

ORIGINAL RESEARCH

Global Longitudinal Strain Is a Superior Predictor of All-Cause Mortality in Heart Failure With Reduced Ejection Fraction



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ABSTRACT

OBJECTIVES The purpose of this study was to investigate the prognostic value of global longitudinal strain (GLS) in heart failure with reduced ejection fraction (HFrEF) patients in relation to all-cause mortality.

BACKGROUND Measurement of myocardial deformation by 2-dimensional speckle tracking echocardiography, specifically GLS, may be superior to conventional echocardiographic parameters, including left ventricular ejection fraction, in predicting all-cause mortality in HFrEF patients.

METHODS Transthoracic echocardiographic examinations were retrieved for 1,065 HFrEF patients admitted to a heart failure clinic. The echocardiographic images were analyzed, and conventional and novel echocardiographic parameters were obtained.

RESULTS Many of the conventional echocardiographic parameters proved to be predictors of mortality. However, GLS remained an independent predictor of mortality in the multivariable model after adjusting for age, sex, body mass index, total cholesterol, mean arterial pressure, heart rate, ischemic cardiomyopathy, percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery, noninsulin dependent diabetes mellitus, and conventional echocardiographic parameters (hazard ratio [HR]: 1.15; 95% confidence interval [CI]: 1.04 to 1.27; $p = 0.008$, per 1% decrease). No other echocardiographic parameter remained an independent predictor after adjusting for these variables. Furthermore, GLS had the highest C-statistics of all the echocardiographic parameters and added incremental prognostic value with a significant increase in the net reclassification improvement ($p = 0.009$). Atrial fibrillation (AF) modified the relationship between GLS and mortality (p value for interaction = 0.036); HR: 1.08 (95% CI: 0.97 to 1.19), $p = 0.150$ and HR: 1.22 (95% CI: 1.15 to 1.29), $p < 0.001$, per 1% decrease in GLS for patients with and without AF, respectively. Sex also modified the relationship between GLS and mortality (p value for interaction = 0.047); HR: 1.23 (95% CI: 1.16 to 1.30), $p < 0.001$ and HR: 1.09 (95% CI: 0.99 to 1.20), $p = 0.083$, per 1% decrease in GLS for men and women, respectively.

CONCLUSIONS GLS is an independent predictor of all-cause mortality in HFrEF patients, especially in male patients without AF. Furthermore, GLS was a superior prognosticator compared with all other echocardiographic parameters. (J Am Coll Cardiol Img 2015;8:1351-9) © 2015 by the American College of Cardiology Foundation.

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Manuscript received April 27, 2015; revised manuscript received June 23, 2015, accepted July 15, 2015.

ABBREVIATIONS AND ACRONYMS

AF	= atrial fibrillation
CABG	= coronary artery bypass graft
CART	= classification and regression tree
DT	= deceleration time
GCS	= global circumferential strain
GLS	= global longitudinal strain
HFrEF	= heart failure with reduced ejection fraction
LAVI	= left atrial volume index
LV	= left ventricular
LVEF	= left ventricular ejection fraction
LVMI	= left ventricular mass index
MAP	= mean arterial pressure
NIDDM	= noninsulin dependent diabetes mellitus
NRI	= net reclassification improvement
PTCA	= percutaneous transluminal coronary angioplasty
TAPSE	= tricuspid annular plane systolic excursion

Echocardiography is the principal cardiac imaging tool used when assessing left ventricular (LV) systolic function in patients with heart failure (HF). Patients with HF who have undergone an echocardiographic examination have a greater chance of survival because of intensified medical treatment and intervention (1), and quantifying LV systolic function is vital in predicting adverse outcomes in patients with HF (2). Two-dimensional echocardiography can be used for evaluating LV systolic function by obtaining left ventricular ejection fraction (LVEF) (3). This parameter is widely used in clinical practice (4) and has been established as a predictor of mortality in HF patients (5). However, a measurement of LVEF depends on factors such as image quality, tracing of the endocardium, and geometric assumptions. Two-dimensional speckle tracking echocardiography has in recent years emerged as a method for assessing LV systolic and diastolic function (6). The technique measures the displacement of speckles on the 2-dimensional echocardiographic image. Speckle tracking offers a directional independence of the ultrasound beam (7,8) and represents myocardial deformation rather than volumetric change as seen by the LVEF

method. Global longitudinal strain (GLS), obtained by 2-dimensional speckle tracking echocardiography, is

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a measurement that has previously been demonstrated to be of prognostic value in patients having a wide array of cardiac diseases (9). There is also evidence supporting the prognostic value of GLS in HF patients (10-13). However, the previous studies on HF were either small or did not consider alternative echocardiographic predictors. Additionally, no other studies have investigated echocardiographic risk stratification models obtained by classification and regression tree (CART) analysis and net reclassification improvement (NRI). The aim of this study was to investigate the predictive value of GLS compared with conventional echocardiographic parameters in predicting mortality in a large cohort of patients with HF with reduced LVEF (HFrEF). In addition, we sought to identify the optimal echocardiographic risk stratification model in this patient population.

METHODS

STUDY POPULATION. In this large-scale retrospective study, we identified 1,102 nonacute consecutive

patients referred to Gentofte Hospital's HFrEF clinic in the period from 2005 to 2013. Patients had an LVEF of 45% or lower at referral. The baseline clinical data for the patients was retrieved from the HFrEF clinic's database, which was registered at the patient's first visit and includes history of diseases and previous procedures performed. All patients had a diagnosis of HFrEF by an experienced clinician and a history of angiography to evaluate coronary artery status. The 1,102 patients were cross-referenced with the hospital's echocardiographic database, in which an echocardiographic examination was retrieved for every patient. We included patients with an echocardiographic examination performed at a maximum of 1 year from the first admittance (median 30 days before admittance; interquartile range [IQR]: 6 to 56 days before admittance). Twenty-two patients did not have an echocardiographic examination within 1 year of admittance and were therefore excluded. Furthermore, 15 patients were excluded due to a poor or inadequate echocardiographic examination. In the end, 1,065 patients had echocardiographic images eligible for analysis. All clinical baseline data were obtained on admission to the HFrEF clinic and registered by an experienced clinician. The relevant status of medication initiated at admission date was retrieved from the database as well. Information on mortality status was retrieved from the Danish National Registry of Mortality, and follow-up was 100%. Ischemic cardiomyopathy was defined as patients who had a history of myocardial infarction and/or having undergone percutaneous transluminal coronary angioplasty (PTCA) and/or coronary artery bypass graft (CABG) surgery.

ECHOCARDIOGRAPHY. All the echocardiograms were obtained using either Vivid 7 or 9 echocardiographic machines (GE Healthcare, Little Chalfont, United Kingdom). The images were stored in a GE Healthcare image vault. The echocardiograms were subsequently analyzed offline in Echopac version 12 (GE Healthcare) by a single investigator blinded to all baseline patient data.

Conventional echocardiography. LVEF was obtained using the modified Simpson rule (4). LV end-diastolic dimensions were measured in the parasternal long-axis view at the tip of the mitral valve leaflets. These include interventricular septum thickness, LV posterior wall dimension, and LV internal dimension (4).

The anatomic LV mass was estimated by the Devereux formula (14). LV mass was then divided by the body surface area to obtain the left ventricular mass index (LVMI). Body surface area (m²) was

obtained using the Du Bois formula (15). Left atrial volume was measured by the area length method and divided by the body surface area to estimate the left atrial volume index (LAVI) (4).

The tricuspid annular plane systolic excursion (TAPSE) was measured using M-mode echocardiography in the 4-chamber apical view to determine the lateral tricuspid annulus motion.

Pulsed-wave Doppler in the 4-chamber apical view was used to assess mitral valve inflow patterns and obtain the peak velocities of early diastolic left ventricular filling (E) and atrial diastolic left ventricular filling (A). We also calculated the E/A ratio and measured the deceleration time (DT) of the E-wave.

With the sample volume placed at the septal and lateral mitral annular sites in the 4-chamber apical view, pulsed-wave tissue Doppler imaging was used to measure the peak longitudinal early diastolic (e') tissue velocity. The mean value was calculated as an average between the septal and lateral velocities. To assess LV filling pressure, we calculated the E/e' (16).

Speckle tracking echocardiography. Two-dimensional speckle tracking analysis was performed in the 2-, 3-, and 4-chamber apical views with an average of 74 ± 18 frames/s. The endocardial border was traced by an automated function that defined a region of interest (ROI) at end-systole. The investigator visually assessed the detected ROI and, if necessary, manually modified the ROI to ensure correct tracking of the speckles. Tracking was satisfactory if it covered the entire cardiac wall from the endocardium through to the myoepicardial border and if there was a visible motion of the speckles. In case of poor speckle tracking, the ROI was readjusted. A segment was excluded if it did not fulfill these criteria or were compromised by a shadow or artifact. In this case, the automatic quality score was also ignored. GLS was calculated as an average of the 3 apical projections and the ROI set to cover the entire left ventricle. If speckle tracking could not be obtained from a chamber view, GLS was averaged from the 2 remaining chamber views (total 4-chamber views: 996; 2-chamber views: 1,009; and apical long-axis views: 922). The peak GLS rate was calculated using the same approach as that for GLS.

Circumferential speckle tracking was analyzed in the parasternal short-axis view at the midventricular level, and we calculated global circumferential strain (GCS) and GCS rate.

STATISTICAL ANALYSIS. SPSS version 19.0 (IBM, Chicago, Illinois), STATA version SE 12.0 (StataCorp, College Station, Texas), and R software version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. For all

analyses performed, a p value in a 2-sided test <0.05 was considered statistically significant.

The continuous variables were compared using the Student *t* test. The chi-square test was used if the variable was categorical. Survival curves were constructed using the Kaplan-Meier method. Cox proportional hazards regression models were constructed, and both univariable and multivariable hazard ratios (HRs) were calculated. The assumption of proportional hazards were graphically asserted and tested based on the Schoenfeld residuals. In the multivariable regression models, we included sex, ischemic cardiomyopathy, and the baseline characteristics that were significant predictors of mortality: age, sex, body mass index, mean arterial pressure (MAP), total cholesterol, heart rate, noninsulin-dependent diabetes mellitus (NIDDM), PTCA, CABG (Table 1), and significant echocardiographic parameters (LVEF, LVMI, LAVI, E, E/e', E/A ratio, DT, and TAPSE) (Table 2). Every strain parameter (GLS, GLS rate, GCS, and GCS rate) was assessed individually in the multivariable regression model to avoid multicollinearity.

TABLE 1 Baseline Characteristics for Heart Failure Patients Alive and Those Who Died During Follow-Up

	Alive at Follow-Up (n = 888)	Dead at Follow-Up (n = 177)	p Value
Age, yrs	66 ± 12	72.5 ± 9	<0.001
Heart rate, beats/min	74 ± 16	78 ± 18	0.002
BMI, kg/m ²	26.6 ± 5	25.8 ± 5	0.028
MAP, mm Hg	94 ± 13	89 ± 14	<0.001
Cholesterol, mmol/l	4.5 ± 1	4.3 ± 1	0.014
Atrial fibrillation/atrial flutter	127 (14)	45 (25)	<0.001
Male	648 (73)	136 (77)	0.29
History of MI	408 (46)	88 (50)	0.36
Angina pectoris	195 (22)	49 (28)	0.098
IDDM	17 (2)	5 (3)	0.44
NIDDM	78 (9)	28 (16)	0.004
PTCA	267 (30)	32 (18)	0.001
CABG	175 (20)	48 (27)	0.027
Pacemaker	45 (5)	14 (8)	0.13
Implantable cardioverter-defibrillator	23 (3)	6 (3)	0.55
ICM	503 (57)	105 (59)	0.51
RAS blockade	709 (80)	137 (77)	0.46
Beta-blocker	590 (66)	120 (68)	0.73
Spirinolactone	132 (15)	22 (12)	0.50
Diuretic	462 (52)	81 (46)	0.12
Anticoagulants	168 (19)	33 (19)	0.93
Antiarrhythmics	40 (5)	9 (5)	0.74
Calcium channel blocker	8 (1)	1 (1)	0.66

Values are mean ± SD or n (%).
 BMI = body mass index; CABG = coronary artery bypass graft; ICM = ischemic cardiomyopathy;
 IDDM = insulin-dependent diabetes mellitus; MAP = mean arterial pressure; MI = myocardial infarction;
 NIDDM = noninsulin-dependent diabetes mellitus; PTCA = percutaneous transluminal coronary angioplasty;
 RAS = renin-angiotensin system.

TABLE 2 Conventional Echocardiographic and 2-Dimensional Speckle Tracking Parameters of Heart Failure Patients Alive and Deceased at the Date of Follow-Up

Echocardiographic Parameters	Alive at Follow-Up (n = 888)	Dead at Follow-Up (n = 177)	p Value
LVEF, % (888;177)	28.2 ± 9.1	23.8 ± 9.9	<0.001
LVIDd, cm (882;177)	5.6 ± 1.0	5.7 ± 1.1	0.27
LVMI, g/m ² (888;177)	117 ± 37	122 ± 38	0.040
LAVI, ml/m ² (870;175)	30 ± 13	38 ± 19	<0.001
E, m/s (856;166)	0.8 ± 0.3	0.9 ± 0.3	0.002
A, m/s (741;124)	0.7 ± 0.3	0.7 ± 0.3	0.124
E/A, (740;124)	1.4 ± 1.0	1.7 ± 1.2	0.05
DT, ms (850;166)	191 ± 80	176 ± 71	0.025
e', cm/s (806;157)	6.9 ± 2.5	6.7 ± 2.6	0.35
E/e' (797;155)	12.8 ± 6.0	14.7 ± 6.7	0.002
TAPSE, cm (888;177)	1.9 ± 0.6	1.6 ± 0.6	<0.001
GLS rate, 1/s (846;166)	-0.6 ± 0.3	-0.5 ± 0.2	<0.001
GCS rate, 1/s (760;138)	-0.6 ± 0.3	-0.5 ± 0.3	0.25
GCS, % (728;136)	-10.6 ± 4.06	-9.1 ± 4.5	<0.001
GLS, % (878;176)	-9.9 ± 3.2	-8.1 ± 3.0	<0.001

Values are mean ± SD and the values in parentheses specify patients with measurement available for the specific parameter.

A = peak transmitral late diastolic inflow velocity; DT = deceleration time of early diastolic ventricular inflow; E = peak transmitral early diastolic inflow velocity; e' = average peak early diastolic mitral annular velocity; GCS = global circumferential strain; GLS = global longitudinal strain; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; LVIDd = left ventricular internal dimension in diastole; LVMI = left ventricular mass index; TAPSE = tricuspid annular plane systolic excursion.

To assess the prognostic strength of the examined parameters, Harrell C statistics were calculated from the univariable Cox regression models.

Using logistic regression, models were constructed for predicting the risk of future mortality in patients during follow-up of 40 months (IQR: 22 to 57 months). Reclassification analysis by arbitrary risk categories of <5%, 5% to <30%, 30% to <50%, and ≥50% was performed to assess NRI when adding GLS or LVEF to the significant clinical and echocardiographic predictors of mortality in the population.

We also performed a CART analysis (17) to identify the optimal echocardiographic risk stratification for HFREF patients and all-cause mortality. CART analysis is an empirical, statistical technique based on recursive partitioning of the data space to predict the response (17). The models are obtained by binary splitting of the data by the value of predictors, and the split variable and split-point are automatically selected from possible predictive values to achieve the best fit. Then, 1 or both “child nodes” are split into 2 or more regions recursively, and the process continues until a stopping rule is applied. Finally, the result of this process is represented as a binary decision tree.

ETHICS. The study was approved by the Danish Data Protection Agency, journal no. 03240 (I-Suite), ID: GEH-2014-047.

RESULTS

PREDICTORS OF ALL-CAUSE MORTALITY IN PATIENTS WITH HFREF. During a median follow-up of 40 months (IQR: 22 to 57 months), 177 patients (16.7%) died.

Patients who died during follow-up were significantly older, had lower MAP, higher heart rate, and lower total cholesterol. There were a higher proportion of patients with NIDDM and of patients who had CABG surgery and PTCA performed (Table 1).

With regard to the echocardiographic examination, patients who died during follow-up had significantly lower LVEF, GLS, GCS, and GCS rate. Patients who died had larger LVMI, larger LAVI, lower TAPSE, higher peak inflow E-wave velocity, shorter DT of early mitral inflow, higher E/A ratio and higher E/e' ratio (Table 2).

The patient population was stratified into tertiles of GLS. The risk of dying increased with decreasing tertile of GLS, being approximately 3 times higher for patients in the lowest tertile compared with patients in the highest tertile (tertile 1 vs. tertile 3, HR: 3.38, 95% CI: 2.3 to 5.1, p < 0.001) (Figure 1). In the multivariable Cox regression, GLS was the only echocardiographic parameter that was an independent predictor of mortality: HR 1.15 (95% CI: 1.04 to 1.27), p = 0.008 per 1% decrease (Table 3). Further analysis with multivariable models including medication (Online Table 1) and tissue Doppler imaging parameters (Online Table 2) did not influence the prognostic significance of GLS. In addition, GLS was the parameter with highest Harrell C-statistics of all the

FIGURE 1 Kaplan-Meier Curves for Patients Stratified Into Tertiles of GLS

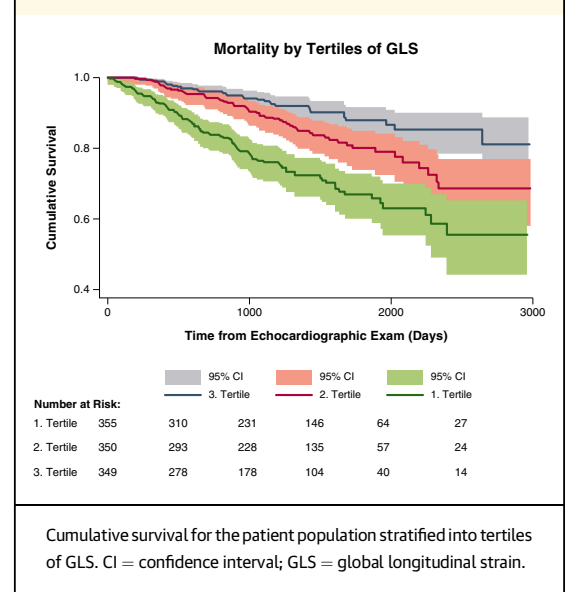


TABLE 3 Univariable and Multivariable Cox Proportional Hazard Models

	Univariable Analysis			C-Statistic	Multivariable Analysis*		
	HR	95% CI	p Value		HR	95% CI	p Value
Age, per 1-yr increase	1.05	1.03-1.06	<0.001		1.05	1.02-1.07	<0.001
MAP, per 1-mm Hg increase	0.97	0.96-0.98	<0.001		0.97	0.95-0.98	<0.001
Heart rate, per 1-beat/min decrease	1.01	1.00-1.02	0.015				
Ischemic cardiomyopathy	1.14	0.84-1.53	0.39		1.32	0.78-2.26	0.305
CABG	1.41	1.01-1.96	0.043				
PTCA	0.56	0.38-0.82	0.003				
Cholesterol, per 1-mmol/l increase	0.83	0.72-0.96	0.013				
NIDDM	1.88	1.25-2.81	0.002		2.66	1.55-4.30	<0.001
BMI, per 1-kg/m ² increase	0.97	0.93-0.99	0.036				
LVEF, per 1% increase	0.95	0.94-0.97	<0.001	0.6533			
LVMI, per 1-g/m ² decrease	1.04	1.00-1.01	0.036	0.5641			
LAVI, per ml/m ² decrease	1.02	1.01-1.03	<0.001	0.6048			
TAPSE, per 1-cm increase	0.44	0.34-0.58	<0.001	0.6319			
E, per 1-m/s increase	1.88	1.20-2.96	0.006	0.5694			
DT, per 1-ms decrease	0.99	0.99-1.00	0.031	0.5638			
E/A, per 1 increase	1.23	1.08-1.41	0.003	0.5709			
e', per 1-cm/s increase	0.004	0.00-1.96	0.08	0.5502			
E/e', per 1 decrease	1.06	1.02-1.06	0.001	0.5902			
GCS rate, per 1-s ⁻¹ decrease	1.85	0.96-3.60	0.067	0.5833			
GCS, per 1% decrease	1.11	1.06-1.16	<0.001	0.6371			
GLS rate, per 1-s ⁻¹ decrease	11.02	4.64-26.20	<0.001	0.6450			
GLS, per 1% decrease	1.20	1.14-1.26	<0.001	0.6735	1.15	1.04-1.27	0.008

*Multivariable model includes age, sex, BMI, total cholesterol, MAP, heart rate, Ischemic cardiomyopathy, PTCA, CABG, NIDDM, LVEF, LVMI, LAVI, TAPSE, DT, E velocity, E/e' ratio, E/A ratio, and GLS. Only HRs for variables that are significant in the multivariable analysis are shown.
 CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

echocardiographic parameters. Only age, MAP, and NIDDM also remained independent predictors of mortality in the multivariable model.

PROGNOSTIC UTILITY OF GLS IN RELATION TO SEX AND THE PRESENCE OF ATRIAL FIBRILLATION. A substantial proportion of the patient population who were deceased at follow-up had atrial fibrillation (AF) (25.4%). We therefore sought to investigate whether GLS could be used to predict mortality in patients with AF. We found that AF modified the relationship between GLS and mortality (p value for interaction = 0.036). From the Cox regression we estimated an HR of 1.08 (95% CI: 0.97 to 1.19; p = 0.150) and an HR of 1.22 (95% CI: 1.15 to 1.29; p < 0.001) per 1% decrease in GLS for patients with and without AF, respectively (Online Figures 1A and 1B). We also performed a subgroup analysis of the AF patients to investigate whether the GLS rate would be a better prognosticator. In the univariable Cox regression, the GLS rate did not significantly predict mortality (p = 0.07); however, LVEF did (p = 0.014). None was significant in the multivariable model.

Sex also modified the relationship between GLS and mortality (p value for interaction = 0.047; HR: 1.23

[95% CI: 1.16 to 1.30; p < 0.001] and HR: 1.09 [95% CI: 0.99 to 1.20; p = 0.083]) per 1% decrease in GLS for men and women, respectively (Online Figures 1C and 1D). In a subgroup analysis including only male patients without AF (n = 510), GLS remained an independent predictor of mortality in the multivariable model: HR: 1.16 (95% CI: 1.03 to 1.31; p = 0.010) per 1% decrease in GLS including the same covariates as listed in Table 3.

INCREMENTAL PROGNOSTIC VALUE OF ADDING GLS IN RELATION TO PREDICTING MORTALITY.

Adding GLS to the significant clinical parameters (age, sex, MAP, NIDDM, PTCA, CABG, body mass index, heart rate, total cholesterol) and the conventional echocardiographic parameters (LVEF, LVMI, LAVI, TAPSE, E, DT, E/A, E/e') resulted in an improved prediction model with a significant increase in the categorical NRI of 9.27% (95% CI: 9.18% to 9.36%; p = 0.009) (Online Table 3). A similar result was found when confining the analysis to male patients without AF (NRI of 8.26%, 95% CI: 8.17% to 8.34%; p = 0.040) (Online Table 4). In comparison, adding LVEF to the same model did not result in a better predicting model (p = 0.38).

ECHOCARDIOGRAPHIC RISK STRATIFICATION IN PATIENTS WITH HFrEF

Performing a CART analysis including all the echocardiographic parameters resulted in the risk stratification tree depicted in Figure 2. The statistical stratification obtained by the CART analysis demonstrated that GLS is especially useful for stratifying patients with very severe HF as defined by an LVEF <22%. Even though GLS seems to be the single-handedly strongest echocardiographic prognosticator in HFrEF, the optimal echocardiographic risk stratification strategy includes an evaluation of several echocardiographic predictors (TAPSE, LVEF, E, and GLS).

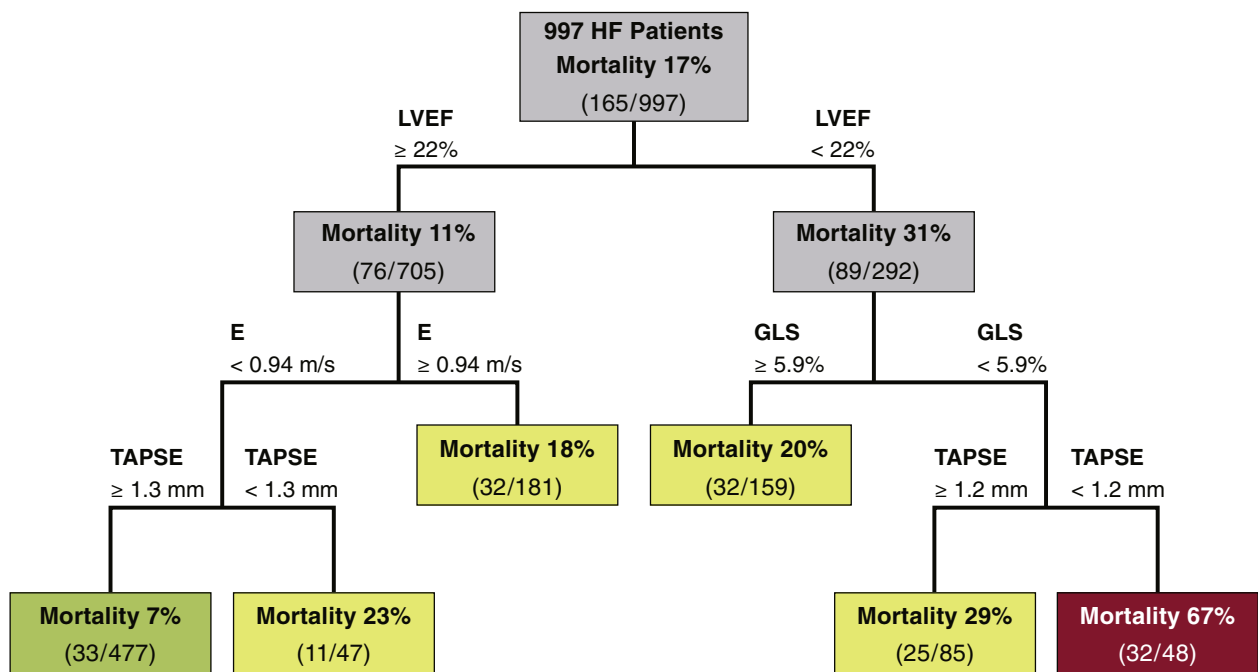
DISCUSSION

The present study is, as far as the authors are aware, the largest study determining the prognostic utility of

GLS in patients with HFrEF. We demonstrate that GLS seems to be a superior prognosticator compared with all other conventional echocardiographic parameters. In addition, we found GLS to be of limited prognostic value in females and patients with AF. GLS also resulted in a better risk prediction model when added to the baseline clinical risk factors and echocardiographic parameters. Finally, we provide an echocardiographic risk stratification tree that allocates patients with HFrEF into several clearly defined risk groups.

PROGNOSTIC VALUE OF GLS IN RELATION TO MORTALITY. Our findings are consistent with most previous studies conducted examining GLS in relation to all-cause mortality (11-13,18). However, we demonstrate that GLS is not only superior to the systolic echocardiographic parameter in predicting mortality, but also preferable to conventional echocardiographic parameters, as reflected by the highest

FIGURE 2 Risk Stratification Tree Using LVEF, GLS, E, and TAPSE as Obtained by CART Analysis



Risk Categories for Mortality

- Low Risk: 0 – 15% (green)
- Intermediate Risk: 15 – 30% (yellow)
- High Risk: > 30% (red)

CART analysis stratifying patients into a binary risk tree for predicting mortality when assessing LVEF, GLS, E, and TAPSE combined. All echocardiographic parameters were included in the initial model, but the CART analysis resulted in selecting the 4 parameters depicted in the risk stratification tree. CART = classification and regression tree; E = peak transmitral early diastolic inflow velocity; GLS = global longitudinal strain; HF = heart failure; LVEF = left ventricular ejection fraction; TAPSE = tricuspid annular plane systolic excursion.

C-statistic value. In addition, GLS as the only echocardiographic parameter remained an independent predictor of mortality after adjustment for all the univariable predictors. However, compared with other studies, our study did not include data on New York Heart Association functional class.

Our results are the first to demonstrate an incremental predictive value of adding GLS to established risk factors. NRI analysis yielded a significant reallocation of patients in the respective risk groups (Online Table 3). This was not the case when adding LVEF to a model already including GLS ($p = 0.38$). Therefore, LVEF does not improve our risk prediction model if an assessment of GLS has already been performed. This finding, together with GLS having a higher C-statistic and being the only significant echocardiographic parameter in the multivariable model, suggests that GLS is a superior systolic prognosticator. Nevertheless, in accordance with the risk stratification tree obtained from our CART analysis, an assessment of both LVEF and GLS is especially useful in identifying high-risk patients (Figure 2). Thus, our results do not suggest using GLS as a replacement for conventional echocardiographic predictors, but rather that an assessment of GLS conveys detailed information about the LV systolic function and adds information on the risk of mortality beyond the information that we can gain from our conventional measures.

Another factor to consider is that the images used in the present study were retrieved from a clinical examination. Our study reflects the quality obtained in the daily clinical practice. This could suggest that GLS can be used in the clinical setting to predict mortality and is a more robust method than previously considered.

In the present report, we are the first to incorporate GLS in a risk stratification tree, together with the conventional echocardiographic measurements, as depicted in the CART analysis (Figure 2). Because it can be difficult to interpret isolated GLS values, this risk stratification tree gives a very simple decision algorithm for the clinician to place HFrEF patients in risk categories. This information could prove valuable in the clinical setting and potentially optimize certain aspects of HF treatment plans. In addition, the algorithm could prove useful as a research tool when initiating new clinical trials of HF drugs or devices to identify high-risk patients.

GCS has previously been proved to be a better prognosticator than both LVEF and GLS (19). In our study, we found GCS to be a significant predictor of mortality in the univariable analysis. When we adjusted for the baseline characteristics and conventional echocardiographic parameters, GCS did

not remain an independent predictor of mortality (Table 3). We also examined GCS and GLS rate parameters to see whether the deformation velocities added any incremental value in predicting mortality. These parameters proved to be significant in the univariable models but failed to be significant in the multivariable model (Table 3).

GLS AS A PREDICTOR OF MORTALITY IN FEMALE HFrEF PATIENTS WITH AF. This study is the first to demonstrate the interaction between AF and GLS in predicting mortality in HFrEF. GLS was not a significant predictor of mortality in patients with AF (Online Figure 1A).

Patients with AF have higher heart rates (20), and this was also the case in our study, with a significant difference in heart rate for patients without AF (73.1 ± 15.0 beats/min) and patients with AF (80 ± 21 beats/min) ($p < 0.001$). The increased heart rate will cause a lower stroke volume and consequently a lower GLS. Another hemodynamic consequence of AF is the beat-to-beat variations of the systolic performance that could affect the GLS measurements (21). Together these factors may contribute to a systematic underestimation of GLS and thus explain the limited prognostic capability of GLS in AF patients. This underestimation could possibly be bypassed by recording up to 10 cardiac cycles to ensure that the GLS measurement is representative of the true peak value.

We also found that sex modified the relationship between GLS and mortality in HFrEF. GLS did not predict mortality in women (Online Figure 1C). It is known that women have a significantly lower amount of cardiac muscle mass as measured by LVMI (22,23) and lower volumetric measurements (4). LVEF has also been demonstrated to be higher in women (24,25) as has GLS (26). Even though we found some significant differences between men and women (Online Table 5), these differences do not explain the marked difference in the prognostic capability of GLS in men and women. Nevertheless, our differences in echocardiographic measurements between men and women are in accordance with those of previous studies (22-26). Together, these findings may indicate an intrinsic difference in the cardiac architecture, physiology, and LV systolic performance between men and women. This information must be taken into account when making sex-specific risk stratification of HFrEF patients, but further studies are needed to clarify the exact underlying mechanism of the cardiac differences between sexes. In both the multivariable analysis (Table 3) and NRI analysis (Online Tables 3 and 4), GLS remained a significant and incremental predictor of mortality even when confining our analysis to include only men without AF.

STUDY LIMITATIONS. There are several limitations of this study, which should be taken into consideration. The time from admittance to the HFrEF clinic to the echocardiographic examination was in some patients relatively long (up to a year). Under optimal circumstances, the echocardiographic examinations would have been performed on the same day as the patients were admitted to reflect the in-clinic cardiac performance. However, the large majority of patients had their echocardiographic examination performed very near to the admission to the heart failure clinic (median 30 days before admittance; IQR: 6 to 56 days before admittance). In addition, we performed a sensitivity analysis including patients with an echocardiographic examination within 3 months before admission, which yielded the same results as those seen when using our inclusion criteria.

Our study did not account for clinical characteristics such as New York Heart Association functional class and brain natriuretic peptide, which have been shown to be of importance when assessing the prognosis in HFrEF (11,27). In addition, patients' medications were registered at admission to the heart failure clinic, but adjustments of the treatment after consecutive visits to the heart failure clinic could affect both mortality and GLS.

As this study was retrospective and performed in a clinical setting, we were only able to retrieve a single cardiac cycle and could not obtain information on QRS duration, serum creatinine, and cardiac resynchronization therapy. Lastly, we only calculated GCS from the papillary muscle level. GCS obtained from other views might have improved the predictive value of GCS.

CONCLUSIONS

In the present study, we found GLS to be a strong prognosticator of all-cause mortality in patients with HFrEF. Additionally, GLS was superior to LVEF and all other conventional echocardiographic parameters

in predicting mortality. However, GLS was not a significant prognosticator of mortality in HFrEF patients with AF or in women. Furthermore, GLS provided incremental prognostic information when added to a model already including significant echocardiographic and clinical predictors. Finally, the optimal echocardiographic risk stratification tree in HFrEF patients includes an assessment of measures of systolic (LVEF and GLS), diastolic (E), and right ventricular (TAPSE) function.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1:

GLS has previously been shown to predict outcome in heart failure. This study shows that GLS is a powerful predictor of mortality compared with all the conventional echocardiographic parameters in HFrEF. The use of GLS to identify patients at high risk of mortality could lead to changes in follow-up or therapy.

COMPETENCY IN MEDICAL KNOWLEDGE 2:

It is important when risk-stratifying HFrEF patients to make a comprehensive echocardiographic assessment of the entire heart, which includes systolic, diastolic, and right heart function.

TRANSLATIONAL OUTLOOK:

This study provides new information on prognosis and sex-specific differences of GLS. Additional research is needed to validate this finding and clarify a possible physiological explanation for the sex differences.

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KEY WORDS echocardiography, GLS, prognosis, risk stratification, speckle tracking, systolic function

APPENDIX For supplemental tables and a figure, please see the online version of this article.