Supplementary Online Content

Tröbs S-O, Prochaska JH, Schwuchow-Thonke S, et al. Association of global longitudinal strain with clinical status and mortality in patients with chronic heart failure. *JAMA Cardiol*. Published online February 3, 2021. doi:10.1001/jamacardio.2020.7184

This supplementary material has been provided by the authors to give readers additional information about their work.

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eMethods. Detailed Methods

Resting heart rate and blood pressure were measured in a temperature-regulated room after a rest period of five minutes three times in intervals of three minutes utilizing an Omron 705-CP electronic oscillometer. Subsequent anthropometric measurements, including weight, height, waist- and hip circumference, were obtained. Smokers were dichotomized into non-smoker (never and ex-smokers) and smoker including occasional, and permanent smokers, according to anamnestic data. Current smoking was defined through the computer-assisted computer interview if one of the following criteria was met: smoking one cigarette per day, smoking at least seven cigarettes per week, smoking one package per month, smoking one cigarillo per day, smoking at least seven cigarillos per week or smoking two pipes per day. Obesity was defined as a body mass index higher than $30 m/kg^2$. Type-2 diabetes mellitus was defined by glycated hemoglobin ≥ 6.5%, current intake of antidiabetic drugs, or a diagnosis by a physician. Dyslipidemia was defined by a low-density lipoprotein/high-density lipoprotein ratio > 2.5, proper current medication, triglyceride concentration > 150, or if a physician previously diagnosed dyslipidemia. Arterial hypertension was assumed if anti-hypertensive drugs were taken or mean systolic blood pressure was ≥ 140 mmHg, or if diastolic blood pressure was ≥ 90 mmHg, respectively. Positive family history of myocardial infarction or stroke was defined as a first-degree family member with myocardial infarction or stroke at age > 60 if male or > 65 if female. Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 ml/min/1.73m² (according to CKD-EPI formula).[1] Information on venous thromboembolism (VTE) and stroke were collected through computer-assisted personal interview or medical records. VTE was defined as ever occurred pulmonary artery embolism and/or deep vein thrombosis. Stroke was defined as a previous history stroke.

Blood samples were drawn from a cubital vein after a fasting period of at least 5h and subsequently processed for biobanking and measurement of an ad hoc available set of laboratory markers. NT-proBNP was measured via a commercially available Elecsys® 2010 proBNP II immunoassay (Roche Diagnostics, Mannheim, Germany).

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eTable 1. Inclusion and exclusion criteria of the study sample

Inclusion criteria	Exclusion criteria
Age: 35 to 84 years Documented (via echocardiography) asymptomatic cardiac functional abnormality or symptomatic heart failure Competent to compliance at the time of written consent German-speaking	Individuals who are not able to travel to the study center and to cooperate in the investigations due to psychological or physical impairment Acute form of endocarditis, myocarditis or pericarditis Acute infectious disease Acute myocardial infarction Decompensated heart failure

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eTable 2. Clinical characteristics of study participants in sinus rhythm stratified for the availability of data on GLS

	GLS available (n=2,186)	GLS missing (n=514)
Age [years]	65.1±10.5	65.9±9.9
Sex (female), No. (%)	768 (35.1)	183 (35.6)
NYHA functional class ≥II, No. (%)	700 (32.0)	201 (39.1)
Cardiovascular risk factors, No. (%)		
Arterial hypertension	1734 (79.3)	395 (76.8)
Diabetes mellitus	498 (22.8)	145 (28.2)
Dyslipidemia	1569 (71.8)	399 (77.6)
FH of MI/Stroke	529 (24.2)	118 (23.0)
Obesity	714 (32.7)	205 (39.9)
Smoking	289 (13.2)	67 (13.1)
Comorbidities, No. (%)		
Atrial fibrillation*	373 (17.1)	104 (20.2)
Coronary artery disease	866 (39.6)	248 (48.2)
Chronic kidney disease	361 (16.5)	82 (16.0)
COPD	301 (13.8)	64 (12.5)
Myocardial infarction	542 (24.8)	170 (33.1)
Peripheral artery disease	153 (7.0)	38 (7.4)
Stroke	187 (8.6)	54 (10.5)
Venous thromboembolism	191 (8.7)	45 (8.8)
Left ventricular function		
LVEF [%]	55.3±10.4	52.3±11.8
E/E'	8.48 (6.54/11.29)	8.70 (6.75/11.93)
Left ventricular geometry		
LVMi [$g/m^{2,7}$]	45.1 (37.2/54.5)	46.8 (38.4/58.5)
RWT	0.42±0.12	0.42±0.12
LVEDV [ml]	98.0 (78.0/125.0)	107.3 (82.2/141.6)
LVESV [ml]	41.0 (30.7/59.9)	47.0 (33.5/73.9)
NT-proBNP [pg/ml]	155.0 (69.0/369.0)	182.0 (86.0/451.7)
Heart failure stages according to AHA, No. (%)		
Stage A	434 (19.9)	60 (11.7)
Stage B	629 (28.8)	115 (22.4)
Stage C/D	1123 (51.4)	339 (66.0)
Medication, No. (%)		
ACE inhibitor (C09A)	783 (35.8)	225 (43.8)
ARA (C03DA)	274 (12.5)	88 (17.1)
ARB (C09C)	677 (31.0)	173 (33.7)
Beta-blocker (C07)	1206 (55.2)	309 (60.1)
Diuretics (C03)	618 (28.3)	178 (34.6)
Ivabradine (C01EB17)	145 (6.6)	36 (7.0)
Statins (C10AA)	975 (44.6)	263 (51.2)

Continuous data are expressed as mean ± standard deviation or as median with interquartile range. Categorical variables are presented as % (n). ACE, angiotensin-converting enzyme; ARA, Aldosterone receptor antagonist; ARB, Angiotensin receptor blocker; COPD, chronic

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obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; FH, family history; LVEF, left ventricular ejection fraction; MI, myocardial infarction. Chronic kidney disease was defined by estimated glomerular filtration rate; * in sinus rhythm during the examination

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eTable 3. Predictive value of left ventricular ejection fraction and E/E' ratio in addition to global longitudinal strain for survival.

	Adjustment for age, sex, GLS, LVEF, E/E' ratio, observer, image quality		Additional adjustment for CVRF[a], comorbidities[b], eGFR		Additional adjustment for cardiac structure[c], NYHA class, HF medication[d]	
	HR [95%CI] [per SD]	P-value	HR [95%CI] [per SD]	P-value	HR [95%CI] [per SD]	P-value
All-cause mortality						
E/E'	1.06 [0.92 – 1.22]	.43	0.95 [0.82 – 1.10]	.5	0.95 [0.82 – 1.10]	.49
$LVEF^{-1}$	1.22 [0.96 – 1.54]	.11	1.05 [0.83 – 1.34]	.66	0.98 [0.75 – 1.28]	.89
Cardiac death						
E/E'	1.16 [0.98 – 1.37]	.089	1.11 [0.93 – 1.31]	.24	1.11 [0.93 – 1.32]	.25
$LVEF^{-1}$	1.21 [0.82 – 1.79]	.33	1.04 [0.69 – 1.59]	.84	1.03 [0.61 – 1.73]	.91

Multivariable Cox-regression analysis with all-cause mortality and cardiac death (all-cause mortality as competing risk) as the dependent variable and global longitudinal strain as an independent variable with adjustment for the denoted parameters. CI, confidence interval; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; SD, standard deviation. [a]i.e. diabetes mellitus, dyslipidemia, family history of myocardial infarction or stroke, hypertension, obesity, smoking. [b]i.e., atrial fibrillation, coronary artery disease, chronic obstructive pulmonary disease, myocardial infarction, peripheral artery disease, stroke, venous thromboembolism. [c]i.e., left ventricular mass index and relative wall thickness. d, heart failure medication comprises intake of aldosterone antagonists, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, beta-blockers and/or diuretics.

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eTable 4. *C*-statistics of Cox models for predicting all-cause and cardiac death.

	All-cause death	Cardiac death
	C-Index	**C-Index**
Model 1: Adjusted for age, sex, cardiovascular risk factors[a], comorbidities[b] and eGFR	0.76	0.76
Model 1 + log-transfromed NT-proBNP	0.79	0.79
Model 1 + GLS	0.77	0.81
Model 1 + GLS and log-transfromed NT-proBNP	0.80	0.81

C-index of multivariable Cox-regression models with all-cause mortality or cardiac death (here with all-cause mortality as competing risk) as dependent variable adjusted for denoted parameters. eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain. [a], cardiovascular risk factors include diabetes mellitus, dyslipidemia, family history of myocardial infarction or stroke, arterial hypertension, obesity, smoking. [b], comorbidities include atrial fibrillation, coronary artery disease, chronic obstructive pulmonary disease, myocardial infarction, peripheral artery disease, stroke, venous thromboembolism.

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eTable 5. Cause-specific hazard ratios for global longitudinal strain, left ventricular ejection fraction and E/E' ratio for cardiac death.

	Adjustment for age, sex, GLS, LVEF, E/E' ratio		Additional adjustment for CVRF[a], comorbidities[b], eGFR		Additional adjustment for cardiac structure[c], NYHA class, HF medication[d]	
	HR [95%CI] [per SD]	P-value	HR [95%CI] [per SD]	P-value	HR [95%CI] [per SD]	P-value
Cardiac death						
GLS	2.10 [1.47 – 3.00]	<.0001	2.23 [1.54 – 3.22]	<.0001	2.00 [1.35 – 2.97]	.00058
E/E'	1.17 [0.98 – 1.40]	.084	1.11 [0.92 – 1.33]	.27	1.20 [0.97 – 1.47]	0.091
$LVEF^{-1}$	1.32 [0.95 – 1.86]	.10	1.13 [0.80 – 1.61]	0.48	1.08 [0.71 – 1.64]	.71

Multivariable Cox-regression analysis with cardiac death (cause-specific) as the dependent variable and global longitudinal strain as an independent variable with adjustment for the denoted parameters. CI, confidence interval; eGFR, estimated glomerular filtration rate; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; SD, standard deviation. [a]i.e. diabetes mellitus, dyslipidemia, family history of myocardial infarction or stroke, hypertension, obesity, smoking. [b]i.e., atrial fibrillation, coronary artery disease, chronic obstructive pulmonary disease, myocardial infarction, peripheral artery disease, stroke, venous thromboembolism. [c]i.e., left ventricular mass index and relative wall thickness. [d], heart failure medication comprises intake of aldosterone antagonists, angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, beta-blockers and/or diuretics

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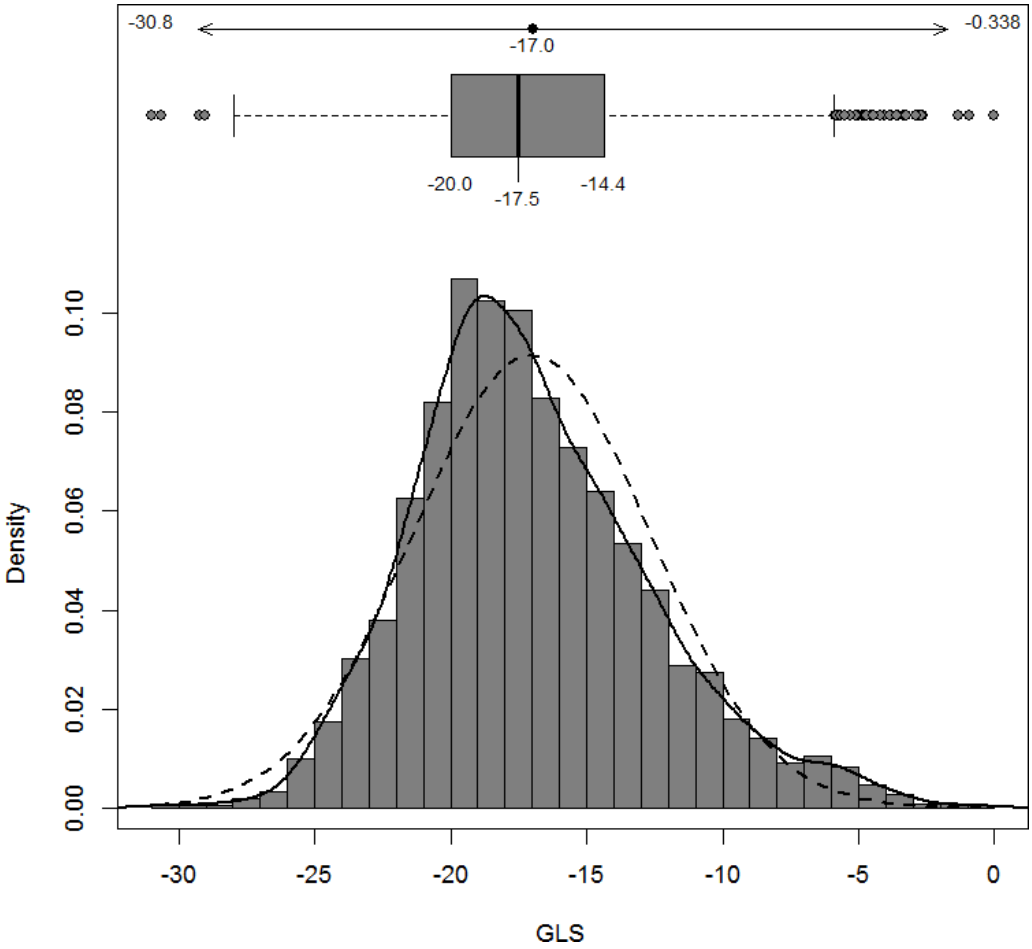
eFigure 1. Distribution of global longitudinal strain in the sample.



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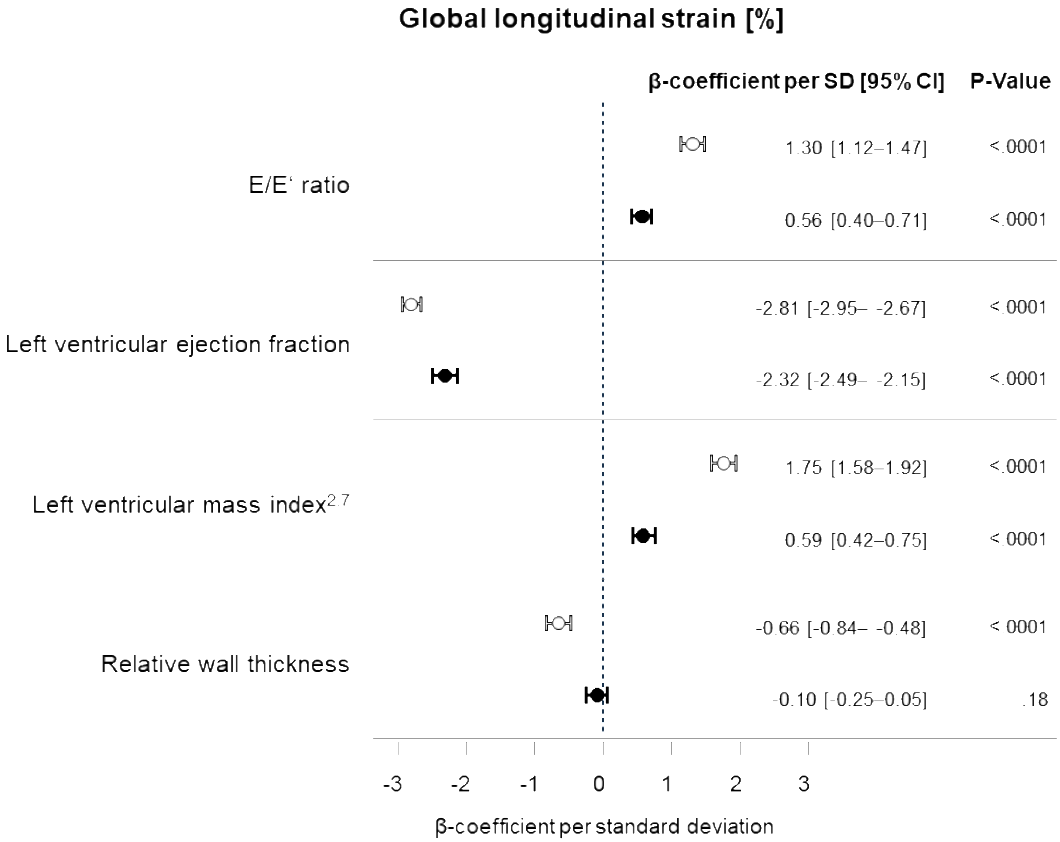
eFigure 2. Relation between established measures of cardiac function and structure with global longitudinal strain.



○ crude
● adjusted for age, sex, CVRF (i.e., arterial hypertension, diabetes mellitus, dyslipidemia, FH of MI/stroke, obesity, smoking), comorbidities (i.e., atrial fibrillation, coronary artery disease, chronic obstructive pulmonary disease, estimated glomerular filtration rate, myocardial infarction, peripheral artery disease, venous thromboembolism, stroke), cardiac function (i.e., E/E' ratio and left ventricular ejection fraction) and structure (i.e., left ventricular mass index$^{2.7}$ and relative wall thickness)

Univariate and multivariable regression analysis with global longitudinal strain as the dependent variable. β-estimates presented per one standard deviation are presented for each independent variable. Multivariable model adjusted for denoted covariates. SD, standard deviation.

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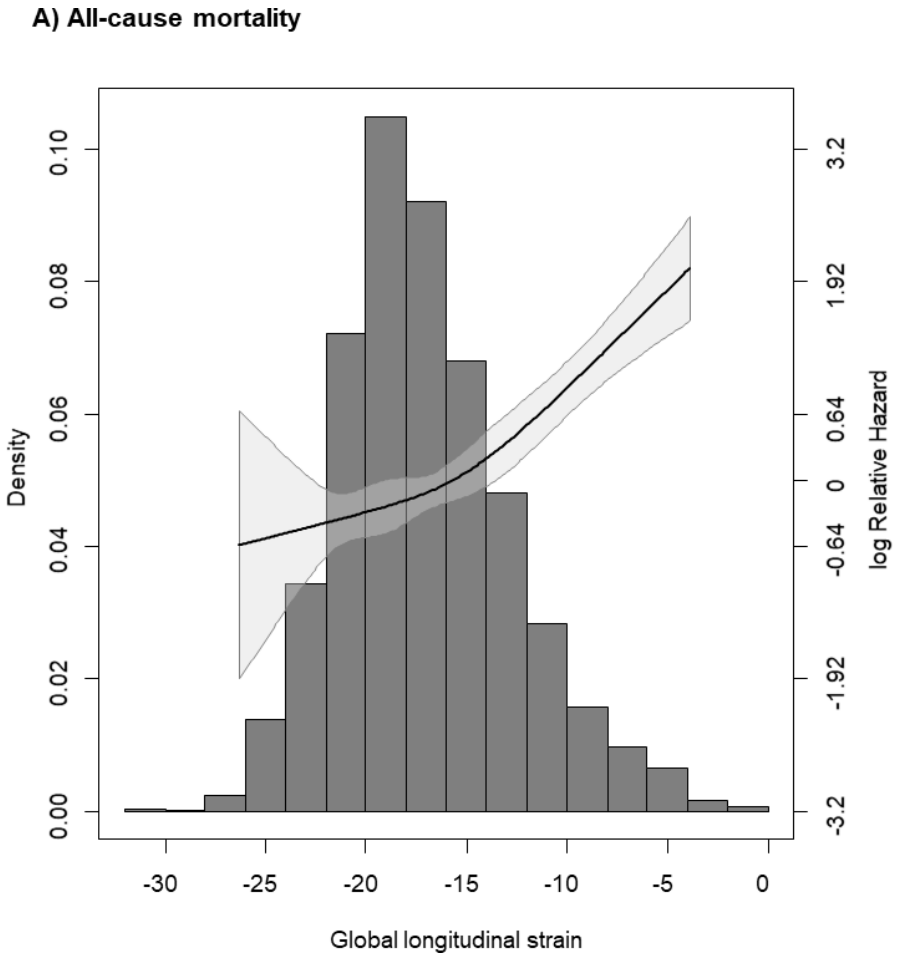
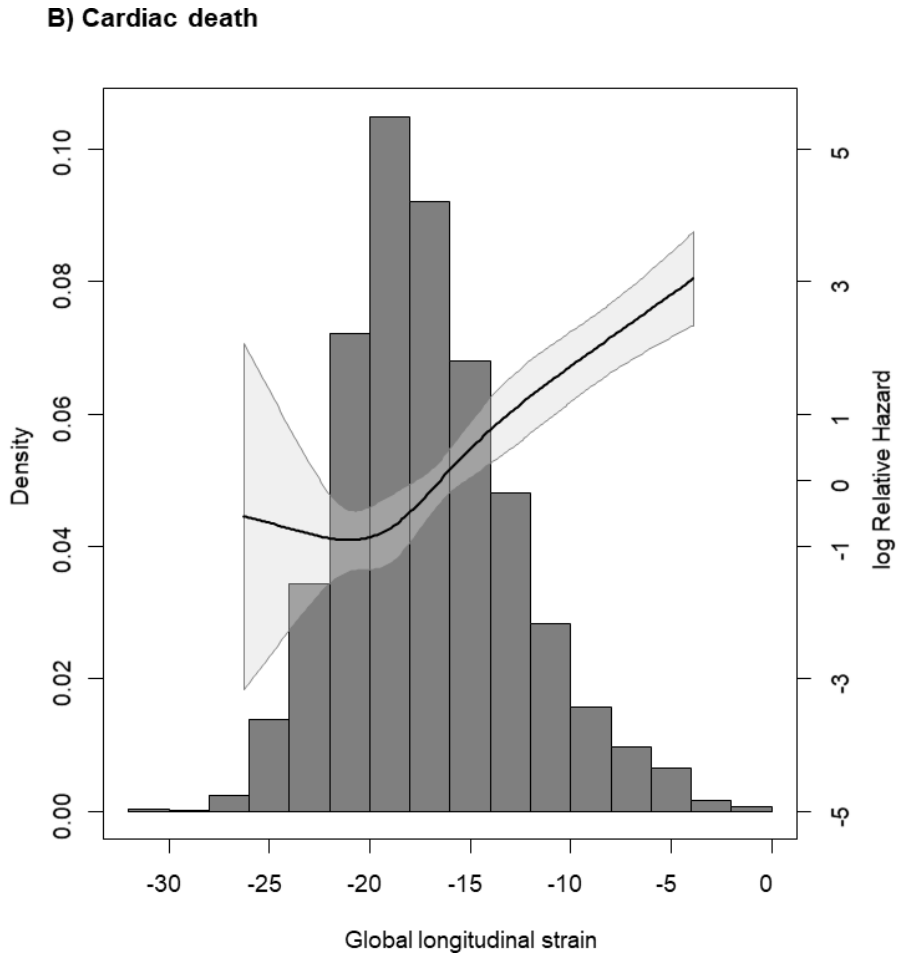
eFigure 3. Cox models with restricted cubic splines for the relation of GLS with survival.





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eReference

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.

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