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ORIGINAL RESEARCH ARTICLE

Left ventricular dysfunction in atrial fibrillation and heart failure risk

Jen-Yuan Kuo[1,2,3], Sheng-Hsiung Chang[1,2,3], Kuo-Tzu Sung[1,2], Po-Ching Chi[4], Jo-Nan Liao[5,6], Tze-Fan Chao[5,6], Cheng-Huang Su[1,2,3], Hung-I Yeh[1,2,3] and Chung-Lieh Hung[1,2,3,7]*

[1]*Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan;* [2]*Department of Medicine, Mackay Medical College, New Taipei, Taiwan;* [3]*Mackay Junior College of Medicine, Nursing and Management, Taipei, Taiwan;* [4]*Department of Cardiology, Taoyuan General Hospital, Ministry of Health and Welfare, Taoyuan, Taiwan;* [5]*Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan;* [6]*Cardiovascular Research Center and Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan;* [7]*Institute of Biomedical Sciences, Mackay Medical College, New Taipei City, Taiwan*

Abstract

Aims This study aimed to investigate the functional correlate, clinical relevance, and prognostic implications of novel left ventricular (LV) deformations in patients with atrial fibrillation (AF).

Methods and results LV deformational indices, including peak global longitudinal strain (GLS), systolic strain rates (SRs), and early diastolic strain rates (SRe) were measured in a large-scale AF population. We related such measures to key clinical heart failure (HF) markers, conventional echocardiographic ventricular parameters, and clinical outcomes. Among 1483 subjects with newly diagnosed AF (mean age, 71.6 ± 12.4 years; 55.5% male), worsened GLS (mean, − 12.6 ± 3.9%) and strain rates (SRs and SRe: mean, − 0.86 ± 0.27 and 1.25 ± 0.41 1/s, respectively) by our three-beat measures were independently correlated with higher C-reactive protein, N-terminal pro-B-type natriuretic peptide, higher E/e', more impaired LV ejection fraction (LVEF < 50%), lower estimated glomerular filtration rate, permanent AF, and prevalent HF (all $P < 0.05$). LV deformations by three-beat analysis well correlated with the respective results of traditional methods. Abnormal GLS (> − 14.7%) was common in our cohort (67.8%) despite an averaged preserved LVEF (58.4 ± 14.2%), with worse GLS and SRe being associated with higher composite HF re-admissions/death during the 2.9 year follow-up (inter-quartile range, 1.6–4.1 years) in multivariate models incorporating key LV indices (LVEF, LV mass index, and E/e') (all $P < 0.001$). Sensitivity analysis by excluding those with regional wall motion abnormality showed broadly similar findings. An improved risk reclassification was observed when GLS and SRe were separately added to the LVEF. Comparison of the AF cohort with a fully matched independent non-AF cohort at the same baseline LVEF level showed a substantially lower GLS [− 13.2 ± 3.8% (AF) vs. 18.1 ± 3.2% (non-AF)] and higher clinical events rate (hazard ratio, 1.41 [95% confidence interval, 1.14–1.75]; log-rank $P = 0.002$) in the AF cohort.

Conclusions Impaired LV function defined by myocardial deformation was common in patients with AF and provides independent prognostic values over conventional measures with improved risk prediction. Our data highlight the need for implementing cardiac deformations in daily practice for patients with AF.

Keywords Left ventricular deformation; Global longitudinal strain; Strain rate; Atrial fibrillation; Heart failure; Mortality

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**Correspondence to: Chung-Lieh Hung, Cardiovascular Center and Division of Cardiology, Mackay Memorial Hospital, 92, Sec 2, Zhongshan North Road, Taipei 10449, Taiwan. Tel: 886-2-2543-3535 ext. 2456; Fax: 886-2-2543-3535 ext. 2459. Email: jotaro3791@gmail.com*

Introduction

Atrial fibrillation (AF) remains the most common sustained type of cardiac arrhythmia worldwide and is associated with significant morbidity, including ischaemic stroke and heart failure (HF), and mortality.[1] With the rapid increase in the elderly population, AF prevalence is expected to rise substantially, with estimates ranging from 5.6 million to > 10 million in the USA by 2050.[2,3] Left ventricular ejection fraction (LVEF) measured by echocardiography remains the cornerstone for determining the left ventricular (LV) systolic performance in clinical practice. However, structural cardiac anomalies and LV systolic dysfunction are common among subjects with an established diagnosis of AF.[1,4] As HF and

AF frequently coexist, better LV functional characterization is warranted to provide valuable information on the extent of pathological ventricular involvement and to improve risk stratification in patients with AF.

Recently, two-dimensional (2D) speckle-tracking strain and strain rate imaging has provided new insights into cardiac mechanical properties and has been shown to be a more robust measure because of its angle-independent and load-independent characteristics and a higher reproducibility in evaluating intrinsic ventricular contractility.[5] LV global longitudinal strain (GLS) is a widely utilized surrogate marker of myocardial systolic function shown to detect subtle LV systolic dysfunction in various conditions, even when the LVEF is in the normal range.[6] On the other hand, novel diastolic index by speckle-tracking technique, for example, early diastolic strain rate, has been shown to better reflect LV relaxation and filling condition over traditional measures.[7] These advanced deformational indices have also recently demonstrated to be superior predictor of cardiovascular outcomes for subjects with either sinus rhythm or AF independent of LVEF.[8–11] Despite these, prior reports using LV deformational indices in AF population are largely limited by small sample size, confined to index beat method, and lack of testing across a broad spectrum of cardiovascular disorders.[11,12] As LVEF for ventricular performance evaluation in AF is less sensitive and has cycle-to-cycle variations,[13] in this regard, the superiority of the GLS measure may likely render it a useful and alternative measure to conventional parameters (i.e. LVEF) when AF is present.[14,15]

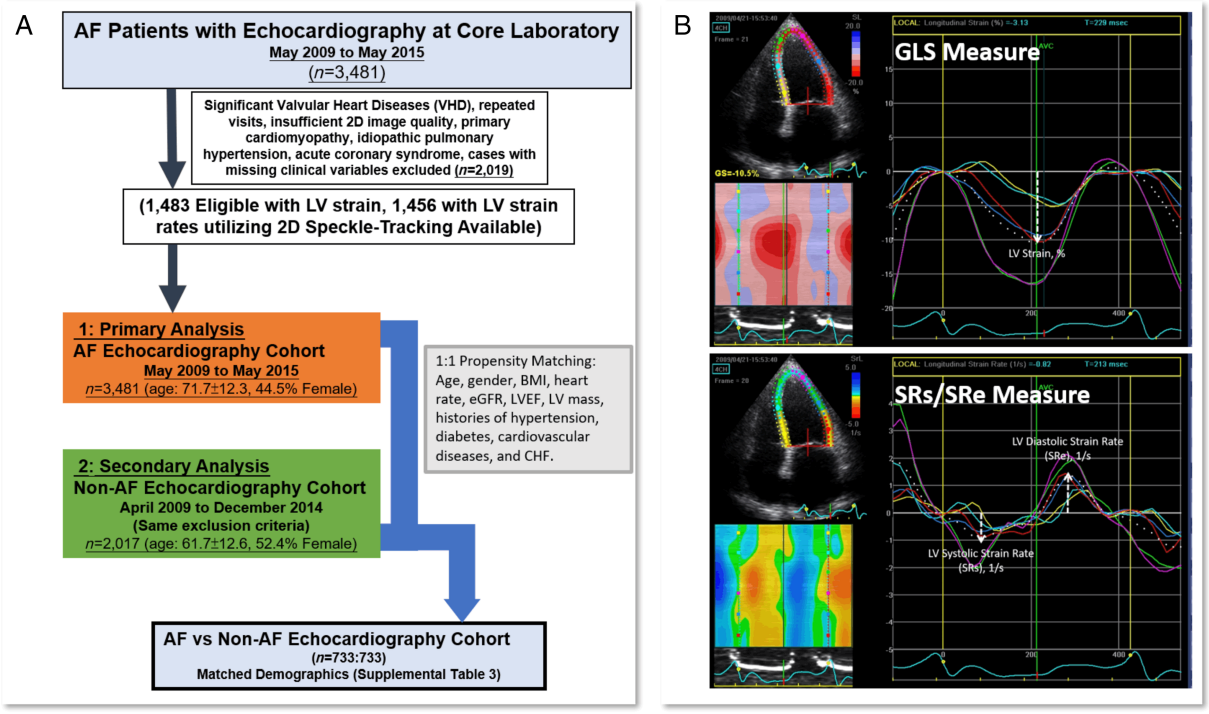
Hence, we investigated the burden of mechanical functional impairment, clinical correlates, and prognostic associations using LV deformations assessed by 2D speckle-tracking method in a large AF patient population.

Methods

Study population

Patients with first-diagnosed AF were retrospectively reviewed, and only those who underwent comprehensive transthoracic echocardiography with sufficient image quality were eligible for our primary analysis. Study subjects were enrolled from May 2009 to May 2015. Baseline characteristics, underlying diseases, medications used, and laboratory results were all obtained by reviewing medical records and information from electronic *medical records*. The detailed study workflow is shown in *Figure 1A*. Hypertension or diabetes mellitus medical history was defined from known diagnosed medical history or current medications use by electronic chart review. History of HF in current study was defined as adjudicated prior HF hospitalization (as Stage C HF). Types of AF in current study were classified as (i) paroxysmal AF: episodes of

FIGURE 1 (A) Study flowchart. (B) Illustration of the speckle-tracking measurement of the left ventricular global longitudinal strain (right upper panel) and strain rate curves (right lower panel) in the apical four-chamber view.



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observed AF that terminate within 1 week interval; (ii) persistent AF: observed AF rhythm that lasted for more than 1 week interval; with (iii) permanent AF: the presence of observed AF rhythm that persisted for more than 1 year. For statistical ease, we further categorized patients according to types of AF as non-permanent (paroxysmal + persistent AF) and permanent AF.

To examine whether the presence of AF rhythm may interfere with the longitudinal systolic function when using ventricular deformation GLS and clinical endpoints as key outcome measures, we also performed a second analysis including a non-AF cohort. This cohort was used as a comparator group and fulfilled the same study criteria as those for the study participants but did not have a known prior AF diagnosis (April 2009 to December 2014) (*Figure 1A*). We conducted propensity matching between AF and non-AF cohorts for key baseline demographics, including age, sex, body mass index (BMI), baseline heart rate (HR), estimated glomerular filtration rate (eGFR), LVEF, LV mass, and medical history [hypertension, diabetes, cardiovascular diseases (presence of coronary artery, cerebrovascular, and peripheral arterial disease), and HF] (*Figure 1A*).

This study was approved by the local ethics institutional committee (Mackay Memorial Hospital) for retrospective analysis (institutional review board no. 16MMHIS142e). The investigation conforms with the principles outlined in the Declaration of Helsinki. Given the retrospective study design, informed consent was waived from the institutional review board for the current work.

Conventional echocardiography examination

Conventional echocardiography was performed using the GE system (Vivid 7, E-VingMed) equipped with a 2–4 MHz transducer (M4S). All conventional parameters including the left atrial (LA) diameter, LV wall thickness, internal diameter, LV mass, and LV mass index (LVMi) were measured based on the American Society of Echocardiography criteria.[16] LA and LV volumes were assessed by a modified biplane Simpson's method, using the apical four-chamber and two-chamber views, and averaged for continuous three beats (or five, if available). LVEF and LA emptying fraction were calculated as follows: 100 × (maximal LV or LA volume − minimal LV or LA volume)/maximal LV or LA volume.

LV diastolic haemodynamic indices, including transmitral inflow early (E) and late diastolic filling (A) velocities of pulsed-wave Doppler, deceleration time of E, A-wave duration, and isovolumic relaxation time, were all obtained from five consecutive beats. Further, high-temporal-resolution tissue Doppler imaging (TDI) was adopted to determine the early phase mitral annular velocities of motion, with both peak systolic (s′) and early diastolic (e′) values averaged from the septal and lateral annuli. We also obtained information on the E/e′ ration, a well-documented non-invasive estimate of LV filling condition, by using the ratio of the E transmitral Doppler velocity to TDI-derived average early diastolic e′.

Key study variables, methods, and definitions

All echocardiographic images were stored digitally and reviewed offline. Deformation measurements were performed on 2D images with an average acquired frame rate of 50–90 frames (mean 67 ± 8 frames) per second by an experienced technician using proprietary software (version 10.8, EchoPAC, GE Vingmed Ultrasound, Norway). LV endocardial border was traced manually in the apical two-chamber, three-chamber, and four-chamber views at end-systole.[17] The software automatically generated an epicardial LV silhouette, which delineated a region of interest (ROI) comprising six segments in each apical view. Manual ROI adjustment was allowed to encompass the entire LV myocardial layer followed by an automated segmental tracking. LV strain and strain rate (SR) curves, as the *derivative* of the strain measure for each ventricular segment, were generated from the apical two-chamber, three-chamber, and four-chamber views. The strain pattern was characterized by a predominant down-sloping wave that peaked at the end of the ventricular systole, followed by an up-sloping wave from the baseline. The LV SR curves were shown as a ventricular function of the time throughout the cardiac cycle and could be divided into two main components representing different phases of the LV, with peak systolic SR (SRs) during the systolic and early diastolic SR (SRe) phases, during the early diastolic phase (*Figure 1B*). Larger absolute values $|x|$ of the strain or SR measurements indicated better functions of LV myocardial deformations. Representative global LV deformational indices of strain (GLS) and SR components were derived from the averaged value of the apical two-chamber, three-chamber, and four-chamber data from three continuous beats.

Statistical analysis

Normally distributed continuous variables are presented as mean and standard deviation; categorical variables are presented as proportions. Continuous variables were compared using an unpaired two-tailed *t* test; nominal/categorical variables were compared by χ^2 analysis or Fisher's exact test, as appropriate. Continuous variables among different clinical categories were analysed using a one-way analysis of variance with post-hoc paired comparisons.

Patients were divided into tertile groups on the basis of the original LV GLS, SRs, and SRe values. The first tertile of the LV GLS and SRs referred to the best LV GLS and systolic SR, whereas the first tertile of SRe referred to the worst early

diastolic SR. A linear trend of all continuous baseline demographics and echocardiography variables across the GLS or all SR tertiles was also tested. From a previous community-based study for incident AF, we defined GLS $> -14.7\%$ as an abnormal GLS threshold and examined the distribution of abnormal GLS in the entire study cohort and in clinical subgroups (*Figure 2*).[18] Associations of several key clinical markers or echocardiography predictors of LV systolic/diastolic indices (as an independent variable) with GLS/SR components (as a dependent variable) were evaluated with adequate adjustment. To determine the extent to which the presence of AF rhythm (compared with non-AF as reference) influences the intrinsic myocardial contractility (using GLS as dependent surrogate marker) and clinical outcomes, we introduced propensity matching between AF and non-AF subjects by controlling key clinical demographics, LV mass, and LVEF, using SAS version 9.4e software (SAS Institute, Cary, NC) (*Table S1*); a mediator analysis was performed to confirm the potential effect of the LV GLS on clinical endpoints after matching.

The incidence of combined endpoint of HF re-admission and death was assessed by Cox linear regression models using GLS and SR components as continuous variables. The models were adjusted for several clinical variables (including types of AF) and key LV indices (i.e. LVEF, LVMi, and E/e') separately. We repeated the Cox analysis using the GLS and SR variables as tertiles. Under the speculations that LV regional wall motion abnormalities may affect LV deformational values to an extent, we further conducted sensitivity analysis by examining the predictors and prognostic values of LV deformations again after excluding those with recognizable regional wall motion abnormality (RWMA, n = 145). We further tested the possible non-linearity in the assumption of the associations with the strain/SR using restricted cubic splines (RCSs), according to the tertile cut-points in addition to the lower (fifth) and upper (95th) percentile threshold values. Analyses with RCSs were conducted using the R Statistical Package (version 3.5.1; R Development Core Team) and '*rms*' package (version 5.1-2 updated on 6 January 2018). The incremental values and improvement in the reclassification with LV deformation measurements over the LVEF were assessed using the following: Harrell's concordance index (*C*-index), category-free continuous net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

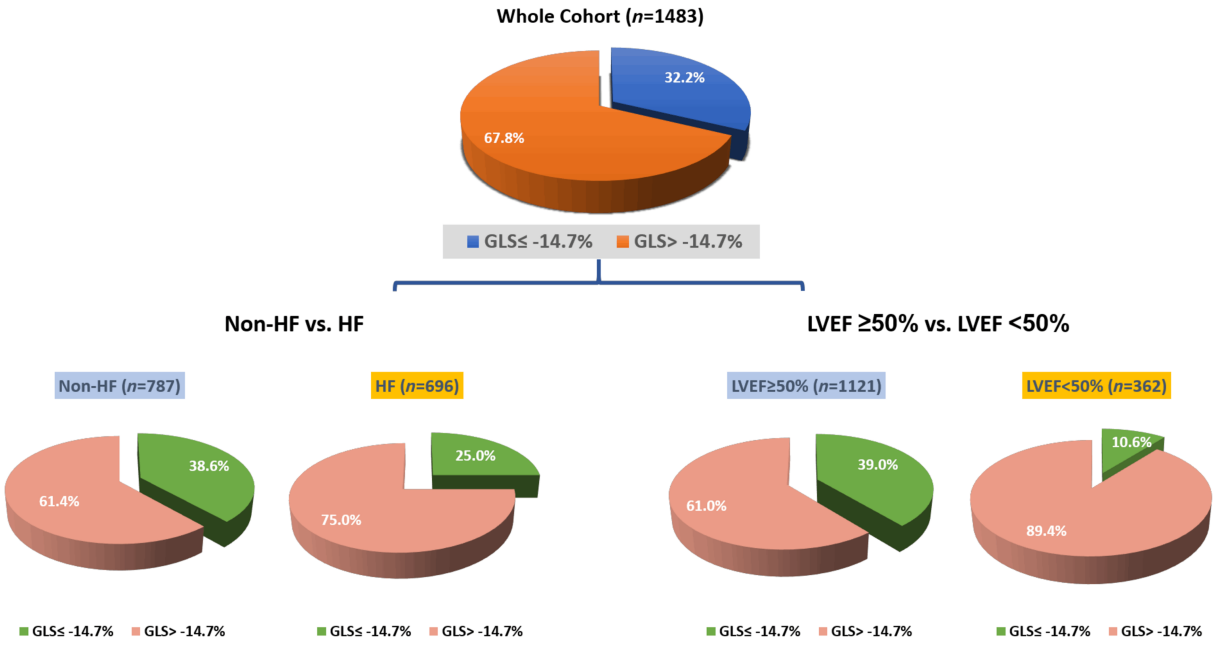
All statistical analyses were performed using SPSS version 17.0 statistical software (SPSS, Chicago, IL, USA) and STATA software (version 11.0, Stata Corp., College Station, TX, USA). Statistical significance was set at $P < 0.05$.

Results

Baseline characteristics

Among 1483 patients with AF (mean age, 71.6 ± 12.4 years; 55.5% male) who met the study criteria, were eligible for a

FIGURE 2 Burden and distribution of abnormal GLS (defined as GLS $> -14.7\%$) using community-derived cut-off for high risk of AF incidence in the current study population, by the presence of either prevalent HF or preserved/impaired LVEF categories (refer to Lang *et al.*[16] for GLS cut-off). AF, atrial fibrillation; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction.



2D speckle-tracking echocardiographic analysis, and were enrolled in our final analysis, the mean LV GLS, SRs, and SRe values were − 12.6 ± 3.9%, − 0.86 ± 0.27, and 1.25 ± 0.41 1/s, respectively, as assessed by the three-beat method. The mean LVEF was 58.4 ± 14.2%. There were totally 343 paroxysmal AF, 230 persistent AF, and 858 permanent AF. Compared with patients in other LV GLS tertiles, patients in the first (best) tertile had the lowest HR; the lowest diastolic blood pressure; fewest co-morbidities, including diabetes mellitus, HF, vascular diseases, and permanent AF; the least anticoagulant use; the lowest serum fasting glucose; the highest high-density lipoprotein and eGFR; and the lowest N-terminal pro-B-type natriuretic peptide (BNP) and C-reactive protein (CRP) levels (all $P < 0.05$; *Table 1*). Conventional echocardiography data analysis showed a smaller end-systolic and end-diastolic LV volume, lower LVMi, higher LV s′ and e′, lower E/e′, and better LV SRs/SRe values but a higher LVEF in the best GLS group than in the other groups (all $P < 0.05$). Continuous relationships between GLS and SR indices vs. LVEF, LVMi, and E/e′ were displayed as RCS (*Figure S1*). In general, patients in SRs/SRe tertiles showed similar baseline demographics and clinical features as those in the GLS tertiles (*Tables* S1 and *S2*).

Associations of atrial fibrillation, left ventricular systolic dysfunction, and heart failure

By defining − 14.7% as the abnormal GLS cut-off, we determined that 67.8% of the whole study cohort had abnormal GLS. Moreover, abnormal GLS was observed in 75.0% of patients with HF (n = 696) vs. 61.4% of those without HF (n = 787), and in 89.4% of patients with impaired LVEF (< 50%; n = 362) vs. 61.0% of those with preserved LVEF (≥50%; n = 1121; *Figure 2*). Patients with permanent AF had markedly lower GLS (− 11.5 ± 3.8% vs. − 14.4 ± 3.2%), LV SRs (−0.80 ± 0.26 1/s vs. − 0.95 ± 0.25 1/s), and LV SRe (1.17 ± 0.40 1/s vs. 1.37 ± 0.39 1/s, all $P < 0.001$) than those classified as non-permanent AF (all $P < 0.001$). Worsened renal function (per 10-unit increment), history of coronary artery disease, permanent AF, higher CRP (per 1-unit increment), BNP > 1000 pg/mL, E/e′ ≥ 14 or ≥11, LVEF < 50%, and prevalent HF were all independently associated with reduced LV GLS, LV SRs, and LV SRe (*Figure 3A, B*). When we classified participants into three clinical categories according to LVEF and HF (LVEF ≥ 50% without HF, n = 613 [42.0%]; LVEF ≥ 50% with HF, n = 486 [33.3%]; and LVEF < 50%, n = 360 [24.7%]), we observed a significant reduction in GLS across these three categories (− 16.8 ± 1.7%, − 12.9 ± 1.0%, − 8.2 ± 2.1%; P for trend < 0.001; *Figure 3C*). Similarly, significant trends towards decreasing LV SRs (0.86 ± 0.28, 0.80 ± 0.26, and 0.70 ± 0.27 1/s) and SRe (− 1.28 ± 0.48, − 1.11 ± 0.39, and − 1.05 ± 0.46 1/s) across the three categories were observed (P for trend < 0.001; *Figure 3D*). Sensitivity analysis showed broadly similar associations (except for the relationship with CRP) after excluding those with RWMA (*Figure S2*).

Comparison between three-beat method and index beat or multiple-beat methods

The reproducibility of calculating the GLS using our averaged three-beat method among 80 study participants was tested. Coefficients of variance for the intra-observer and inter-observer analyses using the same beat (same cycle length of any of the subjects with AF) were 5.52% and 6.05%, with LV SRs as 6.43 and 7.08, and LV SRe as 6.67%, and 7.14%, respectively. We examined the correlations of the LV end-diastolic volume, end-systolic volume, LVEF, and GLS among beats 1, 2, and 3 [beat 3 (index beat) as standard value, defined as the RR1/RR2 ratio by beats 1 and 2, ranging from 0.96 to 1.04] for 80 subjects with available index beat data. We found that the GLS tended to have a higher reproducibility than the LV volume and LVEF,[11] with the LVEF demonstrating the worst reproducibility (*Figure S3*). The correlation of the GLS, LV SRs, and SRe between our averaged three-beat and index beat methods was 0.936, 0.954, and 0.947 (all $P < 0.001$), with the mean bias estimated to be − 0.13, − 0.098, and 0.02; limits of agreement (reference range for difference): − 2.848 to 2.585, 95% confidence interval [CI], − 0.43 to 0.17, for GLS; − 0.287 to 0.09, 95% CI, − 0.119 to − 0.077, for LV SRs; and − 0.31 to 0.349, 95% CI, − 0.017 to 0.057, for LV SRe. The correlations of the GLS, LV SRs, and SRe between the averaged three-beat and 10-beat methods were 0.943, 0.954, and 0.958 (all $P < 0.001$), with the mean bias estimated to be 0.07, −0.064, and 0.01, limits of agreement (reference range for difference): − 2.532 to 2.669, 95% CI, − 0.43 to 0.17, for GLS; − 0.24 to 0.111, 95% CI, − 0.084 to − 0.045, for LV SRs; and − 0.282 to 0.295, 95% CI, − 0.026 to 0.039, for LV SRe, respectively.

Prognostic value of the left ventricular deformations

During a median follow-up of 2.89 years (interquartile range, 1.60–4.14 years), 286 patients were re-admitted because of HF, while 228 patients died. Lower LV GLS, SRs, and higher SRe conferred independent prognostic values for the composite endpoint of HF re-admission and death, as assessed by Cox regression models, even after adjusting for key LV indices (all $P < 0.001$; *Table 2*). RCS curves demonstrated the continuous relationship of LV GLS, SRs, and SRe with incident HF re-admission and all-cause death (*Figure S3*). Worsened LV GLS and SRe rather than SRs remained independent predictors for the composite endpoint of HF re-admission and death after adjusting for baseline covariates and key LV

Table 1 Baseline characteristics and echocardiography parameters of all study participants with atrial fibrillation stratified by global longitudinal strain tertiles

Patient characteristics	All study subjects	GLS, T1	GLS, T2	GLS, T3	*P* (test)	*P* (trend)
GLS range (%)	(− 24.4% to − 1.2%)	(−24.4% to − 14.6%)	(−14.6% to − 11.2%)	(− 11.2% to − 1.2%)		
Number, *n*	(*n* = 1483)	(*n* = 498)	(*n* = 496)	(*n* = 489)		
Baseline demographics						
Age, years	71.6 ± 12.4	71.6 ± 11.4	71.5 ± 12.5	71.7 ± 13.2	0.97	0.91
Male sex (%)	811 (55.5)	270 (55.3)	271 (55.5)	271 (55.6)	> 0.99	0.92
BSA, m^2	1.7 ± 0.2	1.71 ± 0.20	1.73 ± 0.23	1.71 ± 0.23	0.36	0.76
BMI, kg/m^2	25.3 ± 4.6	25.2 ± 4.22	25.7 ± 4.69	25.0 ± 4.84	0.046	0.65
HR, per min	88.2 ± 24.8	78.7 ± 20.4	86.5 ± 22.0*	99.4 ± 26.9*,†	< 0.001	< 0.001
SBP, mmHg	131.1 ± 21.3	130.6 ± 19.6	130.7 ± 20.2	132.1 ± 23.8	0.46	0.60
DBP, mmHg	74.5 ± 14.2	72.7 ± 12.6	74.3 ± 13.7	76.4 ± 15.8*	< 0.001	0.75
Underlying co-morbidities						
Hypertension (%)	943 (64.5)	300 (61.5)	314 (64.3)	330 (67.8)	0.12	0.04
Diabetes mellitus (%)	561 (38.3)	148 (30.3)	181 (37.1)	232 (47.6)	< 0.001	< 0.001
Dyslipidaemia (%)	461 (31.5)	156 (32.0)	157 (32.2)	148 (30.4)	0.81	0.61
Heart failure (%)	696 (46.9)	182 (36.5)	236 (47.6)	278 (56.9)	< 0.001	< 0.001
Vascular disease (PAD + CAD) (%)	275 (18.8)	41 (8.4)	67 (13.7)	89 (18.3)	< 0.001	< 0.001
ESRD (with dialysis) (%)	58 (4.0)	13 (2.7)	19 (3.9)	26 (5.3)	0.10	0.032
Ischaemic stroke or TIA (%)	402 (27.1)	130 (26.6)	125 (25.6)	147 (30.2)	0.24	0.22
Types of AF						
Non-permanent (%)	573 (40)	292 (61.1)	194 (40.3)	87 (18.4)	< 0.001	< 0.001
Permanent (%)	858 (60)	186 (38.9)	287 (59.7)	385 (81.6)	< 0.001	< 0.001
Medication use						
Antiplatelet agents (%)	756 (51.7)	267 (54.7)	251 (51.4)	238 (48.9)	0.19	0.07
Anticoagulant (%)	530 (36.2)	184 (37.7)	196 (40.2)	149 (30.6)	0.01	0.02
Beta-blocker (%)	550 (37.1)	182 (36.6)	195 (39.3)	173 (35.4)	0.42	0.60
ACEI/ARB (%)	658 (45.0)	219 (44.9)	220 (45.1)	220 (45.2)	> 0.99	0.95
CCB (%)	599 (40.9)	212 (43.4)	204 (41.8)	184 (37.8)	0.18	0.07
Statin (%)	226 (15.4)	66 (13.5)	82 (16.8)	79 (16.2)	0.32	0.25
Laboratory data						
Fasting glucose, mg/dL	129.4 ± 5.6	122.1 ± 55.7	128.4 ± 75.6	137.6 ± 63.2*	0.002	< 0.001
Cholesterol, mg/dL	171.1 ± 54.6	170.2 ± 43.4	175.0 ± 70.9	167.7 ± 45.0	0.15	0.51
HDL, mg/dL	46.7 ± 15.1	48.2 ± 15.3	46.7 ± 15.2	45.1 ± 14.8*	0.03	0.01
LDL, mg/dL	101.2 ± 30.7	99.0 ± 30.2	103.1 ± 28.8	101.3 ± 33.0	0.21	0.33
eGFR, mL/min/1.73 m^2	59.1 ± 33.1	61.6 ± 29.8	61.2 ± 34.2	54.5 ± 34.6*,†	0.001	0.001
BNP, pg/mL (*n* = 1010), median, 25th–75th	357.5 (172–714)	269.5 (130.5–510)	321.5 (137–596)*	516.5 (253–1055)*,†	< 0.001	< 0.001
CRP, mg/dL *n* = 1037, median, 25th–75th	0.98 (0.224–3.33)	0.72 (0.17–2.87)	0.64 (0.17–2.76)*	1.47 (0.39–4.14)*,†	< 0.001	< 0.001
Conventional LV echocardiography parameters						
IVS, mm	9.8 ± 1.7	9.6 ± 1.4	9.7 ± 1.7*	10.0 ± 1.9*,†	< 0.001	< 0.001
LVEDV, mL	78.8 ± 35.0	103.9 ± 27.9	106.0 ± 27.8	117.0 ± 38.2*,†	< 0.001	< 0.001
LVESV, mL	34.1 ± 23.9	37.6 ± 13.9	42.4 ± 17.2*	57.6 ± 31.9*,†	< 0.001	< 0.001
LV mass index (BSA), g/m^2	90.9 ± 25.7	85.8 ± 22.8	87.4 ± 23.0	99.6 ± 28.8*,†	< 0.001	< 0.001
LVEF, %	58.4 ± 14.2	64.7 ± 10.0	60.3 ± 11.8*	50.3 ± 16.0*,†	< 0.001	< 0.001
LVEF < 50 (%)	359 (24.6)	41 (8.5)	83 (17.0)	235 (48.8)	< 0.001	< 0.001
LV s′, cm/s	5.88 ± 1.51	6.43 ± 1.53	5.96 ± 1.38*	5.22 ± 1.37*,†	< 0.001	< 0.001
LV e′, cm/s	8.38 ± 2.20	9.25 ± 2.17	8.53 ± 2.14*	7.33 ± 1.83*,†	< 0.001	< 0.001
E/e′ (average) (*n* = 1387)	11.2 ± 5.7	10.3 ± 5.01	10.8 ± 5.26	12.1 ± 5.17*,†	< 0.001	< 0.001
E/e′ (average) ≥ 14	438 (31.6%)	108 (23.3%)	127 (27.5%)	203 (43.8%)	< 0.001	< 0.001
E/e′ (average) ≥ 11	752 (54.2%)	212 (45.7%)	230 (49.9%)	310 (67.0%)	< 0.001	< 0.001
PAP, mmHg	38.9 ± 11.0	38.8 ± 10.3	38.2 ± 10.6	39.7 ± 12.0	0.11	0.23
LAV (max), mL	90.4 ± 45.0	91.5 ± 47.8	91.2 ± 45.5	88.3 ± 41.4	0.48	0.27
LA emptying fraction, %	28.9 ± 14.1	29.6 ± 13.7	28.8 ± 14.5	28.4 ± 14.1	0.38	0.18
LV speckle-tracking indices						
GLS, %	− 12.6 ± 3.9%	− 15.7 ± 2.67	− 13.9 ± 2.39	− 9.21 ± 3.94*,†	< 0.001	< 0.001
LV SRs, 1/s	− 0.86 ± 0.27	− 1.07 ± 0.20	− 0.88 ± 0.18*	− 0.62 ± 0.20*,†	< 0.001	< 0.001
LV SRe, 1/s	1.25 ± 0.41	1.56 ± 0.34	1.27 ± 0.30*	0.91 ± 0.30*,†	< 0.001	< 0.001

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II-receptor blocker; BMI, body mass index; BNP, N-terminal pro-B-type natriuretic peptide; BSA, body surface area; CAD, coronary artery disease; CCB, calcium channel blocker; CRP, C-reactive protein; DBP, diastolic blood pressure; E/e′, ratio of the early diastolic transmitral flow velocity to the motion velocity of the lateral mitral annulus at the early phase of diastole; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLS, global longitudinal strain; HDL, high-density lipoprotein; HR, heart rate; IVS, septal wall thickness, LA, left atrial; LAV max, maximal LA volume; LDL, low-density lipoprotein; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular

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end-systolic volume; LVMi, left ventricular mass index; MI, myocardial infarction; PAD, peripheral arterial disease; PAP, pulmonary arterial pressure; SBP, systolic blood pressure; SRe, early diastolic strain rate; SRs, systolic strain rate; TIA, transient ischaemic attack.
Data are expressed as mean ± standard deviation or as percentage.
*P value < 0.05 for comparisons with Group 1.
†P value < 0.05 for comparisons with Group 2.

indices (all $P < 0.001$; *Table 3*). Subjects achieving the composite HF/death endpoint consistently presented with worsened GLS and SRe regardless of LVEF or HF (*Figure 3C, D*). Kaplan–Meier survival estimates showed that the lowest GLS tertile had the worst clinical outcomes (all log-rank $P < 0.05$; *Figure 4*). Prognostic utilizations of LV GLS, SRs, and SRe (as continuous variables) by Cox regression models were broadly similar in sensitivity analysis after excluding RWMA (*Table S5*).

Both GLS and SRe, but not SRs, had a larger area under the receiver operating characteristic curve than LVEF for the combined HF re-admission and death endpoint (Harrell's *C*-index: GLS: 0.63 vs. 0.58, $P = 0.021$; SRe: 0.64 vs. 0.58, $P = 0.002$; SRs: 0.59 vs. 0.58, $P = 0.91$). GLS, SRs, and SRe set at

FIGURE 3 CRP, BNP, eGFR levels, E/e', LVEF < 50%, and HF were associated with reduced LV GLS and strain rates (A, B). The global LV strain and strain rate were adjusted for age, sex, BMI, HR, HTN, HF, DM, dyslipidaemia, vascular disease, eGFR, ACEI/ARB, diuretics, and beta-blockers. LV deformation measurements and cardiac outcomes according to the three clinical categories: LVEF ≥ 50% without HF, LVEF ≥ 50% with HF, and LVEF < 50% (C, D). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II-receptor; BNP, N-terminal pro-B-type natriuretic; CAD, coronary artery disease; CRP, C-reactive protein; DM, diabetes mellitus; eGFR, estimate glomerular filtration rate; GLS, global longitudinal strain; HF, heart failure; HTN, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction; PAD, peripheral arterial disease.

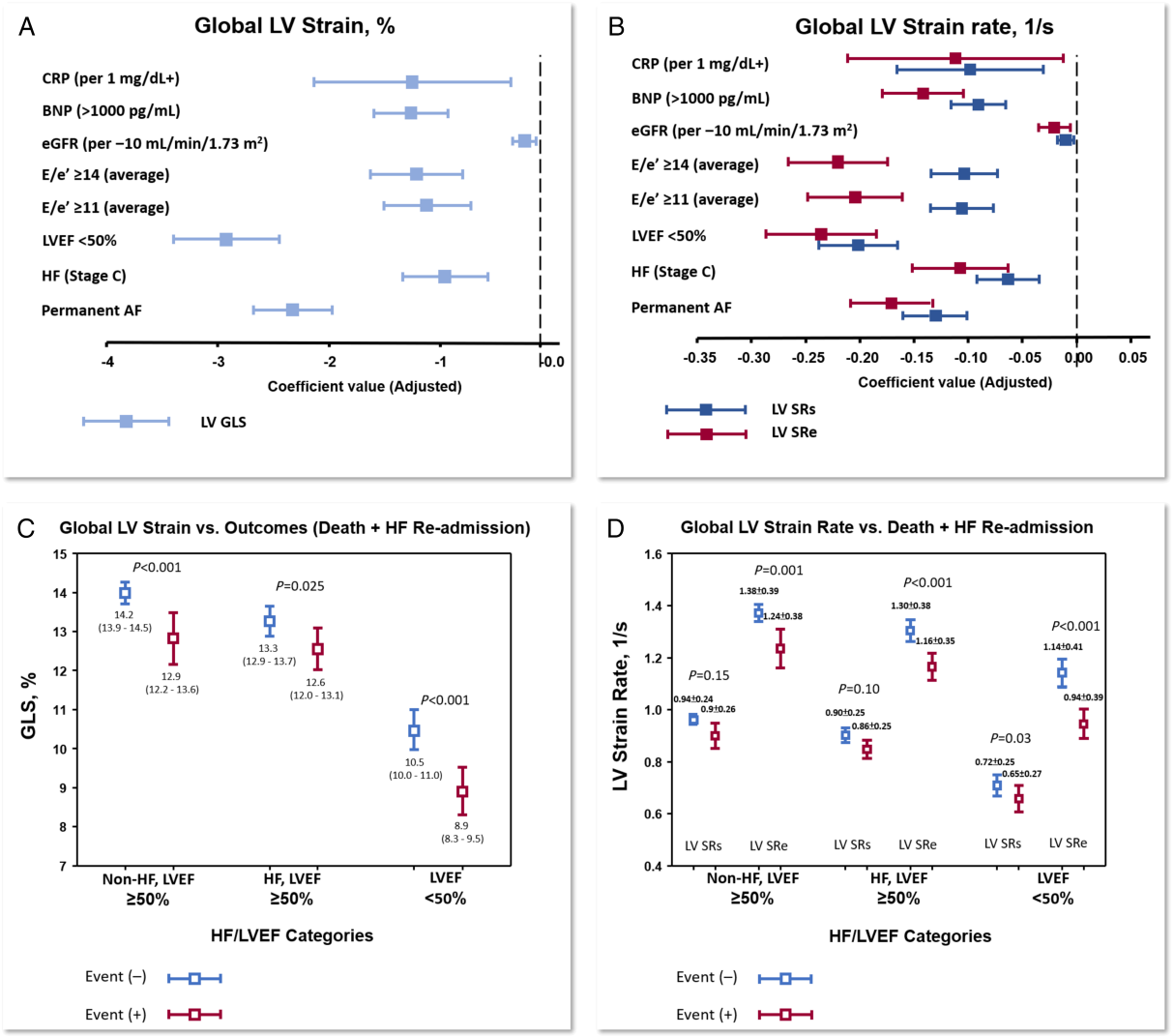

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Table 2 Univariable and multivariable Cox hazard regression models for the combined outcome of heart failure re-admissions and death

	Data range		
	GLS, % (−24.43, −1.17)	LV SRs, 1/s (−2.23, −0.17) Cox linear regression models	LV SRe, 1/s (0.22, 2.88)
	Hazard ratio (95% CI)		
Crude, hazard ratio [95% CI]	1.12 [1.09–1.15], $P < 0.001$	3.18 [2.20–4.61], $P < 0.001$	0.31 [0.25–0.40], $P < 0.001$
Multivariate model, hazard ratio [95% CI]			
Model 1	1.12 [1.10–1.15], $P < 0.001$	3.40 [2.34–4.95], $P < 0.001$	0.32 [0.25–0.41], $P < 0.001$
Model 2	1.12 [1.10–1.15], $P < 0.001$	3.47 [2.38–5.06], $P < 0.001$	0.32 [0.25–0.41], $P < 0.001$
Model 3	1.07 [1.04–1.11], $P < 0.001$	1.95 [1.31–2.91], $P = 0.001$	0.45 [0.34–0.59], $P < 0.001$
Model 3 + LVEF	1.05 [1.02–1.09], $P = 0.001$	1.49 [0.97–2.29], $P = 0.068$	0.51 [0.38–0.67], $P < 0.001$
Model 3 + LVMi[a]	1.06 [1.03–1.09], $P < 0.001$	1.65 [1.09–2.50], $P = 0.017$	0.49 [0.37–0.64], $P < 0.001$
Model 3 + E/e′	1.07 [1.04–1.11], $P < 0.001$	1.99 [1.33–3.00], $P = 0.001$	0.43 [0.32–0.57], $P < 0.001$

Model 1: crude model adjusted for age. Model 2: Model 0 adjusted for age and sex. Model 3: Model 0 adjusted for age, sex, body mass index (BMI), heart rate, types of AF, hypertension, diabetes, dyslipidaemia, heart failure, and coronary artery disease, estimated glomerular filtration rate, angiotensin-converting enzyme inhibitor/angiotensin II-receptor blocker, diuretics, and beta-blockers.
CI, confidence interval; LVMi, left ventricular mass index; SRe, early diastolic strain rate; SRs, systolic strain rate.
[a]BMI was not included in the models.

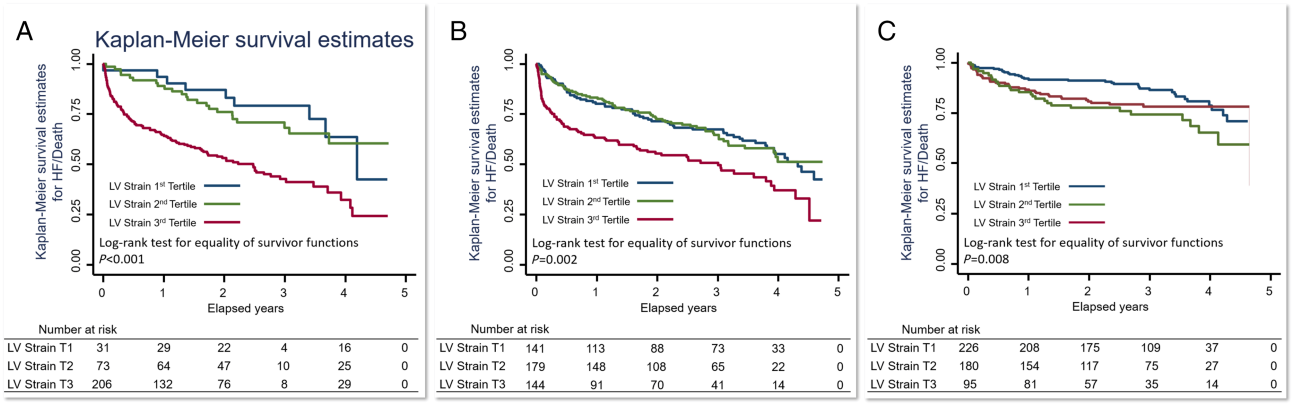
−12.0%, −0.80 1/s, and 1.23 1/s, respectively, according to ROC analysis, served as useful cut-offs for the composite endpoint, with GLS/SRe remaining significant after multivariate adjustment incorporating key LV indices (all $P < 0.001$; *Table S4*). Patient classification for the combined HF/death endpoint was significantly improved when the GLS and LV SRe were added to the LVEF [continuous NRI, 17.1% and 27.7 ($P = 0.003$ and $P < 0.001$, respectively); IDI, 2.0% and 2.4% ($P = 0.008$ and $P = 0.013$, respectively)]. LV SRs did not exhibit improved risk reclassification over the LVEF.

Table 3 Univariate and multivariable Cox hazard regression models for the combined heart failure re-admissions and death based on left ventricular global longitudinal strain, systolic strain rate, and early diastolic strain rate tertiles

	T1	T2	
GLS Range	(−24.4% to −14.6%)	(−14.6% to −11.2%)	(−11.2% to −1.2%)
Crude, hazard ratio [95% CI]	(Reference)	1.27 [0.98–1.64], $P = 0.07$	2.45 [1.94–3.10], $P < 0.001$
Multivariate Model, hazard ratio [95% CI]			
Model 1	(Reference)	1.26 [0.97–1.63], $P = 0.08$	2.38 [1.89–3.02], $P < 0.001$
Model 2	(Reference)	1.26 [0.98–1.64], $P = 0.08$	2.39 [1.89–3.02], $P < 0.001$
Model 3	(Reference)	1.01 [0.76–1.35], $P = 0.92$	1.25 [1.1–1.92], $P = 0.008$
Model 3 + LVEF	(Reference)	1.00 [0.76–1.30], $P = 0.97$	1.32 [1.02–1.88], $P = 0.02$
Model 3 + LVMi[a]	(Reference)	1.02 [0.74–1.38], $P = 0.90$	1.33 [1.02–1.77], $P = 0.03$
Model 3 + E/e′	(Reference)	0.94 [0.70–1.23], $P = 0.76$	1.44 [1.09–1.92], $P = 0.01$
	LV SRs, T1	LV SRs, T2	LV SRs, T3
LV SRs range	(−2.23 1/s to −0.97 1/s)	(−0.97 1/s to −0.75 1/s)	(−0.75 1/s to −0.17 1/s)
Crude, hazard ratio [95% CI]	(Reference)	1.19 [0.93–1.52], $P = 0.16$	1.69 [1.34–2.13], $P < 0.001$
Multivariate Model, hazard ratio [95% CI]	(Reference)	1.20 [0.94–1.53], $P = 0.15$	1.69 [1.34–2.13], $P < 0.001$
Model 1	(Reference)	1.20 [0.94–1.53], $P = 0.15$	1.71 [1.35–2.15], $P < 0.001$
Model 2	(Reference)	1.13 [0.88–1.45], $P = 0.32$	1.34 [1.05–1.71], $P = 0.02$
Model 3	(Reference)	1.10 [0.85–1.42], $P = 0.46$	1.28 [0.99–1.65], $P = 0.058$
Model 3 + LVEF	(Reference)	1.03 [0.80–1.33], $P = 0.84$	1.06 [0.81–1.39], $P = 0.64$
Model 3 + LVMi[a]	(Reference)	1.06 [0.83–1.37], $P = 0.63$	1.16 [0.89–1.51], $P = 0.26$
Model 3 + E/e′	(Reference)	1.07 [0.83–1.39], $P = 0.59$	1.27 [0.98–1.64], $P = 0.07$
	LV SRe, T1	LV SRe, T2	LV SRe, T3
LV SRe range	(0.22 1/s to 1.05 1/s)	(1.05 1/s to 1.42 1/s)	(1.42 1/s to 2.88 1/s)
Crude, hazard ratio [95% CI]	(Reference)	0.68 [0.55–0.84], $P < 0.001$	0.36 [0.28–0.46], $P < 0.001$
Multivariate Model, hazard ratio [95% CI]	(Reference)	0.69 [0.55–0.85], $P < 0.001$	0.37 [0.29–0.48], $P < 0.001$
Model 1	(Reference)	0.68 [0.55–0.84], $P < 0.001$	0.37 [0.29–0.48], $P < 0.001$
Model 2	(Reference)	0.83 [0.67–1.04], $P = 0.10$	0.49 [0.38–0.64], $P < 0.001$
Model 3	(Reference)	0.86 [0.69–1.08], $P = 0.19$	0.51 [0.39–0.67], $P < 0.001$
Model 3 + LVEF	(Reference)	0.92 [0.73–1.16], $P = 0.49$	0.57 [0.43–0.75], $P < 0.001$
Model 3 + LVMi[a]	(Reference)	0.88 [0.70–1.10], $P = 0.26$	0.55 [0.42–0.73], $P < 0.001$
Model 3 + E/e′	(Reference)	0.83 [0.67–1.05], $P = 0.12$	0.51 [0.39–0.68], $P < 0.001$

Model 1: crude model adjusted for age. Model 2: Model 0 adjusted for age and sex. Model 3: Model 0 adjusted for age, sex, body mass index (BMI), heart rate, types of AF, hypertension, diabetes, dyslipidaemia, heart failure, coronary artery disease, estimated glomerular filtration rate, angiotensin-converting enzyme inhibitor/angiotensin II-receptor blocker, diuretics, and beta-blockers.
Other abbreviations as in *Tables* 1 and 2.
[a]BMI was not included in the models.

FIGURE 4 Kaplan–Meier survival estimates according to LV GLS tertiles and LVEF categories (LVEF ≥ 50% without HF, LVEF ≥ 50% with HF, and LVEF < 50%). GLS, global longitudinal strain; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction.



Comparisons of global longitudinal strain in the matched atrial fibrillation and non-atrial fibrillation cohorts

Of the 2017 patients in the non-AF cohort (mean age, 61.7 ± 12.6 years), 52.4% were female, 76.7% had hypertension, 32.4% had diabetes, and 26.8% had cardiovascular diseases (mean LVEF, 59.3 ± 7.1%). A total of 733 patients from each cohort (AF and non-AF) could be successfully matched (*Table S3*) with comparable clinical characteristics and LVEF (*Table S1*), although the LV mass in the AF cohort was slightly higher after matching (P = 0.02). Generally, the GLS was nearly 30% lower in patients with AF than in those without (−13.2 ± 3.8% vs. −18.1 ± 3.2%) and seemed to decrease as the EF decreased in both groups ($p_{interaction}$ = 0.60 between AF and non-AF; LVEF with respect to GLS measurement). Moreover, the composite HF/death events' rate during the follow-up was significantly higher among patients with than without AF (event number, 189/733 vs. 145/733; incidence rate, 3.43 [2.97–3.96] vs. 2.35 [2.00–2.77] per 100 person-years; hazard ratio, 1.41 [95% CI, 1.14–1.75]; log-rank P = 0.002; *Figure 5*).

Discussion

Main findings

In this study, we analysed the LV GLS and SR during the systolic and early diastolic phases and explored the clinical and prognostic implications in a large population with AF and a broad clinical spectrum. Compared with the volumetric metrics, the GLS based on the three-beat method tended to be more reproducible in AF. A higher CRP, BNP, and E/e', a lower LVEF (< 50%), worsened renal function, and permanent AF and HF history were closely associated with reduced LV GLS and SR. Patients with AF and with clinical events (HF re-admissions and mortality) had worse LV GLS and SRe regardless of their clinical HF or LVEF phenotypes. Compared with an independent, non-AF cohort, with fully matched clinical features, and the same LVEF level, the AF cohort showed substantial GLS reduction and higher composite clinical endpoints, indicating a meaningful intrinsic myocardial dysfunction during AF rhythm. The consistent and independent prognostic associations of worse LV GLS and SRe as continuous variables or in tertiles with composite HF re-admissions and death were further verified after multivariate adjustment.

Systolic left ventricular functional evaluation by global longitudinal strain in atrial fibrillation

LV systolic dysfunction is a strong prognostic marker of adverse cardiovascular events.[9,19] Patients with AF are at a higher risk of developing HF, and especially HF preserved EF (HFpEF).[20,21] GLS, as a non-invasive imaging surrogate mainly reflecting subendocardial longitudinal myofiber shortening, is a sensitive myocardial marker of several cardiovascular risks, including aging,[22] hypertension, diabetes mellitus, obesity, LV hypertrophy,[6] HF,[23] and metabolic abnormalities combined with a pro-inflammatory status.[24] Interestingly, these are all notable clinical risk factors for AF development.[1,2] Reduced GLS reflecting pre-clinical myocardial injury may occur prior to overt chamber dilation[8] and has been shown to reflect subclinical systolic dysfunction and myocardial stiffness in paroxysmal AF.[25] Previous studies have proposed that AF, even in patients with a preserved LVEF (> 50%), is characterized by impaired intrinsic systolic properties, compared with those in sinus rhythm,[26,27] and that certain LV dysfunctions can be restored when AF is converted back to sinus rhythm.[28–30] In our study, we further demonstrated a marked and meaningful GLS reduction in the AF cohort compared

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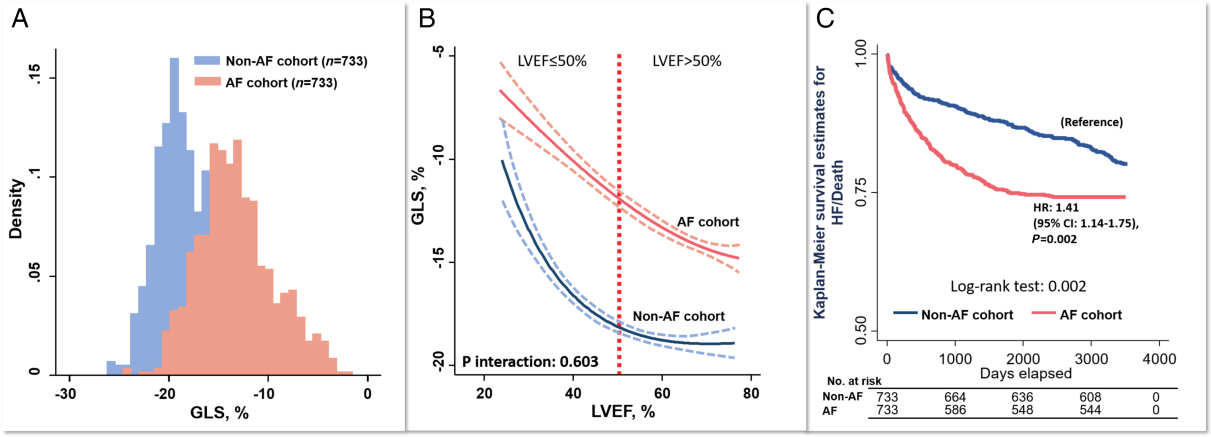
FIGURE 5 GLS distribution, associations of GLS with LVEF, and comparisons of the composite outcome of HF/all-cause death between AF and non-AF cohorts. AF, atrial fibrillation; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction.



with the respective value in the non-AF cohort with fully matched baseline demographics and a similar LVEF level. These findings, when taken collectively, imply the presence of LV dysfunction in AF to a certain degree regardless of the chamber-level pump function.

Notably, our three-beat method for quantifying GLS in AF showed a good correlation to the index beat method (r = 0.936), which also tended to have a more consistent reproducibility among the RR1, RR2 (corresponding to beats 1 and 2 in the current study, respectively), and index beat data when compared with the LVEF and LV volume measures.

Prognostic utilization of global longitudinal strain and left ventricular systolic strain rate in atrial fibrillation

The prognostic value of GLS has been widely tested in unselected populations, such as patients with chronic HF,[5,6,8,9,23] including those with reduced[31] or preserved global ventricular systolic function.[32] GLS also showed prognostic superiority over LVEF in determining subclinical LV systolic dysfunction,[33] as a more robust LV-contractility assessment with less variability,[6] and has been tested in a small sample of subjects with AF post myocardial infarction.[34] However, data on the utilization and prognostic value of GLS and its derivative index of systolic SR in subjects with AF have not been clearly established. To the best of our knowledge, no other study has investigated the prognostic value of GLS in a large AF population with a relatively preserved LVEF (mean LVEF, 60.7 ± 16.9%). Moreover, our study also provides outcome data from a non-AF comparator cohort. The systolic mechanical measurements of GLS and SR, either as continuous data or in tertiles, successfully predicted the composite clinical endpoint of HF re-admission and death. Collectively, our findings further expand the clinical use of GLS in subjects with AF across a wide clinical spectrum of HF/LVEF categories.

Left ventricular early diastolic strain rates as a useful mechanical diastolic property in atrial fibrillation

Impaired diastolic properties due to either a diminished LV active relaxation or increased passive stiffness, especially in patients with HFpEF as a common AF co-morbidity,[35,36] may be detrimental to the mechanical function of the LA. Proposed mechanisms of the relationship between AF pathophysiology and impaired diastolic function and HF may involve myocardial energy depletion, calcium regulation anomaly, and extracellular matrix remodelling.[37] Beat-to-beat variations in cycle lengths in patients with AF may lead to a shorter diastolic filling time, impaired haemodynamics, and sympathetic activation, thereby resulting in diastolic disturbances.[13] Furthermore, loss of effective atrial contraction with AF further deteriorates LV filling and haemodynamics, which in turn aggravates HF development or progression.[30,38] As intrinsic myocardial relaxation utilizing global LV early diastolic strain rate (SRe) by speckle tracking has been proposed to correlate better with invasive haemodynamic measures than conventional echocardiography (such as E/e′),[7,39] we speculated that global SRe likely provides better pathological insights into diastolic dysfunction in AF patients. Indeed, we observed that global SRe provided additive and independent prognostic values to LV E/e′ in our AF population.

Although GLS remains the most well-established standard marker among various LV deformational parameters and is widely investigated as a clinical predictor,[8,29] speckle tracking-derived SRe has also been introduced for clinical

use as a novel parameter reflecting early LV diastolic phase conduit property.[7,11,40] In our study, the SRe independently predicted combined HF re-admission and death even after considering baseline covariates and key conventional LVEF, diastolic index E/e′, and degree of LV remodelling (i.e. LVMi). In the present study, SRe appeared to be a better predictor of cardiac outcomes than SRs, possibly because it was more prone to beat-to-beat cycle length variations in patients with AF, which may interfere with diastolic LV filling, partially reflective of atrial dysfunction independent of LV systolic functions. However, further large-scale prospective studies are warranted to confirm these findings.

Clinical implications

Despite the increasing recognition and broader clinical implementation of deformational parameters in daily practice, clinical correlates that are useful in identifying impaired ventricular function along with the cut-off values for adverse clinical events in patients with AF remain largely unexplored. Our study provides useful clinical information on LV deformation measurements. Further, by implementing novel LV myocardial imaging using GLS and SR, we could identify certain AF patients with a higher risk of subsequent HF development. Importantly, the predictive value of such deformational measurements may be uniformly effective and useful across a broad clinical spectrum, regardless of the baseline LVEF and HF history. Identification of high-risk patients with AF in daily practice may allow for a more aggressive rhythm control and for earlier and more intensive pharmacological interventions, which could in turn prevent adverse cardiovascular events.

Limitations

Our study has several limitations. First, as AF many exist without a definite clinical diagnosis in a paroxysmal manner under detection, our AF cohort may not be representative of all subjects with various clinical phenotypes of AF. Moreover, a case initially presenting as sinus rhythm may progress to AF during clinical follow-up before reaching any pre-specified endpoints. Second, as AF and HF both have high co-morbidities and disease complexities, determining an appropriate clinical cut-off for any specific clinical purpose is frequently a subject of debate and relies on the target in terms of sensitivity and specificity. Third, some confounders that may potentially influence ventricular contractility could still exist and may not have been identified or included in our multivariate analysis. Finally, as speckle-tracking technique may heavily rely on 2D echocardiographic image quality or those with limited acoustic window, it that may largely impact its accuracy and reproducibility.

In conclusion, our study demonstrated that LV deformation measurement is readily available and may serve as non-invasive myocardial mechanical assessment and could provide more reproducible and novel mechanistic insights into LV pathology, which paralleled several established key clinical markers of deteriorated cardiac systolic/lusitropic properties. Compared with sinus rhythm, AF rhythm could cause detrimental effects on global LV systolic function regardless of LVEF. Utilization of LV deformational indices in AF patients, especially global LV strain or early diastolic SR, further provided independent prognostic values and markedly improved risk classification of HF and death beyond conventional LV parameters. Our findings support the clinical implications of utilizing LV deformational indices in AF patients in daily practice.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics and echocardiography parameters stratified by LV SRs tertiles
Table S2. Baseline characteristics and echocardiography parameters stratified by LV SRe tertiles
Table S3. Baseline characters between AF and non-AF cohort after propensity matching process (n = 733 for each cohort)
Table S4. Uni- and Multi-variable Cox Hazard Regression Models for HF re-admission based on LV GLS, and strain rates (SRs and SRe) tertile groups
Table S5. Sensitivity analysis for univariable and multivariable Cox hazard regression models for combined HF re-admissions and death after excluding those with regional wall motion abnormality (total n = 1,338)

Figure S1. Unadjusted restricted cubic spline (RCS) graphs displaying the association of global LV remodeling (LVMi), pump function using conventional LVEF, LV filling E/e' (averaged) with ventricular longitudinal strain (GLS), and strain rates (SRs and SRe).

Figure S2. Sensitivity analysis for multi-variate associations of LV deformational indices with key clinical co-morbidities, biomarkers and conventional LV parameters after excluding those with regional wall motion abnormality (total n = 1,338)

Figure S3. Comparisons on reproducibility of LVEF, volumes, and GLS using index beat methods by within-subject coefficients of variance (COV) and *Bland–Altman plot* statistics. Beat 1 and 2 with a ratio of RR interval ranging from 0.96 to 1.04 was defined RR1/RR2, with index beat defined as beat number 3. EDV: end-diastolic volume, ESV: end-systolic volume, GLS: global longitudinal strain. LVEF: left ventricular ejection fraction. COV of LV SRs and SRe (with index beat as reference) for RR1 and RR2 were 7.4%, 7.6% (SRs) and 7.3%, 7.8% (SRe), respectively,

Figure S4. Multivariate-adjusted splines displaying the association of ventricular longitudinal strain (GLS, A) and strain rate components (SRs and SRe, B and C) with risk for composite heart failure and all-cause death.

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