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ORIGINAL RESEARCH

# Cardiac Magnetic Resonance Feature Tracking Global Longitudinal Strain and Prognosis After Heart Transplantation

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## ABSTRACT

**OBJECTIVES** This study determined the long-term prognostic significance of GLS assessed using CMR-FT in a large cohort of heart transplant recipients.

**BACKGROUND** In heart transplant recipients, global longitudinal strain (GLS) assessed using echocardiography has shown promise in the prediction of clinical outcomes. We hypothesized that CMR feature tracking (CMR-FT) GLS is independently associated with long-term outcomes in heart transplant recipients.

**METHODS** In a cohort of consecutive heart transplant recipients who underwent routine CMR for clinical surveillance, CMR-FT GLS was calculated from 3 long-axis cine CMR images. Associations between GLS and a composite endpoint of death or major adverse cardiac events (MACE), including retransplantation, nonfatal myocardial infarction, coronary revascularization, and heart failure hospitalization, were investigated.

**RESULTS** A total of 152 heart transplant recipients (age 54 ± 15 years; 29% women; 5.0 ± 5.4 years after heart transplantation) were included. The median GLS was −11.6% (interquartile range: −13.6% to −9.2%). Over a median follow-up of 2.6 years, 59 recipients reached the composite endpoint. On Kaplan-Meier analyses, recipients with GLS worse than the median had a higher estimated cumulative incidence of the composite endpoint compared with recipients with GLS better than the median (log rank $p = 0.004$). On multivariate Cox proportional hazards regression, GLS was independently associated with the composite endpoint after adjustment for cardiac allograft vasculopathy, history of rejection, left ventricular ejection fraction (LVEF), right ventricular EF, and presence of myocardial fibrosis, with a hazard ratio of 1.15 for every 1% worsening in GLS (95% confidence interval: 1.06 to 1.24; $p < 0.001$). Similar results were seen in subgroups of recipients with LVEF >50% and with no myocardial fibrosis. GLS provided incremental prognostic value over other variables in the multivariate model as determined by the log-likelihood chi-squared test.

**CONCLUSIONS** In a large cohort of heart transplant recipients, CMR-FT GLS was independently associated with the long-term risk of death or MACE. (J Am Coll Cardiol Img 2020;13:1934–42) © 2020 by the American College of Cardiology Foundation.

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In appropriately selected patients, heart transplantation improves survival and provides a favorable quality of life (1). Heart transplantation outcomes have significantly improved because of advances in immunosuppressive therapy and the management of complications. However, cardiac allograft vasculopathy (CAV) and allograft failure continue to be frequent causes of late morbidity, death, and retransplantation (1).

Recently, assessment of myocardial mechanics using echocardiographic strain imaging has shown promise in predicting clinical outcomes in heart transplant recipients (2–7). Cardiac magnetic resonance (CMR) is increasingly used in heart transplant recipients because of its ability to characterize myocardial tissue, particularly the detection of myocardial fibrosis by using late gadolinium enhancement (LGE). Recent developments in CMR feature tracking (CMR-FT) techniques now allow the assessment of strain by using standard cine CMR images with no specialized pulse sequences or complex post-processing (8). CMR-FT-derived global longitudinal strain (GLS) has been shown to have prognostic value in patients with ischemic and nonischemic cardiomyopathies incremental to left ventricular ejection fraction (LVEF) and LGE (9,10).

Whether CMR-FT GLS is independently associated with long-term adverse cardiac outcomes in heart transplant recipients has not been studied. Therefore, this study sought to determine the independent prognostic significance of CMR-FT GLS in a large consecutive cohort of heart transplant recipients with long-term follow-up. The hypothesis of this study was that CMR-FT GLS is associated with a higher risk of long-term cardiovascular events after heart transplantation.

## METHODS

**PATIENTS.** Consecutive adult heart transplant recipients were included who underwent CMR for surveillance between January 2004 and December 2017 at the University of Minnesota (Minneapolis, Minnesota). To identify the study patients, the institutional heart transplant database was cross-matched with the University of Minnesota Cardiovascular Magnetic Resonance Registry (11–15). For recipients with multiple CMRs, the earliest one was included. This retrospective cohort study was approved by the University of Minnesota's Institutional Review Board with a waiver of informed consent.

**BASELINE MEASUREMENTS.** Demographic data, medical history, co-morbidities, and outcomes data blinded to CMR data were collected. CAV and rejection were defined according to the nomenclature recommended by the International Society for Heart and Lung Transplantation (16,17).

**CMR PROTOCOL.** CMR was performed using clinical 1.5-T Avanto or Aera scanner (Siemens, Malvern, Pennsylvania), using phased array receiver coils according to standard recommendations. A typical protocol included steady-state free precession cine CMR images acquired in the short axis (every 10 mm to cover the entire LV from the mitral valve plane through the apex) and 3 long-axis views (2-, 3-, and 4-chamber). Typical cine CMR parameters consisted of repetition times of 3.0 to 3.5 ms; echo times of 1.2 to 1.5 ms; in-plane spatial resolution of 1.8 × 1.4 mm; and temporal resolutions of 35 to 40 ms. Standard LGE CMR imaging was performed 10 to 15 min after the patient received gadolinium contrast (0.15 mmol/kg), using a 2-dimensional (2D) segmented inversion recovery gradient-echo sequence in views identical to cine CMR imaging. Typical LGE CMR parameters consisted of inversion time set to null viable myocardium, typically 280 to 360 ms; in-plane spatial resolution of 1.8 × 1.5 mm; temporal resolution of 180 to 200 ms; and a slice thickness of 6 mm. The same CMR protocol was used during the entire study period.

**CMR ANALYSES.** CMRs were reinterpreted and analyzed for this study, blinded to all other patient data. LV and right ventricular (RV) ejection fractions (LVEF and RVEF) were determined by quantitative analysis according to standard recommendations (18). For CMR-FT analysis, a single expert physician

**ABBREVIATIONS AND ACRONYMS**

**CAV** = cardiac allograft vasculopathy

**CMR** = cardiac magnetic resonance

**EDVI** = end-diastolic volume index

**ESVI** = end-systolic volume index

**FT** = feature tracking

**GLS** = global longitudinal strain

**LGE** = late gadolinium enhancement

**LV** = left ventricular

**LVEF** = left ventricular ejection fraction

**MACE** = major adverse cardiovascular event(s)

**RV** = right ventricle

**RVEF** = right ventricular ejection fraction

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Imaging* author instructions page.

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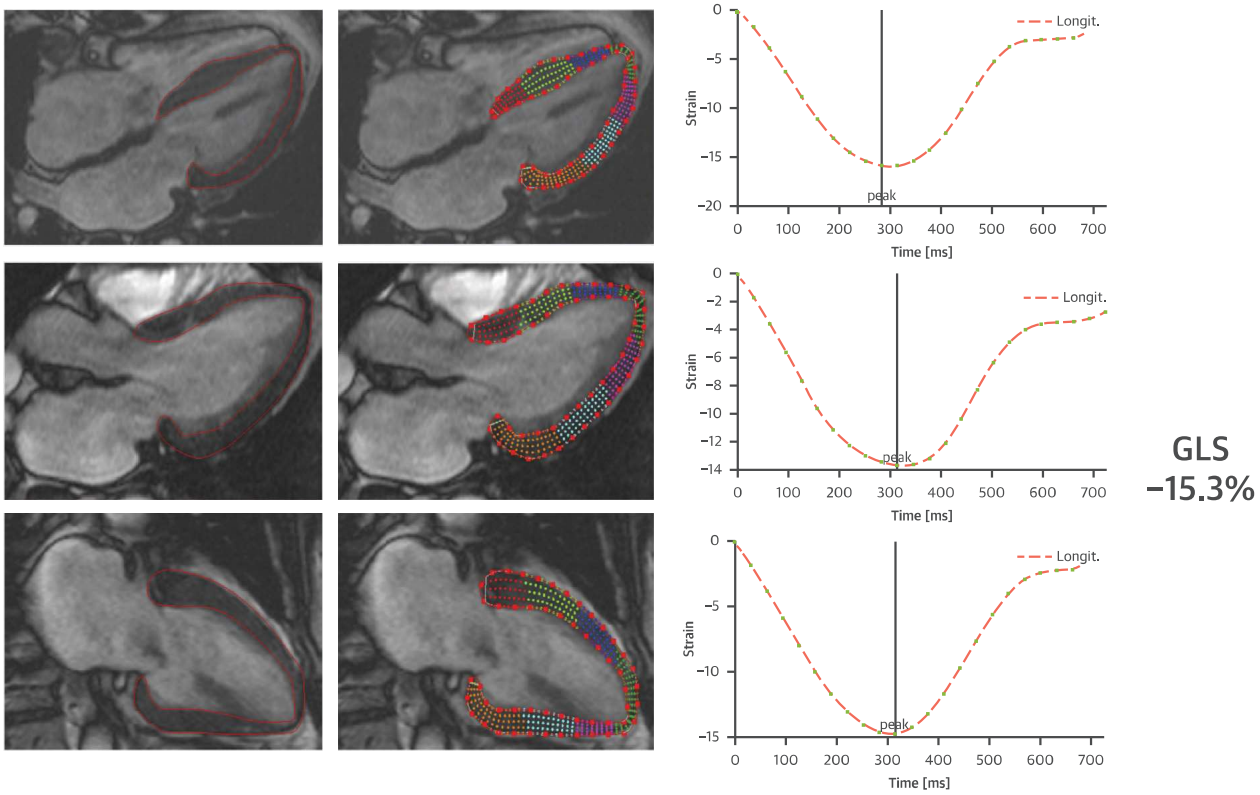
**FIGURE 1 Measurement of CMR-FT GLS**




Endo-cardial and epicardial LV contours were manually traced in all 3 long-axis cine views to derive GLS. GLS in this recipient was −15.3%. CMR-FT = cardiac magnetic resonance feature tracking; GLS = global longitudinal strain; LV = left ventricle.

blinded to all other patient data manually traced the LV endo- and epicardial borders at end-diastole in all 3 long-axis cine views (2-, 3-, and 4-chamber views) to derive GLS by using Segment CMR software (Medviso AB, Lund, Sweden) (Figure 1). The GLS value was provided by the software by integrating data from all 3 long-axis views in every patient (19). End-diastole was identified as the frame just before the closure of the mitral valve. For LGE analysis, the investigators first identified the presence or absence of focal myocardial fibrosis based on visual assessment. For patients with myocardial fibrosis, the extent was quantified using the full-width-at-half-maximum method and expressed as a percentage of the LV myocardial mass (18,20).

**CLINICAL FOLLOW-UP AND OUTCOMES.** Follow-up data were collected through a review of electronic medical records blinded to CMR data. The pre-specified primary endpoint was a composite of all-cause death or major adverse cardiac events (MACE), retransplantation, nonfatal myocardial infarction, coronary revascularization, or heart failure hospitalization, during follow-up. Myocardial infarction was defined according to the Fourth Universal Definition of Myocardial Infarction (21). Mortality status and death dates were cross-checked with the Minnesota Department of Health Office of Vital Records.

**STATISTICAL ANALYSIS.** Normally distributed continuous variables were expressed as mean ± SD, and non-normally distributed continuous variables were presented as median (interquartile range [IQR]. Categorical variables were expressed as counts with percentages. Comparisons among groups were performed using a 2-sample Student's *t*-test for continuous, normal variables, and a Mann-Whitney rank sum *U* test for continuous, non-normal data. Pearson chi-squared tests were used to compare discrete data among groups. In those cases where the expected cell count was <5, the Fisher exact test was used. Intra-observer variability for GLS was assessed in a random sample of 30 patients. Kaplan-Meier analyses and

**TABLE 1 Patient Characteristics at the Time of CMR for All Recipients and Stratified Using Median GLS**

| | All Recipients (N = 152) | GLS Worse Than Median (n = 76) | GLS Better Than Median (n = 76) | p Value |
|---|---|---|---|---|
| Demographics | | | | |
| Age, yrs | 54.2 ± 15.2 | 53.2 ± 14.8 | 55.3 ± 15.7 | 0.39 |
| Women | 44 (28.9) | 18 (23.7) | 26 (34.2) | 0.15 |
| Time since transplantation, yrs | 5.0 ± 5.4 | 5.3 ± 5.2 | 4.8 ± 5.5 | 0.58 |
| Transplantation indication | | | | |
| Ischemic cardiomyopathy | 53 (34.9) | 32 (42.1) | 21 (27.6) | 0.06 |
| Comorbidities | | | | |
| Body mass index, kg/m$^2$ | 26.6 (23.5–30.2) | 26.5 (23.8–29.6) | 26.7 (23.4–30.9) | 0.97 |
| Hypertension | 95 (62.5) | 52 (68.4) | 43 (56.6) | 0.13 |
| Diabetes mellitus | 54 (35.5) | 30 (39.5) | 24 (31.6) | 0.31 |
| Chronic kidney disease (eGFR <60 ml/min per 1.73 m$^2$) | 65 (42.8) | 34 (44.7) | 31 (40.8) | 0.62 |
| Ischemic time, min | 224.0 ± 61.5 | 231.2 ± 63.5 | 217.0 ± 59.0 | 0.16 |
| Cardiac allograft vasculopathy | 48 (31.6) | 24 (31.6) | 24 (31.6) | 1.00 |
| History of ISHLT grade 2R or 3R cellular rejection or antibody-mediated rejection | 48 (31.6) | 31 (40.8) | 17 (22.4) | 0.015 |
| Immunosuppressant medications | | | | |
| Tacrolimus | 114 (75.0) | 55 (72.4) | 59 (77.6) | 0.46 |
| Sirolimus/everolimus | 28 (18.4) | 13 (17.1) | 15 (19.7) | 0.68 |
| Cyclosporine | 26 (17.1) | 13 (17.1) | 13 (17.1) | 1.00 |
| Mycophenolate mofetil | 123 (80.9) | 61 (80.3) | 62 (81.6) | 0.84 |
| Azathioprine | 9 (5.9) | 4 (5.3) | 5 (6.6) | 0.73 |
| Prednisone | 44 (28.9) | 23 (30.3) | 21 (27.6) | 0.72 |
| Other cardiac medications | | | | |
| Aspirin | 132 (86.8) | 67 (88.2) | 65 (85.5) | 0.63 |
| Statin | 129 (84.9) | 62 (81.6) | 67 (88.2) | 0.26 |
| ACE inhibitor/ARB | 69 (45.4) | 37 (48.7) | 32 (42.1) | 0.42 |
| Beta-blocker | 26 (17.1) | 18 (23.7) | 8 (10.5) | 0.032 |
| Calcium-channel blocker | 46 (30.3) | 22 (28.9) | 24 (31.6) | 0.72 |
| CMR findings | | | | |
| LVEDVI, ml/m$^2$ | 53.8 (44.4–61.8) | 52.2 (42.5–59.3) | 56.1 (47.2–62.8) | 0.020 |
| LVESVI, ml/m$^2$ | 22.3 (17.7–27.8) | 23.4 (18.0–30.6) | 22.0 (17.8–26.1) | 0.30 |
| LVEF, % | 56.4 (50.1–62.2) | 53.0 (44.4–58.9) | 59.0 (56.1–63.3) | <0.001 |
| RVEDVI, ml/m$^2$ | 50.6 (44.3–59.8) | 47.4 (39.6–60.1) | 52.4 (46.5–59.7) | 0.010 |
| RVESVI, ml/m$^2$ | 23.0 (18.2–28.4) | 23.5 (17.6–32.2) | 22.5 (18.8–26.8) | 0.53 |
| RVEF, % | 55.6 (47.0–60.5) | 48.9 (41.9–57.7) | 58.1 (53.8–62.2) | <0.001 |
| Myocardial fibrosis presence | 27 (17.8) | 19 (25.0) | 8 (10.5) | 0.020 |
| Extent of myocardial fibrosis | 2.2 (6.2) | 3.6 (8.0) | 0.7 (3.0) | 0.004 |

Values are mean ± SD, n (%), median (interquartile range).

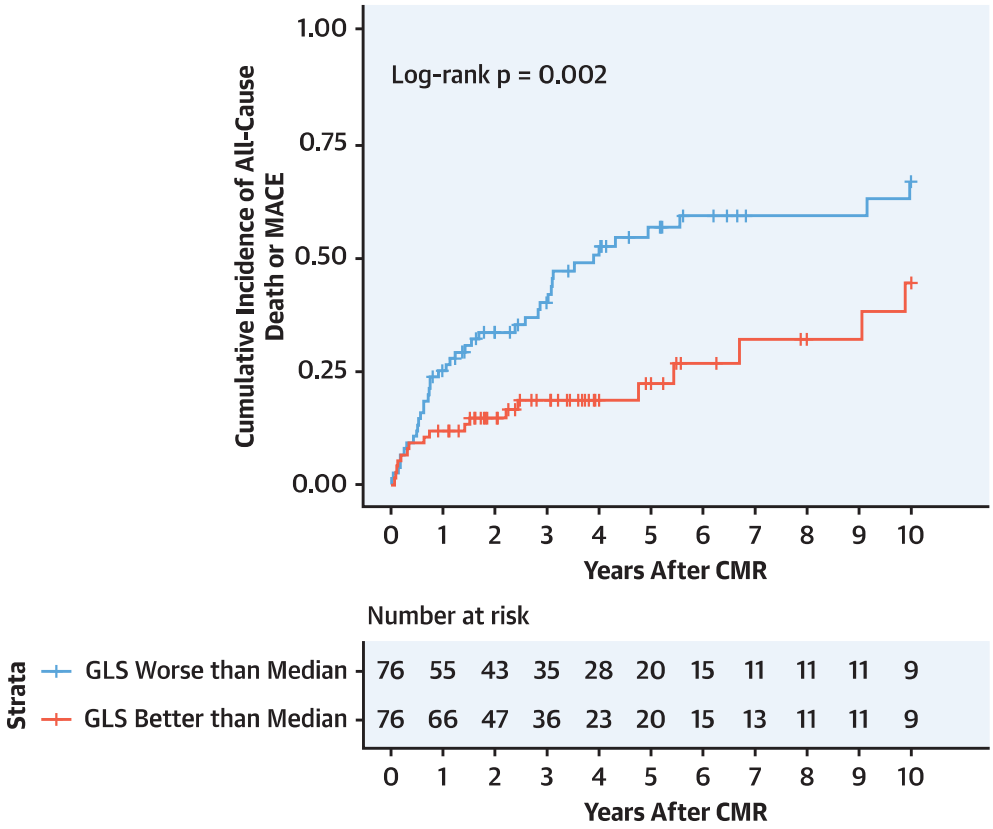
ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CI = confidence interval; CMR = cardiac magnetic resonance; EDVI = end-diastolic volume index; eGFR = estimated glomerular filtration rate; EF = ejection fraction; ESVI = end-systolic volume index; ISHLT = International Society for Heart and Lung Transplantation; IQR = interquartile range; LV = left ventricle; RV = right ventricle.

unadjusted and adjusted Cox proportional hazards regression analyses were used to assess relationships between clinical and imaging variables and all-cause death or MACE. The assumption of proportional hazards was assessed by plotting the scaled Schoenfeld residuals for each independent variable against time. These correlations were nonsignificant for all variables included in the multivariate models. To test the incremental prognostic value of GLS, the final model was compared with a model in which GLS was not included, using the likelihood ratio test. All tests were 2-tailed. A p value of <0.05 was used to denote statistical significance. Analyses were performed using R version 3.4 software (R Foundation, Vienna, Austria).

## RESULTS

**OVERALL PATIENT CHARACTERISTICS.** Table 1 lists the patient characteristics at the time of the index CMR. A total of 152 transplant recipients were included in the study. The mean time from cardiac transplant to CMR was 5.0 years, and the median was 3.1 years. Comorbidities were common (62%

**CENTRAL ILLUSTRATION** **Kaplan-Meier Cumulative Incidence Curves**




**Shenoy, C. et al. J Am Coll Cardiol Img. 2020;13(9):1934–42.**

Cumulative incidence curves comparing all-cause death or MACE among heart transplant recipients with GLS worse than the median **(blue)** and GLS better than the median **(red).** The log-rank p value was 0.002. Each **vertical tick** on the curves displays a censored patient. CMR = cardiac magnetic resonance; GLS = global longitudinal strain; MACE = major adverse cardiac event(s).

hypertension, 35% diabetes mellitus, and 42% chronic kidney disease [glomerular filtration rate: <60 ml/min/1.73 $m^2$]). A total of 32% had CAV, and 32% had a history of either International Society for Heart and Lung Transplantation grade 2R or 3R cellular or antibody-mediated rejection. Mycophenolate mofetil and tacrolimus were commonly used among the varied immunosuppression regimens. Aspirin and statins were also frequently used.

**CMR FINDINGS.** The median LVEFs and RVEFs were >55% (Table 1). The median GLS was −11.6% (IQR: −13.6% to −9.2%). Bland-Altman analysis of intraobserver variability for GLS showed a bias of 0.05%. The 95% limits of agreement were −0.44% and 0.53%, respectively.

Recipients with GLS worse than the median were more likely to have a history of rejection and use beta-blockers compared with recipients with GLS better than the median. On CMR, recipients with GLS worse than the median were more likely to have lower LVEFs, lower RVEFs, and a higher prevalence of myocardial fibrosis than recipients with GLS better than the median.

Myocardial fibrosis was detected in 27 recipients (18%): infarct pattern (subendocardial or transmural) in 10 (37%), noninfarct pattern (mid-myocardial or subepicardial) in 11 (41%), and both in 6 (22%). The mean extent of the myocardial fibrosis was 12.2%, and the median was 9.7%.

**ASSOCIATION OF GLS WITH ALL-CAUSE DEATH OR MACE.** Follow-up data were available for all recipients. A total of 59 recipients (38.8%) experienced all-cause death or MACE over a median follow-up of 2.6 years (IQR: 1.3 to 5.2 years). The individual outcomes were death in 36 (23.7%), retransplantation in 7 (4.6%), nonfatal myocardial infarction in 1 (0.7%),

**TABLE 2 Cox Multivariable Proportional Hazards Modeling for Death or MACE in All Recipients (N = 152)**

| | Model 1* | | Model 2† | |
|---|---|---|---|---|
| | Hazard Ratio (95% CI) | p Value | Hazard Ratio (95% CI) | p Value |
| Cardiac allograft vasculopathy | 1.46 (0.80–2.65) | 0.22 | 1.59 (0.87–2.92) | 0.13 |
| History of ISHLT grade 2R or 3R cellular rejection or antibody-mediated rejection | 0.79 (0.44–1.42) | 0.43 | 0.75 (0.41–1.38) | 0.36 |
| LVEF per 1% decrease | 0.98 (0.95–1.01) | 0.10 | 0.97 (0.94–1.00) | 0.07 |
| RVEF per 1% decrease | 1.04 (1.01–1.08) | 0.007 | 1.04 (1.01–1.07) | 0.011 |
| Presence of myocardial fibrosis | 2.15 (1.15–4.05) | 0.017 | - | - |
| Extent of myocardial fibrosis per 1% increase | - | - | 1.03 (0.99–1.06) | 0.13 |
| GLS worsening per 1% worsening | 1.15 (1.06–1.24) | <0.001 | 1.14 (1.05–1.24) | 0.002 |

*Model 1 included the presence of myocardial fibrosis as a binary variable. †Model 2 included the extent of myocardial fibrosis as a continuous variable.
GLS = global longitudinal strain; other abbreviations as in Table 1.

coronary revascularization in 17 (11.2%), and heart failure hospitalization in 28 (18.4%). Kaplan-Meier analyses stratified by the median GLS showed a significantly higher estimated cumulative incidence of all-cause death or MACE in recipients with GLS worse than the median, compared with recipients with GLS better than the median (log-rank p = 0.002) (Central Illustration).

In multivariable analyses (Table 2), including CAV, history of rejection, LVEF, RVEF, GLS as a continuous variable, and either the presence of myocardial fibrosis (model 1) or the extent of myocardial fibrosis (model 2), GLS was independently associated with all-cause death or MACE in both models. The hazard ratios were 1.15 (95% confidence interval [CI]: 1.06 to 1.24; p < 0.001) and 1.14 (95% CI: 1.05 to 1.24; p = 0.002) respectively, showing that the risk of all-cause death or MACE increased by 14% to 15% for every 1% worsening in GLS.

**INCREMENTAL PROGNOSTIC VALUE.** The addition of GLS to a Cox model that included CAV, history of rejection, LVEF, RVEF, and either the presence of myocardial fibrosis or the extent of myocardial fibrosis resulted in a significantly improved model fit as assessed by using the likelihood ratio test (p < 0.001 for both comparisons).

**SUBGROUP ANALYSES.** In a subgroup analysis of recipients with LVEF >50% (n = 114) (Table 3), GLS was independently associated with all-cause death or MACE after adjustment for CAV, history of rejection, RVEF, and either the presence of myocardial fibrosis (model 3) or the extent of myocardial fibrosis (model 4) with hazard ratios of 1.20 (95% CI: 1.09 to 1.31; p < 0.001) and 1.19 (95% CI: 1.07 to 1.33; p = 0.001), respectively.

In a second subgroup analysis of recipients without myocardial fibrosis (n = 125) (Table 4), GLS was again independently associated with all-cause death or MACE after adjustment for CAV, history of rejection, LVEF, and RVEF, with a hazard ratio of 1.22 (95% CI: 1.10 to 1.34; p < 0.001).

## DISCUSSION

In a large cohort study of 152 heart transplant recipients, CMR-FT GLS was independently associated with long-term death or MACE after adjustment for known clinical and imaging predictors. There was an incremental prognostic value for GLS over known clinical and imaging predictors of long-term clinical outcomes after heart transplantation. The association was also noted in subgroups of recipients with LVEF >50% and no myocardial fibrosis, showing that GLS has prognostic value even in recipients without functional or structural abnormalities by well-established criteria. These findings suggest a role for CMR-FT GLS in the risk stratification of heart transplant recipients.

Other markers with prognostic significance included the presence of myocardial fibrosis and RVEF. RV dysfunction has been described by measurements of echocardiography after heart transplantation (22–24), but the mechanisms of RV dysfunction after heart transplantation are poorly understood.

**ECHOCARDIOGRAPHY-DERIVED GLS IN HEART TRANSPLANT RECIPIENTS.** Prior studies have suggested an association between echocardiography-derived GLS and various adverse clinical outcomes in heart transplant recipients (3,4,6). Our findings of an independent prognostic value for CMR-FT GLS are consistent with these prior echocardiographic studies. Additionally, the prognostic value of CMR-FT GLS is shown incremental to myocardial fibrosis and quantitative LVEF, as assessed by the gold standard

**TABLE 3 Cox Multivariable Proportional Hazards Modeling for Death or MACE in Recipients With LVEF >50% (N = 114)**

| | Model 3* | | Model 4† | |
|---|---|---|---|---|
| | Hazard Ratio (95% CI) | p Value | Hazard Ratio (95% CI) | p Value |
| Cardiac allograft vasculopathy | 1.19 (0.54–2.65) | 0.67 | 1.35 (0.60–3.05) | 0.47 |
| History of ISHLT grade 2R or 3R cellular rejection or antibody-mediated rejection | 0.48 (0.22–1.06) | 0.07 | 0.46 (0.21–1.03) | 0.06 |
| RVEF per 1% decrease | 1.07 (1.02–1.11) | 0.003 | 1.06 (1.02–1.11) | 0.005 |
| Myocardial fibrosis presence | 1.95 (0.84–4.53) | 0.12 | | |
| Myocardial fibrosis extent per 1% increase | | | 1.02 (0.96–1.07) | 0.58 |
| GLS worsening per 1% worsening | 1.20 (1.09–1.31) | <0.001 | 1.19 (1.07–1.33) | 0.001 |

*Model 3 included the presence of myocardial fibrosis as a binary variable. †Model 4 included the extent of myocardial fibrosis as a continuous variable.
Abbreviations are as in Tables 1 and 3.

technique of CMR. In the authors' knowledge, there have been no studies investigating the prognostic association of CMR-derived GLS on clinical outcomes in heart transplant recipients.

**MYOCARDIAL MECHANICS IN HEART TRANSPLANT RECIPIENTS.** LVEF is a global measurement reflecting the combined function of both longitudinal and circumferential fibers, without the ability to distinguish between these components. Possibly because of their subendocardial location, longitudinal myocardial fibers seem to be exquisitely sensitive to disturbance by various pathologies (25–29). Thus, in the early stages of many myocardial diseases, longitudinal impairment appears to precede reduction in circumferential contraction, resulting in subclinical impairment of LV function despite a normal EF. Some studies suggest that an early compensatory increase in circumferential function helps maintain the LVEF despite impaired longitudinal function (30).

In heart transplant recipients, an abnormal GLS may represent an early integrated biomarker of clinical and subclinical pathologies that affect the subendocardium, such as CAV and allograft failure. These processes could adversely affect the subendocardium in various ways, for example, perfusion abnormalities, wall stress abnormalities, myocardial fibrosis, and myocardial edema, and result in myocardial contractile dysfunction manifesting as an abnormal GLS.

**TABLE 4 Cox Multivariable Proportional Hazards Modeling for Death or MACE in Recipients With No Myocardial Fibrosis (N = 125)**

| | Hazard Ratio (95% CI) | p Value |
|---|---|---|
| Cardiac allograft vasculopathy | 1.46 (0.66–3.25) | 0.35 |
| History of ISHLT grade 2R or 3R cellular rejection or antibody-mediated rejection | 0.63 (0.30–1.31) | 0.22 |
| LVEF per 1% decrease | 1.00 (0.97–1.04) | 0.83 |
| RVEF per 1% decrease | 1.04 (1.00–1.08) | 0.07 |
| GLS worsening per 1% worsening | 1.22 (1.10–1.34) | <0.001 |

Abbreviations are as in Tables 1 and 3.

**CLINICAL IMPLICATIONS.** Assessment of echocardiography-derived GLS is recommended by the European Association of Cardiovascular Imaging during routine surveillance in heart transplant recipients for the diagnosis of subclinical allograft dysfunction, and with endomyocardial biopsy to characterize and monitor an acute rejection or "global dysfunction episode" (31). The present data provide evidence to support a role for CMR-FT GLS in determining the long-term prognosis of transplant recipients. We have previously shown a prognostic role for myocardial fibrosis in heart transplant recipients (15). This study showed an independent and incremental prognostic value for CMR-FT GLS over the presence and extent of myocardial fibrosis and an independent prognostic value in a subgroup without LGE. An abnormal GLS could be an early trigger for further investigation and changes in therapy. However, prospective studies are warranted first to investigate whether such a GLS-guided strategy is associated with improved long-term outcomes. The prognostic value of CMR-FT GLS combined with data from cine, perfusion, LGE, $T_1$ mapping, and $T_2$ mapping needs to be established.

Chronic kidney disease is not uncommon among heart transplant recipients and may preclude the use of LGE CMR to detect myocardial fibrosis in some recipients due to the perceived risk of nephrogenic systemic fibrosis. CMR-FT GLS does not require administration of contrast and could help obtain prognostic information even in recipients with chronic kidney disease.

**STUDY LIMITATIONS.** This is a single-center retrospective study and is, therefore, subject to referral bias and all the limitations inherent in the study design. The long (14-year) study period resulted in heterogeneity in the referral of recipients for CMRs

and in the clinical care they received. Newer CMR techniques such as $T_1$ and $T_2$ mapping were not clinically available during the entire study period and may add prognostic information incremental to GLS. Similar to echocardiography-derived GLS, there are algorithmic differences between various CMR-FT strain software programs which may lead to differing values (32). Thus, the present findings would benefit from replication using other CMR-FT strain software programs. Studies comparing echocardiography-derived GLS and CMR-FT GLS are also warranted. Less-validated strain measurements such as global circumferential strain and global radial strain were not measured in this first study of the prognostic value of CMR-FT in heart transplant recipients. Finally, longitudinal changes in CMR-FT GLS were not investigated in this study.

## CONCLUSIONS

In a large cohort of heart transplant recipients, CMR-FT GLS was associated with the long-term risk of death or MACE after adjustment for clinical and CMR risk factors. Each 1% worsening in GLS was independently associated with a 15% increased risk of events. Importantly, CMR-FT GLS was independently associated with the long-term risk of death or MACE even in the subgroups of recipients with LVEF >50% and no myocardial fibrosis. Future studies are needed to explore the role of CMR-FT GLS-guided strategies for clinical decision making in heart transplant recipients.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In heart transplant recipients, CMR-FT GLS is associated with the long-term risk of death or MACE incrementally to clinical and CMR risk factors. This is true even in the subgroups of recipients with LVEF >50%, and no myocardial fibrosis.

**TRANSLATIONAL OUTLOOK:** Future studies are needed to explore the role of CMR-FT GLS-guided strategies for clinical decision making in heart transplant recipients.

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