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ORIGINAL RESEARCH

Feature-Tracking Global Longitudinal Strain Predicts Mortality in Patients With Preserved Ejection Fraction

A Multicenter Study

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ABSTRACT

OBJECTIVES The goal of this study was to evaluate the prognostic value of global longitudinal strain (GLS) derived from cardiac magnetic resonance (CMR) feature-tracking in a large multicenter population of patients with preserved ejection fraction.

BACKGROUND Ejection fraction is the principal parameter used clinically to assess cardiac mechanics and provides prognostic information. However, significant abnormalities of myocardial deformation can be present despite preserved ejection fraction. CMR feature-tracking techniques now allow assessment of strain from routine cine images, without specialized pulse sequences. Whether abnormalities of strain measured by using CMR feature-tracking have prognostic value in patients with preserved ejection fraction is unknown.

METHODS Consecutive patients with preserved ejection fraction (≥50%) and a clinical indication for CMR at 4 U.S. medical centers were included in this retrospective 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 independent association between GLS and death. The incremental prognostic value of GLS was assessed in nested models.

RESULTS Of the 1,274 patients in this study, 115 died during a median follow-up of 6.2 years. By Kaplan-Meier analysis, patients with GLS ≥ median (-20%) had significantly reduced event-free survival compared with those with GLS < median (log-rank test, $p < 0.001$). By Cox multivariable regression modeling, each 1% worsening in GLS was associated with a 22.8% increased risk of death after adjustment for clinical and imaging risk factors (hazard ratio: 1.228 per percent; $p < 0.001$). Addition of GLS in this model resulted in significant improvement in the global chi-square test (94 to 183; $p < 0.001$) and Harrell's C-statistic (0.75 to 0.83; $p < 0.001$).

CONCLUSIONS GLS derived from CMR feature-tracking is a powerful independent predictor of mortality in patients with preserved ejection fraction, incremental to common clinical and imaging risk factors.
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Ejection fraction is the principal parameter used clinically to assess cardiac mechanics. It is frequently used to diagnose myocardial dysfunction and provides prognostic information. However, echocardiographic strain imaging has shown that significant abnormalities of myocardial deformation may be present despite preserved ejection fraction and can be associated with an adverse

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prognosis (1,2). Cardiac magnetic resonance (CMR) feature-tracking techniques now allow assessment of strain from routinely acquired cine images, without specialized pulse sequences. We and others have shown that feature-tracking-derived global longitudinal strain (GLS) is a powerful independent predictor of adverse outcomes in patients with reduced ejection fraction (3–5).

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Whether abnormalities of strain measured by using CMR feature-tracking have prognostic value in patients with preserved ejection fraction is unknown. We hypothesized that feature-tracking-derived GLS may provide prognostic information incremental to clinical and CMR-derived parameters in this patient group. The aim of the current study therefore was to evaluate the prognostic value of GLS derived from CMR feature-tracking in a large multicenter population of patients with preserved ejection fraction undergoing CMR.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

GLS = global longitudinal strain

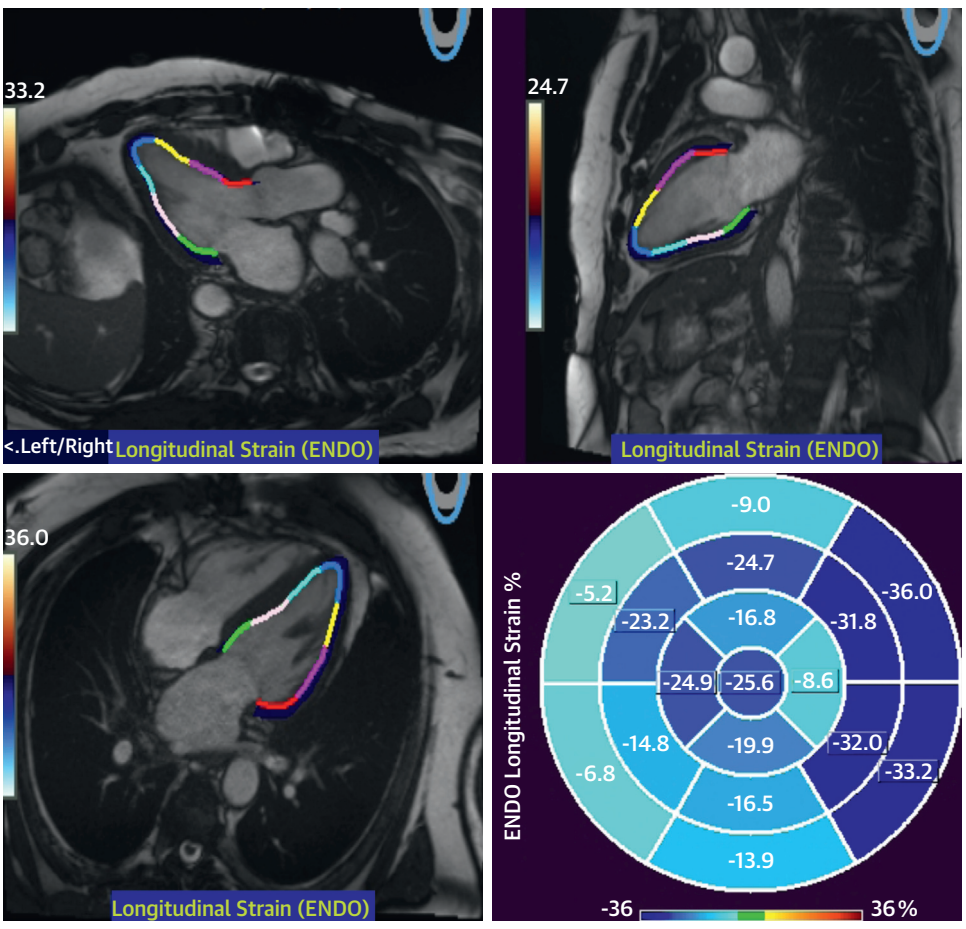
LGE = late gadolinium enhancement

LV = left ventricular

METHODS

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

FIGURE 1 Measurement of GLS



Endocardial (ENDO) left ventricular contours were manually traced in all 3 long-axis cine views to derive 2-dimensional global longitudinal strain (GLS) by using the QStrain package. GLS in this patient was -16.5%.

TABLE 1 Baseline Characteristics of Study Population Stratified According to GLS Above and Below the Median (-20%)

	Total	GLS < Median	GLS ≥ Median	p Value
Clinical history				
Age, yrs	57.1 ± 15.9	56.6 ± 16.0	57.5 ± 15.8	0.287
Male	53.5	48.2	58.9	<0.001
BMI, kg/m^2	28.8 ± 8.0	28.6 ± 6.4	28.9 ± 9.4	0.504
Diabetes	19.2	17.6	20.9	0.139
Hyperlipidemia	41.5	42.7	40.3	0.375
Hypertension	57.0	54.8	59.7	0.074
Smoking	5.7	5.5	5.8	0.808
History of MI	5.7	5.2	6.2	0.466
Aspirin	42.3	40.3	44.2	0.175
Statin	37.4	37.8	36.9	0.753
ACE inhibitor	26.4	25.6	27.3	0.494
Beta-blocker	22.5	20.8	24.1	0.176
CMR variables				
Heart rate, beats/min	71.8 ± 13.9	70.3 ± 13.1	73.4 ± 14.5	<0.001
Systolic BP, mm Hg	133 ± 20	133 ± 19	133 ± 21	0.644
Diastolic BP, mm Hg	75 ± 23	74 ± 11	76 ± 31	0.060
LA volume	50.9 ± 40.0	49.9 ± 34.2	51.8 ± 44.0	0.383
LVEDV index, ml/m^2	60.6 ± 19.7	61.5 ± 19.6	59.8 ± 19.8	0.118
LVESV index, ml/m^2	22.1 ± 11.4	20.7 ± 11.0	23.4 ± 11.8	<0.001
LVEF, %	63.0 ± 6.6	64.6 ± 6.6	61.3 ± 6.1	<0.001
LGE present	18.4	14.3	22.4	<0.001
RVEDV index, ml/m^2	80.6 ± 12.7	81.6 ± 11.9	79.7 ± 13.4	0.006
RVEF, %	54.8 ± 3.2	54.9 ± 2.1	54.6 ± 3.0	0.039

Values are mean ± SD or %.

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; CMR = cardiac magnetic resonance; GLS = global longitudinal strain; LA = left atrial; LGE = late gadolinium enhancement; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume index; MI = myocardial infarction; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction.

STUDY POPULATION. Consecutive patients with preserved ejection fraction (ejection fraction ≥50%) and a clinical indication for CMR who had undergone CMR in 2011 with both cine and late gadolinium enhancement (LGE) imaging formed the study population of 1,274 patients. Exclusion criteria included uninterpretable image quality for GLS assessment, severe valvular disease, as well as hypertrophic and infiltrative cardiomyopathies (total excluded: n = 111). Baseline demographic characteristics (age, sex, body mass index, history of diabetes, hyperlipidemia, hypertension, smoking, myocardial infarction, cardiac medications) were obtained by local site investigators at the time of the clinical study. History of diabetes, hyperlipidemia, hypertension, smoking, or myocardial infarction was assessed based on documentation of the diagnosis in the electronic medical record at the time of the CMR examination.

TABLE 2 Main Indications and Suspected Diagnoses for Performance of Cardiac Magnetic Resonance Imaging

	Prevalence
Suspected myocardial involvement or cardiomyopathy	28
Known or suspected coronary artery disease	23
Known or suspected arrhythmias	13
Known or suspected aortic disease	12
Evaluation before possible ablation of atrial fibrillation	7
Known or suspected cardiac mass	6
Known or suspected valve disease	6
Others (including poor echo windows, syncope, pericardial disease, coronary anomaly, pulmonary hypertension, abnormal electrocardiogram)	5

Values are %.

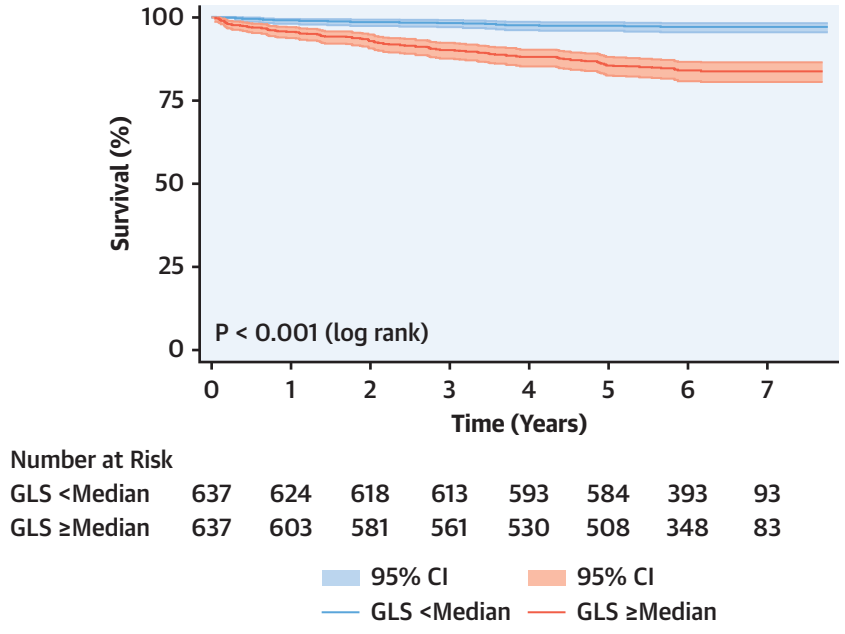
CMR ACQUISITION. Images were acquired with phased-array receiver coils according to the routine scan protocol at each site using a variety of scanners from all 3 major vendors (Siemens, Philips, and General Electric) at both 1.5- and 3-T. A typical protocol included steady-state free-precession cine 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 gadolinium contrast (0.15 mmol/kg) administration by using a 2-dimensional 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. LGE and feature-tracking GLS was assessed as described previously (3,6–10). For feature-tracking analysis, endocardial left ventricular 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 2-dimensional GLS using the QStrain package (Medis Medical Imaging Systems, Leiden, the Netherlands) (Figure 1).

FOLLOW-UP. Patients were followed up for the primary outcome of all-cause mortality using the U.S. Social Security Death Index. Time to event was calculated as the period between the CMR study and death. Patients who did not experience the primary outcome were censored at the time of assessment.

STATISTICAL ANALYSIS. Normally distributed data are expressed as mean ± SD. Differences in baseline characteristics were compared with the Student's *t*-test for continuous variables and the chi-square test for dichotomous variables. Kaplan-Meier methods were used to evaluate the relationship between GLS and time to the primary outcome of all-cause

CENTRAL ILLUSTRATION **Kaplan-Meier Survival Curves**



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Stratified by global longitudinal strain (GLS) above and below the median value. CI = confidence interval.

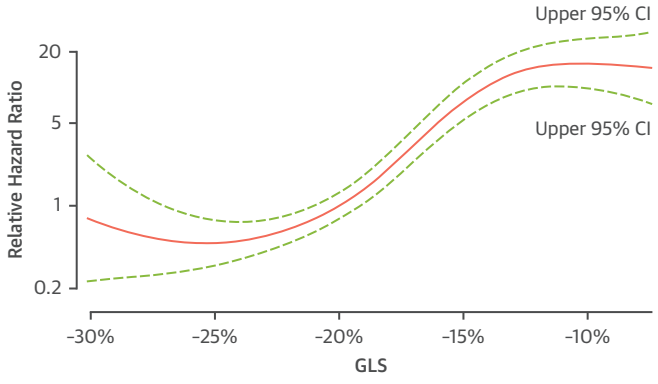
mortality. Cox proportional hazards regression modeling was used to examine the association between GLS and all-cause mortality. All models were assessed for collinearity and proportional hazards assumption. For the multivariable models, clinical and imaging risk factors that were univariate predictors (at $p \leq 0.10$) were considered as covariates.

The incremental prognostic value of GLS was assessed in nested models. Model discrimination was compared by calculating the C-index (11). Risk reclassification analyses were conducted with calculation of continuous net reclassification improvement (12). A p value <0.05 was considered statistically significant. Analyses were performed by using STATA (StataCorp, College Station, Texas).

RESULTS

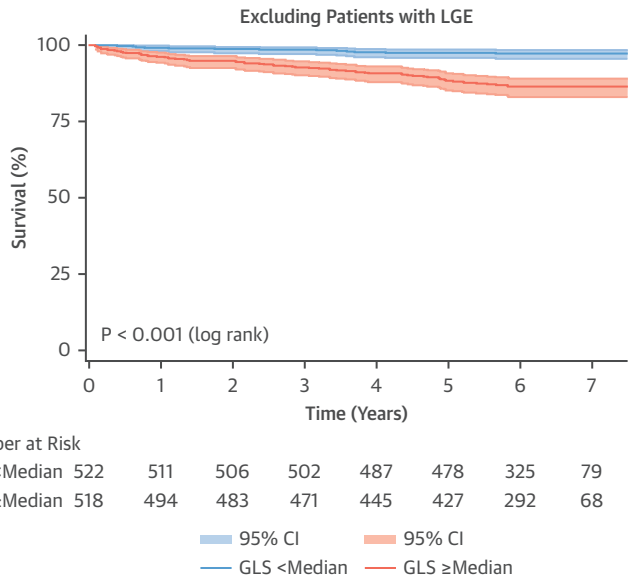
PATIENT CHARACTERISTICS. Table 1 summarizes baseline patient characteristics stratified by GLS above and below the median (-20%). The mean age of the study population was 57.1 ± 15.9 years. Fifty-three percent of patients were male, and 19% had diabetes mellitus. The mean ejection fraction was 63.0 ± 6.6%, and LGE was present in 18.4% of patients. Mean LGE extent was 1.3 ± 4.5% of the myocardium. Of the patients with LGE, 60% had an ischemic pattern (i.e., involving the subendocardium), and 40% had a nonischemic pattern (i.e., mid-myocardial or epicardial, without subendocardial involvement). Atrial fibrillation was present in 56 patients (4.4%) at the time of the CMR scan. The primary indications and suspected

FIGURE 2 **Relationship Between GLS and Hazard of Death (With 95% CIs)**



Hazard ratios are relative to those with median global longitudinal strain (GLS). CI = confidence interval.

FIGURE 3 Kaplan-Meier Survival Curves



Stratified by GLS above and below the median value for the subgroup of patients with no late gadolinium enhancement (LGE). Abbreviations as in Figure 2.

diagnoses for CMR are shown in Table 2. The most common symptoms were dyspnea (29%), chest pain (23%), and palpitations (20%).

PRIMARY OUTCOME. Of the 1,274 patients in this study, 115 died during a median follow-up of 6.2 years (interquartile range: 5.6 to 6.7 years).

OUTCOMES AND GLS. When stratified according to the median value of GLS (-20%), Kaplan-Meier analysis showed a significantly increased risk of death in those with GLS ≥ median (log-rank test, $p < 0.001$) (Central Illustration). The continuous relationship between GLS and the hazard of death is shown in the cubic spline in Figure 2.

In addition, among the subgroup of patients without LGE (n = 1,040; 80 deaths), Kaplan-Meier analysis similarly showed a significantly increased risk of death in those with GLS ≥ median (log-rank test, $p < 0.001$) (Figure 3).

MULTIVARIABLE ANALYSIS AND INCREMENTAL PROGNOSTIC VALUE. After multivariate adjustment for clinical and imaging risk factors (age, body mass index, diabetes, hypertension, heart rate, diastolic blood pressure, left ventricular end-diastolic volume index, left ventricular ejection fraction, left atrial volume, LGE, right ventricular ejection fraction), GLS remained a significant independent predictor of death (hazard ratio: 1.228; $p < 0.001$); that is, each 1% worsening in GLS was associated with a 22.8% increased risk of death (Table 3). In sequential nested Cox models, a model based on clinical variables alone (age, body mass index, diabetes, hypertension, heart rate, and diastolic blood pressure) was significantly improved by the addition of imaging variables (left ventricular end-diastolic volume index, left ventricular ejection fraction, left atrial volume, LGE, right ventricular ejection fraction), and further significantly improved by adding GLS (Figure 4). Addition of GLS into the model with clinical and imaging predictors resulted in a significant increase in the C-statistic (from 0.75 to 0.83; $p < 0.001$) and a significant increase in the model chi-square value (from 94 to 183; $p < 0.001$). This finding was associated with a significant integrated discrimination improvement of 0.134 (95% confidence interval: 0.078 to 0.199) and a continuous net reclassification improvement of 0.916 (95% confidence interval: 0.753 to 1.152).

In addition, among the subgroup of patients without LGE, GLS remained a significant independent predictor of death (hazard ratio: 1.212; $p < 0.001$) after adjustment for clinical and imaging risk factors (age, body mass index, diabetes, heart rate, and left ventricular ejection fraction) (Table 4).

DISCUSSION

This study shows that feature-tracking GLS is a powerful independent predictor of mortality in a large multicenter population of patients with preserved ejection fraction undergoing CMR. We found that GLS provides prognostic information incremental to common clinical and CMR risk factors, including LGE. These findings highlight the importance of

TABLE 3 Multivariable Model for Death in Overall Population

	Multivariable Model for Death	
	HR (95% CI)	p Value
Age	1.031 (1.016–1.046)	<0.001
BMI	0.950 (0.915–0.985)	0.006
Diabetes	1.461 (0.934–2.287)	0.097
Hypertension	1.140 (0.742–1.751)	0.550
Heart rate	1.011 (0.998–1.024)	0.107
Diastolic BP	0.988 (0.973–1.003)	0.127
LVEDV index	0.999 (0.988–1.010)	0.834
LGE	1.319 (0.857–2.030)	0.207
LVEF	0.999 (0.968–1.031)	0.938
LA volume	1.000 (0.997–1.003)	0.912
RVEF	0.969 (0.927–1.014)	0.176
GLS	1.228 (1.178–1.280)	<0.001

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

long-axis function and suggest a role for feature-tracking GLS in identifying patients at the highest risk of death, despite a preserved ejection fraction.

MYOCARDIAL CONTRACTION AND LONG-AXIS FUNCTION. Long-axis function plays a fundamental role in cardiac mechanics. It is well known that the outer contour volume of the heart remains relatively constant throughout the cardiac cycle, with the apex remaining still as the mitral annulus moves longitudinally (13). This action results in reciprocal filling and emptying of the ventricles and atria, such that filling of one chamber occurs at the expense of emptying of the other.

Longitudinal movement of the mitral annulus is the major driver of ventricular ejection and atrial filling. Since the outer contour of the heart remains relatively constant, movement of the annulus in systole results not just in shortening of ventricular length but also increase in wall thickness (radial wall thickening) due to conservation of myocardial volume (14).

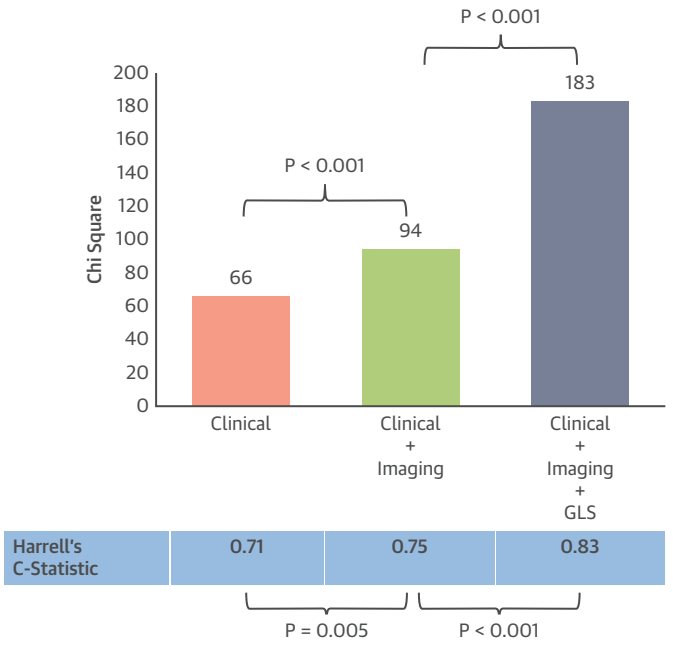
EJECTION FRACTION AND SUBCLINICAL LONG-AXIS DYSFUNCTION. Ejection fraction is a simple global measure reflecting the combined function of both longitudinal and circumferential fibers, without the ability to distinguish between these components. Possibly because of their subendocardial location, the more longitudinal myocardial fibers seem to be exquisitely sensitive to disturbance by various pathologies, and mitral annular motion is very rapidly reduced by ischemia in experimental models (15). This may relate to the presence of greater compressive forces and higher oxygen consumption in the subendocardium (16–19).

Thus, in the early stages of many cardiac diseases, impairment in longitudinal function seems to precede reduction in circumferential contraction, giving rise to subclinical impairment of left ventricular function despite preserved ejection fraction. Early compensatory increase in circumferential function helps maintain ejection fraction despite significantly impaired longitudinal function (2).

In the current study, we showed that reduction of long-axis function as detected by GLS is a powerful independent predictor of mortality in patients with preserved ejection fraction. This occurs possibly because it is an early marker of subclinical pathological processes affecting the subendocardial longitudinal fibers.

CMR FEATURE-TRACKING GLS AND PROGNOSIS. There is a growing body of literature describing the prognostic value of feature-tracking GLS in patients with reduced ejection fraction and heart failure (3–5,20). In a large (N = 1,012) multicenter population of patients with ischemic and nonischemic cardiomyopathy, it was shown that GLS derived from feature-tracking is a powerful independent predictor of mortality, incremental to common clinical and CMR risk factors, including ejection fraction and LGE (4). Buss et al. (5) likewise showed that GLS derived from feature-tracking was an independent predictor of the composite endpoint of cardiac death, heart transplantation, and aborted sudden cardiac death in

FIGURE 4 Sequential Nested Cox Models for Death



A model based on clinical variables alone (age, body mass index, diabetes, hypertension, heart rate, and diastolic blood pressure) was significantly improved by addition of imaging variables (left ventricular end-diastolic volume index, left ventricular ejection fraction, left atrial volume, late gadolinium enhancement, right ventricular ejection fraction). It was further significantly improved by adding global longitudinal strain (GLS).

TABLE 4 Multivariable Model for Death in Patients Without LGE

	Multivariable Model for Death	
	HR (95% CI)	p Value
Age	1.039 (1.022–1.056)	<0.001
BMI	0.938 (0.899–0.979)	0.004
Diabetes	1.504 (0.891–2.540)	0.127
Heart rate	1.008 (0.993–1.023)	0.282
LVEF	0.998 (0.959–1.037)	0.901
GLS	1.212 (1.157–1.270)	<0.001

Abbreviations as in Tables 1 and 3.

a single-center population of 210 patients with dilated nonischemic cardiomyopathy. In a small population of selected patients with heart failure and preserved ejection fraction, Kammerlander et al. (21) reported an association between feature-tracking GLS and a composite endpoint of heart failure hospitalization and cardiovascular death.

Feature-tracking GLS also seems to provide prognostic value after a myocardial infarction. Eitel et al. (22) reported on the incremental prognostic value of feature-tracking GLS early after reperfused myocardial infarction in 1,235 patients (ST-segment elevation myocardial infarction: n = 760; non-ST-segment elevation myocardial infarction: n = 347) from multiple sites across Germany. Similarly, in a single-center study, Gavara et al. (23) showed that feature-tracking GLS was associated with a composite outcome of cardiac death, heart failure hospitalization, and reinfarction in 323 patients post-ST-segment elevation myocardial infarction.

The current study extends these previous observations by showing that feature-tracking GLS is also a powerful independent predictor of mortality in patients with preserved ejection fraction. Ultimately, better identification of high-risk patients may allow closer follow-up and more directed therapies to be applied. How this information will affect clinical care requires further investigation, and future studies are warranted to explore the role of feature-tracking GLS in clinical decision-making. These studies will need to show that imaging-driven patient management improves specific outcomes before such an approach could be advocated.

STUDY LIMITATIONS. Although this is a multicenter study, the patients described in the current paper may not be representative of all patients with preserved ejection fraction in the community. Because this is a CMR study, there is selection bias related to being able to undergo a CMR examination, resulting in exclusion of patients with large body size, severe renal impairment, severe claustrophobia, or those with pacemakers and implantable cardioverter-defibrillators.

Information about downstream cardiovascular resource utilization such as revascularization, implantable cardioverter-defibrillator implantation, or cardiac surgery was not available. However, this does not detract from the main findings of this study, that feature-tracking GLS is a powerful predictor of death in these patients, independent of common clinical and imaging markers available at the time of CMR. Follow-up data 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 unbiased and clinically relevant, which is often not the case for other cardiac outcomes such as revascularization or hospitalization (1,24,25). Use of cardiac death instead of all-cause death as an endpoint can be problematic for many reasons because data obtained from death certificates or from medical records are limited, biased, and not necessarily accurate. In addition, determination of cause of death is often difficult due to multiple comorbidities, low autopsy rates, and poor understanding of complex diseases (25). We therefore believe that all-cause mortality is a very important and valid primary endpoint for this study.

It can be argued that, unsurprisingly, left ventricular ejection fraction was of limited prognostic value in this study because, by design, this was a group of patients with preserved ejection fraction only. Although 23% of patients were undergoing CMR for evaluation of known or suspected coronary artery disease, information regarding the proportion of patients with non-ST-segment elevation versus ST-segment elevation myocardial infarction was not available. Moreover, patients in this study did not systematically undergo coronary angiography. Therefore, accurate and detailed information about the presence or absence of coronary artery disease was not available. A priori, this analysis was not designed as a study of patients with heart failure. Thus, details such as clinical heart failure status, heart failure hospitalization, B-type natriuretic peptide, and right heart catheterization were not systematically assessed or available.

T1 mapping techniques were not clinically widely available at the time of CMR image acquisition and therefore could not be performed on these clinical scans across multiple sites with different vendors and field strengths.

CONCLUSIONS

In this large multicenter study, feature-tracking GLS was a significant independent predictor of mortality in patients with preserved ejection fraction, incremental to common clinical and imaging risk factors. Each 1% worsening in GLS was associated with a 22.8% increased risk of death after adjustment for clinical and imaging risk factors. A major strength of these findings is that they were made in a multicenter group of patients with a large number of hard events (n = 115), which greatly increases the robustness of the results. Importantly, GLS remained an

independent predictor of death even in the subgroup of patients without LGE, potentially allowing early identification of patients at highest risk.

Our findings highlight the importance of long-axis function and suggest that consideration may be given to measurement of GLS even in those with preserved ejection fraction. Further studies are needed to explore the role of feature-tracking GLS in clinical decision-making in these patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this multicenter study, feature-tracking GLS measured during cine CMR was a significant independent predictor of mortality in patients with preserved ejection fraction and a clinical indication for CMR, incremental to common clinical and imaging risk factors.

TRANSLATIONAL OUTLOOK: How this information will affect clinical care requires further investigation, and future studies are warranted to explore the role of CMR-derived feature-tracking GLS in clinical decision-making.

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