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Prognostic Relevance of Left Ventricular Global Longitudinal Strain in Patients With Heart Failure and Reduced Ejection Fraction

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Patients with heart failure (HF) and reduced ejection fraction (HFrEF) are complex patients who often have a high prevalence of co-morbidities and risk factors. In the present study, we investigated the prognostic significance of left ventricular (LV) global longitudinal strain (GLS) along with important clinical and echocardiographic variables in patients with HFrEF. Patients who had a first echocardiographic diagnosis of LV systolic dysfunction, defined as LV ejection fraction ≤45%, were selected. The study population was subdivided into 2 groups based on a spline curve analysis derived optimal threshold value of LV GLS (≤10%). The primary end point was occurrence of worsening HF, whereas the composite of worsening HF and all-cause death was chosen for the secondary end point. A total of 1,873 patients (mean age 63 ± 12 years, 75% men) were analyzed. During a median follow-up of 60 months (interquartile range 27 to 60 months), 256 patients (14%) experienced worsening HF and the composite end point of worsening HF and all-cause mortality occurred in 573 patients (31%). The 5-year event-free survival rates for the primary and secondary end point were significantly lower in the LV GLS ≤10% group compared with the LV GLS >10% group. After adjustment for important clinical and echocardiographic variables, baseline LV GLS remained independently associated with a higher risk of worsening HF (hazard ratio 0.95, 95% confidence interval 0.90 to 0.99, p = 0.032) and the composite of worsening HF and all-cause mortality (hazard ratio 0.94, 95% confidence interval 0.90 to 0.97, p = 0.001). In conclusion, baseline LV GLS is associated with long-term prognosis in patients with HFrEF, independent of various clinical and echocardiographic predictors. **(Am J Cardiol 2023;202:30−40)**

Heart failure (HF) with reduced ejection fraction (HFrEF) is the most common type of HF and is associated with a poor prognosis, even when being compared with other types of HF including HF with midrange or preserved ejection fraction (EF).[1,2] Left ventricular (LV) EF, estimated with 2-dimensional (2D) echocardiography, is the most frequently used imaging technique for the diagnosis and management of HFrEF.[3−5] However, the assessment of LV systolic performance with 2D LVEF has several limitations, including its reliance on geometrical assumptions.[6] Moreover, LVEF underestimates LV forward stroke volume in patients with mitral and aortic regurgitation, because of retrograde flow into the left atrium (LA) or LV, respectively.[7] LV global longitudinal strain (GLS) is a noninvasive, sensitive marker to detect subtle LV systolic dysfunction and can at least partially overcome the limitations that are associated with the assessment of LV systolic performance by 2D LVEF.[8−10] In addition, it has proved its incremental diagnostic and prognostic value over 2D LVEF in multiple cardiovascular diseases, including valvular heart disease and different cardiomyopathies, which are also frequently noted in patients with HFrEF.[1,11,12] Therefore, the assessment of LV systolic function with LV GLS could be more accurate than an LVEF-based approach. The prognostic value of LV GLS, however, has never been evaluated in a real-life, large cohort of patients with HFrEF. The present study, therefore, aims to evaluate the prognostic value of LV GLS in a large cohort of patients with HFrEF.

Methods

From an ongoing registry of patients with chronic HF (Leiden University Medical Center, Leiden, The Netherlands) and first echocardiographic diagnosis of LV dysfunction, defined as an LVEF ≤45%, patients ≥18 years who presented between November 1993 and June 2020 were identified. Patients who had a diagnosis of active cancer at baseline or who died within the first 30 days of follow-up were excluded. Patients underwent complete clinical and echocardiographic evaluation at the time of the

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See page 38 for Declaration of Competing Interest.

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echocardiogram on which an LVEF ≤45% was first documented. Baseline clinical data were collected as documented in the departmental information system (EPD-Vision, Leiden University Medical Centre, Leiden, The Netherlands) at the time of the first echocardiogram on which an LVEF ≤45% was documented. Baseline clinical data including demographic data, cardiovascular risk factors, co-morbidities, and laboratory results were collected as recorded at the date of the index echocardiography. According to the departmental routine clinical workflow, which is based on the European Society of Cardiology guideline recommendations,[4] most patients were initiated on guideline-directed medical therapy (GDMT) or received up-titration of GDMT during the first year after echocardiographic diagnosis of HF with LVEF ≤45%. Accordingly, GDMT was presented within 1 year after the index echocardiography. Similarly, data on invasive procedures including percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy (CRT), and valvular intervention (surgical or transcatheter) were also presented within 1 year after the index echocardiography. All data used in the current analysis were collected for routine clinical purposes and handled anonymously. Written informed consent was waived by the Institutional Review Board. The investigation conforms to the principles outlined in the Declaration of Helsinki.[13]

The index echocardiography was the first examination on which a reduced LVEF (≤45%) was diagnosed. All patients were examined in the left lateral decubitus position using a commercially available echocardiography system (Vivid 7, E9, and E95, GE Vingmed Ultrasound, Horten, Norway). M-mode and 2D images were obtained and saved in a cine-loop format for offline analysis (EchoPac 202 and 203, GE Vingmed Ultrasound, Horten, Norway). The LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were measured on the apical 4-chamber and 2-chamber views and LVEF was calculated according to Simpson's biplane method.[3] LA volume was measured on the apical 4-chamber and 2-chamber views at LV end-systole using the biplane method of disks[3] and indexed for body surface area (left atrial volume index). The severity of mitral regurgitation (MR) and tricuspid regurgitation was evaluated and graded according to current recommendations.[14−16] Echocardiographic loops which had at least 40 frame rates per second and no foreshortening were selected for 2D speckle-tracking echocardiography-derived LV GLS measurements from the apical long-axis, 4-chamber, and 2-chamber views.[3] The region of interest was automatically generated and manually adjusted to the myocardial thickness. LV GLS was subsequently averaged from 17 LV segments. LV GLS measurements in which the regional tracking was suboptimal on more than 2 myocardial segments were excluded from analysis. LV GLS values were reported as positive values.

The primary end point was worsening HF. The secondary end point was the composite of worsening HF and all-cause mortality. Data on mortality were obtained from the departmental cardiology information system (EPD-Vision, Leiden University Medical Centre, The Netherlands), which is linked to the governmental death registry database. Worsening HF was defined as the first hospital admission for worsening signs and symptoms of HF or a visit to the emergency department which required intensification of intravenous diuretics after the index echocardiography. Data on worsening HF were acquired by review of medical records which were archived in the departmental information system. Follow-up time was calculated from the date of index echocardiography at which LVEF ≤45% was first documented. All patients were followed up until the occurrence of the study end point, loss of follow-up, or September 2021.

Normally distributed continuous variables (assessed by the Shapiro-Wilk test and distribution histograms) are presented as mean ± SD and non- normally distributed variables as median and interquartile range (IQR). Categorical variables are presented as frequencies and percentages. To illustrate the change in hazard ratio (HR) for the primary and secondary end point across the range of baseline LV GLS, a spline curve was plotted. A baseline LV GLS value >10% was derived from the spline curve analysis, representing the value where the HR for the end point was >1 (Figure 1). Furthermore, baseline clinical and echocardiographic variables were compared between patients having an LV GLS ≤10% versus >10%. Continuous variables were compared using the independent samples *t* test when normally distributed, whereas the Mann−Whitney *U* test was used to compare continuous variables that were not normally distributed. Categorical variables were compared using chi-square tests. Univariable and multivariable Cox proportional hazard regression models were constructed to determine the relation between individual variables and study end points, and HRs with 95% confidence intervals (CIs) were reported. Variables that had a significant association with the univariable analysis ($p < 0.05$) were included in the multivariable model. To check the incremental value of baseline LVEF and LV GLS, 2 step multivariable analysis was constructed. In the first step, baseline LVEF was included in the multivariable analysis together with other significant variables, while baseline LV GLS was introduced into the second multivariable analysis. Additional unadjusted and adjusted spline curves were built to illustrate the change in HR across the spectrum of LVEF and LV GLS versus risk of worsening HF and the composite of worsening HF and all-cause mortality with overlaid CIs. The 5-year event-free survival rates were estimated by the Kaplan−Meier method and differences between groups were compared with the log-rank test. All statistical tests were 2-sided, and a $p < 0.05$ was considered to be statistically significant. Statistical analysis was performed using SPSS for Windows version 25.0 (IBM Corporation, Armonk, New York) and R version 4.2.0 (survival package v3.1-12, splines2 package v0.3.1, Greg package v1.3.4 and survminer 0.4.9 package, R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 1,873 patients (mean age 64 ± 12 years, 75% male) with a first echocardiographic diagnosis of LVEF ≤45% were included in the present study. Baseline characteristics of the overall population and according to the LV

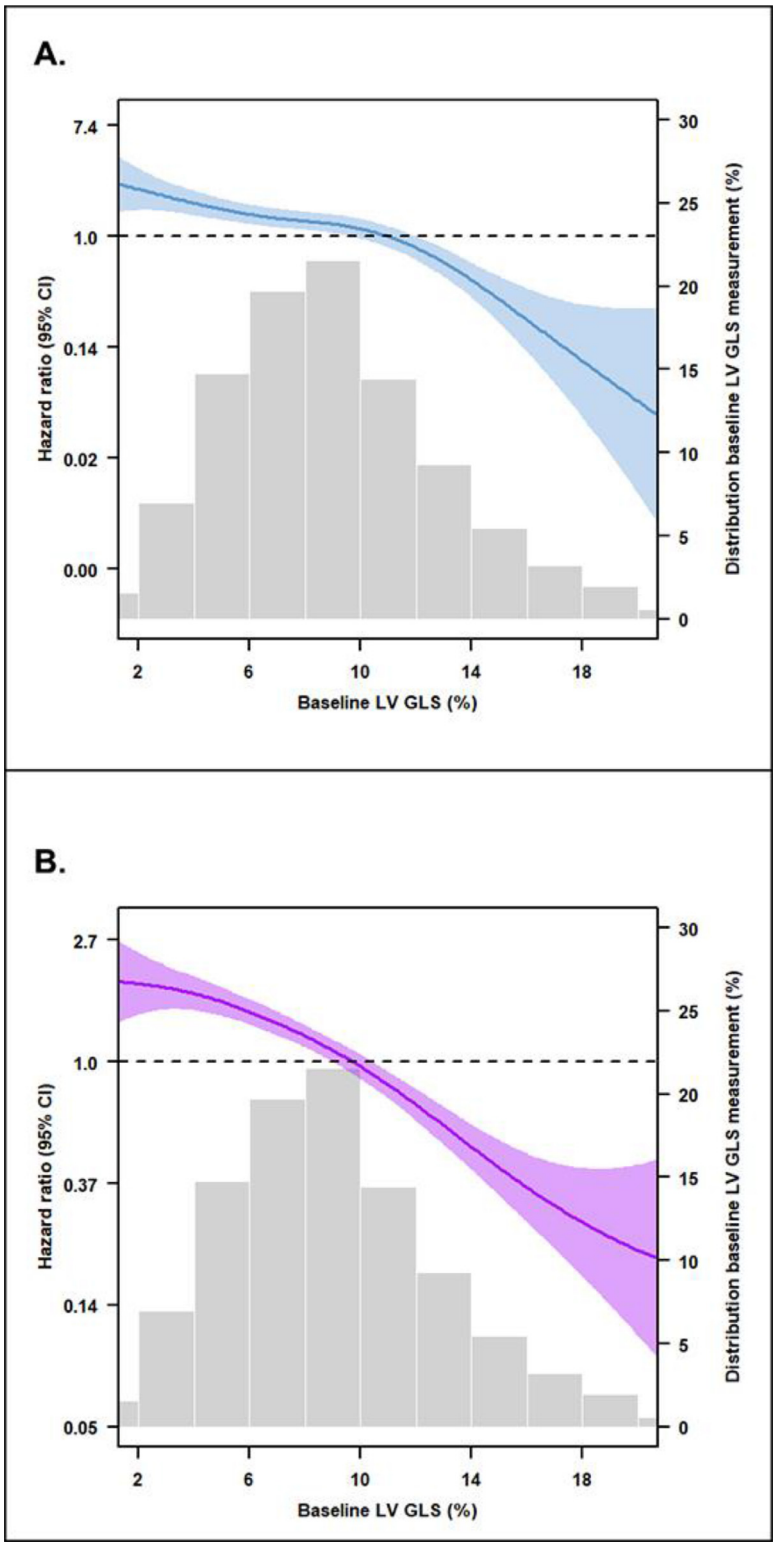

Figure 1. Spline curves for worsening HF (*A*) and the composite of worsening HF and all-cause mortality (*B*) across a range of baseline LV GLS, plotted as a hazard ratio with overlaid 95% confidence intervals.

GLS groups are listed in Table 1. Patients with LV GLS ≤10% were more likely older (65 ± 12 vs 62 ± 13 years, p <0.001), and the prevalence of diabetes mellitus (23% vs 17%, p <0.001), arterial hypertension (42% vs 36%, p <0.001), hyperlipidemia (30% vs 27%, p = 0.044), coronary artery disease (56% vs 53%, p = 0.040), chronic kidney disease (29% vs 16%, p <0.001) and atrial fibrillation (29% vs 16%, p = 0.001) were higher compared to patients

Table 1
Baseline characteristics

	Overall patient population (n=1873)	LV GLS ≤10% (n=1211)	LV GLS >10% (n=662)	p-value
Age (years)	64±12	65±12	62±13	<0.001
Male, n (%)	1405 (75%)	903 (75%)	502 (76%)	0.546
BSA (m^2)	1.98±0.22	1.98±0.23	1.97±0.20	0.184
Current smoker, n (%)	409 (22%)	236 (20%)	173 (26%)	0.006
Ex-smoker, n (%)	427 (23%)	291 (24%)	136 (21%)	0.019
DM, n (%)	385 (21%)	275 (23%)	110 (17%)	<0.001
Arterial hypertension, n (%)	742 (40%)	507 (42%)	235 (36%)	<0.001
Hyperlipidemia, n (%)	537 (29%)	360 (30%)	177 (27%)	0.044
Family history of CAD, n (%)	479 (26%)	271 (22%)	208 (31%)	<0.001
CAD, n (%)	1029 (55%)	676 (56%)	353 (53%)	0.040
MI, n (%)	989 (53%)	545 (45%)	444 (67%)	<0.001
COPD, n (%)	174 (9%)	131 (11%)	43 (7%)	0.134
CKD, n (%)	462 (25%)	355 (29%)	107 (16%)	<0.001
AF, n (%)	451 (24%)	345 (29%)	106 (16%)	0.001
Hemoglobin (g/dl)	14.8±2.5	14.7±2.5	14.9±2.3	0.208
eGFR (ml/min/1.73 m^2)	72±26	68±26	79±24	<0.001
PCI, n (%)	553 (30%)	336 (28%)	217 (33%)	0.022
CABG, n (%)	385 (21%)	283 (23%)	102 (15%)	<0.001
ICD implantation, n (%)	573 (31%)	456 (38%)	117 (18%)	<0.001
CRT implantation, n (%)	355 (19%)	302 (25%)	53 (8%)	<0.001
Valvular intervention, n (%)	399 (21%)	300 (25%)	99 (15%)	0.016
Beta-blocker, n (%)	1332 (71%)	840 (69%)	492 (74%)	0.287
ACEi/ARB, n (%)	1375 (73%)	845 (70%)	530 (80%)	<0.001
MRAs, n (%)	479 (26%)	399 (33%)	80 (12%)	<0.001
Ca2+ channel antagonist, n (%)	216 (12%)	121 (10%)	95 (14%)	0.011
Diuretics, n (%)	954 (51%)	765 (63%)	189 (29%)	<0.001
OACs, n (%)	791 (42%)	612 (51%)	179 (27%)	<0.001
Anti-arrhythmic, n (%)	262 (14%)	213 (18%)	49 (7%)	<0.001
Digoxin, n (%)	156 (8%)	132 (11%)	24 (4%)	<0.001
Statin, n (%)	1260 (67%)	774 (64%)	486 (73%)	0.001
LVEDV (ml)	146±72	160±77	120±51	<0.001
LVESV (ml)	102±58	116±63	76±35	<0.001
LVEF (%)	31±8.7	29±8.4	36±6.7	<0.001
LAVi (ml/m^2)	37±20	41±19	30±20	<0.001
Moderate-to-severe MR, n (%)	638 (34%)	493 (41%)	145 (22%)	<0.001
Moderate-to-severe TR, n (%)	418 (22%)	332 (27%)	86 (13%)	<0.001
LV GLS (%)	9.1±4.0	6.7±2.2	13.4±2.8	<0.001

Values are mean ± SD.

ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BSA = body surface area; CABG = coronary artery bypass graft; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; DM = diabetes mellitus; ICD = implantable cardioverter-defibrillator; LAVi = left atrial volume index; LVEDV = left ventricular end-diastolic volume; LVEDV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; MR = mitral regurgitation; OACs = oral anticoagulants; PCI = percutaneous coronary intervention; TR = tricuspid regurgitation.

with LV GLS >10%. In contrast, patients with LV GLS ≤10% were less likely to have a family history of coronary artery disease (22% vs 31%, p <0.001) and previous history of myocardial infarction (MI) (45% vs 67%, p <0.001) compared to patients with LV GLS >10%.

After the initial echocardiographic diagnosis of LVEF ≤45%, invasive procedures (including PCI, CABG, ICD, and CRT implantation and valvular interventions [surgical or transcatheter]), were performed within 1-year if indicated. Patients with LV GLS ≤10% were more likely to be treated with CABG (23% vs 15%, p <0.001), ICD implantation (38% vs 18%, p <0.001), CRT implantation (25% vs 8%, p <0.001), and valvular intervention (25% vs 15%, p = 0.016), but were less likely to be treated with PCI (28% vs 33%, p = 0.022) when compared to patients with LV GLS >10%. Similarly, GDMT was started or intensified within 1 year, and use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (70% vs 80%, p <0.001), calcium channel antagonists (10% vs 14%, p = 0.011) and statins (64% vs 73%, p = 0.001) were significantly lower, whereas use of mineralocorticoid antagonists (33% vs 12%, p <0.001), diuretics (63% vs 29%, p <0.001), oral anticoagulants (51% vs 27%, p <0.001), antiarrhythmic therapies (18% vs 7%, p <0.001) and digoxin (11% vs 4%, p <0.001) were significantly higher in the LV GLS ≤10% group compared with the LV GLS >10% group.

LVEDV (160 ± 77 ml vs 120 ± 51 ml, p <0.001), LVESV (116 ± 63 ml vs 76 ± 35 ml, p <0.001), and LA volume index (41 ± 19 ml/m^2 vs 30 ± 20 ml/m^2, p <0.001)

were significantly more dilated in the LV GLS ≤10% group compared with the LV GLS >10% group. The presence of moderate-to-severe MR (41% vs 22%, p <0.001) and tricuspid regurgitation (27% vs 13%, p <0.001) was significantly higher in patients with LV GLS ≤10% compared with patients with LV GLS >10%.

During a median follow-up of 60 (IQR 27 to 60) months, 256 patients (14%) experienced worsening HF. Cumulative event rates for worsening HF at 5 years follow-up were significantly higher in the LV GLS ≤10% group (20%, CI 18% to 22%) compared with the LV GLS >10% group (95%, CI 7% to 11%) (p <0.001). Patients with LV GLS ≤10% had a significantly lower event-free survival rate compared with patients with LV GLS >10% (log-rank p <0.0001) (Figure 2).

The association between baseline LV GLS and worsening HF was tested using univariable and multivariable Cox proportional hazard models (Table 2). Baseline LVEF was significantly associated with worsening HF in the univariable analysis (HR 0.97, 95% CI 0.96 to 0.98, p <0.001). With higher baseline LVEF, there was a gradual decrease in the risk of worsening HF, particularly a baseline LVEF >35% was associated with decreased risk of worsening HF in a spline curve (Figure 3, light blue spline curve). However, the parameter lost the significant association when adjusted for other significant covariates (HR 1.01, 95% CI 0.97 to 1.05, p = 0.541). When adjusted for other significant predictors, baseline LVEF was not associated with risk of worsening HF in spline curve analysis (Figure 3, light blue spline curve).

In contrast, LV GLS was significantly associated with the occurrence of worsening HF, and a higher baseline LV GLS portended a better prognosis in both the univariable (HR 0.88, 95% CI 0.85 to 0.91, p <0.001) (Figure 3, light blue spline curve) and multivariable analysis (HR 0.95, 95% CI 0.90 to 0.99, p = 0.032) (Figure 3, light blue spline curve).

After a median follow-up of 60 (IQR 27 to 60) months, the composite end point of worsening HF and all-cause mortality occurred in 573 patients (31%). Cumulative event rates at 5 years follow-up were significantly higher in the LV GLS ≤10% group (40%, CI 36% to 44%) compared with the LV GLS >10% group (19%, CI 15% to 23%) (p <0.001). The 5-year event-free survival rates for the composite end point of worsening HF and all-cause mortality were significantly lower for patients with LV GLS ≤10% compared with patients with LV GLS >10% (log-rank p <0.0001) (Figure 2).

LVEF was significantly associated with the composite end point on the univariable analysis (HR 0.97, 95% CI 0.96 to 0.98, p <0.001) but not on the multivariable analysis, after adjustment for other prognostically relevant covariates (HR 0.99, 95% CI 0.97 to 1.02, p = 0.576). The unadjusted spline curve demonstrated that baseline LVEF >35% was associated with decreased risk of the composite of worsening HF and all-cause mortality (Figure 3, purple spline curve). However, baseline LVEF was not significantly associated with the composite end point when adjusted for other significant predictors on adjusted spline curve analysis (Figure 3, purple spline curve). In contrast, higher baseline LV GLS values were significantly associated with a reduced risk of the composite end point of worsening HF and all-cause mortality in both the univariable (HR 0.89, 95% CI 0.87 to 0.91, p <0.001) and multivariable analysis (HR 0.94, 95% CI 0.90 to 0.97, p = 0.001; Table 3). Furthermore, baseline LV GLS >10% was significantly associated with decreased risk of the composite end point in both unadjusted and adjusted spline curves (Figure 3, purple spline curve).

Discussion

The results of the present study, including patients with HF and reduced LVEF, can be summarized as follows: (1) LV GLS is independently associated with HF hospitalizations and all-cause mortality; and (2) LV GLS provides incremental prognostic value, even after adjustment for traditional risk factors, including LVEF.

Categorization and risk stratification of patients with HF are mostly based on LVEF, which is calculated from a volumetric estimation of LVEDV and LVESV.[4,5] However, the assessment of LV systolic function with LVEF has several limitations, including its reliance on geometrical assumptions which are influenced by LV shape.[6] In addition, LVEF overestimates LV systolic function in patients with significant mitral and aortic regurgitation because of the retrograde flow into the LA and LV during systole and diastole, respectively.[7]

LV GLS could be a better parameter to assess LV systolic performance and at least partially overcomes the limitations of LVEF. LV GLS quantifies active myocardial deformation, is better associated with longitudinal deformation (which is impaired at an earlier stage), and indirectly reflects structural changes in the myocardium including fibrosis.[6] In a study comparing patients with nonischemic dilated cardiomyopathy who were matched for LVEF and who had significant MR versus those who did not, Kamperidis et al[10] demonstrated that baseline LV GLS had already significantly decreased in the group of patients with significant MR. Moreover, Ewe et al[9] showed that LV GLS was more impaired in symptomatic than in asymptomatic patients with moderate-to-severe aortic regurgitation, despite a preserved LVEF.

LV GLS has also been shown to be a sensitive marker to detect LV myocardial fibrosis in patients with HF. Cameli et al[17] demonstrated in 47 patients who underwent cardiac transplantation because of advanced HF, that LV GLS, but not LVEF, was strongly correlated with myocardial fibrosis on histological examination. In addition, Ota et al[18] examined LV GLS with echocardiography and replacement fibrosis by late-gadolinium-enhanced cardiac magnetic resonance in patients with nonischemic cardiomyopathy (LVEF <50%) and revealed that LV GLS was significantly impaired in patients who had replacement fibrosis. In the present study, the proportion of patients with significant MR was 34% and the prevalence of patients with previous MI was 53%. Significant MR and previous MI are conditions in which LVEF could overestimate LV systolic function or the degree of myocardial fibrosis, respectively. In these conditions, LV GLS could be more accurate than LVEF.

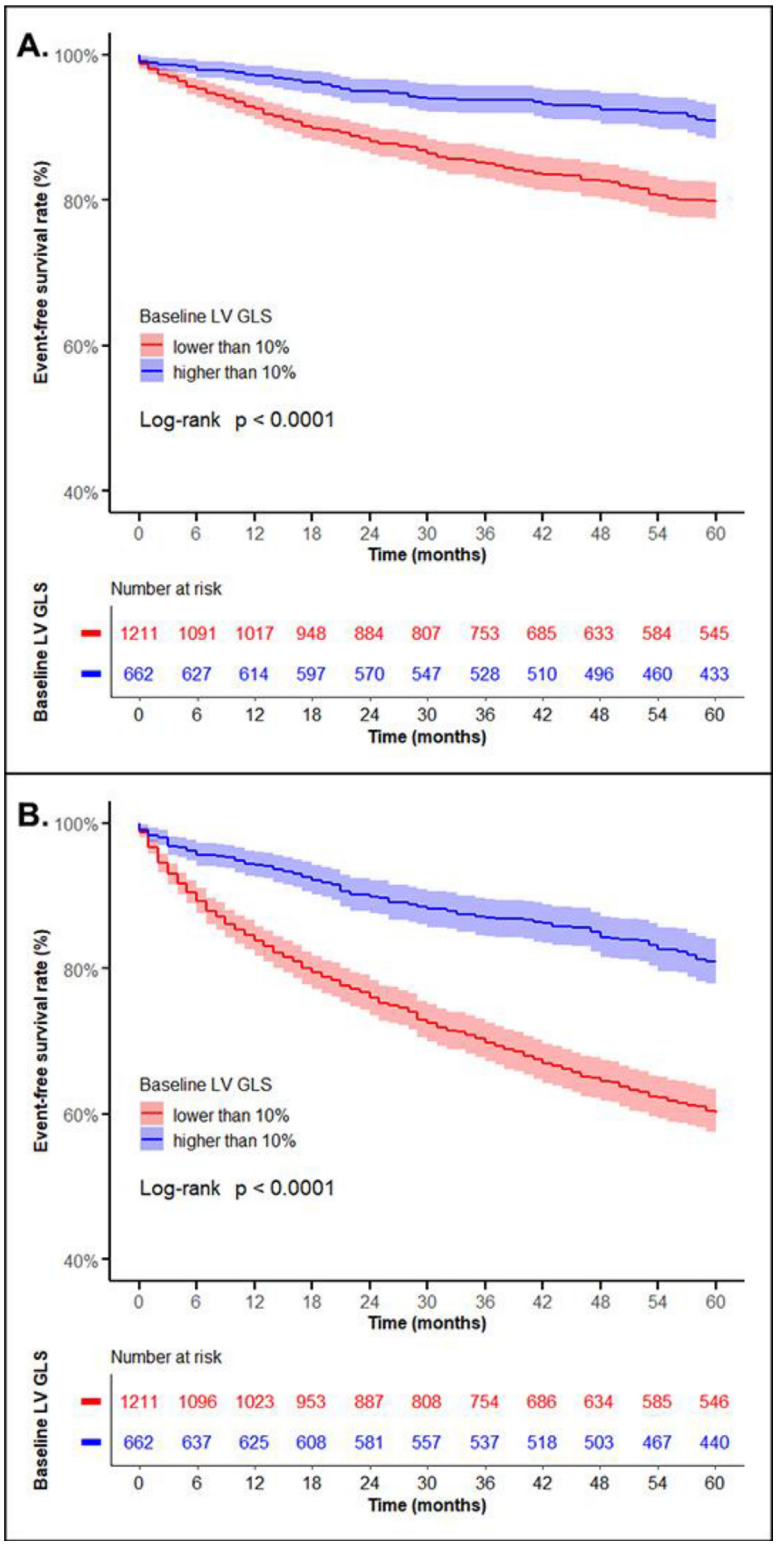

Figure 2. Kaplan−Meier curves for worsening HF (*A*) and the composite of worsening HF and all-cause mortality (*B*) stratified by optimal threshold value of baseline LV GLS.

Besides the observation that LV GLS is a more accurate marker of LV systolic dysfunction, LV GLS could also have prognostic implications in patients with HFrEF. Some studies have already shown the prognostic value of LV GLS in patients with HF.[19,20] However, these studies included a limited number of patients or did not consider alternative echocardiographic variables. In 1,065 patients with HF and reduced LVEF, Sengeløv et al[21] demonstrated that LV GLS was independently associated with all-cause mortality. The present study, which includes an

Table 2
Univariable and multivariable analysis for worsening HF

	Univariable analysis			Multivariable analysis without LV GLS			Multivariable analysis with LV GLS		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.00	0.99-1.01	0.757						
Male	1.31	0.97-1.77	0.081						
BSA	1.26	0.73-2.18	0.405						
Current smoker	0.91	0.67-1.23	0.525						
Ex-smoker	1.17	0.88-1.56	0.286						
DM	1.32	0.99-1.77	0.059						
Arterial hypertension	1.10	0.85-1.42	0.469						
Hyperlipidemia	1.00	0.76-1.31	0.975						
Family history of CAD	1.08	0.82-1.43	0.585						
CAD	1.48	1.12-1.96	0.006	1.09	0.76-1.58	0.635	1.07	0.73-1.55	0.739
MI	1.04	0.80-1.35	0.772						
COPD	1.36	0.93-1.97	0.110						
CKD	1.45	1.09-1.93	0.011	0.77	0.46-1.30	0.327	0.75	0.45-1.27	0.284
AF	1.23	0.94-1.63	0.135						
Hemoglobin*	1.06	1.00-1.13	0.061						
eGFR*	0.92	0.87-0.97	0.001	0.94	0.85-1.05	0.287	0.94	0.85-1.05	0.256
PCI	1.35	1.04-1.76	0.026	1.51	1.07-2.12	0.018	1.54	1.09-2.17	0.014
CABG	1.20	0.90-1.61	0.216						
ICD implantation	2.49	1.88-3.29	<0.001	2.43	1.65-3.57	<0.001	2.42	1.65-3.55	<0.001
CRT implantation	1.96	1.50-2.56	<0.001	0.84	0.58-1.20	0.337	0.84	0.58-1.20	0.332
Valvular intervention	0.88	0.65-1.20	0.422						
Beta-blocker	1.30	0.91-1.88	0.155						
ACEi/ARB	0.97	0.67-1.38	0.849						
MRAs	1.40	1.07-1.84	0.013	0.83	0.60-1.15	0.260	0.82	0.59-1.13	0.216
Ca2+ channel antagonist	1.32	0.93-1.87	0.122						
Diuretics	2.70	1.91-3.81	<0.001	2.02	1.29-3.14	0.002	1.84	1.17-2.87	0.008
OACs	1.54	1.17-2.03	0.002	0.92	0.65-1.29	0.614	0.88	0.63-1.23	0.455
Anti-arrhythmic	1.77	1.32-2.38	<0.001	1.23	0.87-1.74	0.238	1.23	0.87-1.73	0.248
Digoxin	1.98	1.41-2.79	<0.001	1.76	1.20-2.57	0.004	1.70	1.16-2.49	0.007
Statin	1.12	0.82-1.54	0.476						
LVEDV*	1.04	1.03-1.06	<0.001	0.93	0.79-1.08	0.331	0.94	0.80-1.10	0.414
LVESV*	1.05	1.03-1.07	<0.001	1.12	0.92-1.37	0.268	1.10	0.90-1.35	0.365
LAVi	1.01	1.01-1.02	<0.001	1.00	1.00-1.01	0.274	1.00	1.00-1.01	0.278
Moderate-to-severe MR	1.60	1.25-2.06	<0.001	1.09	0.78-1.51	0.612	1.08	0.78-1.50	0.631
Moderate-to-severe TR	1.54	1.17-2.01	0.002	1.36	0.97-1.91	0.078	1.32	0.94-1.86	0.108
LVEF	0.97	0.96-0.98	<0.001	1.01	0.97-1.05	0.541	1.02	0.98-1.06	0.399
LV GLS	0.88	0.85-0.91	<0.001	-	-	-	0.95	0.90-0.99	0.032

* 10 unit increase.

ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BSA = body surface area; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; DM = diabetes mellitus; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LAVi = left atrial volume index; LVEDV = left ventricular end-diastolic volume; LVEDV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; LV GLS = left ventricular global longitudinal strain; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; MR = mitral regurgitation; OACs = oral anticoagulants; PCI = percutaneous coronary intervention; TR = tricuspid regurgitation.

even larger population, expands on these results and confirms that LV GLS is independently associated with all-cause mortality and provides incremental prognostic value over LVEF in patients with HFrEF. In addition, the present study adjusted for many more baseline clinical and echocardiographic variables, and medical and surgical (including coronary revascularization, valvular intervention, ICD, and CRT) treatments for HF. Consequently, these results show that baseline LV GLS remains strongly and independently associated with outcomes, even after starting or optimizing GDMT for HFrEF. Interestingly, in the present study, LV GLS was also significantly associated with worsening HF which was not evaluated previously.[21] Worsening HF despite optimal GDMT may indicate progression of underlying disease,[22,23] which has been shown to be associated with poor prognosis in large population-based registries,[24–26] and is increasingly used as an outcome parameter in major HF trials.[27–29] As such, the prognostic value of LV GLS for the end point of worsening HF provides additional value in patients with HF and LV systolic dysfunction.

The assessment of LV GLS may improve risk stratification and clinical decision-making in patients with HF and reduced LVEF. In patients with a recovered LVEF after introduction of optimal GDMT, an abnormal LV GLS value (≤16%) predicted the likelihood of developing a decreased LVEF during follow-up, whereas a normal LV GLS (>16%) predicted the likelihood of stable LVEF during

Table 3
Univariable and multivariable analysis for the composite of worsening HF and all-cause mortality

	Univariable analysis			Multivariable analysis without LV GLS			Multivariable analysis with LV GLS		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.02	1.02-1.03	<0.001	1.01	1.00-1.02	0.118	1.01	1.00-1.02	0.240
Male	1.28	1.05-1.57	0.015	1.22	0.93-1.60	0.145	1.26	0.96-1.65	0.101
BSA	0.88	0.60-1.28	0.491						
Current smoker	0.89	0.72-1.09	0.251						
Ex-smoker	1.07	0.88-1.30	0.518						
DM	1.71	1.42-2.06	<0.001	1.21	0.96-1.52	0.102	1.19	0.95-1.50	0.134
Arterial hypertension	1.12	0.94-1.33	0.219						
Hyperlipidemia	1.13	0.94-1.35	0.197						
Family history of CAD	0.87	0.72-1.06	0.165						
CAD	1.38	1.15-1.66	0.001	1.16	0.92-1.46	0.211	1.15	0.91-1.45	0.250
MI	0.94	0.79-1.12	0.471						
COPD	1.59	1.25-2.02	<0.001	1.29	0.98-1.71	0.075	1.28	0.97-1.69	0.084
CKD	2.28	1.90-2.74	<0.001	1.07	0.74-1.53	0.730	1.05	0.73-1.50	0.807
AF	1.33	1.10-1.60	0.003	0.98	0.76-1.26	0.873	0.96	0.75-1.24	0.766
Hemoglobin*	0.96	0.92-1.00	0.025	1.02	0.97-1.07	0.461	1.01	0.97-1.06	0.609
eGFR*	0.83	0.80-0.86	<0.001	0.92	0.85-0.99	0.034	0.92	0.85-0.99	0.024
PCI	1.11	0.93-1.34	0.249						
CABG	1.20	0.98-1.46	0.072						
ICD implantation	1.36	1.13-1.63	0.001	1.23	0.93-1.63	0.139	1.24	0.94-1.63	0.135
CRT implantation	1.28	1.05-1.56	0.013	0.84	0.63-1.11	0.211	0.83	0.63-1.10	0.195
Valvular intervention	0.98	0.80-1.20	0.826						
Beta-blocker	0.83	0.67-1.03	0.092						
ACEi/ARB	0.62	0.50-0.77	<0.001	0.72	0.56-0.94	0.016	0.75	0.57-0.97	0.030
MRAs	1.28	1.06-1.54	0.010	0.95	0.76-1.19	0.661	0.93	0.74-1.17	0.531
Ca2+ channel antagonist	1.19	0.94-1.52	0.155						
Diuretics	2.91	2.28-3.70	<0.001	2.14	1.56-2.93	<0.001	1.95	1.42-2.68	<0.001
OACs	1.46	1.21-1.76	<0.001	1.09	0.84-1.40	0.527	1.03	0.80-1.33	0.806
Anti-arrhythmic	1.57	1.27-1.93	<0.001	1.21	0.94-1.56	0.136	1.20	0.93-1.55	0.158
Digoxin	1.59	1.24-2.04	<0.001	1.29	0.96-1.73	0.096	1.25	0.93-1.68	0.137
Statin	1.02	0.83-1.25	0.872						
LVEDV*	1.03	1.01-1.04	<0.001	1.01	0.90-1.13	0.884	1.03	0.92-1.15	0.653
LVESV*	1.04	1.02-1.05	<0.001	1.00	0.87-1.16	0.971	0.97	0.84-1.13	0.711
LAVi	1.01	1.01-1.01	<0.001	1.00	0.99-1.01	0.802	1.00	0.99-1.01	0.837
Moderate-to-severe MR	1.65	1.40-1.95	<0.001	1.00	0.80-1.26	0.977	1.00	0.79-1.26	0.974
Moderate-to-severe TR	1.59	1.33-1.91	<0.001	1.15	0.90-1.46	0.257	1.12	0.88-1.43	0.342
LVEF	0.97	0.96-0.98	<0.001	0.99	0.97-1.02	0.576	1.00	0.97-1.02	0.811
LV GLS	0.89	0.87-0.91	<0.001	-	-	-	0.94	0.90-0.97	0.001

* 10 unit increase.

ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BSA = body surface area; CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; DM = diabetes mellitus; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LAVi = left atrial volume index; LVEDV = left ventricular end-diastolic volume; LVEDV = left ventricular end-systolic volume; LVEF = left ventricular ejection fraction; LV GLS = left ventricular global longitudinal strain; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; MR = mitral regurgitation; OACs = oral anticoagulants; PCI = percutaneous coronary intervention; TR = tricuspid regurgitation.

follow-up.[30] Mandoli et al[31] investigated the value of LV GLS to predict LV reverse remodeling in 341 patients with HFrEF who were treated with an angiotensin receptor neprilysin inhibitor. Patients who showed complete LV reverse remodeling (>10% reduction in LVESV and LVEF ≥35%) at 6 months follow-up had higher LV GLS values at baseline compared with those showing incomplete reverse remodeling (≤10% reduction in LVESV but LVEF ≥35%) or no reverse remodeling (≤10% reduction in LVESV and LVEF <35%). LV GLS also showed an incremental prognostic value compared with LVEF when used for risk stratification of patients with HF and significant secondary MR.[32,33] In patients who were treated with transcatheter mitral valve repair in the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation), LV GLS was independently associated with outcomes at 10 months follow-up.[32] In 829 HF patients who received CRT, Khidir et al[34] demonstrated that baseline LV GLS was significantly associated with the composite end point of all-cause mortality, heart transplantation and LV assist device implantation. Altogether, the previously mentioned studies suggest that LV GLS provides incremental prognostic value over LVEF when risk-stratifying patients with HFrEF who underwent HF-directed medical or device therapy.

The present study has several limitations. Data used in the present study were derived from a single center and

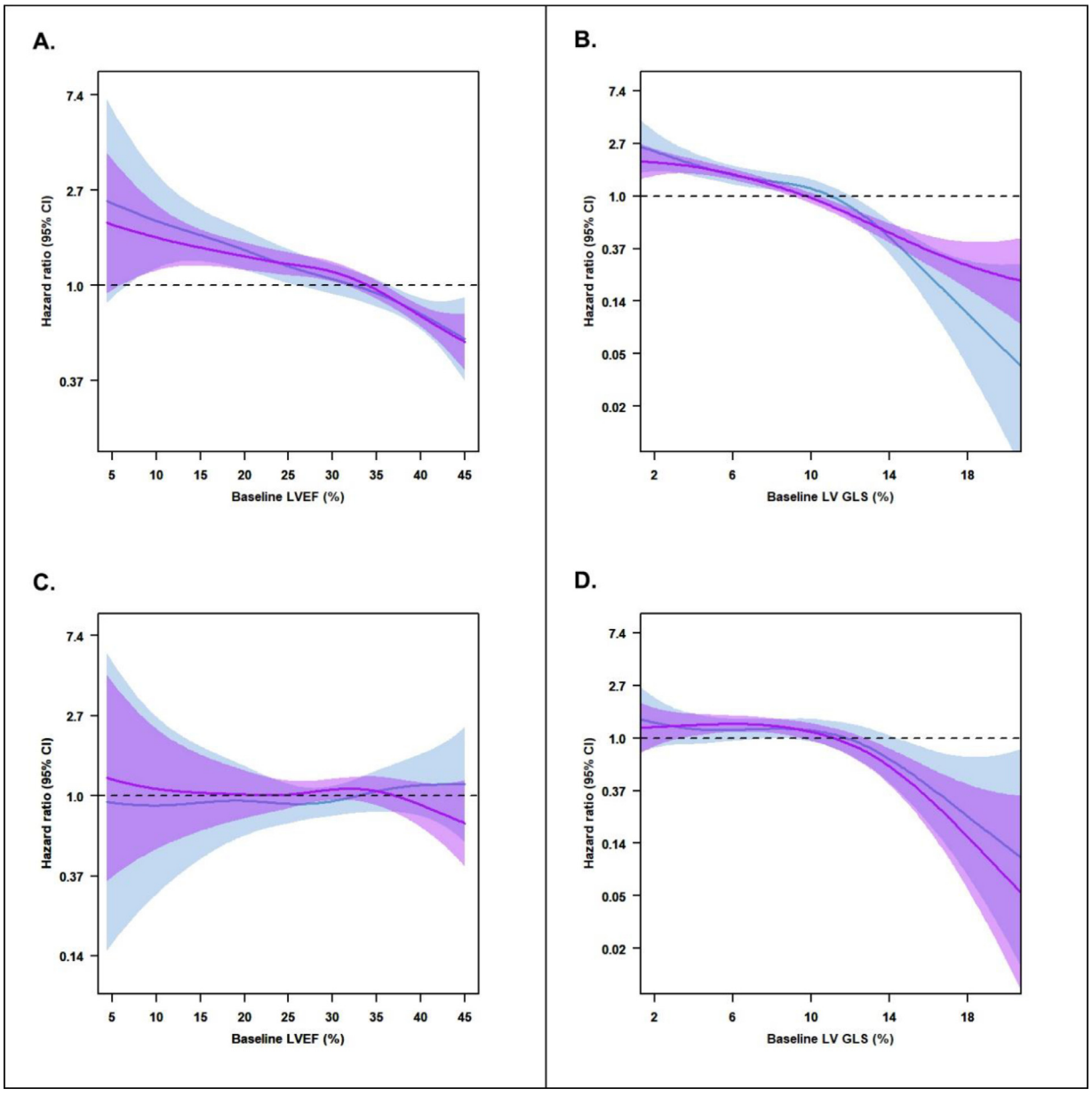

Figure 3. Unadjusted (*A, B*) and adjusted (*C, D*) spline curves for worsening HF (*light blue*) and the composite of worsening HF and all-cause mortality (*purple*) across a range of baseline LVEF (*A, C*) and baseline LV GLS (*B, D*), plotted as a hazard ratio with overlaid 95% confidence intervals.

were analyzed retrospectively. Patients with insufficient echocardiographic image quality for LV GLS analysis were excluded, which could result in selection bias. LV GLS is vendor-dependent, and values cannot be compared directly across different echo platforms. Mortality data were limited by all-cause death, and it was not possible to differentiate between cardiac versus noncardiac causes of death.

In conclusion, baseline LV GLS is a sensitive parameter to estimate LV systolic function and is independently associated with long-term outcomes in patients with HFrEF. LV GLS showed incremental prognostic value when compared to LVEF and the incorporation of LV GLS in clinical practice should therefore be considered to improve risk stratification of patients with HFrEF.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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