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ORIGINAL RESEARCH

Prognostic Value of T1 Mapping and Feature Tracking by Cardiac Magnetic Resonance in Patients With Signs and Symptoms Suspecting Heart Failure and No Clinical Evidence of Coronary Artery Disease

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BACKGROUND: The ability of left ventricular ejection fraction (LVEF) and late gadolinium enhancement (LGE) by cardiac magnetic resonance for risk stratification in suspected heart failure is limited. We aimed to evaluate the incremental prognostic value of cardiac magnetic resonance-assessed extracellular volume fraction (ECV) and global longitudinal strain (GLS) in patients with signs and symptoms suspecting heart failure and no clinical evidence of coronary artery disease.

METHODS AND RESULTS: A total of 474 consecutive patients (57±21 years of age, 56% men) with heart failure-related symptoms and absence of coronary artery disease underwent cardiac magnetic resonance. After median follow-up of 18 months, 59 (12%) experienced the outcome of all-cause death or heart failure hospitalization (DeathCHF). In univariate analysis, cardiac magnetic resonance-assessed LVEF, LGE, GLS, and ECV were all significantly associated with DeathCHF. Adjusted for a multivariable baseline model including age, sex, LVEF and LGE, ECV, and GLS separately maintained a significant association with DeathCHF (ECV, hazard ratio [HR], 1.44 per 1 SD increase; 95% CI 1.13–1.84; P=0.003, and GLS, HR, 1.78 per 1 SD increase; 95% CI, 1.06–2.96; P=0.028 respectively). Adding both GLS and ECV to the baseline model significantly improved model discrimination (C statistic from 0.749 to 0.782, P=0.017) and risk reclassification (integrated discrimination improvement 0.046 [0.015–0.076], P=0.003; continuous net reclassification improvement 0.378 [0.065–0.752], P<0.001) for DeathCHF, beyond LVEF and LGE.

CONCLUSIONS: In patients with signs and symptoms suspecting heart failure and no clinical evidence of coronary artery disease, joint assessment of GLS and ECV provides incremental prognostic value for DeathCHF, independent of LVEF and LGE.

Key Words: cardiovascular magnetic resonance imaging ■ feature tracking ■ outcome ■ T1 mapping

Currently, left ventricular ejection fraction (LVEF)-based risk stratification plays a fundamental role in heart failure (HF) management[1] and the prognosis in patients with the absence of coronary artery disease (CAD), where an HF diagnosis may be suspected based on clinical impression.[2] Furthermore, the

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CLINICAL PERSPECTIVE

What Is New?

- The ability of left ventricular ejection fraction and late gadolinium enhancement by cardiac magnetic resonance for risk stratification in patients with signs and symptoms suspecting heart failure is limited.
- We investigated the incremental prognostic value of feature-tracking global longitudinal strain and extracellular volume by cardiac magnetic resonance in patients with signs and symptoms of heart failure and no clinical evidence of coronary artery disease.
- In patients with suspected heart failure and no clinical evidence of coronary artery disease, joint assessment of global longitudinal strain and extracellular volume provided incremental prognostic value for all-cause death and heart failure hospitalization, independent of left ventricular ejection fraction and late gadolinium enhancement.

What Are the Clinical Implications?

- Systematic combined assessment of global longitudinal strain—incremental to left ventricular ejection fraction—and extracellular volume—incremental to late gadolinium enhancement, significantly improves risk stratification in patients with signs and symptoms suspecting heart failure and no clinical evidence of coronary artery disease.
- Our findings suggest that evaluation of global longitudinal strain and extracellular volume using cardiac magnetic resonance—incremental to the evaluation of traditional imaging prognosticators—should be part of the standard of care in patients with the absence of coronary artery disease, where a heart failure diagnosis is not yet established but suspected based on clinical impression.

Nonstandard Abbreviations and Acronyms

ECV	extracellular volume
GLS	global longitudinal strain
LGE	late gadolinium enhancement

presence and extent of myocardial scar as assessed by late gadolinium enhancement (LGE) imaging have consistently demonstrated a significant association with mortality in patients with nonischemic cardiomyopathy.[3–6] However, these traditional cardiac magnetic resonance (CMR) markers may miss subtle changes in left ventricular (LV) myocardial systolic function or may be unable to capture diffuse myocardial fibrosis.

Myocardial T1 mapping and feature-tracking (FT) are novel noninvasive imaging techniques that are able to overcome these limitations. Contrast-enhanced T1 mapping can quantify diffuse myocardial fibrosis by estimating extracellular volume fraction (ECV),[7,8] and strain imaging, using FT, can assess myocardial deformation and provide prognostic information incremental to LVEF, without the need for specialized pulse sequences or extra scan time.[9–11] Previous studies have suggested that ECV by T1 mapping or global longitudinal strain (GLS) by FT-CMR may be associated with cardiac events in different patient populations.[12,13] However, the association between ECV and GLS, and whether they provide incremental prognostic value in patients with signs and symptoms suspecting—though not yet established HF—and no clinical evidence of CAD, has not been well studied. Therefore, using a retrospective cohort of patients with signs and symptoms suspecting HF and no clinical evidence of CAD, our goal was to evaluate the prognostic value of CMR-assessed ECV and GLS for death and HF hospitalization (DeathCHF) beyond established clinical and CMR markers.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

We included consecutive patients referred to undergo CMR for assessing suspected HF but without clinical evidence of CAD between May 2015 and July 2018. We included patients referred to undergo CMR specifically for assessing suspected HF but without clinical evidence of CAD. Clinical suspicion of HF was based on presenting signs or symptoms of HF, as determined by the treating physician. The main symptoms at presentation included dyspnea (46%), exercise intolerance (15%), arrhythmia (10%), orthopnea/edema/paroxysmal nocturnal dyspnea (8%), syncope (7%), abnormal ECG (7%), or other (7%). Exclusion criteria included any of the following: (1) any medical documentation of CAD (by angiography or history of myocardial infarction or any coronary intervention); (2) any imaging evidence of myocardial infarction or ischemia; (3) any history or imaging evidence of cardiac amyloidosis, cardiac sarcoidosis, hypertrophic cardiomyopathy, or Chagas disease; (4) moderate-to severe valvular heart disease; and (5) any absolute contraindications to performing CMR. The rationale for studying this patient population was bifold. First, it is a common real-world practice for

CMR to be referred to study heterogeneous groups of patients with a clinical suspicion of HF regardless of the status of LVEF. Second, HF is a syndrome rather than a specific disease. Thus, we found clinical importance in identifying prognostic imaging markers that may apply universally to patients suspected to have signs and symptoms of HF.

CMR Imaging Protocol and Postprocessing

A 3T CMR system (Tim Trio, Siemens, Erlangen, Germany) was used for imaging of all subjects. The CMR protocol consisted of cine steady-state free precession imaging (repetition time 3.4 ms; echo time 1.2 ms; in-plane spatial resolution 1.6×2 mm) for LV function and mass, LGE, and serial T1 mapping. Cine imaging was obtained in 8 to 14 short-axis (8 mm thick with no gap) and 3 radial long-axis planes. LGE imaging (repetition time 4.8 ms; echo time 1.3 ms; inversion time 200–300 ms) was performed to detect fibrosis in matching slice planes, using a segmented inversion-recovery pulse sequence starting 10 to 15 minutes after a weight-based injection (cumulative dose 0.15 mmol/kg) of gadolinium diethylenetriamine penta-acetic acid (Magnevist, Bayer HealthCare Pharmaceuticals, Wayne, NJ). In patients with estimated glomerular filtration rate <60 mL/min per 1.73 m^2, contrast dose was restricted to 0.1 mmol/kg or 20 mL, whichever was lower in volume based on our institutional policy. T1 measurements were acquired in a LV short-axis slice corresponding to midventricular level using a validated cine Look-Locker sequence, with a non-slice-selective adiabatic inversion pulse, followed by segmented gradient-echo acquisition for 17 cardiac phases or times after inversion (echo time 2.5 ms; repetition time 5.5 ms; flip angle 10°; 192×128 matrix; 6-mm slice), spread over 2 cardiac cycles (inversion time increments for T1 measurements of 100 ms precontrast, and 55 ms pos-contrast, slice thickness 8 mm). T1 mapping imaging was acquired once before and 3 times after the injection of gadolinium, at 3, 10, and 25 minutes, spanning across a postcontrast period of ≈30 minutes (Figure 1C). ECV was estimated by least-squares regression from measured R1s to reduce the variance of the ECV estimates, compared with 2-point method. The global mean ECV was calculated by averaging the ECV values without LGE. A commercially available software (Medis Suite v3.1, Medis, Leiden, the Netherlands) was used to postprocess and quantify all CMR images. Epicardial and endocardial contours were placed manually on all LGE images, then LGE mass (in both grams and percentage) was quantified by using the full width half maximum technique.[14] Presence of LGE was assessed visually according to presence/absence, pattern (subendocardial, midwall, epicardial, patchy, and other), and location (anterior, septal, inferior, lateral). Feature tracking analysis was performed using balanced steady-state-free precession cine images (Figure 1D). Global circumferential strain and GLS were obtained from 2-, 3-, and 4-chamber long axis sequences by LV epi- and endocardial contours. Global radial strain was obtained from LV short-axis view.

Follow-Up of Clinical Outcomes

Clinical events of all subjects were assessed by both electronic medical records and direct patient contact with a standardized checklist, blinded to all CMR variables. The mortality status of all study subjects was further verified by the Social Security Death Index at the end of the study period. The retrospective screening and the follow-up were performed until August 8, 2019, after which the data set was locked. The primary outcome included (1) all-cause death and (2) HF admission for decompensated HF requiring an increase of at least 1 HF medication and hospital admission.[1] All study procedures were approved by our institutional review board at Brigham and Women's Hospital. Written informed consent was waived per recommendation of our institution's institutional review board for this study, but all patients had the option of refusing follow-up contact.

Statistical Analysis

Continuous variables were expressed as mean±SD or as median (interquartile range) depending on normality of distributions. Categorical variables were shown as number with percentages. LV dilatation was defined by the recent published reference ranges (female with left ventricular end-diastolic volume index >70 mL/m^2, or male with left ventricular end-diastolic volume index >89 mL/m^2).[15] Comparisons for continuous and categorical variables were performed using a 2-sample Student *t* test or Wilcoxon rank-sum test, and chi-square test, respectively. Spearman's rank correlation coefficient was used to measure the correlations between continuous variables. Univariable and multivariable associations of risk covariates with clinical events were determined by Cox proportional hazards regression with time to event measured from the day of CMR. The proportional hazards assumption was evaluated using the Schoenfeld residuals test and visual inspection of the log-log survival curves. Cumulative incidence curves were displayed using Kaplan-Meier and compared with the log-rank test. We performed a multivariable analysis by inclusion of key baseline variables including patient age, sex, LVEF, and LGE presence. Because the relationship between the log(hazard) and LVEF as a continuous variable in our Cox model was nonlinear, we categorized LVEF in 5 groups by increments of 10% as follows: (1)

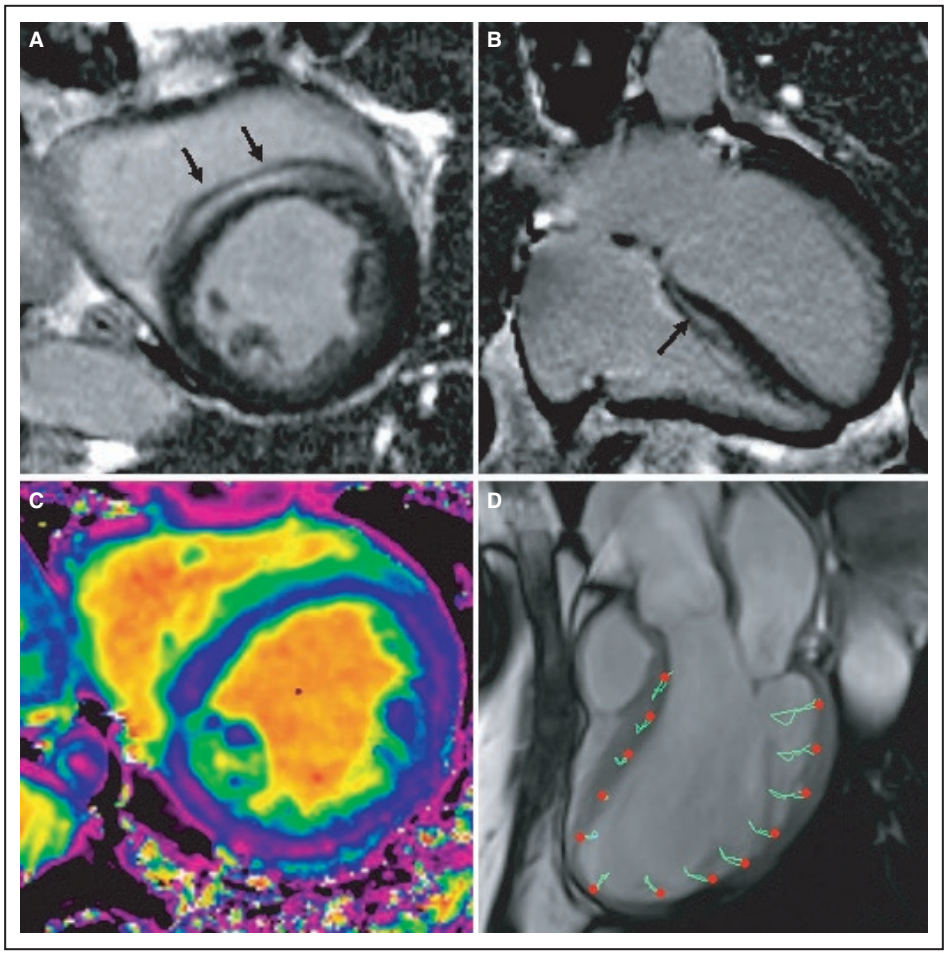

Figure 1. Typical CMR images for non-ischemic cardiomyopathy.
A, Short axis image with midwall LGE in the septal wall (black arrows). B, Long axis image with midwall LGE in the septal wall (black arrow). C, ECV map in the short axis image, midslice. D, Feature tracking image in long axis image.

LVEF <30% (severe dysfunction), (2) 30% to 40% (moderate dysfunction), (3) 40% to 50% (mild dysfunction), and (4) 50% to 60% (normal-low), >60% (normal-high). GLS and ECV were added to the multivariable baseline model to assess their incremental prognostic value, beyond the traditional prognosticators LVEF and LGE. Assessment of variance inflation factors for significant multicollinearity between any variables in the multivariable model was negative (all variance inflation factors <10). To evaluate the model's performance before and after addition of GLS and ECV to the multivariate baseline model, we further calculated (1) the change in model discrimination by the Harrell's C-statistic, (2) reclassification improvement by the category-free continuous net reclassification improvement and integrated discrimination index,[16,17] and (3) the change in model goodness-of-fit based on the –2log likelihood test, compared by the likelihood ratio test.[18]

The prognostic value of GLS for DeathCHF was further assessed in 7 prespecified subgroups stratified by presence or absence of established risk factors for DeathCHF, according to presence or absence of history of HF, hypertension, diabetes, left ventricular end-diastolic volume index, LVEF <50%, and diffuse fibrosis by ECV and LGE. A 2-sided *P* value of <0.05 was considered statistically significant. SAS was used for all statistical analysis version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Demographics and CMR Characteristics

In total, 544 consecutive subjects met inclusion criteria. Of those, a total of 70 subjects were excluded, because of medically documented CAD (n=35), infiltrative cardiomyopathy (n=20), and moderate-severe valvular disease (n=15). The remaining 474 formed the study cohort. Overall baseline characteristics are displayed in Table 1. The mean age of the overall cohort was 57±21 years with 56% men. The prevalence of coronary risk factors in hypertension, hypercholesterolemia, and

Table 1. Baseline Characteristics of the Cohort

	GLS≥median (≥ –17.4) (n=237)	GLS<median (< –17.4) (n=237)	*P* value
Clinical data			
Age, y	60.2±21.5	53.9±23.9	<0.001
Male sex	132 (59)	105 (48)	0.012
Body mass index, kg/m^2	27.4±7.3	26.4±7.8	0.144
Risk factors, n (%)			
Hypertension	104 (47)	78 (36)	0.017
Hypercholesterolemia	78 (35)	68 (31)	0.362
Diabetes	30 (14)	15 (7)	0.021
Smoking	57 (26)	27 (12)	<0.001
Family history of coronary artery disease	8 (4)	12 (6)	0.339
History of heart failure	89 (40)	21 (10)	<0.001
Cardiac magnetic resonance imaging			
LV ejection fraction, %	39.5±25.0	59.5±8.5	<0.001
Right ventricular ejection fraction, %	44.9±15.2	54.7±9.2	<0.001
LV end-diastolic volume index, mL/m^2	102.6±54.5	79.7±25.0	<0.001
LV end-systolic volume index, mL/m^2	63.0±58.4	31.5±14.3	<0.001
LV mass index, g/m^2	67.5±26.2	52.3±17.7	<0.001
Global circumferential strain, %	–13.0±9.2	–24.2±4.9	<0.001
GLS, %	…	…	…
Global radial strain, %	24.9±38.2	68.1±43.1	<0.001
LGE presence	111 (51)	31 (14)	<0.001
LGE pattern			
Midwall	51 (46)	7 (23)	<0.001
Subendocardial	21 (19)	6 (19)	0.002
Epicardial	9 (8)	6 (19)	0.410
Patchy	20 (18)	4 (13)	0.001
Right ventricular insertion	22 (20)	7 (23)	0.003
LGE location			
Anterior	52 (24)	11 (5)	<0.001
Lateral	59 (27)	18 (8)	<0.001
Inferior	68 (31)	20 (9)	<0.001
Septal	85 (39)	17 (8)	<0.001
LGE mass, g	0±4.2	0±0	<0.001
LGE mass, %	0±4.6	0±0	<0.001
Extracellular volume, %	32.3±8.4	28.1±5.3	<0.001
Native T1, ms	1132.0±90.8	1117.7±83.4	0.009

GLS indicates global longitudinal strain; LGE, late gadolinium enhancement; and LV, left ventricular.

diabetes was 42%, 34%, and 10%, respectively. With regard to baseline CMR characteristics, mean LVEF was 49±16%, mean GLS was –16±6%, and mean remote ECV was 30.6±6.0%. A total of 161 subjects (34%) had presence of LGE. The prevailing LGE pattern was midwall in 67 subjects (14%) (Figure 1A and 1B), whereas the most common LGE location was the interventricular septum in 114 subjects (24%).

Univariable Associations With DeathCHF

Over a median follow-up of 1.5 years interquartile range (1.0–2.1). 59 (12.4%) out of 474 patients experienced DeathCHF, including 42 HF hospitalizations and 25 deaths. Among those cases, 6 patients received a ventricular assist device, and 3 underwent heart transplantation. All of these patients experienced HF hospitalization as an adverse event before receiving a left ventricular assist device or a heart transplant. The univariable associations of clinical and CMR characteristics with DeathCHF are shown in Table 2.

CMR-assessed LVEF (hazard ratio [HR] per 10%, 0.62; 95% CI, 0.53–0.73; *P*<0.001), LGE (HR, 2.99; 95% CI, 1.76–5.06; *P*<0.001), GLS (HR per 1 SD, 2.37; 95% CI, 1.80–3.11; *P*<0.001), native T1 (HR per 1 SD, 1.43; 95% CI, 1.13–1.81; *P*=0.003) and ECV (HR per 1 SD, 1.52; 95% CI, 1.27–1.81; *P*<0.001) were all significant univariable markers of DeathCHF.

Among these covariates, GLS showed the strongest association with DeathCHF (χ^2=40.84). In Kaplan-Meier analysis, patients with GLS above median experienced a substantial decrease in event-free survival compared with patients with GLS below median (GLS above versus below median HR, 3.98; 95% CI, 2.06–7.71; *P*<0.001, Figure 2).

With regard to the pattern and location of LGE, midwall and patchy involvement were strongly associated with DeathCHF (HR, 2.87; 95% CI,1.63–5.06; *P*<0.001 and HR, 2.97; 95% CI, 1.41–6.27; *P*=0.004 respectively), whereas a significant association was also noted for septal LGE location (HR, 3.24; 95% CI, 1.93–5.42; *P*<0.001). Finally, LVEF had a strong inverse correlation with GLS (R^2 0.68, *P*<0.001, Figure S1A), whereas ECV had a weak correlation with GLS (R^2 0.11, *P*<0.001, Figure S1B).

Multivariable Models for DeathCHF

We constructed a parsimonious baseline multivariable model based on clinical relevance: LVEF and LGE were included in the model as established CMR prognosticators in this patient population, together with age and sex. Then, we sequentially added GLS and ECV on top of the baseline multivariable model. Taken into account the number of observed outcomes, adjusting for additional variables was avoided to avoid overfitting. After adding GLS to the baseline model, GLS emerged as the only significant covariate of DeathCHF (HR per 1 SD, 1.78; 95% CI, 1.06- 2.96; *P*=0.028). Adding ECV to the baseline model further revealed a significant association between ECV and DeathCHF (HR per 1 SD, 1.44; 95% CI, 1.13–1.84; *P*=0.003). When GLS and ECV were added

Table 2. Univariable Associations With All-Cause Death and Heart Failure Hospitalization

All-cause death and heart failure hospitalization	Chi-square	HR	95% CI	*P* value
Baseline				
Age, y	3.42	1.17	(0.99–1.39)	0.071
Sex	0.74	0.80	(0.47–1.34)	0.392
Body mass index, kg/m^2	0.90	1.02	(0.98–1.07)	0.335
History				
Diabetes	4.07	2.02	(1.07–3.81)	0.03
Hypertension	4.42	1.73	(1.04–2.89)	0.036
Hypercholesterolemia	2.30	1.50	(0.89–2.52)	0.124
Smoking	1.10	1.39	(0.76–2.54)	0.279
Heart failure	21.49	3.42	(2.05–5.71)	<0.001
CMR characteristics				
LVEF, %	37.45	0.95	(0.94–0.97)	<0.001
>60%		1.00	(Ref)	
50% – 60%		0.94	(0.35–2.52)	0.899
40% – 50%		1.26	(0.47–3.39)	0.643
30% – 40%		1.27	(0.42–3.78)	0.673
<30%		6.20	(2.95–13.04)	<0.001
RVEF, %	37.35	0.94	(0.92–0.96)	<0.001
LVEDVI, per 10 mL/m^2 increase	30.38	1.17	(1.11–1.23)	<0.001
LVESVI, per 10 mL/m^2 increase	38.88	1.18	(1.13–1.23)	<0.001
LV mass index, per 10 g/m^2 increase	17.69	1.28	(1.15–1.42)	<0.001
Strain				
GCS, % per 1 SD	33.76	2.22	(1.68–2.94)	<0.001
GLS, % per 1 SD	40.84	2.37	(1.80–3.11)	<0.001
GRS, % per 1 SD	7.83	0.75	(0.64–0.89)	0.001
T1 mapping				
ECV, % per 1 SD	16.39	1.52	(1.27–1.81)	<0.001
native T1, ms per 1 SD	7.76	1.43	(1.13–1.81)	0.003
LGE				
LGE mass, g	2.72	1.02	(1.00–1.04)	0.057
LGE mass, %	5.10	1.03	(1.01–1.05)	0.011
LGE presence	17.04	2.99	(1.76–5.06)	<0.001
LGE pattern				
Midwall	11.24	2.87	(1.63–5.06)	<0.001
Subendocardial	3.08	2.08	(0.98–4.38)	0.055
Epicardial	0.26	1.38	(0.43–4.41)	0.59
Patchy	6.27	2.97	(1.41–6.27)	0.004
RV insertion	5.55	2.60	(1.28–5.30)	0.009
LGE location				
Anterior	8.32	2.44	(1.39–4.31)	0.002
Lateral	8.05	2.29	(1.33–3.93)	0.003
Inferior	13.71	2.79	(1.66–4.69)	<0.001
Septal	18.90	3.24	(1.93–5.42)	<0.001
Segment LGE	17.47	1.11	(1.06–1.16)	<0.001
Segment (1–2)	3.03	2.14	(0.96–4.81)	0.063
Segment (3–7)	8.92	2.86	(1.49–5.48)	0.002
Segment (7<)	12.97	4.14	(2.06–8.35)	<0.001

DeathCHF indicates death and heart failure hospitalization; CV, extracellular volume; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; LGE, late gadolinium enhancement; LV, left ventricle; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; and RVEF, right ventricular ejection fraction.

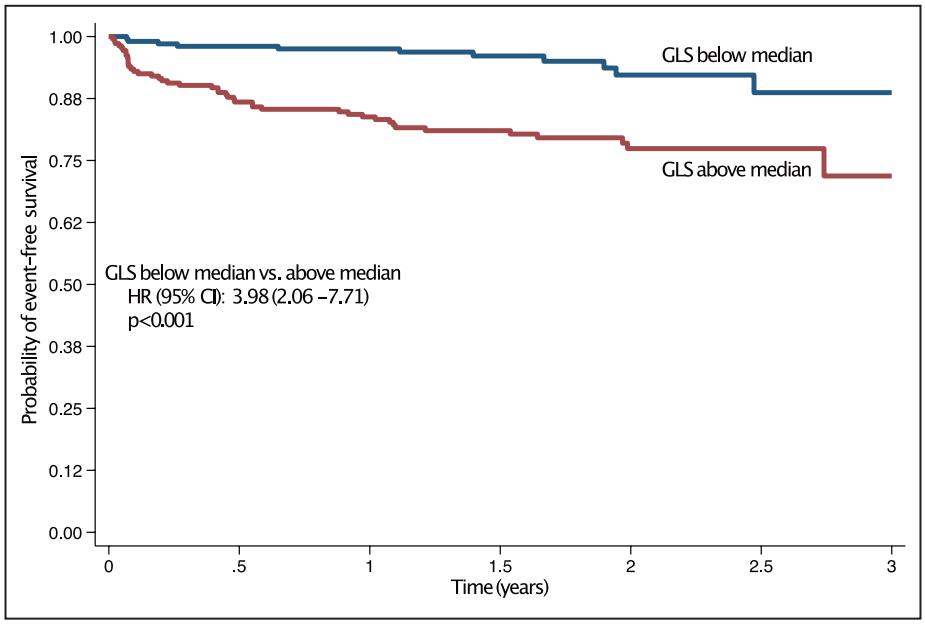

Figure 2. Time-to-event curves for death and/or heart failure hospitalization.
Event-free survival for patients with GLS below median vs above median are shown in blue and red respectively. Statistical analysis using log-rank test. GLS indicates global longitudinal strain; and HR, hazard ratio.

simultaneously to the multivariate baseline model, only ECV maintained a significant association with DeathCHF (HR per 1 SD, 1.37; 95% CI, 1.06–1.78; *P*<0.001, Table 3).

Model Discrimination and Reclassification Improvement After Addition of GLS and ECV

We further determined the discriminative capacity, goodness-of-fit, and reclassification improvement of the multivariable model for DeathCHF before and after addition of CMR-assessed GLS and ECV (Table 4). The baseline model demonstrated a C-statistic of 0.749 (95% CI, 0.680–0.819), which gradually improved after addition of ECV or GLS and peaked after addition of both GLS and ECV (C-statistic 0.782; 95% CI, 0.718–0.846; *P*=0.017).

Then, we assessed improvement in risk reclassification by the integrated discrimination improvement and the continuous net reclassification improvement. Adding GLS and ECV to the baseline model yielded a significant improvement in integrated discrimination index at 0.046 (95% CI, 0.015–0.076) as well as in continuous net reclassification improvement at 0.378 (95% CI, 0.065–0.752) for DeathCHF (Table 4). Finally, addition of GLS and ECV significantly improved the model's goodness-of-fit as assessed by the –2log likelihood test (–2log improvement: 515–505, *P*=0.012) (Table 4).

Subgroup Analysis

This study was not powered for subgroup analysis, and thus this analysis was performed for exploratory purposes.

GLS showed consistent prognostic value across subgroups stratified by established risk factors. In specific, GLS remained positively associated with DeathCHF independent of a history of HF, hypertension, or diabetes, presence of LV dilation, LVEF <50%, presence of diffuse fibrosis by ECV, or presence of LGE. The effect of GLS on DeathCHF was not modified by any of these parameters (*P* value for interaction effect >0.05 in all cases, Figure 3).

DISCUSSION

In this retrospective cohort of patients with signs and symptoms suspecting HF and no clinical evidence of CAD, our main findings indicate that joint assessment of GLS by FT and ECV by serial T1 mapping by CMR provides complementary and incremental prognostic association with DeathCHF over LVEF and LGE. In a real-world practice where patients presenting with nonspecific signs and symptoms and suspected HF were referred for CMR assessment, our findings indicate that CMR-assessed GLS and ECV provided effective risk stratification in this heterogeneous patient population.

Previous studies have demonstrated that LVEF and LGE are powerful predictors of adverse outcomes in patients with cardiac disease.[2,3] However, the identification of high-risk populations by LVEF and LGE is limited.[19–23] First, LVEF-based stratification presents limitations as it is affected by the preload, arterial resistance, heart rate, and valvular function.[2]

Table 3. Multivariable Associations With All-Cause Death and Heart Failure Hospitalization

	Baseline+LGE			Baseline+LGE+GLS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.01	(0.99–1.03)	0.345	1.01	(0.99–1.03)	0.344
Sex	1.01	(0.59–1.74)	0.966	1.10	(0.63–1.92)	0.744
LVEF categories						
>60%		Ref			Ref	
50% – 60%	0.84	(0.30–2.38)	0.747	0.78	(0.27–2.21)	0.635
40% – 50%	1.13	(0.42–3.06)	0.807	0.60	(0.19–1.91)	0.389
30% – 40%	1.04	(0.34–3.17)	0.946	0.51	(0.14–1.86)	0.307
<30%	4.80	(2.21–10.4)	<0.001	1.35	(0.38–4.77)	0.642
LGE presence	1.80	(1.01–3.21)	0.048	1.77	(0.94–3.35)	0.079
GLS, % per 1 SD				1.78	(1.06–2.96)	0.028
ECV, % per 1 SD						
	Baseline+LGE+ECV			Baseline+LGE+GLS+ECV		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.00	(0.98–1.02)	0.703	1.00	(0.98–1.02)	0.805
Sex	1.10	(0.63–1.93)	0.730	1.21	(0.68–2.16)	0.514
LVEF categories						
>60%		Ref			Ref	
50% – 60%	0.86	(0.30–2.50)	0.781	0.75	(0.25–2.23)	0.606
40% – 50%	0.72	(0.23–2.30)	0.582	0.32	(0.08–1.36)	0.123
30% – 40%	0.82	(0.25–2.71)	0.751	0.48	(0.12–1.91)	0.294
<30%	4.49	(1.95–10.31)	<0.001	1.62	(0.41–6.44)	0.491
LGE presence	1.25	(0.67–2.33)	0.479	1.26	(0.63–2.49)	0.513
GLS, % per 1 SD				1.58	(0.91–2.74)	0.106
ECV, % per 1 SD	1.44	(1.13–1.84)	0.003	1.37	(1.06–1.78)	0.018

ECV indicates extracellular volume; GLS, global longitudinal strain; LGE, late gadolinium enhancement; and LVEF, left ventricular ejection fraction.

Early subtle changes in systolic myocardial function may not be detected by a decline in LVEF.[24] Cikes and Solomon have shown that impairment in longitudinal function precedes the reduction in circumferential function, resulting in subclinical impairment of LV function despite preserved LVEF.[21] Thus, numerous studies have consistently indicated that GLS assessed by speckle-tracking echo can be a more sensitive marker of impaired systolic function and a more powerful predictor of cardiac outcomes than

Table 4. Discrimination, Reclassification, and Goodness-of-Fit Statistics for Death and Heart Failure Hospitalization, After Addition of CMR-Assessed ECV and GLS to the Baseline Model

	Model discrimination	Model reclassification		Goodness-of-fit
	C-statistic (95% CI), *P* value	IDI (95% CI), *P* value	cNRI (95% CI), *P* value	–2 log likelihood, *P* value
Baseline model*	0.749 (0.680 to 0.819)			515
+GLS	0.774 (0.709 to 0.839), *P*=0.053†	0.026 (0.010 to 0.043), *P*=0.002	0.344 (0.048 to 0.697), *P*=0.001	508, *P*=0.012
+ECV	0.761 (0.693 to 0.828), *P*=0.315†	0.030 (0.005 to 0.056), *P*=0.020	0.215 (–0.112 to 0.541), *P*=0.087	510, *P*=0.052
+GLS, ECV	0.782 (0.718 to 0.846), *P*=0.017	0.046 (0.015 to 0.076), *P*=0.003	0.378 (0.065 to 0.752), *P*<0.001	505, *P*=0.012

CMR indicates cardiac magnetic resonance; cNRI, continuous net reclassification improvement; ECV, extracellular volume; GLS, global longitudinal strain; IDI, integrated discrimination improvement; LGE, late gadolinium enhancement; and LVEF, left ventricular ejection fraction.

*Baseline model adjusted for age, sex, LVEF, LGE.

†Compared with the baseline model.

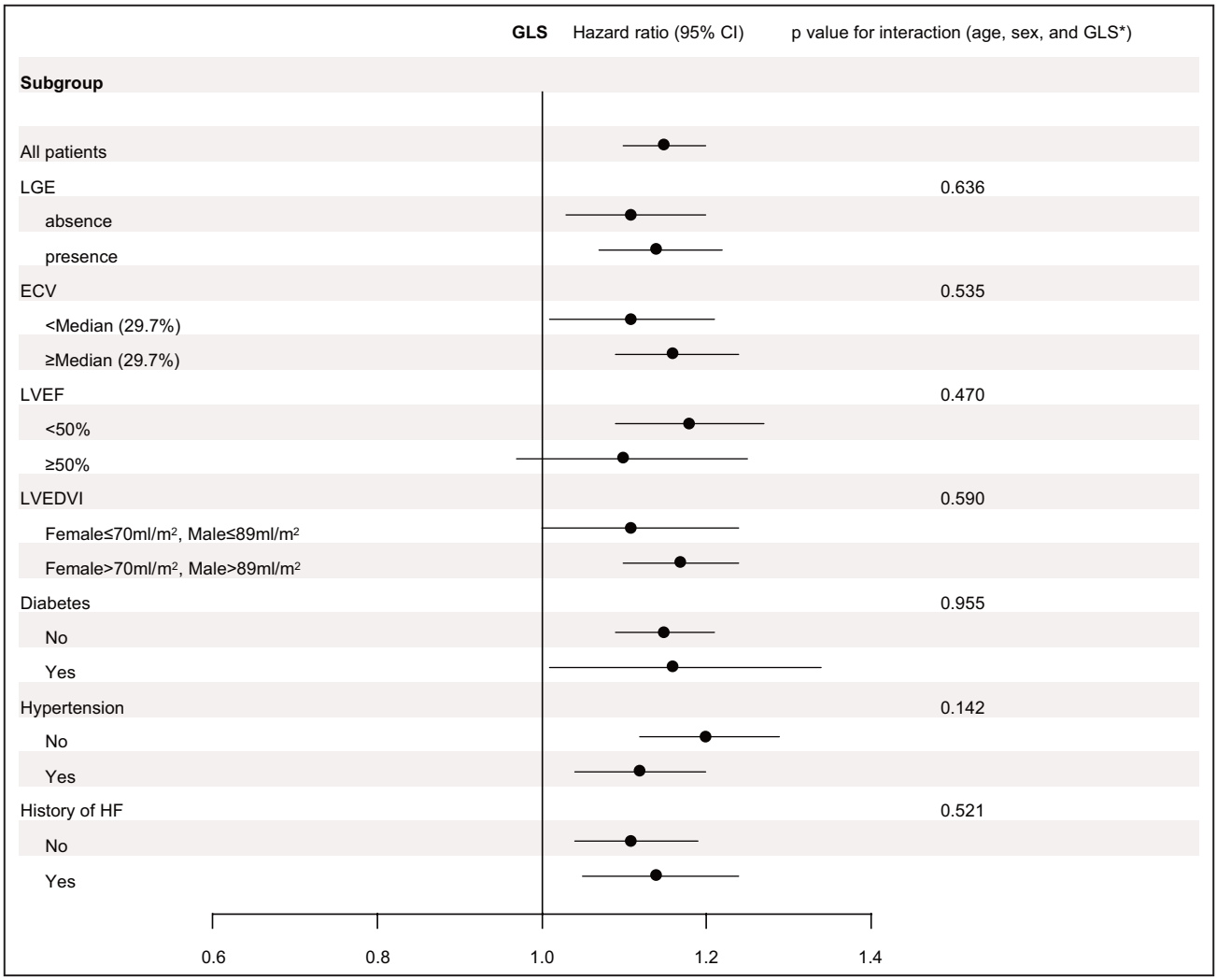

Figure 3. Subgroup analyses for GLS on DeathCHF.
GLS showed positively associated with DeathCHF independent of a history of HF, hypertension, or diabetes, presence of LV dilatation, LVEF <50%, presence of diffuse fibrosis by ECV, or presence of LGE. DeathCHF indicates death and heart failure hospitalization; ECV, extracellular volume; GLS, global longitudinal strain; HF, heart failure; LV, left ventricle; LVEDVI, left ventricular end-diastolic volume index; and LVEF, left ventricular ejection fraction.

LVEF.[25–28] CMR feature-tracking techniques have been developed for the evaluation of myocardial deformation and have been proven as a reliable, alternative method to conventional STE.[9,10,12] Buss et al previously reported that GLS by CMR-FT was independently associated with survival in 210 patients with dilated cardiomyopathy and LVEF ≤50%.[12] In 470 patients with ischemic and nonischemic cardiomyopathy and LVEF <50%, Romano et al found that GLS measured by CMR-FT was independently associated with mortality.[29] The same group further demonstrated an incremental prognostic value of GLS by CMR-FT in patients with preserved ejection fraction (LVEF ≥50%).[30] In our cohort, GLS provided an incremental prognostic value for HF and all-cause death beyond LVEF-based stratification.

Although LGE presence and a specific midwall LGE pattern are recognized as incremental predictors of cardiac events beyond LVEF in patients with nonischemic cardiomyopathy,[3–6] risk stratification based on LGE extent, pattern, and location also comes with limitations. The frequency of LGE presence is limited to one third of patients with nonischemic cardiomyopathy,[3,4] and the prognosis for patients with nonischemic cardiomyopathy and myocardial fibrosis but without "visual" LGE cannot be determined. ECV assessment by T1 mapping techniques can identify diffuse myocardial fibrosis[22,23] and has demonstrated robust associations with cardiac outcomes compared with other surrogate CMR myocardial fibrosis measures, including LGE, native T1, and postcontrast T1.[31,32] Diffuse myocardial fibrosis measured by ECV leads to LV stiffness and

dysfunction,[33] resulting in adverse outcomes including HF and death, which also performs better than LVEF in patient risk stratification.[34,35] In our study, ECV provided an incremental prognostic association for DeathCHF incremental to LGE. Furthermore, in the fully adjusted multivariable model, ECV was retained as the only significant predictor for DeathCHF, whereas associations of LVEF, LGE, and GLS were attenuated.

Fröjdh et al suggested that diffuse myocardial fibrosis diagnosed by ECV and subtle contractile dysfunction diagnosed by GLS might represent principal but distinct cardiac vulnerability.[36] Given that GLS and ECV correlated minimally, combining ECV and GLS may provide a more advanced pathophysiological understanding of underlying myocardial pathology. In this line, our findings indicate that combined GLS and ECV assessment may improve risk stratification in patients with features—but not yet an established diagnosis—of HF and absence of CAD, and, therefore be beneficial for the development of treatment strategies.

Finally, we demonstrated that there was no significant effect modification by established risk factors such as myocardial scar on the significant association of GLS with DeathCHF. These findings indicated that GLS was a robust covariate on DeathCHF regardless of age, sex, LGE presence or absence, ECV, LVEF, LV dilatation, and history of hypertension, diabetes, and HF. In the subgroup of patients without LGE specifically, GLS maintained its significant association with DeathCHF. Similar results were observed by Romano et al who showed that GLS was an independent predictor of death in patients without LGE; however, their populations were limited to preserved EF, and HF outcomes were not included.[30]

Limitations

Our study has several limitations. First, although all patients studied were specifically referred to CMR for "suspicion of HF," as documented by the treating physicians based on the overall clinical impression, CMR could not establish the definitive diagnosis of HF or cardiomyopathy in some patients, especially because natriuretic peptides were not clinically assessed. Second, we overall observed a limited number of events over the follow-up period, which did not allow for comprehensive multivariate adjustments of a diverse set of risk markers. Including LVEF as a categorical variable across clinically relevant categories further added degrees of freedom in the final multivariable model. However, additional analyses treating LVEF as a continuous or dichotomous variable did not change our results. Third, our study may not be powered for subgroup analyses. Finally, there is likely a selection bias from CMR referral for suspected HF but without CAD, severe chronic kidney disease, or presence of pacemakers or implantable cardioverter-defibrillator.

CONCLUSIONS

In patients with signs and symptoms suspecting HF and no clinical evidence of CAD, CMR-assessed GLS and ECV were independently associated with all-cause death and HF hospitalization and provided incremental prognostic value, beyond LVEF and LGE assessment. Systematic assessment of GLS and ECV in this patient population may improve risk stratification and patient care.

ARTICLE INFORMATION

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Supplemental Material

Figure S1

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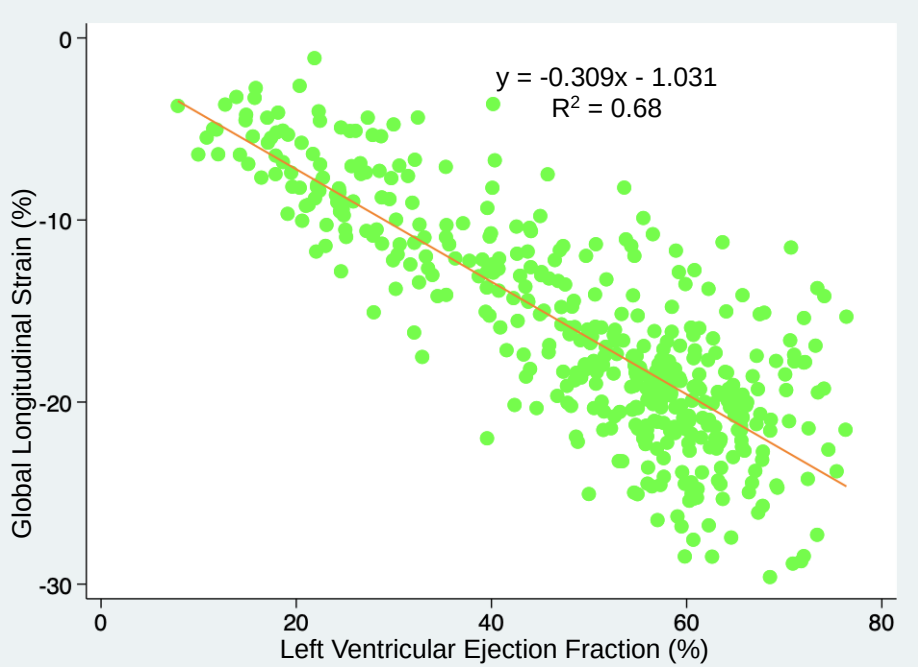
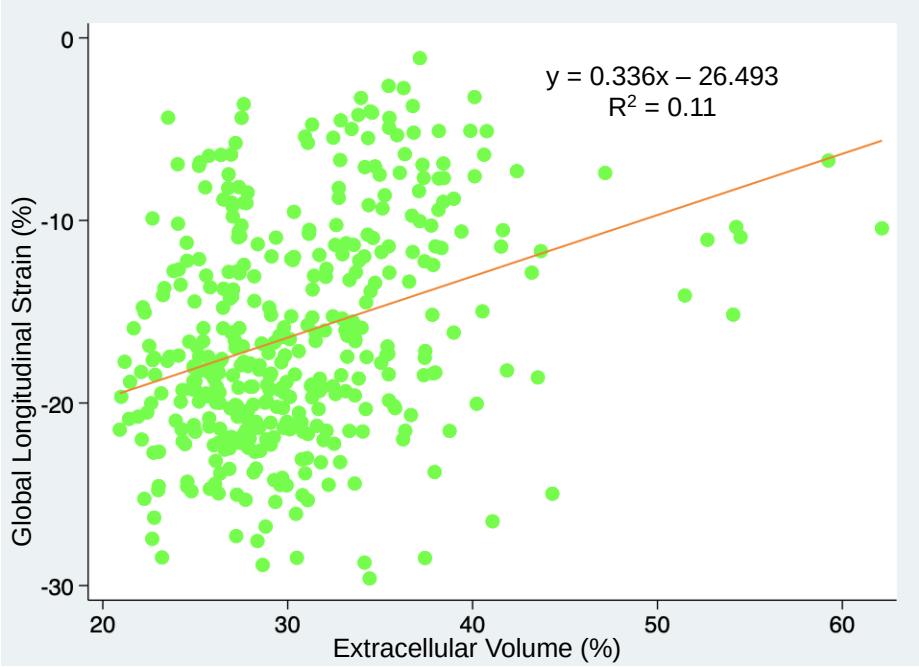
SUPPLEMENTAL MATERIAL

Figure S1. Spearman correlation between: a) GLS by CMR-FT and LVEF, b) GLS by CMR-FT and ECV. inverse correlation between LVEF and GLS; weak positive correlation between ECV and GLS.





LVEF: left ventricular ejection fraction, GLS: global longitudinal strain, ECV: extracellular volume