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ORIGINAL RESEARCH

Global Longitudinal Strain is Incremental to Left Ventricular Ejection Fraction for the Prediction of Outcome in Optimally Treated Dilated Cardiomyopathy Patients

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BACKGROUND: Speckle tracking echocardiographic global longitudinal strain (GLS) predicts outcome in patients with new onset heart failure. Still, its incremental value on top of left ventricular ejection fraction (LVEF) in patients with nonischemic, nonvalvular dilated cardiomyopathy (DCM) after optimal heart failure treatment remains unknown.

METHODS AND RESULTS: Patients with DCM were included at the outpatient clinics of 2 centers in the Netherlands and Italy. The prognostic value of 2-dimensional speckle tracking echocardiographic global longitudinal strain was evaluated when being on optimal heart failure medication for at least 6 months. Outcome was defined as the combination of sudden or cardiac death, life-threatening arrhythmias, and heart failure hospitalization. A total of 323 patients with DCM (66% men, age 55±14 years) were included. The mean LVEF was 42%±11% and mean GLS after optimal heart failure treatment was –15%±4%. Twenty percent (64/323) of all patients reached the primary outcome after optimal heart failure treatment (median follow-up of 6[4–9] years). New York Heart Association class ≥3, LVEF, and GLS remained associated with the outcome in the multivariable-adjusted model (New York Heart Association class: hazard ratio [HR], 3.43; 95% CI, 1.49–7.90, P=0.004; LVEF: HR, 2.13; 95% CI, 1.11–4.10, P=0.024; GLS: HR, 2.24; 95% CI, 1.18–4.29, P=0.015), whereas left ventricular end-diastolic diameter index, left atrial volume index, and delta GLS were not. The addition of GLS to New York Heart Association class and LVEF improved the goodness of fit (log likelihood ratio test P<0.001) and discrimination (Harrell's C 0.703).

CONCLUSIONS: Within this bicenter study, GLS emerged as an independent and incremental predictor of adverse outcome, which exceeded LVEF in patients with optimally treated DCM. This presses the need to routinely include GLS in the echocardiographic follow-up of DCM.

Key Words: deformation imaging ■ dilated cardiomyopathy ■ global longitudinal strain ■ optimal medical treatment ■ prognosis

Dilated cardiomyopathy (DCM) is characterized by the presence of left ventricular (LV) systolic dysfunction and LV dilation, in the absence of significant coronary artery disease and abnormal loading conditions, such as valvular and hypertensive heart disease.[1] The prognosis of DCM significantly improved over the past years as a result of the cumulative benefit of evidence-based heart failure (HF) therapy.[2,3] A

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CLINICAL PERSPECTIVE

What Is New?

- This is the first study that evaluates the prognostic value of global longitudinal strain with respect to left ventricle ejection fraction in patients with dilated cardiomyopathy whot are optimally treated with heart failure medication.
- In the present bicenter study, global longitudinal strain emerged as an independent and incremental predictor of adverse outcome, which exceeded left ventricle ejection fraction in patients with dilated cardiomyopathy who are optimally treated.

What Are the Clinical Implications?

- Considering its quality to detect more subtle myocardial dysfunction, accompanied by its incremental value in risk stratification of patients with dilated cardiomyopathy who are optimally treated, global longitudinal strain should be routinely included in the management and prognostic risk stratification of patients with dilated cardiomyopathy on top of left ventricle ejection fraction, especially after the first year of heart failure therapy optimization has taken place.

Nonstandard Abbreviations and Acronyms

DCM	dilated cardiomyopathy
GLS	global longitudinal strain
LTA	life-threatening arrhythmias
OMT	optimal medical therapy

substantial number of patients with DCM have a significant improvement of cardiac function, and thereby their prognosis may also improve.[4–7] In a group of 5010 patients with HF and an initial LV ejection fraction (LVEF) <35%, 9% improved to a LVEF>40% within 12 months follow-up and had a better survival compared with patients with persistent reduced LVEF.[6] Patients with improved LVEF (≥40%) had fewer HF hospitalizations and a lower mortality rate.[4] Still, event rates—even after improvement upon optimal medical therapy (OMT)—are highly prevalent within this relatively young (30–50 years of age) patient population, and patients with DCM and improved/recovered LVEF still have a worse prognosis compared with healthy patients.[2,6,8] Risk stratification remains challenging, especially during the chronic phase, also because of the dynamic course of this heterogeneous disease.[3,9]

Currently, LVEF is seen as an important echocardiographic parameter for risk stratification of patients with DCM.[3,5,10,11] However, LVEF does not take into account the amount of myocardial tissue that is responsible for this volumetric change.[12] In-depth assessment of cardiac systolic function using global longitudinal strain (GLS) reveals systolic abnormalities despite normal LVEF, which are associated with worse outcome.[13,14] These findings could be explained by the fact that LVEF is predominantly related to LV circumferential shortening, whereas GLS depicts LV longitudinal shortening.[15,16] Because myofibers in the vulnerable subendocardium are responsible for longitudinal shortening, GLS may better detect subtle changes in myocardial tissue[17,18] and is able to predict recovery of LVEF.[19] Previous studies acclaimed GLS also as an important predictor of prognosis in patients with HF and reduced systolic function.[20–23] These studies, however, did not take into account the fact that LVEF can improve or even recover upon OMT, which assumably results in better prognosis. In addition, a substantial group of patients with HF and recovered LVEF still tends to have a bad prognosis.[13] Therefore, we tested the hypothesis that GLS is the best predictor of outcome in patients with DCM on OMT for at least 6 months, irrespective of (recovered) LVEF.

METHODS

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

Study Design

Two European DCM registries participated in this retrospective multicenter study. Consecutive patients were prospectively enrolled in both Trieste Heart Muscle Disease Registry, Italy (between 2006 and 2018) and Maastricht Cardiomyopathy Registry, the Netherlands (between 2004 and 2018). The DCM diagnosis was defined in accordance with the World Health Organization criteria.[1] The diagnosis of DCM was confirmed using the World Health Organization/International Society and Federation of Cardiology definition, based on reduced LVEF and increased LV end-diastolic diameter indexed to body surface area, compared with published age- and sex-specific reference values.[24] In keeping with guidelines,[24–26] exclusion criteria included (1) myocardial infarction and/or significant coronary artery disease (stenosis>50%, ruled out by coronary artery angiography or computed tomography); (2) primary valvular disease; (3) hypertensive or congenital heart disease; (4) acute myocarditis; (5) arrhythmogenic right ventricular dysplasia; and (6) hypertrophic, restrictive, or peripartum cardiomyopathy.

Patients presented themselves at the specialized outpatient clinic after a diagnostic workup and initiation and

optimization of HF therapy to evaluate the improvement of cardiac function. All patients underwent a physical examination and an echocardiogram, at least 6 months after achieving OMT. Patients included in both registries were selected for this study based on the following criteria: (1) time between evaluation echocardiography and achieving OMT at least 6 months; and (2) echocardiographic images available and of sufficient quality for offline analysis. The study was performed according to the Helsinki declaration and was approved by local ethics committees. All patients gave written informed consent.

Follow-Up

Information about the occurrence of adverse events during follow-up was retrieved from the medical records up to December 2020. Follow-up data on sudden or cardiac death, heart transplantation or left ventricular assistant device, life-threatening arrhythmias (LTA), and HF hospitalization were collected. LTAs were defined as nonfatal ventricular fibrillation and/or hemodynamic unstable ventricular tachycardia (with or without appropriate implantable cardioverter-defibrillator shock). Information about the occurrence of LTAs was retrieved from medical patient records; dismissal letters, Holter monitoring, device readouts, and available ECGs. The primary end point was a combination of sudden or cardiac death including heart transplantation or left ventricular assistant device, HF hospitalization, and LTAs.

Echocardiography and Measurement of GLS

Echocardiographic measurements were performed on a phased-array echocardiographic Doppler system (iE33 system with S5-1 or X5-1 transducers, Philips Medical Systems, Best, the Netherlands), following the latest guidelines for cardiac chamber quantification.[27] Normal or recovered LVEF was defined as LVEF ≥50% upon OMT, as described in the current European Society of Cardiology guideline.[24] Patients with recovered LVEF showed improvement to LVEF ≥50% after having either an initial LVEF <40% or having an absolute increase in LVEF of at least 10%. Two-dimensional speckle tracking echocardiography was performed in the apical 2-, 3-, and 4-chamber views according to current recommendation.[15] The measurements were performed offline using dedicated software (TomTec Arena v2.0, TomTec imaging Systems, Unterschleissheim, Germany) by 2 trained independent investigators (AR – Maastricht and AB – Trieste), blinded to outcome. The endocardial border was traced automatically in the end-diastolic frame; the software subsequently and automatically traced the borders in the other frames. The investigators visually assessed the detected endocardial border and, if necessary, manually adapted the tracing to ensure correct tracing of the contours. GLS was calculated by the software as a composite of all values from the 3 views. Delta GLS was calculated by subtracting the baseline GLS value from the follow-up GLS value. A random selection of 27 echocardiograms was analyzed twice by 2 independent analyzers to evaluate the interobserver variability. In addition, to assess the intraobserver variability, both analyzers reanalyzed 20 echocardiograms.

Statistical Analysis

Variables are displayed as numbers (percentage), mean±SD, or median (interquartile range) as appropriate. Normality was assessed by the Shapiro-Wilk test visually using qq-plots and histograms. Comparisons between groups were performed using X^2 tests (or Fisher exact where necessary) for categorical variables and independent samples *t* test for normally distributed, or Mann-Whitney *U* test for not normally distributed, continuous variables. Inter- and intraobserver variability was assessed by Bland-Altman plots. The mean difference and 95% limits of agreement (LOA), which are defined as the average difference (assumed to be 0 in cases of no consistent bias) ±1.96 SD, were calculated. The strength of the inter- and intraobserver variability was analyzed using intraclass correlation coefficients based on absolute agreement, 2-way mixed-effects model. Missing data (4%, <2% per variable) was imputed using multiple imputations by chained equations with predictive mean matching (MICE-Package in R) creating 10 imputed data sets. Pooling of the downstream analysis was performed by applying Ruben's rule. Linearity was visually assessed using Martingale residual plots. Given the nonlinearity of age, systolic blood pressure, LVEF, LV end-diastolic diameter index, left atrial volume index, and GLS, cubic spline analysis was performed to adjust for nonlinearity. After spline adjustment, all continuous variables were dichotomized. The cutoff for dichotomization was defined as hazard ratio (HR)=1 to provide easily interpretable parameters for clinical use. Spline-adjusted associations for GLS and delta GLS with the outcome are depicted in Figure S1 as example. Univariable and multivariable Cox proportional hazards regression analyses were applied to determine the HR and subsequent 95% CI. To take possible center differences into account, center-specific regression models were performed. To test whether GLS improved risk prediction of the clinical parameters, we performed a likelihood ratio test and calculated Harrel's C-indexes. A Kaplan-Meier survival curve was produced and differences between groups were assessed by the log-rank test and pairwise comparison. Statistical analysis was performed using SPSS 26.0 (IBM Corp., Armon, NY) software and R (figures were produced using the packages ggplot2, forest plot) (22–24). A *P* value <0.05 was considered statistically significant.

Table 1. Clinical Characteristics of Total Population With DCM and in Patients With DCM With and Without Events Upon OMT

	All (N=323)	Maastricht (N=192)	Trieste (N=131)	*P* value
Age, y	56±14	55±13	56±15	0.62
Male sex	212 (66)	120 (63)	92 (70)	0.16
Medical history				
Hypertension	89 (28)	58 (30)	31 (24)	0.21
Diabetes	33 (10)	22 (12)	11 (8)	0.46
Atrial fibrillation	65 (20)	43 (22)	22 (17)	0.26
Systemic diseases	37 (12)	11 (6)	26 (20)	<0.01
Heart failure hospitalization	64 (20)	50 (26)	14 (11)	<0.01
Life-threatening arrhythmias	12 (4)	10 (5)	2 (2)	0.13
Implantable cardioverter-defibrillator	47 (15)	30 (16)	17 (13)	0.53
Cardiac resynchronization therapy defibrillator	30 (9)	21 (11)	9 (7)	0.25
Clinical presentation				
New York Heart Association ≥3	12 (4)	6 (3)	6 (5)	0.56
Heart rate, bpm	70 [61 to 79]	73 [64 to 83]	64 [56 to 70]	<0.01
Systolic blood pressure, mm Hg	125 [110 to 140]	132 [115 to 145]	120 [110 to 130]	<0.01
Diastolic blood pressure, mm Hg	75 [70 to 84]	78 [69 to 85]	70 [70 to 80]	0.05
Echocardiographic parameters				
LVEF (%)	43 [35 to 50]	43 [35 to 50]	43 [35 to 50]	0.88
LVEF ≥50%	92 (28)	57 (30)	35 (27)	
LVEF 40%–50%	109 (34)	57 (30)	52 (40)	
LVEF <40%	121 (38)	78 (40)	43 (33)	
LV end-diastolic diameter, indexed by BSA, mm/m^2	29 [26 to 32]	28 [25 to 31]	30 [28 to 33]	<0.01
LV end-systolic diameter, indexed by BSA, mm/m^2	22 [19 to 25]	22 [19 to 25]	22 [19 to 26]	0.36
Left atrial volume, indexed by BSA, mL/m^2	34 [29 to 43]	34 [28 to 43]	35 [29 to 43]	0.49
GLS				
GLS (%)	–15 [–12 to –17]	–15 [–13 to –18]	–14 [–12 to –16]	<0.01
Delta GLS (%)	2.6 [0.0 to 5.8]	3.0 [0.3 to 6.3]	2.4 [–0.2 to 5.1]	0.19
Medication				
Beta blocker	299 (93)	177 (92)	122 (38)	0.83
Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or angiotensin receptor neprilysine inhibitor	311 (96)	185 (96)	126 (96)	1.00
Mineralocorticoid receptor antagonist	160 (50)	89 (46)	60 (19)	1.00
Diuretics	171 (53)	116 (60)	55 (45)	0.02
Outcomes separately				
Combined	64 (20)	42 (22)	22 (17)	0.32
Separately				
Death/heart transplantation/LV assist device	37 (11)	26 (14)	11 (8)	0.21
Life threatening arrhythmias	20 (6)	11 (6)	9 (7)	0.82
Heart failure hospitalization	20 (6)	11 (6)	9 (7)	0.82
Follow-up time, y	6 [4 to 9]	6 [3 to 9]	5 [4 to 9]	0.94

Values are mean±SD, median [interquartile range] or n (%). BSA indicates body surface area; DCM, dilated cardiomyopathy; delta GLS, absolute difference between baseline and follow-up GLS; GLS, global longitudinal strain; LV, left ventricular; LVEF, left ventricular ejection fraction; and OMT, optimal medical therapy.

Table 2. Differences in HF Medication Between First Presentation and Follow-Up

	All (n=323)	No event (N=259)	Event (N=64)	*P* value
All patients (n=323)				
Beta blocker	299 (93)	240 (93)	59 (92)	1.00
At least 50% of recommended OMT	245 (76)	195 (75)	50 (78)	0.75
ACEi, ARB, or ARNI	311 (96)	249 (96)	62 (97)	1.00
At least 50% of recommended OMT	262 (81)	210 (81)	52 (81)	1.00
Combination of beta blocker and ACEi/ARB/ARNI	291 (90)	233 (90)	58 (91)	1.00
MRA	160 (50)	122 (47)	38 (59)	0.09
At least 50% of recommended OMT	156 (48)	118 (46)	38 (59)	0.05
	All (n=91)	**No event (N=30)**	**Event (N=23)**	***P* value**
Left ventricular ejection fraction ≤35% and symptomatic (n=53)				
Beta blocker	50 (94)	29 (97)	21 (91)	0.57
At least 50% of recommended OMT	43 (81)	26 (87)	17 (74)	0.30
ACEi, ARB, or ARNI	51 (96)	29 (97)	22 (96)	1.00
At least 50% of recommended OMT	45 (85)	26 (87)	19 (83)	0.72
Combination of beta blocker and ACEi/ARB/ARNI	48 (91)	28 (93)	20 (87)	0.64
Mineralocorticoid receptor antagonist	43 (81)	22 (73)	21 (91)	0.16
At least 50% of recommended OMT	43 (81)	22 (73)	21 (91)	0.16

ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysine inhibitor; HF, heart failure; MRA, mineralocorticoid receptor antagonist; and OMT, optimal medical therapy. Recommended doses for OMT are based on current guideline[24].

RESULTS

Patient Characteristics

In total, 323 patients were included, 192 patients from Maastricht and 131 patients from Trieste (Figure S2). Clinical characteristics are summarized in Table 1. The mean age at presentation upon OMT was 56±14 years, 66% were men and the minority (4%) of the patients presented with New York Heart Association (NYHA) class 3 or 4. The median follow-up time was 5.6 (3.7–8.9) years. The mean LVEF upon OMT was 42%±11% and the mean GLS was –15%±4%. Guideline-directed medical treatment was optimized in all patients before they visited the outpatient clinic for evaluation (Table 2). The vast majority (90%) of the patients was treated with a beta blocker, combined with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or an angiotensin receptor neprilysine inhibitor. Seventy-six percent of the patients used at least 50% of the recommended target dose of betablockers. For angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, or angiotensin receptor neprilysine inhibitor, this percentage was 81%. In patients who fulfilled the criteria for using a mineralocorticoid receptor antagonist (HF symptoms and LVEF ≤35% [n=53]), a mineralocorticoid receptor antagonist was used with at least 50% of the recommended target dose in 81%.

Ninety-two out of 323 patients (28%) had a recovered LVEF (≥ 50%), at least 6 months after achieving OMT. Six percent of these patients had GLS values worse than the spline-adjusted cutoff (–13%). Patients with recovered LVEF had significantly better GLS values ($P<0.01$) and had less events ($P=0.01$ for all-cause mortality and $P=0.02$ for HF hospitalization). There were no significant differences in clinical presentation. A complete overview of clinical and imaging characteristics of patients with and without recovered LVEF is shown in Table S1.

Differences between the 2 participating centers are summarized in Table 1. In short, patients from the Trieste Heart Muscle Registry had slightly higher LV end-diastolic diameter index compared with patients from the Maastricht Cardiomyopathy Registry ($P=0.02$). More patients from Trieste had a history of systemic disease ($P<0.01$) and more patients from Maastricht had a history of HF hospitalization ($P<0.01$). No other significant or clinically relevant differences were noticed.

Prognostic Value of GLS After Achieving HF Therapy Optimization in Patients with DCM

A total of 64 patients (20%) reached the primary end point after OMT (of which sudden or cardiac death: n=23; heart transplantation or left ventricular assistant device: n=2, LTA: n=20, or HF hospitalization: n=19) during a median follow-up of 5.6 (3.7–8.9) years. Patients with an event had a higher NYHA class, lower LVEF, and worse GLS values (Table S2).

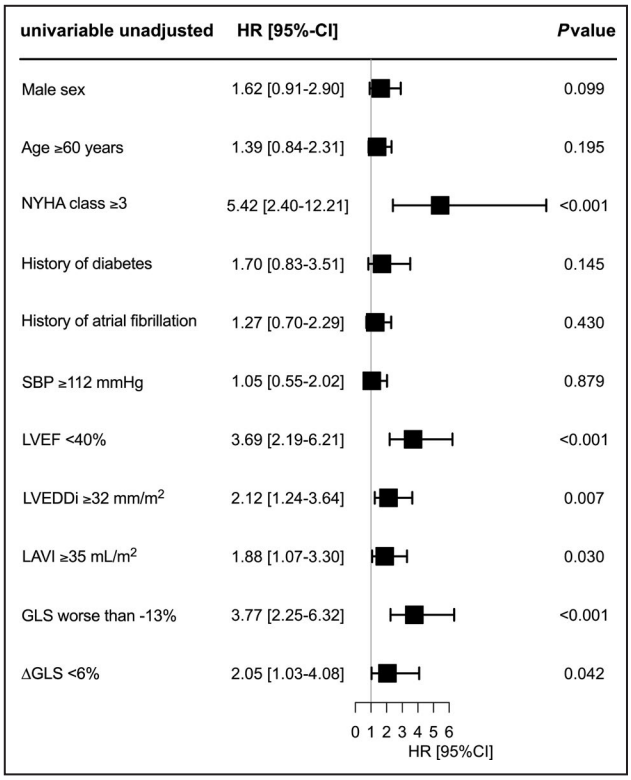

Figure 1. Univariable association of age, sex, NYHA class, diabetes, AF, systolic blood pressure, LVEF, LVEDDi, LAVI, GLS, and delta GLS with the outcome.
NYHA class ≥3, SBP, systolic blood pressure, LVEF <40%, LVEDDi ≥32 mm/m^2, LAVI 35 mL/m^2, GLS worse than –13%, and delta GLS <6% are univariably associated with the outcome. Δ, delta, absolute difference between baseline and follow-up GLS values. AF indicates atrial fibrillation; GLS, global longitudinal strain; HR, hazard ratio; LAVI, left atrial volume, indexed by body surface area; LVEDDi, left ventricular end-diastolic diameter, indexed by body surface area; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

NYHA class, LVEF, LV end-diastolic diameter index, left atrial volume index, GLS, and delta GLS were all univariably associated with the outcome (all P<0.05, Figure 1). NYHA class ≥3, LVEF, and GLS remained associated with the outcome in the multivariable-adjusted model (NYHA class ≥3: HR, 3.43; 95% CI, 1.49–7.90, P=0.004; LVEF: HR, 2.13; 95% CI, 1.11–4.10, P=0.024; GLS: HR, 2.24; 95% CI, 1.18–4.29, P=0.015, Figure 2), whreeas LV end-diastolic diameter index, left atrial volume index, and delta GLS were not. We evaluated the predictive value of GLS upon OMT when added to the other independent predictors (NYHA class and LVEF, Figure 2). The addition of GLS improved the discrimination (Harrell's C NYHA+LVEF=0.673, Harrell's C NYHA+LVEF+GLS=0.703). GLS also significantly improved the goodness-of-fit (log likelihood ratio test, P<0.01). These results indicate that GLS is an incremental predictor of the outcome in patients with DCM who achieved OMT, even after adjusting for other clinical independent predictors.

To take possible relevant center differences into account, we performed center-specific regression models that revealed similar results for the independent predictive value of GLS (Table S3).

GLS as Outcome Predictor, Stratified by LVEF

Next, the prognostic value of GLS was evaluated, stratified by LVEF (both categorized based on spline-adjusted prognostic cutoff values). Impaired GLS was significantly associated with worse outcome in patients with LVEF >40% and patients with LVEF <40% (P=0.026 and P=0.030, respectively), indicating that impaired GLS is associated with worse outcome, irrespective of LVEF (Figure 3).

Interobserver and Intraobserver Variability

Bland-Altman plots of pairs of measurements, indicating the median of differences and 95% LOA for intraobserver (observers A and B) and interobserver variability in measurements of GLS value, are presented in Figure S3. Mean differences were 0.2 (LOA –1.9 to 2.3), 0.1 (LOA –2.3 to 2.4), and 0.1 (LOA –1.3 to 1.5) for interobserver, intraobserver A, and intraobserver B, respectively. The absolute values of intraobserver A and B and the interobserver values did not significantly differ, excluding proportional bias. Both inter- and intraobserver agreement were optimal (intraclass correlation coefficient interobserver=0.98, ICC intraobserver A=0.94, intraclass correlation coefficient intraobserver B=0.99).

DISCUSSION

To the best of our knowledge, this is the first study that evaluates the prognostic value of GLS with respect to LVEF in patients with DCM who are optimally treated

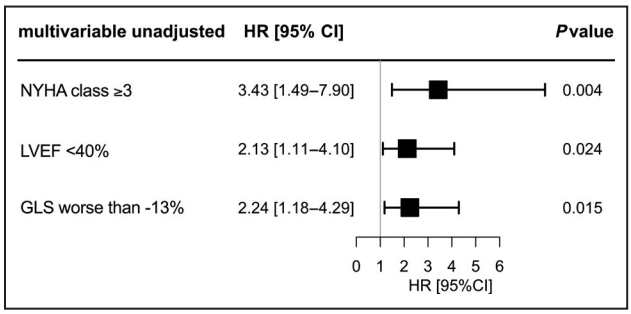

Figure 2. Multivariable model of independent predictors of the outcome.
NYHA class ≥3, LVEF <40%, and GLS worse than –13% are independent predictors of the outcome. GLS indicates global longitudinal strain; HR, hazard ratio; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.

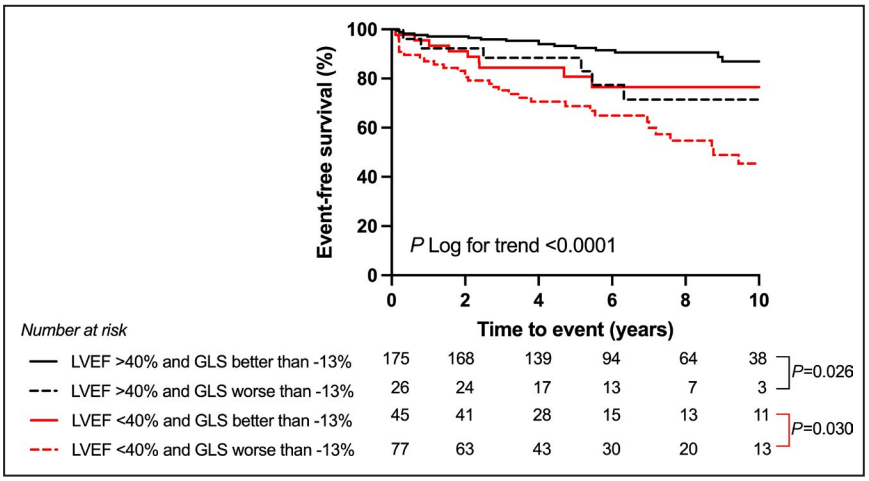

Figure 3. Kaplan-Meier survival analysis of GLS, stratified by LVEF.
Impaired GLS is significantly associated with worse outcome in both patients with LVEF >40% (*P*=0.026) and patients with LVEF <40% (*P*=0.030). GLS indicates global longitudinal strain; and LVEF, left ventricular ejection fraction.

with HF medication. As LVEF may recover in up to 40% of patients with newly diagnosed DCM upon instauration of OMT,[4–7] it is essential to reevaluate the greater value of GLS upon OMT.

In our study, 28% of the patients obtained a recovered LVEF after at least 6 months of OMT. Importantly, GLS appears to be an independent and incremental predictor of adverse outcome in these patients with optimally treated DCM over a median follow-up time of 6 years and exceeded the known prognostic value of LVEF.

Clinical follow-up of patients with DCM after initiation and optimization of HF therapy is necessary to evaluate the effect of therapy on cardiac function and, subsequently, a patients' expected prognosis.[24,26] Guidelines emphasize the importance of optimization of medical therapy, in order to achieve improvement or even recovery of cardiac function.[24,26] The prognosis of DCM significantly improved over the past years as a result of the cumulative benefit of evidence-based HF therapy.[2,3] Nonetheless, HF hospitalization, life-threatening arrhythmias, and sudden cardiac death are—even after achieving OMT—still highly prevalent within this relatively young patient population and risk stratification remains challenging.[3,9]

Unfortunately, studies investigating the prognostic role of clinical parameters and measures of cardiac function after optimization of HF therapy and improvement of cardiac function are scarce. LVEF is still the most commonly used parameter to evaluate cardiac function after reaching OMT. In our study population, 50% of the patients with recovered LVEF after OMT had abnormal GLS based on the most recent reference values,[28] despite normalization of LVEF. Indeed, in patients with an initial reduced LVEF and normalized LVEF at follow-up, abnormal GLS predicted the likelihood of future deterioration of cardiac function based on LVEF.[29] In a study of 212 both ischemic and nonischemic recovered patients with HF (LVEF ≥55%), 79% still had abnormal GLS values that wereassociated with a worse prognosis.[13] This finding was further confirmed in 206 patients with DCM and recovered LVEF (>50%).[30]

Here, GLS is of incremental prognostic value for the prediction of outcome in patients with optimally treated DCM. In previous studies addressing the greater value of GLS on top of LVEF, patients were included at random times, without knowing whether patients had been optimally treated with standard of care HF therapy.[20,31] In our study, patients were echocardiographically evaluated after at least 6 months of optimal medical HF therapy. Medical treatment did not significantly differ between patients with or without events. This strongly indicates that, at least in patients with DCM, GLS is an accurate and subtle measure of systolic (dys)function after optimization of HF therapy. In addition, its incremental value to predict adverse outcome on top of LVEF after optimal treatment advocates that GLS should routinely be included in the standard echocardiography follow-up of patients with DCM, both at baseline and after OMT instauration.

Limitations

The relatively low number of events in patients with DCM in general limited our ability to perform extensive multivariable analysis. Strain measurements were done using dedicated software (TomTec 5.4 TTA 2.0). Significant, but small differences between vendors may exist. However, the reproducibility of GLS is superior to LVEF. GLS has the narrowestCIs compared with other speckle tracking echocardiography parameters.[32,33] Two European centers participated in this study, and both patient groups were merged into 1 study population. Indeed, patients

from the Trieste cohort had less often a history of HF hospitalization and used fewer diuretics, but neither one of these was associated with the outcome. Still, multivariable and center-specific analyses revealed that the main findings were valid for every cohort. To investigate if the results from this merged cohort are reproducible as well as the spline-adjusted prognostic cutoff value of –13%, external validation in other DCM populations would be desirable. In this study, only echocardiographic data have been included and we did not take into account cardiac magnetic resonance parameters such as late gadolinium enhancement, an independent predictor of outcome in DCM as well. However, cardiac magnetic resonance is less widely available and not frequently performed during follow-up.

CONCLUSIONS

In patients with DCM who are optimally treated with HF medical therapy, GLS is an independent and incremental predictor of adverse outcome, exceeding the prognostic value of LVEF. Clinicians should consider routinely including GLS as prognostic marker on top of LVEF, even more so in patients with DCM and improved or recovered LVEF after optimal HF medical therapy.

ARTICLE INFORMATION

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Supplemental Material

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SUPPLEMENTAL MATERIAL

Table S1. Clinical characteristics of DCM patients with and without recovered LVEF upon OMT.

N = 323	**LVEF <50% (n=231)**	**LVEF ≥50% (n=92)**	**p-value**
Age (years)	56 ±14	54 ±14	0.18
Male	154 (67)	58 (63)	0.60
Medical history			
Hypertension	61 (26)	28 (30)	0.49
Diabetes Mellitus	22 (10)	11 (12)	0.54
Atrial fibrillation	47 (20)	18 (20)	1.00
Systemic diseases	24 (10)	13 (14)	0.34
Heart failure hospitalization	45 (20)	19 (21)	0.88
Life threatening arrhythmias	9 (4)	3 (3)	1.00
ICD	39 (17)	8 (9)	0.08
CRT-D	24 (10)	6 (7)	0.40
Clinical presentation			
NYHA ≥ 3	11 (5)	1 (1)	0.19
Heart rate (bpm)	70 [61-79]	70 [60-80]	0.92
Systolic blood pressure (mmHg)	125 [110-140]	130 [117-141]	0.16
Diastolic blood pressure (mmHg)	74 [70-84]	79 [70-85]	0.36
Echocardiographic parameters			
LVEF (%)	39 [31-44]	54 [51-58]	**<0.001**
LVEDDi (mm/m^2)	30 [27-33]	27 [24-30]	**<0.001**
LVESDi (mm/m^2)	24 [21-26]	19 [16-21]	**<0.001**
LAVI (ml/m^2)	35 [29-46]	33 [28-40]	**0.026**
Global longitudinal strain			
GLS	-14 [-11 - -16]	-17 [-15 - -20]	**<0.001**
Delta GLS	2.3 [-0.2 – 4.7]	4.6 [0.2-9.0]	0.001
Outcomes			
Death/HTx/LVAD	33 (14)	4 (4)	**0.01**
Life threatening arrhythmias	17 (7)	3 (3)	0.21
Heart failure hospitalization	19 (8)	1 (1)	**0.02**
Follow-up time (years)	6 [3-9]	6 [4-9]	0.27

Values are mean ± SD, median [IQR] or n (%). NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; LVEDDi: Left Ventricular End Diastolic Diameter, indexed by BSA; LA volume: Left Atrial volume; GLS: Global Longitudinal Strain; ACE-i: Angiotensin Converting Enzyme inhibitor; ARB: Angiotensin Receptor Blocker; MRA: Mineralocorticoid Receptor Antagonist; ARNI: Angiotensin Receptor Neprilysine Inhibitor; HTx: Heart transplant; LVAD: Left Ventricular Assist Device.

Table S2. Clinical characteristics of total DCM population and in DCM patients with and without events upon OMT.

	No event (N=259)	**Event (N=64)**	**p-value**
Age (years)	55 ±14	56 ±14	0.57
Male	165 (64)	47 (73)	0.19
Medical history			
Hypertension	71 (27)	18 (28)	1.00
Diabetes Mellitus	24 (9)	9 (14)	0.26
Atrial fibrillation	50 (19)	15 (23)	0.49
Systemic diseases	29 (11)	8 (13)	0.83
Heart failure hospitalization	48 (19)	16 (25)	0.29
Life threatening arrhythmias	8 (3)	4 (6)	0.26
ICD	30 (12)	17 (27)	**<0.01**
CRT-D	24 (9)	6 (9)	1.00
Clinical presentation			
NYHA ≥ 3	5 (2)	7 (11)	**<0.01**
Heart rate (bpm)	69 [60-78]	72 [64-81]	0.08
Systolic blood pressure (mmHg)	125 [110-140]	130 [115-140]	0.68
Diastolic blood pressure (mmHg)	75 [70-82]	80 [70-85]	0.25
Echocardiographic parameters			
LVEF (%)	45 [38-51]	34 [26-41]	**<0.01**
LVEDDi (mm/m^2)	29 [26-31]	30 [25-33]	0.07
LVESDi (mm/m^2)	22 [19-25]	25 [19-28]	**<0.01**
IVS (mm)	9 [8-10]	9 [8-10]	0.93
LVPW (mm)	9 [8-10]	9 [8-10]	0.68
LVMI (g/m^2)	72 [67-77]	74 [66-80]	0.23
LAVI (ml/m^2)	34 [29-41]	42 [29-53]	**0.01**
Global longitudinal strain			
GLS (%)	-15 [-13 - -18]	-12 [-8 - -16]	**<0.01**
Delta GLS	2.9 [0.1-6.4]	2.2 [-0.2 – 4.8]	0.07

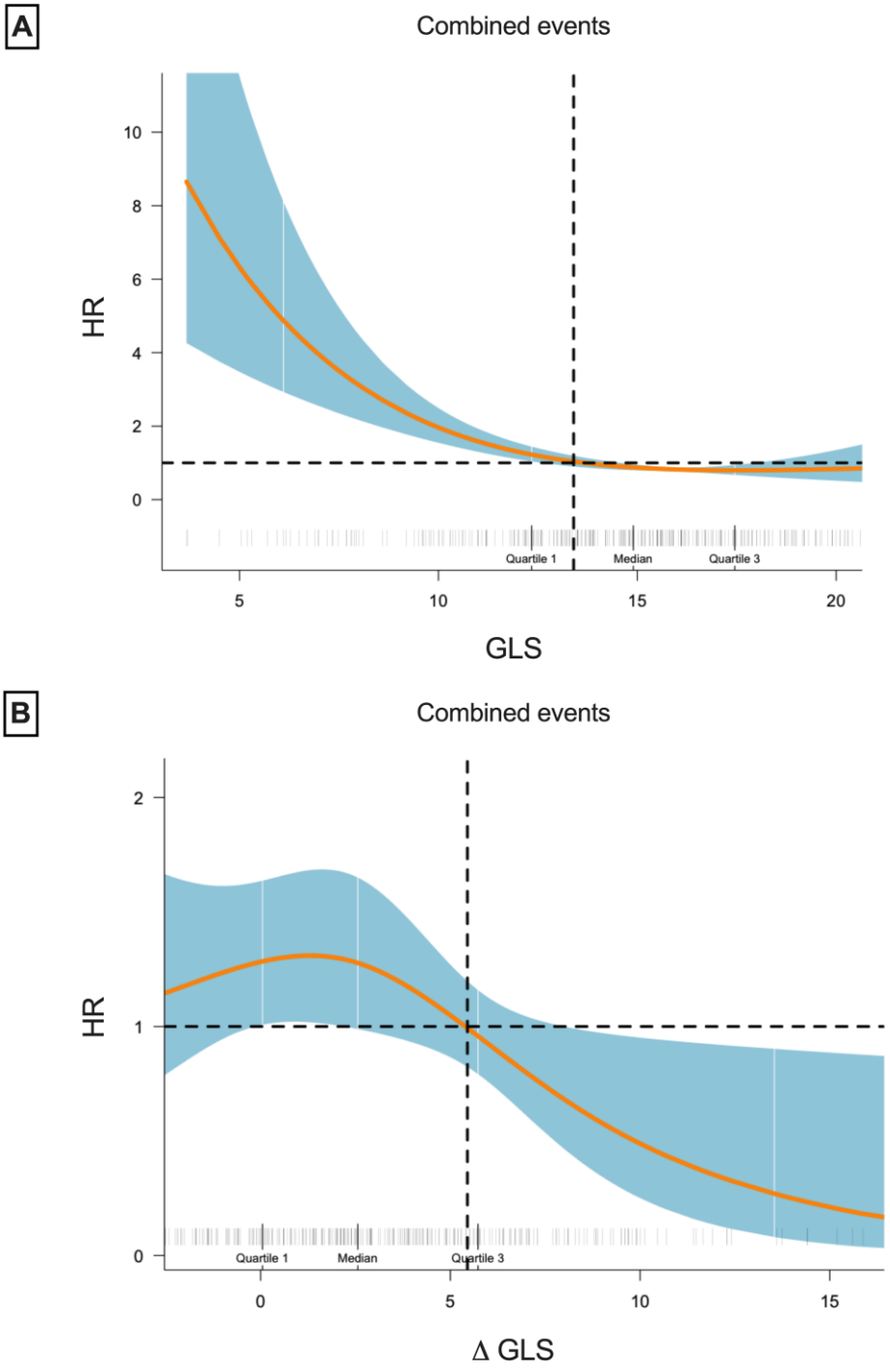
Values are mean ± SD, median [IQR] or n (%). Abbreviations: NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; LVEDDi: Left Ventricular End Diastolic Diameter, indexed by BSA; IVS: Interventricular septum thickness; LVPW: Left Ventricular Posterior Wall thickness; LVMI: Left Ventricular Mass, indexed by BSA; LAVI: Left Atrial volume, indexed by BSA; GLS: Global Longitudinal Strain.

Table S3. Center-specific regression models.

Variables	Univariable analysis			Multivariable analysis		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
MAASTRICHT						
Male sex	1.80	0.90-3.59	0.09			
Age	1.45	0.79-2.66	0.23			
NYHA >=3	3.23	0.99-10.55	0.05	-	-	-
DM	1.12	0.44-2.86	0.81			
AF	1.27	0.64-2.53	0.49			
SBP	0.86	0.41-1.80	0.69			
LVEF	3.09	1.64-5.81	<0.001	-	-	-
LVEDDi	3.09	1.62-5.87	<0.01	2.53	1.32-4.86	<0.01
LAVI	2.48	1.29-4.78	0.01	2.03	1.04-3.94	0.04
GLS	**3.65**	**1.99-6.70**	**<0.001**	**3.28**	**1.78-6.04**	**<0.001**
Delta GLS	1.96	0.91-4.24	0.09			
TRIESTE						
Male sex	1.25	0.49-3.21	0.64			
Age	1.21	0.52-2.79	0.66			
NYHA >=3	12.56	3.90-40.52	<0.001	8.70	2.65-28.58	<0.001
DM	3.78	1.25-11.42	0.02	-	-	-
AF	1.08	0.37-3.20	0.89			
SBP	1.73	0.58-5.12	0.32			
LVEF	4.97	2.03-12.22	<0.001	-	-	-
LVEDDi	2.06	0.89-4.75	0.09			
LAVI	2.68	1.05-6.87	0.04	-	-	-
GLS	**5.59**	**2.06-15.17**	**<0.01**	**4.89**	**1.78-13.41**	**<0.01**
Delta GLS	2.59	0.60-11.10	0.20			

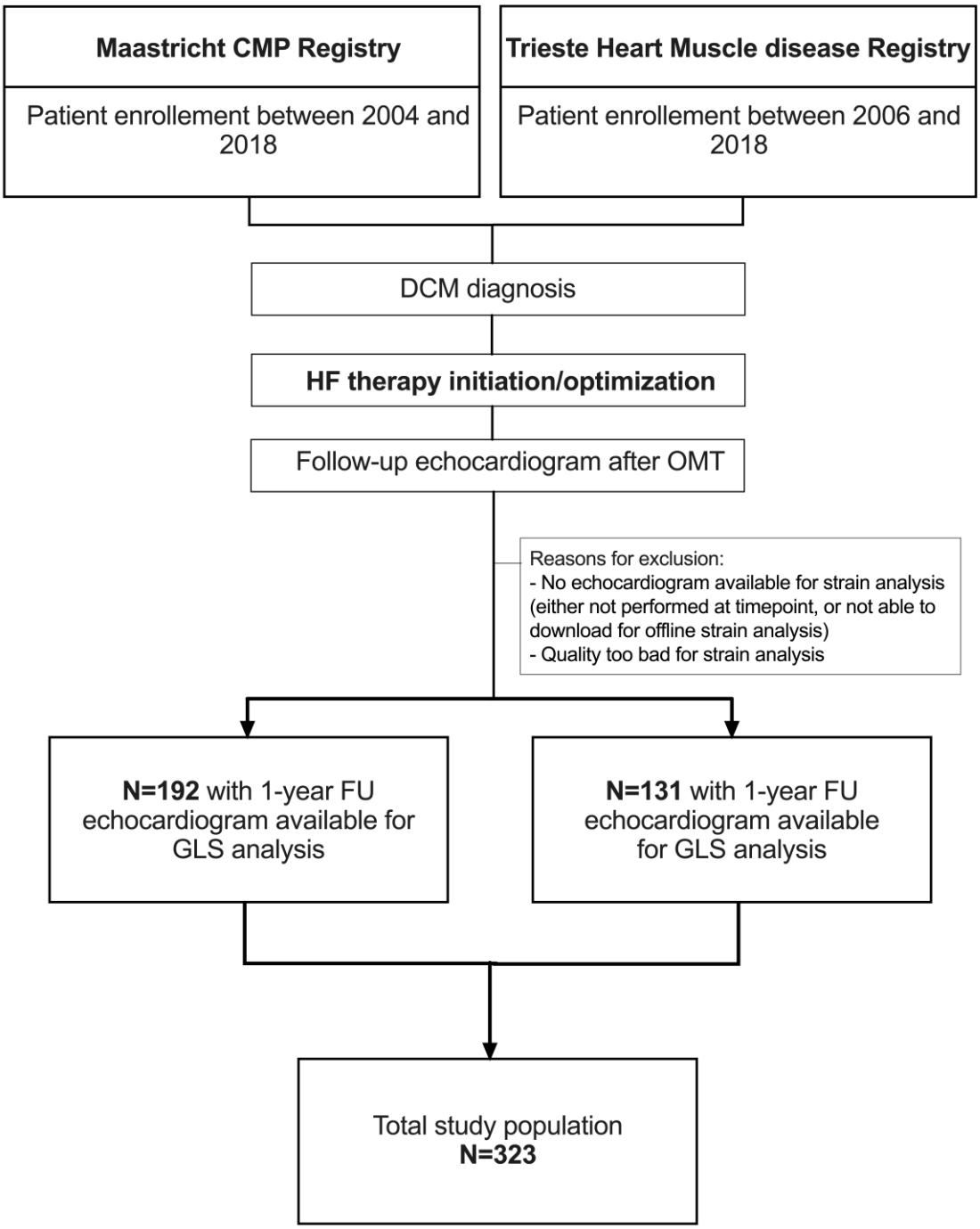
HR: Hazard Ratio; CI: Confidence Intervals; NYHA: New York Heart Association class; LVEF: Left Ventricular Ejection Fraction; LAVI: Left Atrial Volume, indexed; GLS: Global Longitudinal Strain.

Figure S1. Spline adjusted associations of GLS and delta GLS with outcome.



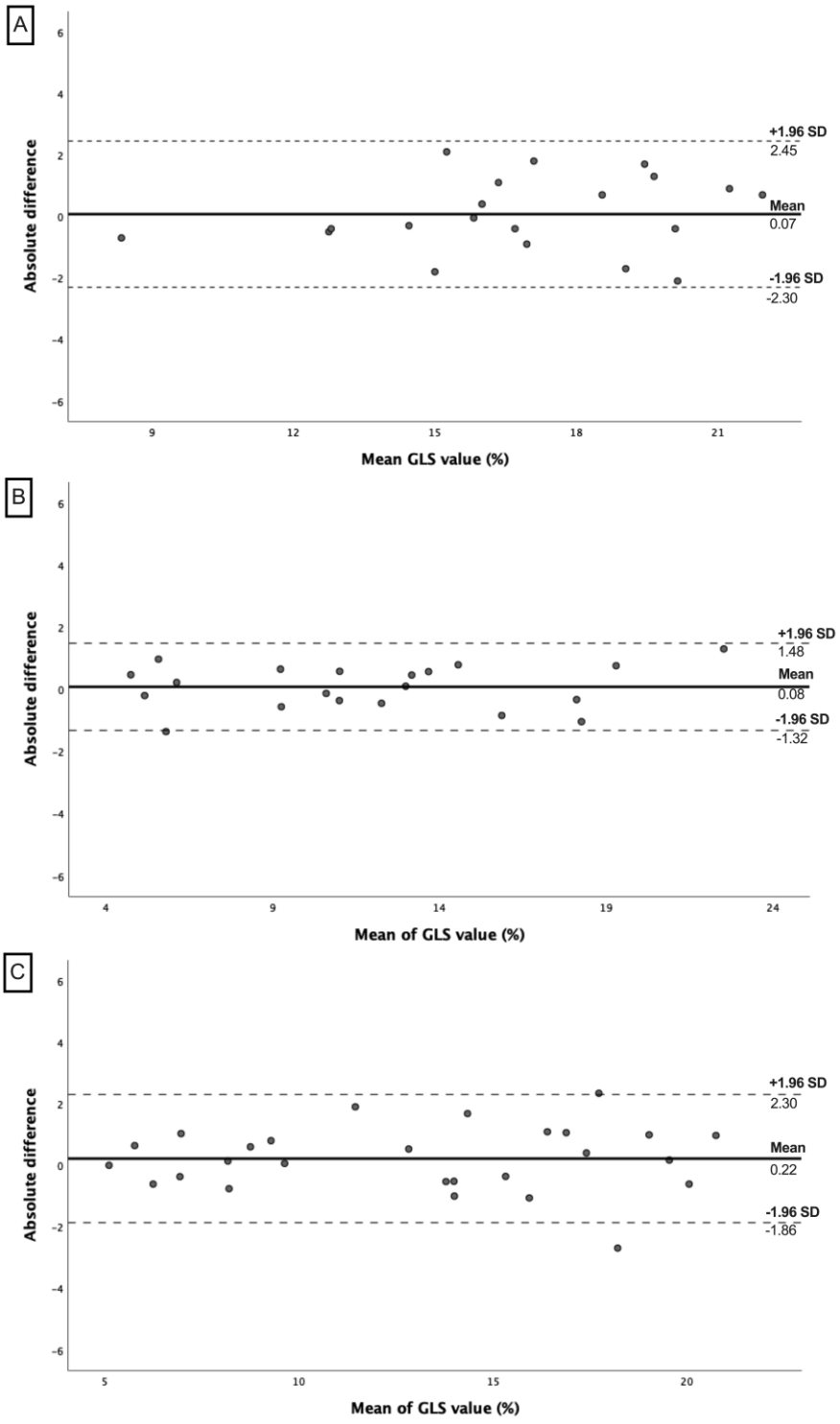
Cubic spline adjusted plots of GLS and delta GLS. The orange line represents the hazard ratio for the different observed strain values, accompanied by 95% confidence intervals in blue. The dashed lines represent the strain value for which the hazard ratio crosses 1. This point is used to dichotomize the strain parameters. GLS = global longitudinal strain, HR = hazard ratio, Δ = delta, the absolute difference.

Figure S2. Flowchart of the selected study population.



In Maastricht, 773 patients were included in the Maastricht CMP registry between 2004 and 2018. In Trieste, 603 patients were included in the Trieste Heart Muscle disease Registry between 2006 and 2018. Both clinical data and echocardiograms at 1-year follow-up were available and eligible for offline GLS analysis in a total of 323 patients. Abbreviations: CMP = cardiomyopathy.

Figure S3. Inter- and intraobserver variability of GLS measurements.



Bland-Altman plots show intraobserver A (A), intraobserver B (B), and interobserver (C) differences of GLS measurements. The solid line indicates the mean value of all measurements, and dotted lines indicate 95% LOA (mean ± 1.96 SDs). There were no significant differences between the absolute values of intraobserver A and B nor between the interobserver values.