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Incremental prognostic value of left atrial strain in patients with heart failure

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Abstract

Aims   The present study aimed to evaluate the prognostic value of atrial strain and strain rate (SR) parameters derived from cardiac magnetic resonance (CMR) feature tracking (FT) in patients with ischaemic and non-ischaemic dilated cardiomyopathy with heart failure with reduced ejection fraction (HFrEF) but without atrial fibrillation.

Methods and results   A total of 300 patients who underwent CMR with left ventricular ejection fraction (LVEF) $\leq$ 40% and ischaemic or non-ischaemic dilated cardiomyopathy were analysed in this retrospective study. Major adverse cardiac events (MACEs) include cardiovascular death, heart transplantation, and rehospitalization for worsening HF. Ninety-four patients had MACEs during median follow-up of 3.84 years. Multivariate Cox regression models adjusted for common clinical and CMR risk factors detected a significant association between LA-εs and MACE in ischaemic (HR = 0.94/%; P = 0.002), non-ischaemic dilated cardiomyopathy (HR = 0.88/%; P = 0.001), or all included patients (HR = 0.87; P < 0.001). LA-εs provided incremental prognostic value over conventional outcome predictors (Uno C statistical comparison model: from 0.776 to 0.801, P < 0.0001; net reclassification improvement: 0.075, 95% CI: 0.0262–0.1301). Kaplan–Meier analysis revealed that the risk of MACE occurrence increased significantly with lower tertiles of left atrial reservoir strain (LA-εs) (log-rank P < 0.0001). Patients in the worst LA-εs tertile faced a significantly increased risk of MACEs irrespective of late gadolinium enhancement (LGE) (log-rank P < 0.0001).

Conclusions   LA-εs derived from CMR FT has a significant prognostic impact on patients with ischaemic or non-ischaemic dilated cardiomyopathy, incremental to common clinical and CMR risk-factors.

Introduction

Heart failure (HF) remains a major challenge for patients and health care systems worldwide, especially with heart failure with reduced ejection fraction (HFrEF), who show rapid progression of HF,[1] despite best care, with approximately 50% dying within 5 years of diagnosis.[2] For patients with HF, prognostic evaluation not only performs risk stratification but is also significant in guiding clinical treatment decisions.[3] Cardiac magnetic resonance (CMR), echocardiography, and other imaging methods can comprehensively evaluate the structure and function of the heart and play a major role in the prognostic evaluation of patients with HF. CMR has the advantages of high spatial resolution, clearer visualization of atrial endocardial borders, and multiplanar imaging. It is increasingly used as a standard tool to assess the heart,[4] while late gadolinium enhancement (LGE) by CMR reflects the extent of tissue fibrosis, determines the underlying cause of left ventricular (LV) dysfunction, and is an independent predictor of adverse cardiovascular outcomes in patients with advanced HF.[5] For patients with advanced HF, the degree of impaired LV function loses its prognostic value.[6] Atrial remodelling and functional changes reflect ventricular systolic and diastolic dysfunction rather sensitively.[7] Atrial

strain from echocardiography or CMR is an independent predictor of prognosis in patients with HF.[8–11] However, these studies either consider only non-ischaemic dilated cardiomyopathy (NIDCM) or focus on a specific atrium. The predictive value of atrial strain in patients with ischaemic and non-ischaemic dilated cardiomyopathy has not yet been studied. The present study aimed to investigate the long-term predictive value of atrial strain derived from CMR in patients with ischaemic cardiomyopathy (ICM) and NIDCM with HFrEF but atrial fibrillation (AF).

Methods

Study population and study design

A total of 326 patients with ICM and NIDCM with HFrEF but AF who visited Beijing Anzhen Hospital, Capital Medical University from January 2015 to April 2020 were included in this retrospective study. These patients underwent electrocardiography, biochemical analysis, standard echocardiography, and CMR examinations, including cine and LGE imaging. ICM was defined as the presence of systolic dysfunction accompanied by one of the following: (i) history of myocardial infarction or revascularization and (ii) presence of at least 75% stenosis in the left main or anterior descending artery or >75% stenosis in at least two coronary arteries.[12] DCM is defined as left or biventricular systolic dysfunction and dilatation that cannot be explained by abnormal loading conditions or coronary artery disease.[13] Chronic kidney disease (CKD) was defined as abnormalities in kidney function or structure present for more than 3 months, with implications for health.[14] The vean contracta(VC) was typically imaged in a view perpendicular to the commissural line. A VC of <3 mm indicated mild mitral regurgitation (MR), whereas a width of ≥7 mm suggested severe MR.[15] Pulmonary hypertension (PH) was considered if patients had a systolic pulmonary arterial pressure (sPAP) of 40 mmHg.[16] PH was categorized as 'mild' (40–54 mmHg), 'moderate' (55–64 mmHg), or 'severe' (>65 mmHg).[17] The inclusion criteria were impaired left ventricular ejection fraction (LVEF) ≤ 40% as determined by CMR.[1] Conversely, patients with congenital heart disease, infiltrative cardiomyopathy, severe valvular heart disease, history of cardiac resynchronization therapy, implantable cardioverter defibrillator, and images from CMR that could not be analysed were excluded. Subsequently, 26 patients were excluded because the image quality could not be assessed, and finally, 300 patients (ICM: $n = 131$, NIDCM: $n = 169$) were included in the study.

Cardiac magnetic resonance acquisition

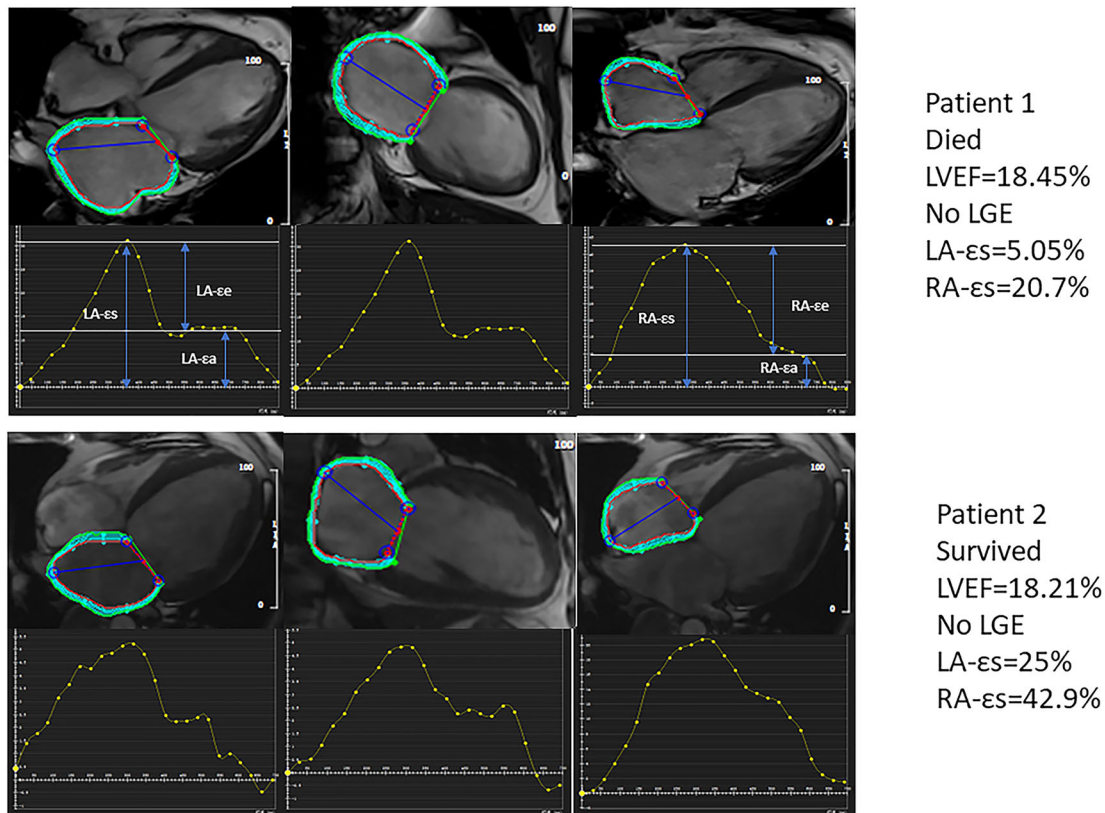All CMR images were electrocardiogram (ECG)-gated. CMR was conducted on a 3.0 T scanner (Magnetom Verio; Siemens AG Healthcare, Erlangen, Germany, or MR750W, General Electric Healthcare, Waukesha, WI, USA). Standard scanning protocols, including steady-state free precession (SSFP) breath-hold cine images and LGE using gadolinium, conforming to current international guidelines, were utilized.[18] The cine images were obtained in multiple short-axis and three long-axis views, with the entire LV and right ventricle (RV) from the base to apex containing slices (8 mm thickness, no cross-gap) at 25 stages per cardiac cycle in consecutive short-axis. The long axis planes had 5-mm slice thickness (2-chamber, 4-chamber, and 3-chamber views) without spacing intersection gap.[6] Using the prospective ECG-gated gradient echo sequence, LGE images were obtained 10 min after intravenous injection of 0.2 mmol/kg gadolinium chelating contrast agent. The sequence parameters were as follows: repetition time/echo time, 4.1/1.6 ms; flip angle, 20°; image matrix, 256 × 130.

Cardiac megnetic resonance analysis and assessment of left ventricular and atrial function

The function of the LV and biatrium was analysed using CVI42 commercial software (Circle Cardiovascular Imaging, Calgary, AB, Canada). Semi-automatic analysis was performed using ventricular short-axis and 4-chamber or 2-chamber or 3-chamber cardiac sequences to identify and delineate the ventricular epicardial and epicardial boundaries at the end of the systole and diastole (papillary muscles were included in the blood pool); the inaccuracies were corrected by cardiovascular imaging professionals with >10 years of experience. LVEF and body surface area (BSA) functional indicators were obtained, including end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), and ventricular mass (MASS). Epicardial and endocardial contours were manually placed on LGE images, which appeared in any area with signal intensity 5 SD above normal myocardium.

Left atrial (LA) strain parameters were analysed using 2-chamber and 4-chamber cine images, while the right atrial (RA) strain parameters were analysed using 4-chamber cine images. LA endocardial and epicardial borders (except pulmonary veins and LA appendages) were traced manually when the LA was the largest and smallest in 2-chamber and 4-chamber cine images, respectively, using a point-matching method by cardiovascular imaging specialists with > 10 years of experience[19] (*Figure 1*). LA endocardial and epicardial borders then propagated automatically to all frames during the heart cycle (25 frames/heart cycle). LA global strain and strain rate were calculated as the average of 2-chamber and 4-chamber views. The endocardial and epicardial contours of the RA were manually drawn in end-systolic images, followed by automatic software-driven tracking of the endocardial and epicardial contours throughout the cardiac cycle[20] (*Figure 1*). In case of unsatisfactory feature tracking (FT), the

Figure 1 Measurement of atrial strain. The top panel shows a patient who died and the bottom panel shows a patient who survived.

Patient 1
Died
LVEF=18.45%
No LGE
LA-εs=5.05%
RA-εs=20.7%

Patient 2
Survived
LVEF=18.21%
No LGE
LA-εs=25%
RA-εs=42.9%

endocardial border was readjusted manually, and the extension algorithm was reapplied.

A total of 30 cases were selected randomly to study the intra-observer and inter-observer variability regarding atrial strain parameters. For interobserver variability, measurements were repeated by a second independent observer, blinded to the results of the first observer. For the intraobserver variability study, these 30 patients were analysed repeatedly by the same observer after an interval of 3 months. Thus, the functional and strain parameters of the atria were obtained, including reservoir strain (εs), conduit strain (εe), booster strain (εa), peak positive strain rate (SRs), peak early negative strain rate (SRe) and peak late negative strain rate (SRa).

Follow-up

Clinical follow-up is the assessment of patients every 6 months by telephone and/or postal questionnaires. The primary outcome was a composite of major adverse cardiac events (MACEs), including cardiovascular death (sudden cardiac death (SCD), HF death, stroke, or thromboembolic event), heart transplantation, and rehospitalization for worsening HF. Patients were followed up until early March 2022. Also, the time point of lost patients was recorded as the last follow-up.

Statistical analysis

All analyses were carried out using SPSS (version 17.0, International Business Machines, Armonk, NY, USA) and R (http://www.R-project.org). For continuous variables, data are presented as mean ± standard deviation (SD) for normal distribution and as median and interquartile range (IQR) for skewed distribution. Discrete data are reported as percentages and frequencies. Herein, we used a five-repetition based multiple interpolation approach to address the missing data issue for the most important variable, type B natriuretic peptide (BNP). The reproducibility of atrial strain parameter measurements was analysed using the intraclass correlation coefficient (ICC), which was <0.4 with poor agreement and >0.75 with good agreement. The differences in baseline characteristics were compared using analysis of variance (ANOVA) or its nonparametric equivalents

Table 1 Clinical baseline characteristics stratified by tertiles of LA-εs

Characteristics	Total	LA εs<8.0%	LA εs8% to 15.9%	LA εs > 15.9%	P-value
Demographic and clinical data					
Age, median (IQR), years	56 (46, 64)	55 (45, 63.75)	59 (48, 65)	57 (43.5, 63.50)	0.352
Male, %	81.00	84.20	83.00	75.80	0.616
BMI, median (IQR), kg/m^2	25.19 (22.28, 27.68)	25.43 (21.92, 28.26)	24.77 (22.89, 26.73)	23.67 (19.76, 27.52)	0.318
Diabetes mellitus, %	31.30	27.80	37.90	29.40	0.209
Hypertension, %	47.70	47.20	49.50	41.20	0.802
CKD, %	6.00	7.20	4.90	0.00	0.406
SBP, median (IQR), mmHg	120 (108, 130)	120 (106, 130)	120 (108, 130)	119 (107.5, 120)	**0.018**
DBP, median (IQR), mmHg	74 (69, 80)	75 (69, 80)	70 (68, 80)	80 (71, 83.5)	0.690
Heart rate, median (IQR), b.p.m.	80 (70, 90)	82 (72, 96)	75 (67, 88)	71 (65.5, 94)	0.248
QRS duration, median (IQR), ms	110 (99, 129)	110 (100, 129.5)	114 (98, 136)	107 (97.5, 117.5)	**0.000**
LBBB on EKG, %	12.30	12.20	14.60	0.00	0.238
RBBB on EKG, %	6.00	7.20	4.90	0.00	0.406
Intraventricular block on EKG, %	8.30	8.90	7.80	5.60	0.883
Smoking, %	68.00	68.30	67.00	70.60	0.947
Drinking, %	50.00	53.30	47.70	41.10	0.362
Medication					
ACEI or ARB, %	85.50	86.40	84.30	85.70	0.929
Beta-blocker, %	84.70	85.90	83.30	84.90	0.895
Diuretic, %	77.30	76.70	78.30	77.00	0.965
Spironolactone, %	78.40	81.20	77.10	76.70	0.744
Blood results					
BNP, median (IQR), pg/mL (n = 270, 90%)	359.50 (142.50, 942.00)	388 (152.05, 915.00)	460.00 (159.00, 1147.00)	178.00 (68.00, 392.50)	**0.024**
ALT, median (IQR), U/L	27.5 (18, 44)	29 (18, 44)	25 (17, 43)	27 (21, 38)	0.502
AST, median (IQR), U/L	25 (20, 37.75)	26 (20, 33)	24 (19, 31)	24 (21, 31)	0.245
Creatinine, median (IQR), μmol/L	82.85 (69.73, 95.98)	84.65 (71.23, 97.30)	80.70 (69.20, 92.90)	80.80 (65.10, 90.90)	0.154
Glucose, median (IQR), mmol/L	5.67 (5.14, 7.38)	5.63 (5.12, 6.79)	5.88 (5.20, 7.77)	5.73 (5.22, 7.64)	0.248
TC, mean (SD), mmol/L	4.14 ± 1.15	4.14 ± 1.10	4.06 ± 1.25	4.48 ± 1.09	0.373
TG, median (IQR), mmol/L	1.23 (0.93, 1.83)	1.21 (0.93, 1.70)	1.41 (1.20, 1.70)	0.94 (0.69, 2.32)	0.128
HDL-C, median (IQR), mmol/L	0.96 (0.81, 1.17)	0.94 (0.80, 1.13)	0.98 (0.83, 1.22)	1.04 (0.91, 1.27)	0.145
LDL-C, median (IQR), mmol/L	2.50 (2.01, 3.17)	2.51 (2.02, 3.20)	2.46 (1.95, 3.05)	2.79 (2.25, 3.43)	0.334
Na+, median (IQR), mmol/L	139.30 (137.70, 141.40)	139.45 (137.80, 141.86)	139.30 (137.60, 141.20)	139.10 (137.10, 140.70)	0.314
Cl−, median (IQR), mmol/L	101.95 (99.40, 104.18)	101.90 (99.32, 104.10)	102.10 (99.60, 104.20)	101.60 (98.85, 104.55)	0.994
hs-CRP, median (IQR), mg/L	2.13 (0.86, 5.86)	2.42 (1.00, 5.65)	2.12 (0.63, 7.21)	1.43 (0.71, 2.23)	0.277
White blood cell, median (IQR), g/L	6.90 (5.67, 8.35)	7.03 (5.73, 8.28)	6.78 (5.73, 8.47)	6.49 (4.38, 8.70)	0.620
Red blood cell, median (IQR), g/L	4.84 (4.42, 5.21)	4.92 (4.45, 5.25)	4.73 (4.38, 5.10)	4.75 (4.52, 5.15)	0.165
Platelets, median (IQR), g/L	203.00 (167.00, 253.30)	203.00 (168.25, 256.00)	210.00 (164.00, 256.00)	191.00 (147.50, 231.50)	0.348
Echocardiographic parameters					
MR severity (n = 288, 96%)					
No, %	8.00	5.10	7.40	11.60	0.246
Mild, %	45.30	37.80	40.40	57.90	**0.010**
Moderate, %	23.00	20.40	27.70	21.10	0.422
Severe, %	23.70	36.40	24.50	9.50	**0.000**

(Continues)

Table 1 (continued)

Characteristics	Total	LA εs<8.0%	LA εs8% to 15.9%	LA εs > 15.9%	P-value
PH severity (*n* = 288, 96%)					
No, %	72.60	58.20	71.30	88.50	**0.000**
Mild, %	13.90	19.40	13.80	8.30	0.084
Moderate, %	11.50	18.40	12.80	3.10	**0.003**
Severe, %	2.10	4.10	2.10	0.00	0.138

ACEI, ACE inhibitor; ARB, angiotensin II receptor blocker; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic pressure at presentation; HDL-C, blood high density lipoprotein cholesterol; hs-CRP, high-sensitivity C reactive protein; LBBB, left bundle branch block; LDL-C, blood low density lipoprotein cholesterol; MR, mitral regurgitation; PH, pulmonary hypertension; RBBB, right bundle branch block; SBP, systolic pressure at presentation; TC, total cholesterol; TG, triglyceride.
Bold items indicate *P*-value < 0.05.

(Kruskal–Wallis test) for continuous variables and the χ^2 test for dichotomous variables. Cox regression was used to assess the prognostic value of various parameters to obtain hazard ratios (HRs) and 95% confidence intervals (CIs). Univariate Cox regression analysis was used to assess the association between each variable and MACEs over 5 years of patient follow-up. The correlations between covariates were evaluated using Pearson's or Spearman's correlation coefficient. A correlation $r > 0.7$ was interpreted as a strong link between the two variables, and $r < 0.3$ was considered as a weak correlation. The association of LA parameters with outcomes was compared using area under curve (AUC) analysis. Clinical and radiographic risk factors for univariate predictors ($P \leq 0.05$) were included as covariates in the multivariate Cox regression model. For variables with correlation >0.7, one variable was selected for inclusion in the multivariate Cox regression model based on clinical experience and previous literature. Because 10% of the patients lacked BNP, we applied the average of the five interpolated data points to the model with BNP and judged whether the interpolation was reliable by estimating the difference in the statistical results before and after interpolation. Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. The final model was compared with a model that did not include LA-εs (LA reservoir strain), and model discrimination was compared by calculating the C-statistic and the integrated discrimination improvement.[21] The incremental prognostic value of LA-εs for the prediction of the primary endpoint was assessed using net reclassification improvement (NRI). A *p*-value < 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 300 patients (131 with ICM and 169 with NIDCM) with HFrEF without AF were included in this study. *Tables 1 and 2* summarize the clinical baseline and CMR characteristics of patients stratified by LA-εs tertiles, respectively. Supporting Information, *Table S1* compares the baseline characteristics of ICM with NIDCM. The median age at baseline was 56 (IQR: 46–64) years, and 81% were men. The LA and RA strain and strain rate (SR) were reduced compared with the corresponding values reported previously in normal subjects.[11] LGE was present in 67.7% of patients. Statistically significant differences were observed in the functional parameters of LA and RA among the three groups. In addition, we counted the echocardiographic findings in 288 patients. There was a weak correlation between the degree of MR and PH and LA-εs ($r < 0.3$).

Table 2 CMR characteristics stratified by tertiles of LA-εs

Characteristics	Total	LA εs < 8.0%	LA εs 8% to 15.9%	LA εs > 15.9%	P-value
CMR-LV functional parameters					
CMR-LVEDV, median (IQR), mL	241.1 (178.21, 321.14)	242.50 (185.56, 323.29)	229.65 (171.21, 297.02)	282.08 (173.62, 348.66)	0.484
CMR-LVSV, median (IQR), mL	46.85 (36.11, 62.34)	44.65 (34.00, 58.98)	50.79 (36.5, 65.17)	49.45 (42.01, 66.06)	0.052
CMR-LVESV, median (IQR), mL	190.24 (136.57, 268.25)	192.37 (143.36, 273.19)	184.48 (120.16, 246.20)	224.09 (140.24, 284.75)	0.293
CMR-LVEF, median (IQR), %	19.88 (14.75, 27.40)	18.77 (13.55, 24.91)	22.54 (15.71, 30.70)	22.09 (16.53, 29.28)	**0.009**
CMR-LVMASS, median (IQR), g	131.58 (107.03, 165.75)	136.44 (110.00, 168.89)	129.69 (105.29, 166.47)	118.70 (106.86, 153.15)	0.327
CMR-LVPGLS, median (IQR), %	−5.40 (−7.32, −3.60)	−4.70 (−6.48, −3.20)	−6.30 (−8.77, −4.37)	−6.80 (−8.20, −6.22)	**0.000**
CMR-LVPGCS, median (IQR), %	−6.56 (−8.99, −4.6)	−6.00 (−8.32, −4.21)	−7.83 (−10.42, −5.10)	−6.70 (−8.25, −4.75)	**0.001**
CMR-LA functional parameters					
CMR-LAVmax, median (IQR), mL	84.67 (60.48, 111.76)	95.39 (64.96, 119.34)	73.36 (56.15, 95.93)	78.60 (57.76, 106.81)	**0.000**
CMR-LAVmin, median (IQR), mL	51.00 (31.40, 79.01)	61.43 (35.80, 87.88)	40.62 (27.21, 62.8)	32.88 (26.00, 63.75)	**0.000**
CMR-LAEF, median (IQR), %	37.72 (24.99, 50.31)	30.74 (22.46, 46.11)	45.62 (36.21, 53.79)	48.51 (34.93, 57.12)	**0.000**
CMR-LA-εs, median (IQR), %	7.10 (4.16, 10.19)	4.95 (2.73, 6.64)	10.55 (9.00, 12.50)	22.40 (17.63, 24.50)	**0.000**
CMR-LA-εe, median (IQR), %	3.00 (1.35, 4.59)	1.83 (0.86, 3.03)	4.85 (3.65, 6.25)	8.05 (4.50, 12.10)	**0.000**
CMR-LA-εa, median (IQR), %	3.65 (2.21, 5.78)	2.60 (1.40, 3.55)	5.90 (4.90, 6.90)	12.90 (9.65, 17.58)	**0.000**
CMR-LA-SRs, median (IQR), s	4.00 (2.05, 5.74)	2.65 (1.55, 4.14)	6.35 (4.95, 7.50)	9.65 (2.08, 13.75)	**0.000**
CMR-LA-SRe, median (IQR), s	−0.68 (−0.95, −0.4)	−0.60 (−0.90, −0.35)	−0.75 (−1.00, −0.50)	−0.95 (−1.10, −0.63)	**0.004**
CMR-LA-SRa, median (IQR), s	−0.80 (−1.40, −0.45)	−0.68 (−1.15, −0.35)	−1.05 (−1.60, −0.65)	−1.55 (−2.03, −0.90)	**0.000**
CMR-RA functional parameters					
CMR-RAVmax, median (IQR), mL	54.07 (40.04, 78.89)	57.83 (41.40, 86.10)	49.92 (37.92, 71.73)	51.35 (44.39, 73.68)	**0.038**
CMR-RAVmin, median (IQR), mL	29.05 (17.42, 44.14)	32.42 (22.10, 50.00)	23.00 (15.25, 36.52)	18.50 (15.40, 38.89)	**0.000**
CMR-RAEF, mean (SD), %	46.79 ± 15.01	42.98 ± 14.84	52.26 ± 13.23	54.99 ± 14.23	**0.000**
CMR-RA-εs, median (IQR), %	15.25 (9.00, 21.23)	11.00 (6.25, 14.45)	22.50 (19.60, 26.60)	39.00 (34.80, 46.70)	**0.000**
CMR-RA-εe, median (IQR), %	6.90 (4.00, 4.90)	4.90 (2.53, 6.80)	11.70 (8.80, 13.50)	20.40 (14.55, 28.65)	**0.000**
CMR-RA-εa, median (IQR), %	7.55 (3.80, 11.075)	4.90 (2.70, 7.80)	11.90 (9.40, 14.50)	18.80 (8.85, 26.95)	**0.000**
CMR-RA-SRs, median (IQR), s	1.00 (0.70, 1.50)	0.80 (0.60, 1.10)	1.40 (1.10, 1.80)	2.10 (1.55, 3.90)	**0.000**
CMR-RA-SRe, median (IQR), s	−0.80 (−1.10, −0.50)	−0.60 (−0.80, −0.40)	−1.10 (−1.40, −0.80)	−1.90 (−3.30, −1.30)	**0.000**
CMR-RA-SRa, median (IQR), s	−1.10 (−1.50, −0.63)	−0.80 (−1.20, −0.50)	−1.40 (−1.80, −1.00)	−2.10 (−2.70, −1.15)	**0.000**
CMR-LGE					
LGE present, %	67.70	63.30	75.30	64.70	**0.012**
LGE extent, median (IQR), %	6.85 (0.00, 22.49)	4.60 (0.00, 22.58)	10.00 (2.10, 23.50)	4.80 (0.00, 19.83)	0.296
ICM, %	43.70	37.20	55.30	41.20	0.097

CMR, cardiac magnetic resonance; ICM, ischaemic cardiomyopathy; LAVmin, minimum left atrial volume; LAEF, left atrial ejection fraction; LGE, late gadolinium enhancementLVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LVMASS, left ventricular mass; LVpGLS, left ventricular peak global longitudinal strain; LVpGCS, left ventricular peak global circumferential strain; LAVmax, maximum left atrial volume; RAEF, right atrial ejection fraction; RAVmax, maximum right atrial volume; RAVmin, minimum right atrial volume; SRe, peak early negative strain rate; SRa, peak late negative strain rate; SRs, peak positive strain rate; εs, reservoir strain; εe, conduit strain; εa, booster strain.
Bold items indicate P-value < 0.05.

Inter-observer and intra-observer variability

The reproducibility of atrial strain and SR parameters was good (ICC = 0.83–0.98, $P < 0.05$) (Supporting Information, *Table S2*). And the reliability of the strain indexes of LA was higher than the strain and SR of the RA.

Primary outcomes

A total of 94 patients experienced MACEs, including 42 with ICM and 52 with NIDCM. The median follow-up time was 3.84 (IQR: 2.4–5.4) years.

Univariate and multivariate analysis and incremental prognostic value

Supporting Information, *Table S3* summarizes the results of the univariate analysis for all patients. AUC was highest for LA-εs (0.765), followed by LA-εe (0.753) and LA-SRs (0.751) (*Figure 2*). The results of correlation analysis are shown in Supporting Information, *Table S4*. We included the covariates in *Table 3* in the Cox regression model based on their clinical value, previous references, and correlation between parameters. After adjustment for clinical and radiographic risk factors, LA-εs remained a significant independent predictor of endpoint events (HR = 0.87/%; $P < 0.001$). Additionally, for each 1% decrease in LA-εs, the risk of MACEs increased by 13% (*Table 3*). Meanwhile, LGE extent (HR = 1.04/%; $P < 0.001$) and LA ejection fraction (LAEF) (HR = 1.03/%; $P < 0.001$) is significantly associated with MACEs. The addition of LA-εs to the model with clinical and radiographic predictors resulted in a significant increase in C statistic from 0.776 to 0.801 ($P < 0.0001$) and a combined differential improvement of 0.261 (95% CI: 0.0722–0.1301) compared
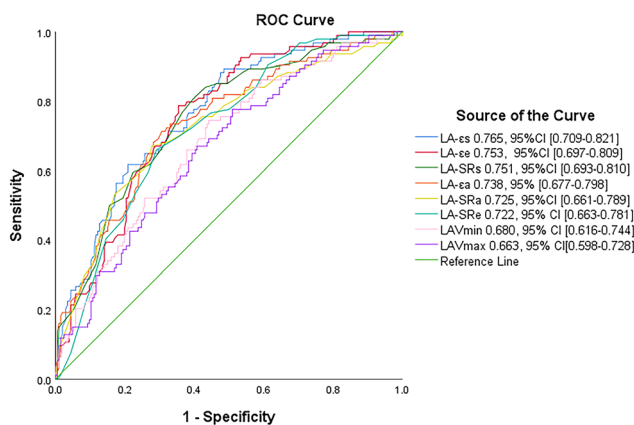
Table 3 Multivariate Cox proportional hazards model analysis for predicting overall survival in patients with HFrEF but without AF

	HR	95% CI	*P*-value
Age, years	1.02	(1.00–1.04)	**0.041**
Male, %	1.07	(0.57–2.03)	0.828
BMI, kg/m^2	0.99	(0.93–1.06)	0.861
SBP, mmHg	0.99	(0.97–1.01)	0.172
QRS duration, ms	1.01	(1.00–1.02)	**0.050**
Diabetes mellitus, %	0.99	(0.60–1.65)	0.971
Medication: ACEI/ARB	0.96	(0.50–1.82)	0.889
BNP, pg/mL	1.00	(1.00–1.00)	**0.039**
ALT, U/L	1.00	(1.00–1.00)	0.084
Creatinine, μmol/L	1.00	(0.99–1.01)	0.682
Cl−, mmol/L	1.00	(1.00–1.01)	0.177
Red blood cell, g/L	0.67	(0.49–0.92)	**0.012**
CMR-LVEDV, mL	1.00	(1.00–1.00)	0.521
CMR-LVPGLS, %	0.92	(0.83–1.03)	0.149
CMR-LVPGCS, %	0.98	(0.89–1.09)	0.718
CMR-LAVmax, mL	1.01	(1.00–1.01)	0.086
CMR-LAEF, %	1.03	(1.01–1.06)	**0.007**
CMR-LA-εs, %	0.87	(0.82–0.92)	**0.000**
CMR-RAVmax, mL	1.01	(1.00–1.01)	0.083
LGE extent, %	1.04	(1.02–1.05)	**0.000**

ACEI, ACE inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement LVEDV, left ventricular end-diastolic volume; LVpGLS, left ventricular peak global longitudinal strain; LVpGCS, left ventricular peak global circumferential strain; LAVmax, maximum left atrial volume; LAEF, left atrial ejection fraction; RAVmax, maximum right atrial volume; SBP, systolic pressure at presentation; εs, reservoir strain.
Bold items indicate *P*-value < 0.05.

with the original model with an NRI of 0.075 (95% CI: 0.0262–0.1301).

Outcomes stratified by left atrial-εs and late gadolinium enhancement

LA-εs was divided into three groups according to the tertile method (<8, 8–15.9, and >15.9). Kaplan–Meier survival analysis (*Figure 3A*) showed a significant difference between patients stratified by LA-εs values; as the LA-εs tertile worsened, the risk of MACE increased significantly (log-rank $P < 0.0001$). According to Kaplan–Meier analysis, the presence of LGE was significantly associated with an increased risk of MACEs (log-rank $P = 0.0001$) (*Figure 4A*). Kaplan–Meier analysis stratified by the highest and lowest LA-εs tertile for those with LGE and without LGE showed that patients in the worst LA-εs tertile faced a significantly increased risk of MACEs irrespective of LGE (log-rank $P < 0.0001$) (*Figure 4B*).

Prognostic value of left atrial-εs in ischaemic and non-ischaemic dilated cardiomyopathy

In both ICM and NIDCM, the dichotomization of LA-εs values was assessed by Kaplan–Meier survival analysis (*Figure 3B, C*), which showed a significant difference between the two

Figure 2 ROC curve. The ROC curve for the overall performance of left atrial indexes for MACEs.

Figure 3 Kaplan–Meier survival curves. (A) Stratified by tertiles of LA-εs in all patients. (B) Stratified by dichotomous of LA-εs in ICM. (C) Stratified by dichotomous of LA-εs in NIDCM.
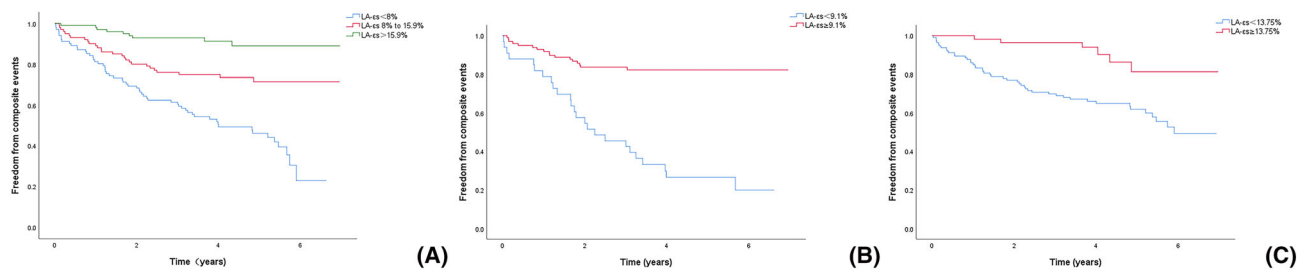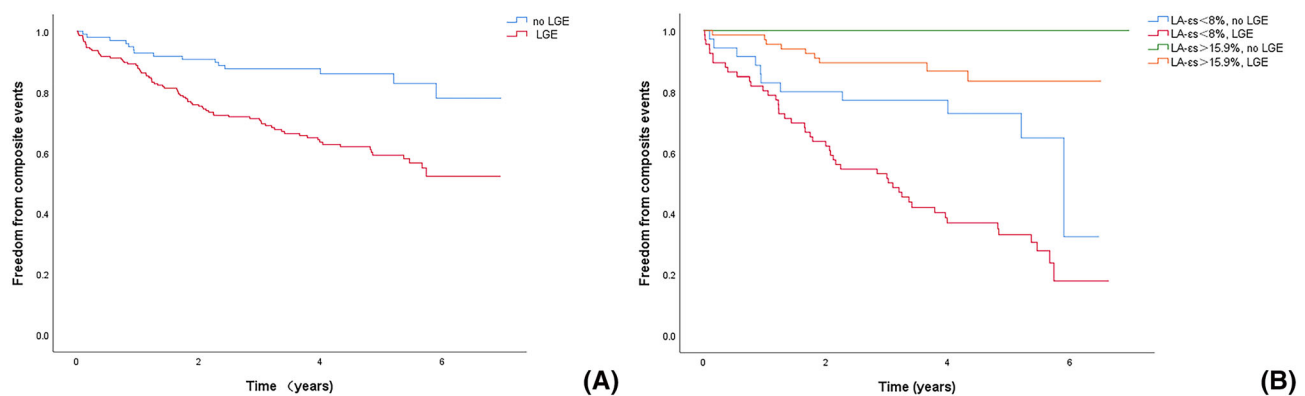

Figure 4 Kaplan–Meier survival curves. (A) Stratified by LGE present in all patients. (B) Stratified by tertiles of LA-εs and LGE present in all patients.

groups of patients. In both ICM and NIDCM patients, LA-εs was significantly associated with the risk of MACEs after adjusting for clinical and radiographic risk factors (ICM: HR = 0.94/%; P = 0.002; NIDCM: HR = 0.88/%; P = 0.001) (*Table 4*). Subsequently, LA-εs remained a critical, independent predictor of the occurrence of MACEs when LGE presence was used instead of extent (*Table 4*).

Discussion

The primary findings of our study were as follows: (i) patients with HFrEF and without AF had reduced reservoir, conduit, and booster deformation indexes (strain and SR) in LA and RA. LA-εs was closely related to LA-εe, LA-εa, LA-SRs, and LA-SRe ($r > 0.5$). (ii) LA-εs, LAEF, and LGE extent were independent predictors of MACEs, and LA-εs increased the incremental predictive value of common clinical and CMR imaging risk factors for outcomes in patients with HFrEF. (iii) LA-εs was an independent predictor of outcome in ICM and NIDCM, respectively, even after adjusting for clinical, laboratory, and CMR variables.

The atrium is a container for storing blood and has been under intensive focus for its role in cardiac function. During the cardiac cycle, it has three main functions: (i) the atrial storage function of pulmonary venous blood flow during ventricular systole; (ii) the conduit function of delivering blood flow into the ventricle during early diastole; (iii) the systolic function of pumping the remaining blood into the ventricle by end-diastole auto-systole.[22] Impaired atrial function indicates an elevated ventricular filling pressures, and the diastolic function of the ventricles determines the degree of relative atrial contribution to ventricular filling.[23] Previous studies suggested that abnormal LA function in the early stages of HF is an early indicator of LV diastolic dysfunction.[24,25] Depletion of compensatory mechanisms translates into overt HF or deteriorated clinical condition.[26] In the advanced stage of HF, LA is enlarged and remodelled to varying degrees with impaired function, which is usually associated with chronic and severe symptoms.[27,28] With the progression of HF, atrial dysfunction may be a late consequence of systemic and pulmonary circulatory changes caused by HF. Melenovsky *et al.*[29] demonstrated that HFrEF is characterized by significant eccentric LA remodelling. The degree of LA deformation is of great value for the prognostic

Table 4 Multivariate Cox proportional hazards model analysis for predicting overall survival in patients with ICM or NIDCM

	Multivariable model using LGE extent						Multivariable model using LGE present					
	ICM			NIDCM			ICM			NIDCM		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age, years	1.03	(0.96–1.03)	0.808	1.04	(1.01–1.07)	**0.016**	1.00	(0.97–1.04)	0.953	1.04	(1.01–1.07)	**0.013**
Male, %	2.91	(0.18–2.91)	0.648	1.44	(0.60–3.47)	0.416	0.55	(0.16–1.96)	0.358	1.64	(0.65–4.13)	0.298
BMI, kg/m^2	1.04	(0.81–1.04)	0.160	1.02	(0.95–1.11)	0.575	0.91	(0.82–1.02)	0.122	1.04	(0.96–1.12)	0.343
SBP, mmHg	1.06	(0.98–1.06)	0.364	0.98	(0.96–1.02)	0.154	1.00	(0.97–1.04)	0.985	0.99	(0.96–1.01)	0.161
QRS duration, ms	1.03	(1.00–1.03)	**0.036**	1.00	(0.99–1.02)	0.716	1.02	(1.01–1.03)	0.005	1.00	(0.99–1.02)	0.778
Diabetes mellitus, %	2.38	(0.43–2.38)	0.976	0.98	(0.40–2.40)	0.960	0.87	(0.38–1.96)	0.733	0.67	(0.25–1.79)	0.422
Medication: ACEI/ARB	2.64	(0.29–2.64)	0.809	0.78	(0.33–1.84)	0.563	0.75	(0.25–2.29)	0.612	0.67	(0.29–1.54)	0.343
BNP, pg/mL	1.00	(1.00–1.00)	0.075	1.00	(1.00–1.00)	0.330	1.00	(1.00–1.00)	0.049	1.00	(1.00–1.00)	0.321
ALT, U/L	1.02	(1.00–1.02)	0.140	1.00	(1.00–1.00)	0.162	1.01	(1.00–1.02)	0.065	1.00	(1.00–1.00)	**0.043**
Creatinine, μmol/L	1.02	(0.99–1.02)	0.972	1.00	(0.99–1.01)	0.965	1.00	(0.99–1.02)	0.963	1.00	(0.99–1.01)	0.988
Cl−, mmol/L	1.16	(0.91–1.16)	0.713	1.00	(1.00–1.01)	0.307	1.02	(0.91–1.15)	0.708	1.00	(1.00–1.01)	0.051
Red blood cell, g/L	1.19	(0.18–1.19)	0.109	0.68	(0.46–0.99)	**0.043**	0.42	(0.17–1.01)	0.052	0.79	(0.55–1.13)	0.201
CMR-LVEDV, mL	1.01	(0.99–1.01)	0.826	1.00	(1.00–1.01)	0.405	1.00	(0.99–1.00)	0.556	1.00	(1.00–1.01)	0.571
CMR-LVpGLS, %	1.34	(0.87–1.34)	0.502	0.88	(0.77–1.01)	0.077	1.06	(0.86–1.31)	0.596	0.91	(0.79–1.05)	0.204
CMR-LVpGCS, %	1.13	(0.78–1.13)	0.473	0.99	(0.87–1.12)	0.836	0.98	(0.81–1.18)	0.801	0.96	(0.85–1.08)	0.460
CMR-LAVmax, mL	1.02	(0.99–1.02)	0.693	1.01	(1.00–1.02)	0.229	1.00	(0.99–1.02)	0.547	1.01	(1.00–1.01)	0.296
CMR-LAEF, %	1.09	(1.00–1.09)	**0.036**	1.02	(0.99–1.06)	0.177	1.04	(1.00–1.08)	0.073	1.01	(0.98–1.05)	0.482
CMR-LA-εs, %	0.94	(0.78–0.94)	**0.002**	0.88	(0.81–0.95)	**0.001**	0.84	(0.76–0.92)	**0.000**	0.89	(0.83–0.96)	**0.002**
CMR-RAVmax, mL	1.02	(0.99–1.02)	0.398	1.01	(1.00–1.02)	0.242	1.01	(0.99–1.02)	0.515	1.00	(0.99–1.01)	0.400
LGE extent, %	1.07	(1.01–1.07)	**0.005**	1.04	(1.01–1.06)	**0.001**	-	-	-	-	-	-
LGE present, %	-	-	-	-	-	-	-	-	-	3.24	(1.51–6.95)	**0.003**

ACEI, ACE inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CMR, cardiac magnetic resonance; LAEF, left atrial ejection fraction; LGE, late gadolinium enhancement; LAVmax, maximum left atrial volume; LVEDV, left ventricular end-diastolic volume; LVpGCS, left ventricular peak global circumferential strain; LVpGLS, left ventricular peak global longitudinal strain; RAVmax, maximum right atrial volume; SBP, systolic pressure at presentation; εs, reservoir strain.
Bold items indicate *P*-value < 0.05.

evaluation of patients with HFrEF. The measurement of LA strain by speckle tracking is challenging due to the low signal-to-noise ratio and a thin atrial wall. CMR has a high spatial resolution and enables rapid and reliable quantification of LA functional parameters with short measurement times and high reproducibility. Leng et al.'s prospective study showed that LA strain measured using CMR can be used as a predictor of long-term outcome in ST-elevation myocardial infarction (STEMI), thus providing additional prognostic information for the established predictors of STEMI.[24] Cojan-Minzat et al. reported that LA total strain had independent predictive value for incremental outcome in NIDCM.[11] Dick et al. assessed the diagnostic value of LA and RA strain parameters for acute myocarditis and demonstrated that LA SRe is the best predictor of condition.[20] To the best of our knowledge, this is the first study to analyse the long-term prognostic value of atrial indexes obtained by CMR in patients with ICM and NIDCM of HFrEF without AF, with a median follow-up of up to 3.84 years. Herein, we showed that LA strain provides additional prognostic information beyond clinical and CMR parameter models in both categories of patients. LAEF was significantly associated with increased filling pressure of LV.[30] As reported by Pellicori et al., in patients with HF, LAEF predicts the adverse outcomes independently of other measures of cardiac dysfunction.[31] The aforementioned conclusions were verified in our study too. When the culprit vessel of ICM causes the three-vessel coronary artery disease and the symptoms of HF are distinct, the cavity will enlarge and the overall movement of the wall will be weakened, which can be easily misdiagnosed as DCM; thus, the distribution of LGE is the key differential point between the two phenomena. Previous studies have shown that the presence and extent of LGE can predict the prognosis of patients with HF caused by ICM and DCM and is an independent predictor of death[32,33]; these findings were confirmed in the current study. In patients with and without LGE, the grouping of LA-εs is valuable for the evaluation of prognostic risk stratification. Romano et al.[32] demonstrated that LV longitudinal strain is an independent predictor of death in patients with ICM or DCM. In this study, the corresponding parameters of the LV did not show independent prognostic value in multivariate Cox analysis. This could be because for patients with advanced HF, the degree of impaired LV systolic function loses its ability for survival prediction. HF can lead to secondary MR and PH.[34] MR and PH have previously been reported in the literature to be associated with the prognosis in patients with HF.[35] However, our results showed that the degrees of MR, PH, and LA-εs were weakly correlated. This correlation could be attributed to the relationship between the severity of HF in our included patients, and the presence of some MR and PH in the three groups of patients categorized by LA-εs. In the subsequent research, we should collect HF with preserved ejection and mildly reduced ejection to verify this aspect. Nonetheless,

some patients with advanced HF can benefit from advanced treatments, such as heart transplantation and LV assist device implantation.[36] The present study has potential clinical implications in the use of LA strains to reclassify such patient populations that would help in making precise HF management decisions in the future.

Limitations

Nevertheless, the present study has some limitations. First, the proportion of men was relatively high. We grouped the baseline characteristics (clinical and CMR characteristics, including LA εs) by sex and showed statistically significant differences for the six parameters of left bundle branch block, intraventricular block, smoking, drinking, CMR-RA-εe, and CMR-RA-SRa (Supporting Information, Table S5). Inclusion of the aforementioned variables in the univariate analysis showed that they were not significantly associated with the outcome. Sex was not statistically significant in univariate analysis. Furthermore, we included the sex indicator in the multivariate Cox model, and after multivariate adjustment, the results showed that there was no significant association between sex and the outcome. We tried to reduce the impact of selection bias via the aforementioned work. Second, this was a single-centre study, and the number of patients was limited, which might affect the accuracy of the results. Third, collecting clinical data was not comprehensive. For example, 10% of patients had missing data for BNP. We input the missing data using statistical methods for multiple interpolation and confirmed our hypothesis of the missing data pattern by demonstrating that BNP was an independent predictor of MACEs before and after data input ($P < 0.05$). In addition, similar to ultrasound tracking techniques,[37] algorithmic differences were detected between different CMR FT software. Further investigation of the applicability of other FT vendors is essential. Finally, our data were all derived from 3 T magnetic resonance, and in subsequent studies, we intend to use 1.5 T magnetic resonance to verify our results, thereby enhancing the generalizability of the conclusions.

Conclusion

LA strain is a robust predictor of MACEs in patients with ischaemic and non-ischaemic dilated cardiomyopathy, independent of common clinical and CMR imaging markers. In HFrEF, LA-εs adds incremental prognostic information on outcomes from common clinical and CMR risk factors (including LGE). The current findings may exert a significant impact on management decisions based on risk stratification in these individuals and contribute to the dynamic assessment of prognosis in patients with HFrEF.

Funding

Conflict of interest

Supporting information

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

Table S1. Baseline characteristics stratified by ICM.
Table S2. Reproducibility of atrial strain parameter measurements.
Table S3. Univariate analysis of major adverse events in 5-year follow-up of patients with ICM or NIDCM.
Table S4. The correlations between covariates.
Table S5. Baseline characteristics stratified by sex.

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