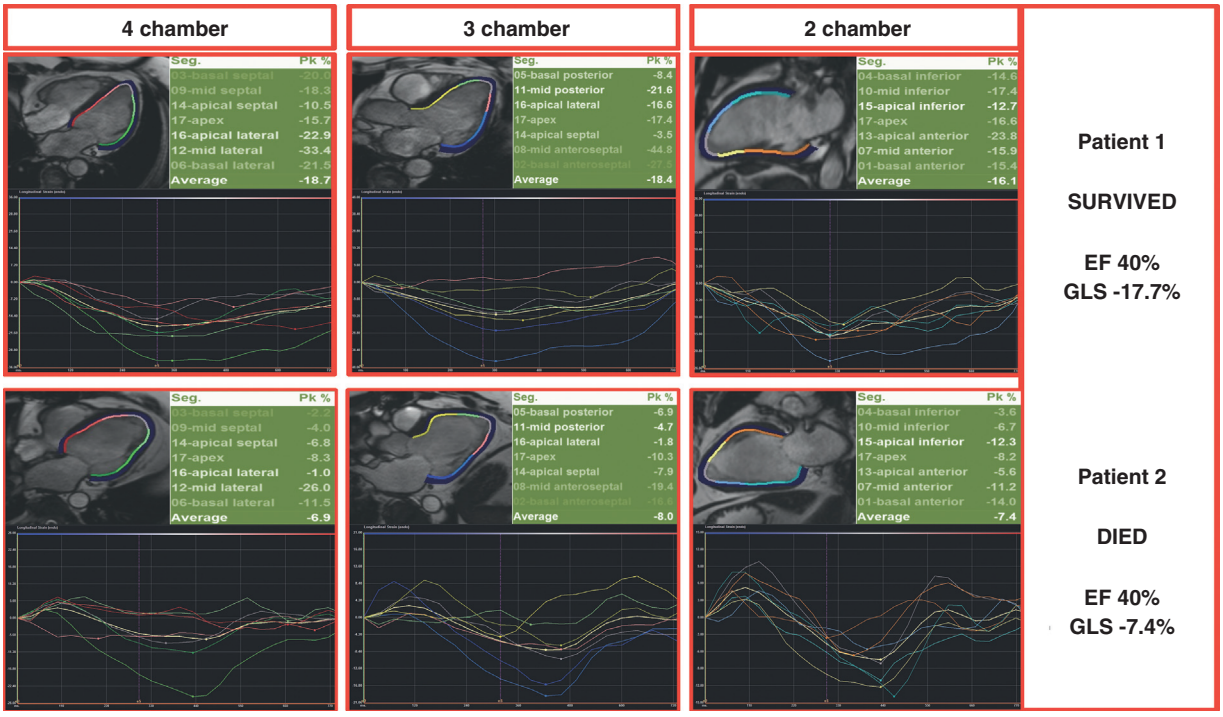
STUDY POPULATION. Consecutive patients (n = 1,047) with EFs <50% and ischemic or nonischemic dilated cardiomyopathy who had undergone clinical CMR in 2011 with both cine- and LGE imaging formed the study population. A subgroup of patients from a single center in this study was used in a previous report (5). Patients with uninterpretable image quality for GLS assessment (n = 35) were excluded, leaving 1,012 patients, which formed the study population. Baseline demographics were obtained by local site investigators at the time of the clinical study.

CMR ACQUISITION. Images were acquired with phased-array receiver coils, according to the routine scan protocol at each site, using a variety of scanners from all 3 major vendors (Siemens, Philips, and General Electric) at both 1.5- and 3-T. A typical protocol included steady-state free-precession cine-images acquired in multiple short-axis and 3 long-axis views with short-axis views obtained every 1 cm to cover the entire left ventricle. Typical temporal resolution of cine-images was <45 ms. LGE imaging was performed 10 to 15 min after administration of gadolinium contrast material (0.15 mmol/kg), using a 2-dimensional (2D) segmented gradient echo inversion-recovery sequence in the same views used for cine-CMR. Inversion delay times were typically 280 to 360 ms.

CMR ANALYSIS AND GLS ASSESSMENT. The study-site investigators analyzed images on locally available workstations and were blinded to follow-up data. Delayed enhancement was assessed as described previously (6–9). In brief, LGE was scored visually on a 17-segment model with a 5-point scale for each segment (0 = no LGE, 1 = 1% to 25%, 2 = 26% to 50%, 3 = 51% to 75%, 4 = 76% to 100%). LGE extent as a percentage of LV myocardium was calculated by summing the regional scores, each weighted by the LGE range midpoint (i.e., 1 = 13%, 2 = 38%, 3 = 63%, 4 = 88%) and dividing by 17. LV volumes and mass were manually quantified at the data coordinating center from short-axis cine-images. At the data-coordinating center, endocardial LV contours were manually traced (by a single physician who was blinded to patient information and outcomes) in all 3 long-axis cine-views to derive GLS using the Q strain feature-tracking package (Medis Medical Imaging Systems, Leiden, the Netherlands) (**Figure 1**). In 100 randomly selected patients, a second blinded CMR physician measured GLS for assessment of interobserver variability. In another 100 randomly selected patients, the same physician remeasured GLS in a blinded fashion for assessment of intraobserver variability.

FOLLOW-UP. Patients were followed for the primary outcome of all-cause mortality using the United States Social Security Death Index. Time to event was calculated as the period between the CMR study and

FIGURE 1 **Measurement of GLS**



Top panel shows a patient that survived and **bottom panel** shows a patient that subsequently died. EF = ejection fraction; GLS = global longitudinal strain.

death. Patients who did not experience the primary outcome were censored at the time of assessment.

STATISTICAL ANALYSIS. Normally distributed data were expressed as mean ± SD. Differences in baseline characteristics were compared with the use of analysis of variance (ANOVA) for continuous variables and the chi-square test for dichotomous variables, as appropriate. Interobserver and intraobserver variability was analyzed using the Bland-Altman method. Kaplan-Meier methods were used to evaluate the relationship between GLS and time to the primary outcome of all-cause mortality. We used Cox proportional hazards regression modeling to examine the association between GLS and all-cause mortality. All models were assessed for collinearity and proportional hazards assumption. For the multivariable models, clinical and imaging risk factors, which were univariate predictors (at $p \leq 0.20$), were considered as covariates. There was no evidence of problematic strong collinearity among GLS and any of the covariates in the multivariable models. The variance inflation factor (VIF) was <1.5 for all the covariates in all the models. To assess the added prognostic value of GLS, the final model was compared with a model in which GLS was not included. Model discrimination was compared by calculating the C-statistic as well as the integrated discrimination improvement (IDI) (10). Formal risk reclassification analyses were conducted with calculation of continuous net reclassification improvement (NRI) (10). A p value of <0.05 was considered statistically significant. Analyses were performed using STATA (StataCorp, College Station, Texas).

RESULTS

PATIENT CHARACTERISTICS. Table 1 summarizes baseline patient characteristics stratified by tertiles of GLS. The mean age of the study population was 60 ± 16 years. Sixty-five percent of patients were male, and 31% had diabetes mellitus. The mean EF was 33.7 ± 10.0%. Mean GLS for the population was −10.9%. Median GLS was −11.0% (interquartile range: −7.8 to −14.0%). A total of 505 (49.9%) patients had ischemic cardiomyopathies, and 507 (51.1%) had nonischemic dilated cardiomyopathies. A total of 484 patients (47.8%) had ischemic LGE patterns (involving the subendocardium), and 144 (14.2%) had nonischemic patterns (midmyocardial or epicardial), with 384

TABLE 1 Baseline Characteristics Stratified by Tertiles of GLS

	Total	GLS <−13.0%	GLS −8.7 to −13.0%	GLS >−8.7%	p Value
Age, yrs	59.8 ± 15.7	56.3 ± 16.6	60.2 ± 14.7	62.8 ± 15.1	<0.001
Male	65.3	66.7	62.5	66.9	0.427
BMI, kg/m^2	28.9 ± 8.6	28.2 ± 6.5	28.9 ± 6.6	29.4 ± 11.6	0.199
Diabetes	30.6	24.9	30.2	36.7	0.004
Hyperlipidemia	54.7	50.2	54.9	58.8	0.078
Smoking	14.8	12.9	13.1	18.3	0.085
Hypertension	66.7	61.1	66.8	72.2	0.010
History of MI	28.9	26.1	25.4	35.1	0.010
Ischemic CM	49.9	43.8	43.7	62.1	<0.001
Nonischemic dilated CM	50.1	56.2	56.3	37.9	<0.001
Aspirin	63.2	57.1	60.3	72.3	0.001
Statin	55.9	53.5	56.4	57.8	0.544
ACE Inhibitor or ARB	66.2	57.0	70.5	70.0	0.001
Beta-blocker	49.6	40.8	54.3	53.4	0.001
Diuretic	44.6	31.8	48.8	53.0	0.001
Heart rate, beats/min	76.5 ± 16.5	70.4 ± 13.8	77.5 ± 16.3	81.3 ± 17.4	<0.001
Systolic BP, mm Hg	123.1 ± 20.7	124.9 ± 20.8	124.7 ± 20.6	119.9 ± 20.3	0.010
Diastolic BP, mm Hg	72.7 ± 13.5	72.0 ± 12.9	73.7 ± 13.3	72.4 ± 14.3	0.371
LVEDV index, ml/m^2	117.9 ± 54.6	102.3 ± 40.6	116.7 ± 55.9	134.5 ± 60.3	<0.001
LVESV index, ml/m^2	67.1 ± 44.2	48.7 ± 26.8	67.1 ± 42.2	85.2 ± 51.9	<0.001
LV mass index, g/m^2	113.7 ± 26.4	110.6 ± 27.0	112.9 ± 52.1	117.5 ± 45.1	0.850
LGE present	62.1	51.7	59.5	74.9	<0.001
LGE extent, %	8.4 ± 10.1	6.3 ± 8.4	7.4 ± 9.3	11.6 ± 11.6	<0.001
LVEF, %	33.7 ± 10.0	40.3 ± 6.8	34.0 ± 8.6	26.8 ± 9.3	<0.001

Values are mean ± SD or %.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CM = cardiomyopathy; GLS = global longitudinal strain; LGE = late gadolinium enhancement; LVEDV = left ventricular end diastolic volume index; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume index; MI = myocardial infarction.

(38.0%) having no LGE. The distribution of GLS with EF and LGE is shown in Online Figures 1 and 2.

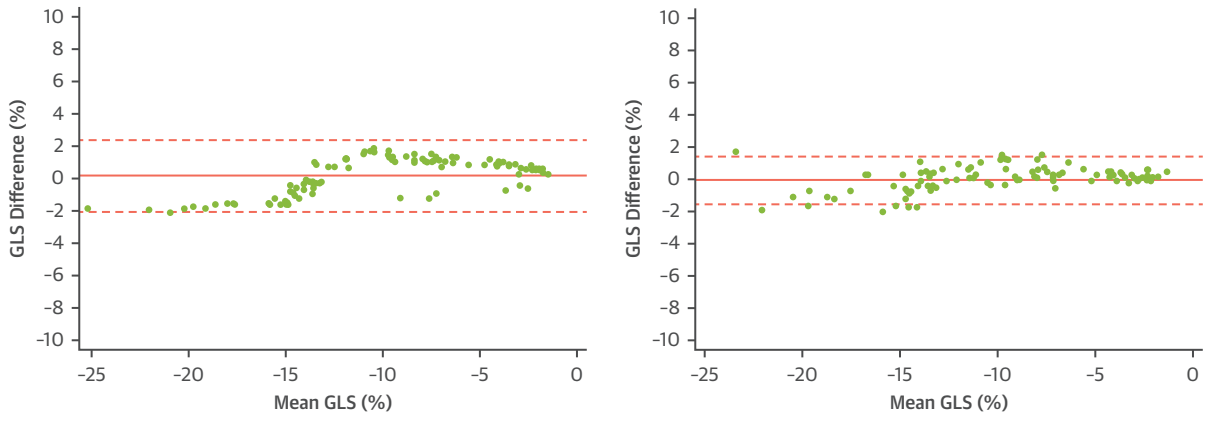
INTEROBSERVER AND INTRAOBSERVER VARIABILITY. Bland-Altman analysis of interobserver repeatability for GLS showed a bias of 0.16%. The 95% limits of agreement were −2.08% to 2.40% (Figure 2). Bland-Altman analysis of intraobserver repeatability for GLS showed a bias of −0.07%. The 95% limits of agreement were −1.59 to 1.45% (Figure 2).

PRIMARY OUTCOME. Of the 1,012 patients in the study, 133 (13.1%) died during a median follow-up of 4.4 years (interquartile range: 3.6 to 5.1 years).

OUTCOMES STRATIFIED BY GLS, LVEF, AND LGE. By Kaplan-Meier analysis, the risk of death increased significantly with worsening tertiles of GLS (log-rank $p < 0.0001$) (Figure 3). LVEF, as a continuous variable, was significantly associated with death (hazard ratio [HR]: 0.980; $p = 0.022$). In other words, every 1% decrease in LVEF was associated with a 2% increased risk of death. Kaplan-Meier analysis of patients with EF ≤35% versus those with EF >35% stratified by the highest and lowest tertiles of GLS shows that mortality was significantly higher in patients in the poorest GLS tertile, irrespective of LVEF (Figure 4). Patients within the poorest GLS tertile and LVEF ≤35% had significantly reduced survival compared with those patients in the poorest GLS tertile with LVEF >35% (log-rank $p = 0.003$). However, in patients within the best-preserved GLS tertile, survival was high and unaffected by LVEF (Figure 4).

LGE extent was significantly associated with all-cause-mortality (HR: 1.030 per %; $p < 0.001$; 95% confidence interval [CI]: 1.015 to 1.050). Thus, every 1% increase in LGE extent was associated with a 3% increased risk of death. Likewise, by Kaplan-Meier analysis, the presence of LGE was associated with a significantly increased risk of death (log-rank $p = 0.0001$) (Figure 5). Kaplan-Meier analysis of patients with LGE versus those without LGE, stratified by the highest and lowest tertiles of GLS, shows that mortality was highest for patients in the poorest GLS tertile, irrespective of LGE (Figure 6). Thus, among patients within the poorest GLS tertile, the presence of LGE did not significantly affect survival (log-rank $p = 0.328$). Likewise, for patients within the best-preserved GLS tertile, presence of LGE did not significantly affect survival (log-rank $p = 0.379$) (Figure 6).

FIGURE 2 Bland-Altman Analysis of GLS for Interobserver and Intraobserver Variability



Interobserver **(left)** and intraobserver **(right)** variability. **Solid line** represents the bias. **Dashed lines** represents the 95% limits of agreement. GLS = global longitudinal strain.

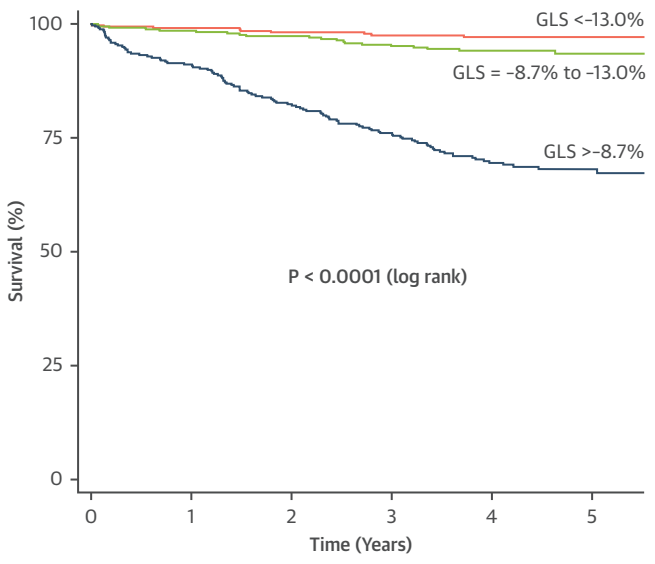
MULTIVARIABLE ANALYSIS AND INCREMENTAL PROGNOSTIC VALUE. After adjustment for clinical and imaging risk factors, which were univariate predictors at $p \leq 0.20$ (age, body mass index, diabetes, hyperlipidemia, LV end-diastolic volume index, LGE extent, EF), GLS remained a significant independent predictor of death (HR: 1.891 per %; $p < 0.001$); that is, each 1% worsening in GLS was associated with an 89.1% increase risk of death (Table 2). Addition of GLS into the model with clinical and imaging predictors resulted in significant increase in the C-statistic (from 0.628 to 0.870; $p < 0.0001$) and an integrated discrimination improvement of 0.256 (95% CI: 0.189 to 0.329), with a continuous NRI of 1.148 (95% CI: 0.996 to 1.318). GLS remained a significant independent predictor of death (HR: 1.890 per %; $p < 0.001$) when presence of LGE was used instead of LGE extent in the multivariable model (Table 2).

PROGNOSTIC VALUE OF GLS IN ISCHEMIC AND NONISCHEMIC DILATED CARDIOMYOPATHY. By Kaplan-Meier analysis, the risk of death increased significantly with worsening tertiles of GLS (log-rank $p < 0.0001$) in both the ischemic and nonischemic dilated cardiomyopathy subgroups (Figure 7). In patients with ischemic cardiomyopathy, each 1% worsening in GLS was associated with a 94.2% increased risk of death after adjustment for clinical and imaging risk factors (HR: 1.942 per %; $p < 0.001$) (Table 3). Similarly, in patients with nonischemic dilated cardiomyopathy, GLS remained significantly associated with death after adjustment for clinical and imaging risk factors (HR: 2.101 per %; $p < 0.001$) (Table 4). GLS remained a significant independent predictor of death when presence of LGE was used instead of LGE extent in the multivariable models for both ischemic and nonischemic cardiomyopathy subgroups (Tables 3 and 4).

DISCUSSION

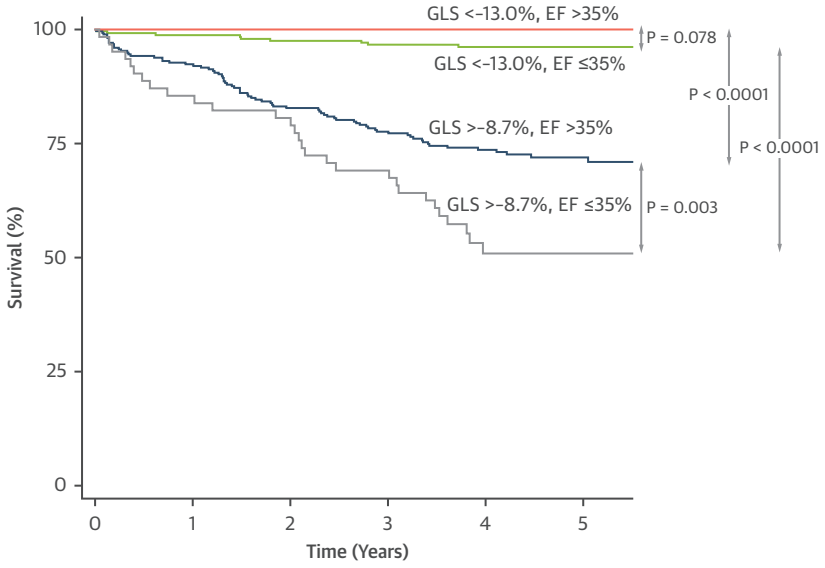
This study shows that GLS measured by feature-tracking CMR was a powerful independent predictor of mortality in a large multicenter population of

FIGURE 3 Kaplan-Meier Survival Curves



Patients are stratified by tertiles of global longitudinal strain (GLS).

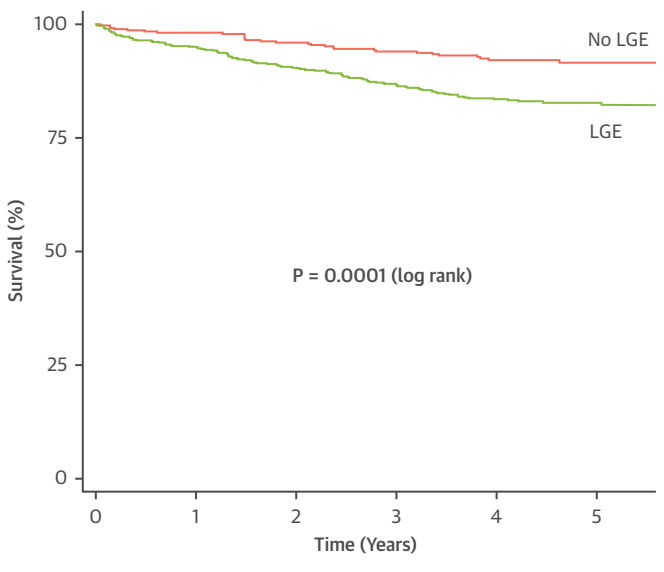
FIGURE 4 Kaplan-Meier Survival Curves Stratified by Ejection Fraction



Patients with ejection fraction (EF) ≤35% versus those with EF >35% are stratified by the highest and lowest tertiles of global longitudinal strain (GLS).

patients with ischemic and nonischemic dilated cardiomyopathy. We have demonstrated that this parameter provides prognostic information incremental to common clinical and CMR imaging risk factors including EF and LGE extent. GLS was an independent predictor of mortality in both ischemic and nonischemic dilated cardiomyopathy subgroups. Thus, these findings have potentially broad application. To the best of our knowledge, this is the largest study validating the use of feature-tracking CMR for prognostic assessment of patients with LV dysfunction. These findings may have significant implications for management decisions based on risk stratification of these patients.

FIGURE 5 Kaplan-Meier Survival Curves Stratified by Presence of LGE

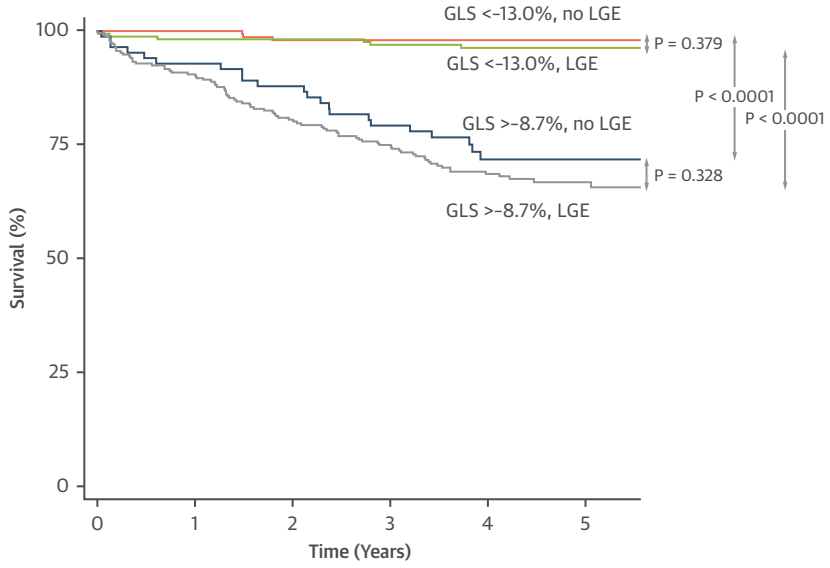


Patients are stratified by presence or absence of late gadolinium enhancement (LGE).

LONG-AXIS FUNCTION IN CARDIAC MECHANICS. Long-axis function plays a fundamental role in cardiac mechanics, contributing to ventricular ejection by reducing long-axis LV cavity size as the mitral annulus is pulled toward the apex (11,12). CMR has been used to measure the contribution of long-axis function to overall stroke volume in normal subjects, elite athletes, and patients with dilated cardiomyopathy (13). These studies suggest that as much as 60% of stroke volume may be explained by long-axis function. In diastole, the mitral annulus springs back to its equilibrium position, moving around the column of blood passing through the mitral valve, thus aiding ventricular filling (11,12).

Possibly because of their subendocardial location, the more longitudinal myocardial fibers seem to be exquisitely sensitive to disturbance by various pathologies, as evidenced by rapid reduction of mitral annular motion with ischemia induction in experimental models (11).

FIGURE 6 Kaplan-Meier Survival Curves Stratified by GLS and Presence of LGE



Patients with late gadolinium enhancement (LGE) versus those without LGE are stratified by the highest and lowest tertiles of global longitudinal strain (GLS).

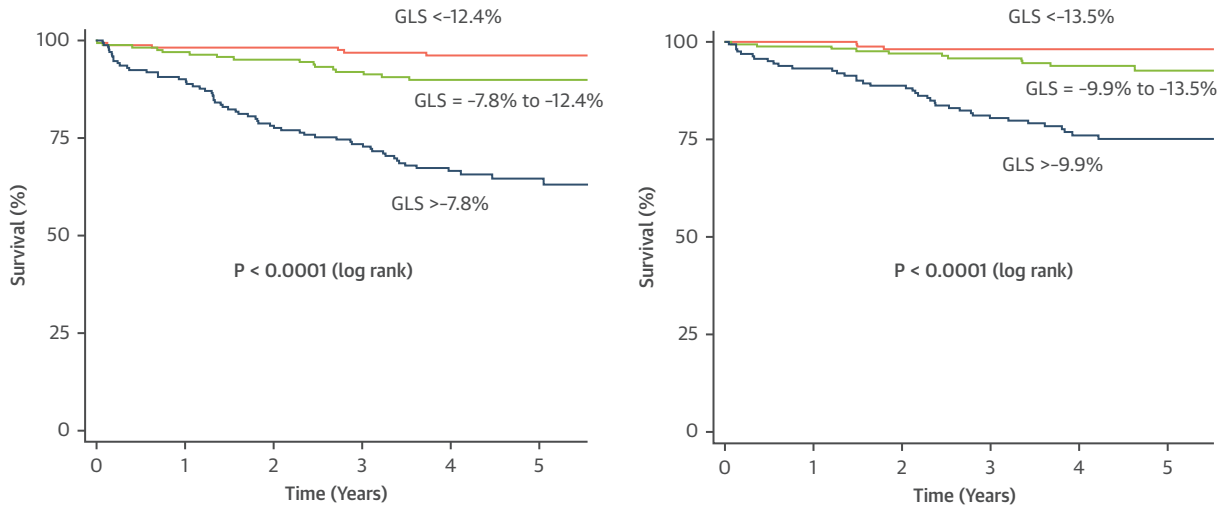
ASSESSMENT OF LONG-AXIS FUNCTION. As the cardiac apex is fixed with respect to the chest wall, long-axis function was initially assessed by measuring changes in the position of the mitral annulus (12). These studies have used M-mode echocardiography and, more recently, CMR to follow the position of the mitral annulus directly and measure mitral annular plane systolic excursion (14-16). However, over the last few years, enormous interest has been generated by development of echocardiographic 2D speckle-tracking techniques to assess long-axis function in a more global manner by measuring GLS (1,2). There is now a large body of literature demonstrating the diagnostic and prognostic utility of echo-derived GLS in various cardiovascular disorders (1,2). However, these echo-strain techniques are dependent on attainment of good-quality imaging (1,2). CMR feature tracking provides an alternative means to obtain GLS in these patients, although with some limitations in those with CMR contraindications such as implanted devices and severe claustrophobia. We have shown that additional measurement of feature-tracking GLS

TABLE 2 Multivariable Models of Mortality With GLS Adjusted to Univariate Clinical and Imaging Predictors (at $p \leq 0.20$) for the Entire Population

	Univariable		Multivariable Using LGE Extent		Multivariable Using LGE Presence	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Age	1.026 (1.014-1.038)	<0.001	1.014 (1.002-1.027)	0.048	1.013 (1.001-1.026)	0.049
BMI	1.010 (0.998-1.022)	0.190	1.000 (0.990-1.009)	0.954	1.000 (0.990-1.010)	0.994
Diabetes	1.771 (1.255-2.499)	0.001	1.574 (1.075-2.304)	0.020	1.574 (1.074-2.308)	0.020
Hyperlipidemia	1.210 (0.859-1.719)	0.160	0.772 (0.512-1.164)	0.217	0.759 (0.502-1.147)	0.191
Hypertension	1.194 (0.885-1.737)	0.192	0.905 (0.599-1.367)	0.636	0.886 (0.585-1.342)	0.567
LVEDV index	1.012 (1.001-1.022)	0.049	0.999 (0.995-1.003)	0.623	0.999 (0.995-1.003)	0.578
GLS	1.347 (1.285-1.411)	<0.001	1.891 (1.546-2.313)	<0.001	1.890 (1.547-2.308)	<0.001
LGE present	2.253 (1.493-3.401)	<0.001	–	–	1.342 (0.872-2.065)	0.182
LGE extent	1.030 (1.014-1.045)	<0.001	1.007 (0.990-1.024)	0.430	–	–
LVEF	0.980 (0.964-0.997)	0.022	1.005 (0.969-1.043)	0.765	1.005 (0.969-1.042)	0.787

CI = confidence interval; other abbreviations as in Table 1.

FIGURE 7 Kaplan-Meier Survival Curves in Patients With Ischemic and Nonischemic Dilated Cardiomyopathy



Ischemic cardiomyopathy **(left)** and nonischemic dilated cardiomyopathy **(right)** patients are stratified by tertiles of global longitudinal strain (GLS).

in patients already undergoing CMR for evaluation of cardiomyopathy provides significant additive prognostic value.

CMR FEATURE TRACKING. Recent development of CMR feature-tracking technology shows promise in allowing measurement of longitudinal strain using routine cine-images in the clinical setting (4). The underlying principle is based on recognition of "patterns of features" or "irregularities" in the image that are tracked and followed in successive frames (4). Importantly, this approach can be applied to routine cine-CMR acquisitions, thus avoiding the need for dedicated pulse sequences, which are required for other specialized CMR-strain techniques such as tagging, harmonic phase (HARP), displacement encoding with stimulated echos (DENSE), and strain-encoded CMR (SENC) (4). Similar to echo-speckle tracking, there are intervendor differences in the exact algorithms used in CMR feature tracking. Moreover, measurements are not necessarily directly comparable among modalities or with those based on dedicated CMR pulse sequences. Nevertheless, several recent studies comparing speckle-tracking echo and CMR feature tracking have suggested good agreement (17,18).

CMR FEATURE TRACKING GLS AND PROGNOSIS. There is a significant and growing body of literature demonstrating the prognostic value of GLS derived

TABLE 3 Multivariable Models of Mortality With GLS Adjusted to Univariate Clinical and Imaging Predictors (at $p \leq 0.20$) for Patients With Ischemic Cardiomyopathy

	Univariable		Multivariable Model Using LGE Extent		Multivariable Model Using LGE Presence	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Age	1.025 (1.006–1.044)	0.008	1.022 (1.002–1.043)	0.031	1.022 (1.002–1.041)	0.029
BMI	1.011 (1.001–1.022)	0.038	1.001 (0.991–1.012)	0.787	1.002 (0.992–1.012)	0.732
Diabetes	1.574 (1.018–2.435)	0.041	1.949 (1.188–3.199)	0.008	1.933 (1.183–3.160)	0.009
Hyperlipidemia	1.351 (0.890–1.816)	0.153	0.834 (0.483–1.438)	0.513	0.837 (0.486–1.442)	0.521
LVEDV index	1.010 (1.001–1.020)	0.049	1.000 (0.994–1.006)	0.986	1.000 (0.994–1.006)	0.987
GLS	1.312 (1.234–1.395)	<0.001	1.942 (1.466–2.573)	<0.001	1.952 (1.475–2.584)	<0.001
LGE Present	2.142 (1.283–3.001)	<0.001	–	–	1.684 (0.228–12.46)	0.609
LGE Extent	1.017 (1.005–1.029)	0.042	1.005 (0.980–1.030)	0.720	–	–
LVEF	0.978 (0.957–0.998)	0.048	1.012 (0.965–1.062)	0.720	1.010 (0.964–1.058)	0.678

Abbreviations as in Tables 1 and 2.

TABLE 4 Multivariable Models of Mortality With GLS Adjusted to Univariate Clinical and Imaging Predictors (at $p \leq 0.20$) for Patients With Nonischemic Dilated Cardiomyopathy

	Univariable		Multivariable Using LGE extent		Multivariable Using LGE presence	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
Age	1.024 (1.008-1.041)	0.004	1.003 (0.985-1.022)	0.717	1.002 (0.984-1.021)	0.791
Diabetes	1.779 (0.996-3.175)	0.061	1.107 (0.588-2.086)	0.752	0.955 (0.510-1.789)	0.885
LVEDV index	1.012 (1.002-1.022)	0.048	0.998 (0.993-1.003)	0.376	0.997 (0.992-1.002)	0.283
GLS	1.402 (1.299-1.513)	<0.001	2.101 (1.546-2.854)	<0.001	2.135 (1.564-2.913)	<0.001
LGE present	2.514 (1.249-3.715)	0.007	–	–	1.914 (1.092-3.355)	0.023
LGE extent	1.057 (1.030-1.085)	<0.001	1.044 (1.015-1.073)	0.002	–	–
LVEF	0.978 (0.958-0.997)	0.020	0.981 (0.927-1.039)	0.511	0.981 (0.926-1.040)	0.525

Abbreviations as in Tables 1 and 2.

using speckle-tracking echo in patients with LV dysfunction (1,19-21). In contrast, data regarding CMR-derived GLS and prognosis have been very limited. Buss et al. (22) recently demonstrated that feature-tracking-derived GLS was an independent predictor of the composite endpoint of cardiac death, heart transplantation, and aborted sudden cardiac death in a small single-center population of 210 patients with dilated nonischemic cardiomyopathy who were followed for a median of 5.3 years.

We have recently reported the prognostic association of GLS with mortality in 470 patients with mixed cardiomyopathy from a single center (5). The findings in the current study are consistent with these earlier observations and build on previous data by demonstrating the independent and incremental prognostic value of CMR feature-tracking GLS in a multicenter population with a significantly greater number of patients and hard events. A major strength of our study is that they were made in a large multicenter group of patients with both ischemic and nonischemic dilated cardiomyopathy. Thus, these findings have potentially broad application to these important patient groups and greatly expand the evidence base for using CMR-derived GLS to assess prognosis.

ROLE OF CMR IN ASSESSMENT OF LV DYSFUNCTION. CMR has evolved into a major tool for diagnosis and prognostic assessment of patients with LV dysfunction by providing data on morphology, function, perfusion, viability, and tissue characterization (3,7,8). It is the reference standard for measurement of ventricular volumes, mass, and function, allowing serial assessment of progression of disease or treatment response in individual patients (3,7). CMR tissue characterization can sometimes help establish the underlying cause of LV dysfunction (3,7). LGE assessment allows prediction of the likelihood of functional recovery after revascularization, medical therapy, or cardiac resynchronization (3,7). In addition, LGE is a powerful predictor of adverse cardiovascular outcome in patients with LV dysfunction (3,7). In this study, we have now shown that GLS provides independent prognostic information in patients with LV dysfunction being evaluated by CMR. Moreover, this was incremental to standard clinical and CMR variables including LGE and EF. How this information will affect clinical care requires further study. However, it is interesting to note that we found that patients with relatively preserved GLS had very few adverse events regardless of whether their EF was above or below 35%. Given that current guidelines recommend implantable cardioverter device (ICD) placement based primarily on an EF ≤35%, it will be interesting to examine the role of GLS on sudden cardiac death in future studies.

STUDY LIMITATIONS. Baseline demographics were obtained by local site investigators at the time of the clinical study and were limited to the prespecified variables presented in this manuscript, which do not represent a comprehensive list of all possible prognostic markers. For example, plasma brain natriuretic peptide levels were not routinely measured at the time of scanning and were not included in our predictive models. Left atrial volumes measurements were not performed.

Information regarding future treatments, such as revascularization or ICD placement, would be interesting to report but were not available. Patients underwent standard clinical care as practiced in the United States with treatments and therapies determined by their physicians. However, this does not detract from the main findings of this study: that feature-tracking GLS is a powerful predictor of death in patients with ischemic and nonischemic dilated

cardiomyopathy, independent of common clinical and imaging markers available at the time of CMR. The findings are reflective of and applicable to patients being evaluated by CMR in daily clinical practice, particularly given the multicenter "real-world" nature of this study.

Because this is a CMR study, there is a degree of selection bias related to being able to undergo a CMR examination, resulting in exclusion of patients with severe symptoms, large body size, severe renal impairment, severe claustrophobia, or those with pacemakers and ICDs.

Information regarding specific cardiovascular outcomes—such as myocardial infarction, sudden death, transplantation, revascularization, or hospitalization—was not available. Follow-up data in this study were limited to the primary endpoint of all-cause death, and the cause of death was not known. However, many have argued that all-cause mortality is an extremely important and appropriate study endpoint because it is objective, clinically relevant, and unbiased, which is often not the case for cardiac mortality or softer outcomes such as revascularization or hospitalization (21,23,24). In a seminal review of this subject, Lauer et al. (24) argued that use of cardiac death instead of all-cause death as an endpoint in clinical investigation is hazardous for various reasons: 1) data obtained from death certificates or from medical records are haphazard, biased, and often grossly inaccurate; 2) determination of cause of death is inherently difficult owing to the presence of concurrent comorbid illnesses, a low autopsy rate, and inadequate understanding of complex disease processes; and 3) coronary artery disease may be present and significant at the time of death and yet not be the primary reason that a patient dies. They concluded that the ultimate result of using specific causes of death as endpoints is that "softness" is introduced into a study that otherwise would be based on the strength of the "hardest" endpoint of all: all-cause mortality. We therefore believe that all-cause mortality is a highly important and valid primary endpoint for this study.

In this study, we prospectively decided to measure GLS only because this measure has the largest and most robust body of prognostic data from echocardiography. Future studies are needed to address the role of feature-tracking-derived radial or circumferential strain.

Phase-sensitive inversion recovery imaging was not used routinely and was not available on all scanners during the study period, which is reflective of real-world practice and Society for Cardiovascular Magnetic Resonance recommendations (25). In this study, we used a semiquantitative assessment of LGE extent. There is no current consensus on the best method of LGE quantification in nonischemic cardiomyopathy (26). However, semiquantitative visual LGE assessment has been validated prognostically in previous studies of nonischemic cardiomyopathy and is rapidly performed in daily practice in many clinical laboratories (27,28). Moreover, we also assessed binary presence or absence of LGE in this study. Presence of LGE by visual analysis has extensive prognostic validation in nonischemic cardiomyopathy from numerous previous studies (26). GLS remained an independent predictor of death, regardless of whether LGE was assessed in a binary or semiquantitative manner.

In similar fashion to echo speckle tracking, there are algorithmic differences among various CMR feature-tracking software platforms, which may result in differing values (4). Thus, the applicability of our findings to other feature-tracking vendors requires further investigation.

CONCLUSIONS

In this large multicenter study, GLS measured during routine cine-CMR is a powerful independent predictor of mortality in patients with ischemic and nonischemic dilated cardiomyopathy, incremental to common clinical and imaging risk factors including EF and LGE. Each 1% worsening in GLS was associated with an 89.1% increased risk of death, adjusted to clinical and imaging risk factors. To the best of our knowledge, this study is the largest CMR analysis of GLS in patients with LV dysfunction. The total number of hard events (n = 133) in our population is significantly higher than previous CMR studies of GLS, which greatly increases the robustness of our findings. A major strength of these findings is that they were made in a large multicenter group of patients. Thus, these observations have potentially broad application to these important patient groups. Our findings highlight the role of long-axis function in patients with LV dysfunction and suggest that consideration should be given to measurement of this parameter in these patients. Future studies are warranted to explore the role of CMR feature-tracking-derived GLS in clinical decision making for these patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this large multicenter study, GLS measured during routine cine-CMR is a powerful independent predictor of mortality in patients with ischemic and nonischemic dilated cardiomyopathy, incremental to common clinical and imaging risk factors including EF and LGE.

TRANSLATIONAL OUTLOOK: Future studies are warranted to explore the role of CMR feature-tracking-derived GLS in clinical decision making for patients with ischemic and nonischemic dilated cardiomyopathy. Given that current guidelines recommend ICD placement based primarily on an EF of ≤35%, it will be interesting to examine the association of feature-tracking-derived GLS with sudden cardiac death.

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