

Left ventricular global longitudinal strain adds incremental value for risk prediction in unselected clinical patients

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Abstract

Aims

Deformation imaging has demonstrated incremental prognostic value compared to left ventricular ejection fraction (LVEF) in specific cardiovascular diseases; however, it remains widely underused. Consequently, we sought to investigate the significance of deformation imaging in an all-comers population to assess its value in a routine in- and outpatient setting.

Methods and results

Patients were prospectively recruited to the single-centre cardiac magnetic resonance registry. Volumetric right and left ventricular (RV/LV) analyses and global circumferential strain were assessed on short-axis stacks, RV and LV global longitudinal strain (GLS) on long-axis views respectively. Follow-up was conducted for primary (all-cause mortality and heart failure hospitalization) and secondary (all-cause mortality, hospitalized angina, infarction, and stroke) endpoints. In total, $n = 1655$ patients met $n = 68$ primary and $n = 107$ secondary endpoints during a median follow-up of 399 days. GLS (HR 1.12, 95%CI 1.04–1.21 $P = 0.002$; HR 1.10, 95%CI 1.03–1.16 $P = 0.002$) but not LVEF ($P = 0.406$; 0.209) was an independent predictor for the primary and secondary endpoint. GLS was an independent predictor for the primary endpoint after correction for commonly considered risk factors including, age, NYHA class, tissue characterization native T1, biomarker NT-proBNP, and glomerular filtration rate (HR 1.09, 95%CI 1.03–1.15, $P = 0.003$). After dichotomization at the median of -16.4% , GLS added incremental value to risk stratification for the primary endpoint on Kaplan-Meier plots in patients with LVEF above ($P = 0.045$) and below ($P = 0.017$) the median of 55% .

Conclusion

In an all-comers, low-risk patient population, GLS emerged as an independent risk predictor with incremental prognostic value relative to LVEF. This finding may support clinical routine implementation of GLS in cardiac in- and outpatient clinics.

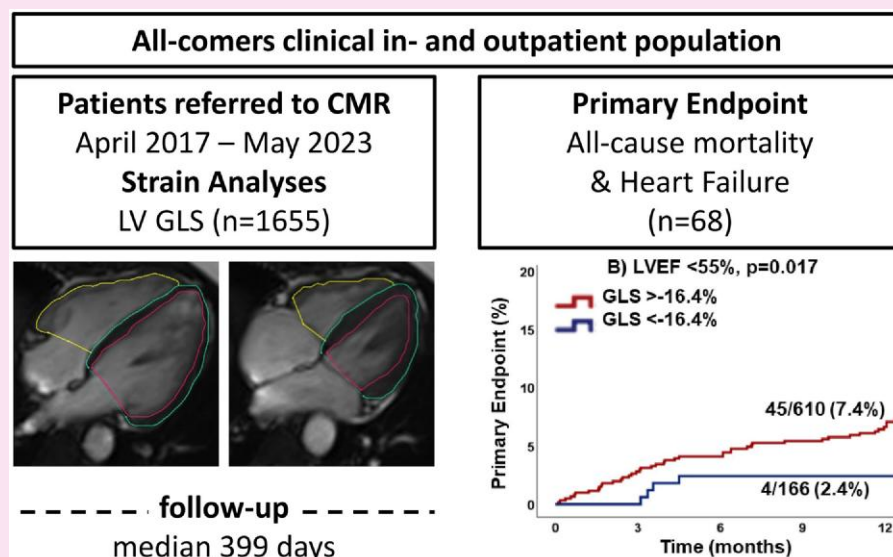
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Graphical Abstract



Keywords

strain • GLS • outcome • incremental value • all-comers

Introduction

The burden of cardiovascular diseases (CVD) remains high¹ despite all progress made in the field of ischaemic² and non-ischaemic heart disease.³ Optimized risk prediction in CVD is a highly debated topic. Despite being continuously challenged as a prognostic indicator, left ventricular ejection fraction (LVEF) remains the clinical go-to standard and is commonly used for heart failure (HF) classification.⁴ Fibrosis has been recognized as an additional risk factor in considering implantable cardioverter defibrillator (ICD) implantation in dilated cardiomyopathy with LVEF >35%. In line with these findings, the ongoing cardiovascular magnetic resonance (CMR)-ICD trial (NCT04558723) was designed to investigate the role of fibrosis in dilated cardiomyopathy with LVEF <35%. Furthermore, fibrosis has long been implicated as a substrate for ventricular arrhythmias in ischaemic heart disease.⁵

Both simple echocardiographic and CMR-derived deformation imaging techniques have already been shown to have incremental prognostic value in the full range of specific CVD,^{6–9} yet clinical routine implementation remains rare. Vendor-dependent reference ranges¹⁰ or potential differing prognostic impacts across the range of CVD may hinder or delay routine clinical application. Although CMR has proven to have incremental value in high-risk patients following acute myocardial infarction,¹¹ advanced heart failure,¹² and even advanced renal disease,⁶ the majority of patients, especially in outpatient clinics, are at lower risk. The additional value of deformation imaging in an unselected, low-risk setting remains unknown and may therefore be underestimated, which in turn may prompt the use of simple LVEF approximation for overall risk evaluation. Consequently, we sought to investigate the role of deformation imaging in an all-comers, low-risk patient population to investigate the prognostic benefit of using this technique in a real-world, routine imaging setting.

Methods

Study population

Patients referred to the imaging unit of the Kerckhoff Heart and Thorax Centre in Bad Nauheim, Germany, were prospectively recruited to the

all-comers CMR/biobank (BioCVI) registry between April 2017 and May 2023 (Figure 1). Clinical indications for CMR comprised assessment of myocardial function and inflammation, ischaemia, and viability testing as well as evaluation of the cardiomyopathy. A follow-up assessment was conducted using a standardized questionnaire one year after recruitment. The registry was approved by the local ethics committee of the University of Giessen and complied with the principles of the Helsinki Declaration. All patients gave written informed consent before participation.

Cardiovascular magnetic resonance

CMR was conducted on a clinical 3.0 Tesla Skyra (Siemens Healthineers, Erlangen, Germany) using a 18-array coil in head-first supine position. Post-processing analyses were performed using commercially available software solutions (CVI42, Calgary, Canada). The clinical protocol followed Society of Cardiovascular Magnetic Resonance guidelines¹³ and included balanced steady-state free precession (bSSFP) cine sequences in 2/3- and 4-chamber views (Ch), long-axis (LAX) orientations, and a short-axis stack (SAX) covering both ventricles. Right and left ventricular (RV/LV) volumetric analyses were conducted on the SAX stack, including end-diastolic/systolic and stroke volumes (EDV/ESV/SV) and EF as well as LV mass excluding trabecularization. LV global longitudinal strain (GLS) was assessed on all LAX orientations and RV GLS on 4 Ch only. LV global circumferential strain was assessed on SAX orientations^{14,15} (Figure 2). Tissue characterization was accomplished by native T1 (MODified Look Locker Inversion recovery sequences 3(2)3(2)5)) (Goethe CVI approaches®) and T2 mapping based on 5-into-3 planning as well as late gadolinium enhancement (LGE) covering the entire SAX. Native T1 and T2 values were taken in the centre of the basal or midventricular septum by means of a region of interest covering at least two voxels that avoided partial volume effects. Inversion recovery-segmented gradient echo sequences were used for LGE assessment 10–15 min after contrast media application (Dotarem®, Guerbet, Villepinte, France; 0.15 mmol/kg bodyweight).

Clinical endpoints

The primary clinical endpoint was defined as all-cause mortality and heart failure hospitalization according to the AHA key data elements and definitions for cardiovascular endpoints in clinical trials.¹⁶ The secondary endpoint comprised all-cause mortality and hospitalized but non-fatal myocardial infarction, stroke, or unstable angina pectoris.

Statistics

Categorical parameters are presented as frequencies with corresponding percentage and were compared using the chi-squared test. Continuous parameters are reported as medians with interquartile ranges (IQR). Independent continuous parameters were compared using the Mann-Whitney U test. Correlations were evaluated using the Spearman's rank correlation coefficient. Outcome analyses were based on 1) univariate and multivariable Cox proportional hazards models using continuous variables reporting hazard ratios (HR) with corresponding 95% confidence intervals (95%CI) and 2) Kaplan-Meier plots with associated log-rank testing. A two-tailed *P*-value <0.05 was considered to be statistically significant. Analyses were performed with SPSS version 29.0.2.0 (IBM, Armonk,

New York, USA) and MedCalc version 23.1.3 (MedCalc Software bvba, Ostend, Belgium).

Results

Study population

The final population consisted of *n* = 1655 patients classified as normal (*n* = 454), chronic coronary syndrome (*n* = 314), ischaemic heart disease (*n* = 279), dilated (*n* = 236), hypertrophic (*n* = 37) or other (*n* = 22) cardiomyopathies, hypertensive heart disease (*n* = 28), storage disorders (*n* = 8), inflammation (*n* = 103), acute myocardial injury (*n* = 11), right heart failure (*n* = 19), and others (*n* = 144). A total of *n* = 68 primary and *n* = 107 secondary endpoints were met during a median follow-up of 395 days (394, 460).

Table 1 reports the baseline characteristics of the study population. Compared to the cohort overall, patients who met the primary or secondary endpoint were, respectively, 9 or 10 years older (*P* < 0.001), suffered from a higher degree of dyspnoea according to the NYHA classification (*P* < 0.001), and showed higher N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) as well as lower estimated glomerular filtration rate (eGFR) on laboratory testing (*P* = 0.001 to <0.001). Whilst the presence of coronary artery disease did not differ between patients without and with event during follow-up (*P* = 0.223 and 0.106, respectively), previous myocardial infarction and interventional or coronary artery bypass graft therapy were more common among those reaching the secondary endpoint (*P* < 0.001).

Cardiac functional evaluation

Table 2 shows echocardiographic and CMR-derived functional characteristics. Cardiac valvular functional assessment by echocardiography was performed in 945 to 949 cases, depending on the valve. The severity of aortic valve stenosis was greater in patients who met either the primary or secondary endpoint (*P* < 0.001), although there was no difference in the severity of regurgitation. Mitral and tricuspid function was impaired in the primary endpoint group only (*P* = 0.004 to <0.001).

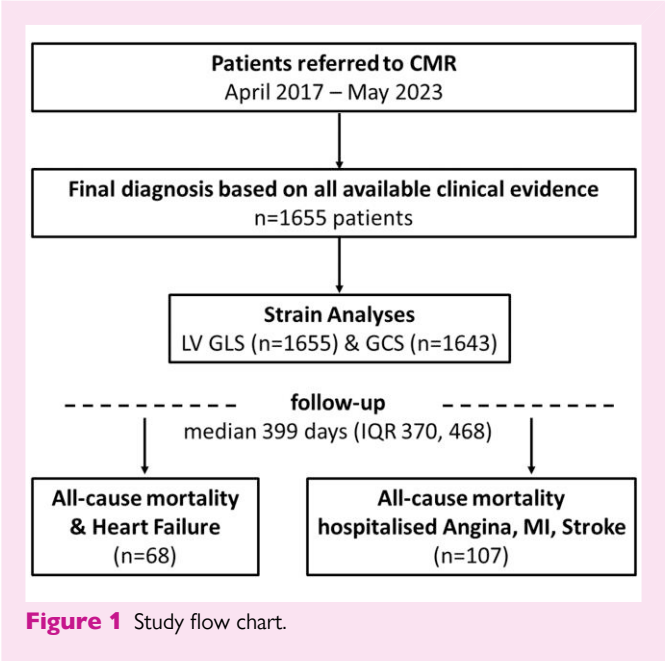


Figure 1 Study flow chart.

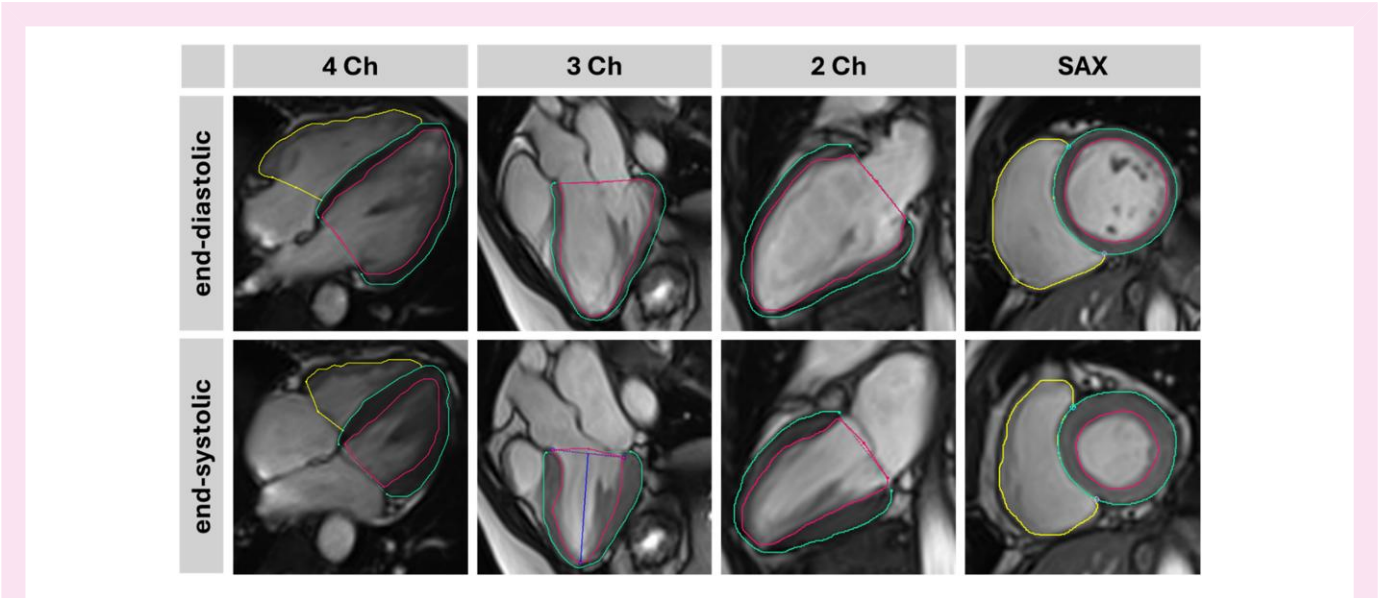


Figure 2 Cardiovascular magnetic resonance feature-tracking. Assessment of left ventricular global longitudinal strain (GLS) on 4/3/2 chamber view (Ch) long axis orientations as well as right ventricular GLS on 4 Ch respectively. Short axis views (SAX) were used for global circumferential strain assessment as well as all volumetric analyses.

Table 1 Baseline characteristics

Variable	All patients n = 1655	No endpoint n = 1518	Primary endpoint n = 68	Secondary endpoint n = 107	P-value
Age	61 (51, 71)	60 (50, 70)	69 (59, 77)	70 (60, 77)	<0.001/<0.001
Sex (m)	589/1655 (35.6)	547/1518	22/68 (32.4)	33/107 (30.8)	0.536/0.278
NYHA class	I 133/1655 (8.0)	I 124 (8.2)	I 7/68 (10.3)	I 5 (4.6)	<0.001/<0.001
	II 325/1655 (19.6)	II 301 (19.8)	II 13/68 (19.1)	II 19 (17.6)	
	III 287/1655 (17.3)	III 246 (16.2)	III 24/68 (35.3)	III 31 (29.0)	
	IV 139/1655 (8.4)	IV 114 (7.5)	IV 14/68 (20.6)	IV 19 (17.6)	
Cardiovascular risk factors					
Active smoking	356/1649 (21.5)	324/1512 (21.3)	13/68 (19.1)	24/107 (22.4)	0.199/0.530
Hypertension	1020/1654 (61.6)	916/1517 (60.3)	52/68 (76.5)	80/107 (74.8)	0.028/0.012
Hyperlipoproteinemia	789/1646 (47.7)	706/1509 (46.5)	40/68 (58.8)	72/107 (67.3)	0.122/<0.001
Diabetes	308/1650 (18.6)	270/1513 (17.8)	25/68 (36.8)	28/107 (26.2)	<0.001/0.083
Family history	571/1621 (34.5)	527/1489 (34.7)	16/67 (23.5)	37/104 (34.6)	0.148/0.429
Body mass index	26.8 (24.1, 30.4)	26.8 (24.1, 30.4)	26.6 (24.1, 31.0)	26.2 (24.2, 29.4)	0.970/0.373
History of coronary heart disease					
Coronary heart disease	613/1646 (37.0)	531/1511 (35.1)	41/67 (60.3)	70/105 (65.4)	0.223/0.106
sclerosis	87	78	8	7	
1-vessel	135	122	7	11	
2-vessel	128	115	3	11	
3-vessel	202	166	15	31	
unspecified	61	50	7	10	
Previous infarction	326/1647 (19.7)	283/1512 (18.6)	20/68 (29.4)	33/105 (30.8)	0.078/<0.001
Previous PTCA	392/1654 (23.7)	335/1517 (22.1)	25/68 (36.8)	49/107 (45.8)	0.018/<0.001
Previous CABG	99/1655 (6.0)	79/1518 (5.2)	7/68 (10.3)	18/107 (16.8)	0.070/<0.001
Sudden cardiac death	77/1642 (4.7)	67/1507 (4.4)	5/67 (7.4)	8/106 (7.5)	0.224/0.036
Atrial fibrillation	361/1647 (21.8)	310/1511 (20.4)	26/68 (38.2)	42/106 (39.3)	0.002/<0.001
Systolic blood pressure	125 (115, 137)	125 (116, 138)	120 (110, 136)	127 (117, 138)	0.407/0.854
Diastolic blood pressure	79 (70, 83)	80 (70, 84)	70 (63, 80)	72 (64, 80)	0.016/0.057
Laboratory Testing					
NTproBNP	247 (82, 887)	233 (80, 794)	1736 (588, 4506)	555 (101, 1652)	<0.001/0.001
eGFR	91 (72, 109)	92 (74, 110)	67 (46, 95)	80 (57, 99)	<0.001/<0.001
Medication					
Beta-blocker	848/1652 (51.2)	758/1515 (49.9)	45/68 (66.2)	69/107 (64.5)	0.031/0.014
ACE inhibitor	459/1650 (27.7)	414/1514 (22.9)	23/68 (33.8)	36/107 (33.6)	0.452/0.313
AT1 antagonist	385/1651 (23.3)	348/1514 (22.9)	13/68 (19.1)	30/107 (28.0)	0.693/0.425
Sacubitril/valsartan	63/1245 (3.8)	54/1146 (4.7)	5/49 (10.2)	6/85 (5.6)	<0.001/0.490
Aldosterone antagonist	234/1652 (14.1)	198/1515 (13.0)	23/68 (33.8)	22/107 (20.6)	<0.001/0.082
Ca channel blocker	255/1652 (15.4)	226/1515 (14.9)	14/68 (20.6)	22/107 (20.6)	0.414/0.263
Loop diuretic	358/1652 (21.6)	294/1515 (19.4)	41/68 (60.3)	45/107 (42.1)	<0.001/<0.001
Statin	636/1652 (38.4)	567/1515 (37.4)	33/68 (48.5)	60/107 (56.1)	0.169/<0.001
Aspirin	559/1651 (33.8)	501/1515 (33.0)	25/67 (36.8)	49/106 (45.8)	0.095/0.007
Malignancy <5 years	100/1649 (6.0)	88/1514 (5.8)	9/68 (13.2)	9/105 (8.4)	0.042/<0.001

Data presented as n/N (%) or median (IQR). P-values were calculated for primary/secondary endpoint compared to no endpoint met. NT-proBNP in pg/mL.

NYHA, New York Heart Association; PTCA, Percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate (mL/min/1.73 m²); ACE, angiotensin converting enzyme; AT1, angiotensin II receptor type 1; Ca, Calcium.

In patients who met the primary endpoint, LV EDV and ESV were higher with consequently lower SV and EF ($P < 0.001$), whilst no volumetric changes were observed in patients who met the secondary endpoint. In contrast, both GLS and global circumferential strain were impaired in the primary ($P < 0.001$) and secondary ($P < 0.001/0.032$) endpoint groups. Volumetric and deformation-based RV function was impaired in patients who reached the primary ($P < 0.001$) but not secondary endpoint.

Outcome

Table 3 reports uni- and multivariable Cox regression models for the primary and secondary endpoint. Whilst GLS was associated with both the primary (HR 1.15, 95%CI 1.10–1.21, $P < 0.001$) and secondary endpoints (HR 1.06, 95%CI 1.03–1.11, $P = 0.001$), LVEF was only significantly associated with the primary endpoint (HR 0.96, 95%CI 0.95–0.97, $P < 0.001$). GLS but not LVEF was an independent predictor for

Table 2 Functional assessments

Variable	All patients n = 1655	No endpoint n = 1518	Primary endpoint n = 68	Secondary endpoint n = 107	P-value
Echocardiography					
Aortic valve stenosis	0 822 I 25 II 18 III 14	0 748 I 23 II 11 III 12	0 39 I 2 II 4 III 0	0 54 I 1 II 6 III 2	<0.001/<0.001
Aortic valve regurgitation	0 703 I 158 II 17 III 2	0 646 I 135 II 14 III 2	0 30 I 11 II 3 III 0	0 40 I 20 II 2 III 0	0.051/0.066
Mitral valve stenosis	0 857 I 10 II 5 III 3	0 778 I 9 II 3 III 3	0 39 I 1 II 2 III 0	0 59 I 1 II 2 III 0	0.004/0.121
Mitral valve regurgitation	0 485 I 357 II 36 III 9	0 444 I 323 II 28 III 6	0 20 I 16 II 8 III 2	0 32 I 25 II 4 III 2	<0.001/0.339
Tricuspid valve regurgitation	0 517 I 322 II 25 III 9	0 474 I 291 II 21 III 4	0 23 I 13 II 4 III 5	0 31 I 27 II 2 III 2	<0.001/0.078
Cardiovascular magnetic resonance imaging					
Left ventricle					
LV mass	51 (41, 64)	51 (41, 63)	60 (46, 73)	53 (42, 65)	0.013/0.201
LV EDV	82 (69, 101)	81 (68, 100)	97 (75, 124)	83 (69, 106)	<0.001/0.743
LV ESV	36 (27, 52)	35 (26, 51)	49 (33, 93)	38 (27, 54)	<0.001/0.253
LV SV	43 (36, 50)	43 (36, 50)	39 (28, 47)	41 (32, 49)	<0.001/0.068
LVEF	55 (43, 63)	56 (44, 63)	41 (24, 55)	52 (39, 62)	<0.001/0.060
FT LV GLS	-16.4 (-12.4, -19.3)	-16.6 (-12.6, -19.5)	-11.8 (-7.0, -15.5)	-14.8 (-11.6, -18.3)	<0.001/0.002
FT LV GCS	-17.6 (-13.1, -20.9)	-17.7 (-13.4, -21.0)	-12.5 (-7.8, -17.0)	-16.1 (-11.8, -20.1)	<0.001/0.026
Right ventricle					
RV EDV	78 (65, 93)	78 (65, 93)	81 (65, 106)	78 (65, 95)	0.159/0.827
RV ESV	38 (29, 50)	38 (29, 50)	45 (35, 60)	41 (30, 52)	0.002/0.234
RV SV	39 (31, 46)	39 (32, 46)	34 (25, 45)	36 (30, 44)	0.021/0.072
RVEF	50 (47.4, 57)	51 (44, 57)	45 (38, 53)	49 (42, 56)	<0.001/0.086
FT RV GLS ^a	-23.9 (-19.1, -27.6)	-24.0 (-19.4, -27.6)	-17.6 (-13.4, -23.6)	-23.2 (-16.9, -27.8)	<0.001/0.363
Tissue characterization					
Native T1	1126 (1090, 1169)	1125 (1089, 1167)	1168 (1119, 1238)	1131 (1096, 1188)	<0.001/0.053

Data presented as n/N (%) or median (IQR). P-values were calculated for primary/secondary endpoint compared to no endpoint met.

LV, left ventricular; RV, right ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; SV, stroke volume; FT, Feature-Tracking; LVEF, left ventricular ejection fraction; GLS/GCS, global longitudinal/circumferential strain.

^an = 1074/983/71/38. Volumes are given in mL/m² body surface area, EF and strain in % and T1 in ms.

the primary endpoint (GLS HR 1.12, 95%CI 1.04–1.21, $P = 0.002$ vs. LVEF HR 0.99, 95%CI 0.97–1.01, $P = 0.406$). GLS emerged as an independent risk predictor for the primary endpoint (HR 1.09, 95%CI 1.03–1.15, $P = 0.003$) in a multivariable model based on clinical factors (age, NYHA classification), laboratory testing (eGFR and NTproBNP), and CMR tissue characterization (native T1). LV GLS dichotomized at the median (16.4%) added incremental value for risk prediction of the primary endpoint in patients with an LVEF below ($P = 0.017$) and above

($P = 0.045$) 55% dichotomized at the median (Figure 3). In a model accounting for RV function for primary endpoint prediction which included the same clinical (age, NYHA) and laboratory (eGFR and NTproBNP) parameters in addition to LV GLS and RV EF, NYHA (HR 1.44, $P < 0.001$), eGFR (HR 0.99, $P = 0.014$) and GLS (HR 1.09, $P = 0.012$) but not RV EF (HR 0.99, $P = 0.404$) emerged statistically significant. Considering the same model, neither LV GLS ($P = 0.623$) nor RV EF ($P = 0.287$) predicted the secondary endpoint.

Table 3 Risk assessment

Variable	Univariate primary endpoint	Multivariable primary endpoint	Univariate secondary endpoint	Multivariable secondary endpoint
Clinical factors				
Age	1.04 (1.02–1.06) <i>P</i> < 0.001	1.01 (0.98–1.03) <i>P</i> = 0.656	1.05 (1.03–1.07) <i>P</i> < 0.001	1.04 (1.02–1.06) <i>P</i> < 0.001
NYHA class	1.63 (1.38–1.94) <i>P</i> < 0.001	1.36 (1.11–1.67) <i>P</i> = 0.003	1.39 (1.22–1.60) <i>P</i> < 0.001	1.31 (1.12–1.54) <i>P</i> < 0.001
Laboratory testing				
eGFR	0.98 (0.97–0.99) <i>P</i> < 0.001	0.99 (0.98–1.00) <i>P</i> = 0.046	0.99 (0.98–0.99) <i>P</i> < 0.001	1.00 (0.99–1.01) <i>P</i> = 0.477
NT-proBNP	1.00 (1.00, 1.00) <i>P</i> < 0.001	1.00 (1.00–1.00) <i>P</i> = 0.455	1.00 (1.00, 1.00) <i>P</i> = 0.002	1.00 (1.00–1.00) <i>P</i> = 0.659
Echocardiography				
Aortic valve stenosis	1.00 (0.99–1.02) <i>P</i> = 0.553		1.00 (0.99, 1.01) <i>P</i> = 0.890	
Mitral valve regurgitation	1.00 (0.99–1.02) <i>P</i> = 0.445		1.00 (0.99, 1.01) <i>P</i> = 0.931	
Cardiovascular magnetic resonance				
Native T1	1.01 (1.01–1.01) <i>P</i> < 0.001	1.01 (1.00–1.01) <i>P</i> = 0.001	1.01 (1.00–1.01) <i>P</i> = 0.001	1.00 (1.00–1.01) <i>P</i> = 0.100
LVEF	0.96 (0.95–0.97) <i>P</i> < 0.001		0.99 (0.98–1.00) <i>P</i> = 0.089	
LV GLS	1.15 (1.10–1.21) <i>P</i> < 0.001	1.09 (1.03–1.15) <i>P</i> = 0.003	1.06 (1.03–1.11) <i>P</i> = 0.001	0.99 (0.95–1.04) <i>P</i> = 0.747
LV GCS	1.12 (1.07–1.17) <i>P</i> < 0.001		1.03 (1.00–1.07) <i>P</i> = 0.064	
RVEF	0.96 (0.94–0.98) <i>P</i> < 0.001		0.98 (0.97–1.00) <i>P</i> = 0.045	
RV GLS ^a	1.05 (1.02–1.08) <i>P</i> < 0.001		1.02 (0.99–1.05) <i>P</i> = 0.137	

The data is presented as hazard ratios with associated 95% confidence intervals in parentheses. Variables with univariate significance (*P* < 0.05) were included in multivariable Cox regression models and are presented if they emerged as statistically significant (*P* < 0.05). Due to collinearity of functional parameters, only GLS was considered as a CMR-derived functional parameter in multivariable models.

NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; LV EF/GLS/GCS, left ventricular ejection fraction/global longitudinal/circumferential strain.

^aRV GLS assessment only available in *n* = 1074 (*n* = 37/60 primary/secondary endpoints). RV function was not considered in this specific multivariate analysis.

Discussion

The results of this monocentric longitudinal registry demonstrate the high prognostic yield of GLS in an unselected, real-world in- and outpatient clinical setting. GLS but not LVEF was found to be a predictor for both the primary and secondary endpoints. GLS was a predictor for the primary and secondary endpoints independent of LVEF and provided incremental prognostic value in patients with LVEF either below or above the median of 55% for primary endpoint prediction. Finally, GLS remained independent in a multivariable model including clinical, laboratory, and CMR-derived information for primary endpoint prediction.

LVEF is commonly used for HF classification⁴ and is the most commonly established parameter for risk assessment.¹⁷ Park et al.¹⁸ demonstrated the incremental value of GLS in patients classified as having HF with reduced, mildly reduced, or preserved EF. Nevertheless, multiple limitations for general clinical practice warrant further consideration. Whilst an acute HF population with a 5-year mortality rate of 40%¹⁸ is in line with data from the ESC guidelines,⁴ this may not be a representative of the day-to-day population of in- and outpatient cardiology clinics. Thus, application of the results presented by Park et al.¹⁸ especially to general outpatient clinics with lower risk profiles and fewer events, may be limited. The present population consisted of 1655 patients across the full spectrum of cardiovascular diseases, both ischaemic and non-ischaemic in nature, including cardiomyopathies, rare storage diseases, myocarditis, and chronic coronary syndrome. Furthermore, there was a distinct percentage of patients with no abnormal findings, as may be expected from a specialized outpatient clinic based on referrals from external cardiologists and internal medicine specialists. As a consequence, this population may better reflect the general cardiological population: only about 4.1% primary and 6.4% secondary endpoints were met by patients during the 1-year timeframe. Despite this low frequency, GLS emerged as a highly significant outcome predictor, which underlines its clinical significance across the full spectrum of CVD.

As all patients presented with acute heart failure,¹⁸ the vast range of EF values across these patients intrinsically demonstrates the limited value of EF for HF hospitalization prediction. Indeed, the presence of HF with preserved EF (HFpEF) itself limits EF as the sole risk assessment tool.^{19,20} In addition, different subtypes of HFpEF have been described based on the range of LVEF that differentiate between HFpEF patients with LVEF from 50% to 60% and >60%²¹: The former group demonstrated impaired contractility and ventriculo-arterial coupling on invasive catheterization in conjunction with ventricular fibrotic remodelling, whereas the latter was associated with increased contractility but higher diastolic and systolic stiffness despite less fibrotic remodelling.²¹ Indeed, CVD may not be adequately described by volumetric assessments alone, neither by overall cardiac volume nor by EF. As a result, the recent ESC guideline on cardiomyopathies has introduced the non-dilated LV cardiomyopathy subtype.³ Whilst in the present population both GLS and EF predict the primary endpoint of all-cause mortality and HF hospitalization, only GLS emerged as an independent predictor. Furthermore, when dichotomized at the median, GLS provided incremental prognostic value in patients both below and above the LVEF median. These findings underline the significance of GLS for detailed, prognosis-relevant functional characterization. Beyond GLS, LA strain has demonstrated incremental diagnostic¹⁹ and prognostic value^{22–24} across the spectrum of HFrEF and HFpEF, even in addition to GLS.²⁵ On the one hand, LA function may reflect LV functional deterioration and congestion, on the other hand, it may add specific value stemming from intrinsic atrial dysfunction. This may underline the future role of LA functional analyses even compared to GLS which warrants further clinical trials. Notwithstanding, GLS alone has demonstrated prognostic value both in HFpEF and HFrEF.¹⁸

The broad spectrum of CVD calls for more than one parameter for detailed patient classification and risk assessment. In that regard, patient characteristics such as age and symptom severity (NYHA class), laboratory findings such as eGFR and NT-proBNP, and the presence of additional valvular dysfunction and tissue remodelling such as T1 should all

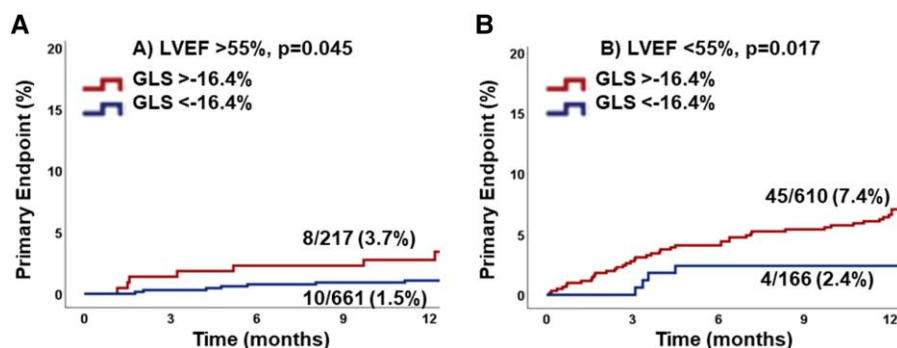


Figure 3 Kaplan-Meier plot—primary endpoint. (A) The graph shows the percentage of patients with LVEF above the median of 55% who met the primary endpoint dichotomized according to the median of GLS. (B) The graph shows the percentage of patients with LVEF below the median of 55% who met the primary endpoint dichotomized according to the median of GLS.

be taken into account for the evaluation of CVD. However, GLS emerged as a predictor for the primary endpoint independent of the aforementioned characteristics. Most hospitalizations of HF patients (63%) do not qualify as HF hospitalizations as reported by the ESC heart failure guideline.⁴ Indeed, GLS was the only functional parameter with prognostic significance in univariate Cox regression analysis for the secondary endpoint of all-cause mortality and hospitalized angina, myocardial infarction, and stroke, although significance was not retained on the multivariable clinical model. Consequently, GLS emerges as the best functional parameter, but further clinical risk assessment is warranted for overall patient classification. Although RV function, both volumetric and deformation imaging derived, held prognostic impact on univariate analyses for primary endpoint prediction, multivariate analyses considering the same clinical and laboratory baseline parameters in addition to LV GLS and RV EF continuously supported the role of LV GLS.

Cardiac deformation assessment based either on echocardiography or CMR imaging remains widely underused. Although the availability of CMR imaging may be limited to tertiary centres, this is not the case for echocardiography, and thus limited availability is not the main reason for limited application. Vendor-specific differences in reference ranges^{10,26} do impact overall applicability²⁷; a reference population may be established for about 30 patients, as is the case for mapping in CMR according to general recommendations. Data from speckle-tracking echocardiography²⁸ as well as CMR-FT using CVI 42^{29,30} show that roughly -16% GLS is the lower limit of normal, which would be in line with the present population showing a median value of -16.4% for myocardial strain. Thus, this value may be used as a landmark for overall interpretation of GLS as it provided incremental prognostic value. Finally, whilst a body of evidence exists for specific CVD such as ischaemic heart disease following acute myocardial infarction,^{8,11} non-ischaemic dilated cardiomyopathy,³¹ and even chronic kidney disease,⁶ the present findings underline the applicability of GLS in patients presenting for the first time with yet unknown specific underlying cardiovascular disease. GLS may serve as a rather universal risk assessment tool upon initial patient contact.

Limitations

The underlying data and conclusions are derived from an observational registry with its associated general limitations. Whilst both in- and outpatients were prospectively recruited to the registry, this poses an inherent limitation in terms of selection bias, as inpatients unfit for CMR were not included. The low number of endpoints met impacts statistical power; however, multivariable models were not overfitted, and the low number of events may be due to a population that is more

homogeneous than that seen in an unselected outpatient setting on a daily basis. RV GLS was not available for all patients which may have resulted in underestimated statistical power and clinical significance.

Conclusion

In an all-comers, low-risk patient population, GLS emerged as an independent risk predictor compared to LVEF as well as established clinical parameters associated with poor outcome. In addition, GLS adds prognostic value to that of LVEF evaluation. As a result, these findings promote clinical routine implementation of GLS for all patients irrespective of their cardiovascular background.

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Author contributions

SB and AR designed the study protocol, performed data acquisition, performed statistical analyses and drafted the manuscript. JT was involved in conceptualization. JSW, SK and DS performed data acquisition/analysis. All authors revised the manuscript and participated in the scientific discussion during the study. All authors read and approved the final manuscript.

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Consent

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Ethics approval and consent to participate

The study was approved by the Ethics Committee of the University Hospital Giessen and complied with the Declaration of Helsinki. All

individuals gave written informed consent before participating in the study.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Data availability

Regarding data availability, we confirm that all relevant data are within the paper and all data underlying the findings are fully available without restriction and can be accessed at the Kerckhoff Heart Research Institute (KHFI) by researchers who meet the criteria for access to confidential data.

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