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Cardiac MRI-derived left atrial remodeling during breast cancer therapy: a prospective study Short Title: Left Atrial Remodeling in Breast Cancer

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Abstract

Background

Cancer therapy-related cardiac dysfunction (CTRCD) may be incompletely characterized by left ventricular ejection fraction (LVEF), whereas the relevance of left atrial (LA) remodeling remains uncertain. We investigated whether early cardiac magnetic resonance (CMR)-derived LA remodeling was associated with 3-month CTRCD during breast cancer therapy.

Methods

This prospective longitudinal study included 68 women with breast cancer who underwent CMR before systemic therapy and at 3 months; 38 also underwent 12-month CMR. LVEF, global longitudinal strain (GLS), LA volume indices, emptying fractions, and phasic strain were assessed. Serial changes were evaluated using linear mixed-effects models. Associations between changes from baseline to 3 months and 3-month CTRCD were assessed using Firth logistic regression adjusted for age and baseline LVEF, with false discovery rate correction.

Results

CTRCD occurred in 15 patients (22.0%) during follow-up, including 11 events at 3 months. LVEF decreased without a significant time-by-group interaction, whereas GLS and maximum LA volume index showed differential trajectories according to CTRCD occurrence ($P < 0.001$ and $P = 0.016$, respectively). Per 1-SD adverse change, increased maximum LA volume index was associated with 3-month CTRCD (adjusted odds ratio: 2.40; 95% CI: 1.16–5.71; FDR-adjusted $P = 0.036$). Decreases in LA reservoir, conduit, and booster strain were also associated with 3-month CTRCD after FDR correction.

Conclusions

Early CMR-derived LA volume expansion and phasic strain impairment were associated with 3-month CTRCD. These measures may complement ventricular assessment but require validation before use for risk prediction.

Introduction

Advances in breast cancer therapy have markedly improved survival; however, cancer therapy–related cardiac dysfunction (CTRCD) remains a clinically important complication, especially in patients treated with anthracycline-based chemotherapy and human epidermal growth factor receptor 2 (HER2)-targeted therapy[1–3]. In routine surveillance, CTRCD is commonly recognized by an asymptomatic decline in left ventricular ejection fraction (LVEF), impaired myocardial deformation, or abnormal cardiac biomarkers before overt heart failure develops. Identifying early cardiac changes is essential, not only to guide closer surveillance and timely cardioprotective therapy, but also to reduce avoidable interruption of effective anticancer treatment[4,5].

Cardiovascular magnetic resonance (CMR) provides accurate and reproducible quantification of cardiac chamber volumes, ventricular function, and myocardial deformation, making it particularly suitable for serial assessment during cancer therapy. Compared with echocardiography, CMR is less dependent on acoustic windows and

operator experience for volumetric assessment, and cine imaging allows simultaneous evaluation of ventricular and atrial structure and function[6,7]. Most previous CMR studies in cardio-oncology have focused on LVEF, ventricular strain, and myocardial tissue characterization[8–11]. By contrast, CMR-derived left atrial (LA) remodeling has received less attention, and its relevance to early CTRCD in patients undergoing breast cancer therapy remains insufficiently defined.

The left atrium reflects the combined effects of ventricular relaxation, filling pressure, longitudinal systolic mechanics, and atrioventricular coupling[12–14]. LA volume represents cumulative loading, whereas LA strain captures reservoir, conduit, and booster function. In non-oncologic cardiovascular populations, LA enlargement and impaired LA deformation have been associated with subclinical dysfunction and adverse outcomes[15–18]. These findings suggest that LA assessment may provide information beyond conventional ventricular indices.

In patients receiving potentially cardiotoxic breast cancer therapy, early LA strain impairment or LA volume expansion may reflect subtle atrioventricular dysfunction before overt LVEF decline. Recent studies have suggested that atrial functional impairment may occur after breast cancer therapy and that LA dysfunction may be related to subsequent cardiotoxicity. However, available evidence remains limited with respect to serial CMR-based assessment of LA remodeling during active treatment, particularly the integrated evaluation of LA volume, emptying function, and phasic strain in relation to early CTRCD[19,20]. Moreover, whether LA remodeling derived from routine cine CMR provides complementary information beyond conventional ventricular parameters remains insufficiently defined.

Therefore, this prospective longitudinal study evaluated CMR-derived LA structure and function in patients with breast cancer receiving anthracycline-based chemotherapy and/or HER2-Targeted therapy. We aimed to characterize serial changes in LA volume indices, LA emptying fractions, and LA reservoir, conduit, and booster strain, and to examine whether early LA remodeling from baseline to 3 months was associated with 3-month CTRCD. Given the modest sample size and limited number of events, the study focused on imaging associations rather than definitive risk prediction.

Methods

Study Design and Population

This prospective longitudinal study was approved by the institutional ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences (IRB number: NCC2020C-508), and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. Patients with pathologically confirmed breast cancer scheduled to receive anthracycline-based chemotherapy and/or HER2 therapy were recruited between January 2022 and September 2025. Exclusion criteria were cancer therapy performed at external institutions, lack of follow-up CMR, pre-existing cardiovascular disease, inadequate image quality, or inadequately controlled hypertension. Among 95 screened patients, 68 were included in the final cohort. All included patients underwent CMR at baseline and 3 months, and 38 patients underwent an additional CMR examination at 12 months.

Cancer Therapy and Clinical Data

Cancer treatment exposure was obtained from electronic medical records. Patients were classified according to systemic therapy regimen, including trastuzumab monotherapy, trastuzumab plus pertuzumab, anthracycline followed by trastuzumab, or anthracycline followed by trastuzumab plus pertuzumab. Baseline demographic and clinical variables included age, body mass index, body surface area, heart rate, hypertension, diabetes mellitus, and hyperlipidemia.

CMR Acquisition

CMR was performed on a 3.0-T scanner (GE Healthcare) with electrocardiographic gating and repeated breath-hold acquisition. Cine images were acquired using a fast imaging employing steady-state acquisition sequence. Standard 2- and 4-chamber long-axis cine views were obtained for left atrial volume and strain analysis. A contiguous short-axis cine stack covering the left ventricle from base to apex was acquired for left ventricular volume, mass, and ejection fraction assessment. Representative short-axis cine parameters were as follows: repetition time/echo time, 3.8/1.7ms; flip angle, 60°; slice thickness, 7mm; interslice spacing, 10 mm; interslice gap, 3mm; field of view, 350 mm; matrix, 512×512; in-plane resolution, 0.68×0.68 mm; and 20 reconstructed cardiac phases per cardiac cycle. Imaging parameters were kept consistent across serial examinations whenever possible.

CMR Image Analysis

CMR images were analyzed offline using cvi42 software (Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada) by experienced observers blinded to CTRCD status and clinical outcomes. Left ventricular volumes, mass, and ejection fraction were quantified from short-axis cine images using standard contouring methods and indexed to body surface area when appropriate. Global longitudinal strain was derived using feature-tracking analysis.

Left atrial volumes were measured from long-axis cine images at maximum volume, pre-atrial contraction volume, and minimum volume, and indexed to body surface area as LAVImax, LAVIpre, and LAVImin. Total, passive, and active left atrial emptying fractions were calculated from phasic left atrial volumes. Left atrial reservoir, conduit, and booster strain were assessed using feature-tracking analysis from standard 2- and 4-chamber cine views. Representative left atrial volumetric and strain measurements are shown in Fig. 2.

Definition of CTRCD

Cancer therapy-related cardiac dysfunction (CTRCD) was defined and graded according to the 2022 European Society of Cardiology cardio-oncology guidelines[1]. Mild asymptomatic CTRCD was defined as new LVEF ≥ 50% with a relative GLS decline > 15% from baseline. Moderate asymptomatic CTRCD was defined as new LVEF of 40% to 49%, and severe asymptomatic CTRCD as new LVEF < 40%. For patients with persistent CTRCD, only the first event was included in the primary analysis. Because cardiac biomarkers were not systematically available, CTRCD was adjudicated using CMR-derived LVEF and GLS criteria. The primary outcome was CTRCD occurring at 3 months. The secondary outcome was CTRCD occurring during follow-up, defined as CTRCD detected at either the 3-month or 12-month CMR examination. For patients with CTRCD detected at more than one time point, only the first event was considered for event classification. In exploratory analyses, patients were further categorized according to CTRCD trajectory as no observed CTRCD, early transient CTRCD, persistent CTRCD, or late-onset CTRCD.

Statistical Analyses

Continuous variables are presented as mean ± SD or median with interquartile range, and categorical variables as counts and percentages. Baseline characteristics were compared between patients with and without CTRCD using Student's t-test or the Mann-Whitney U test for continuous variables and the chi-square or Fisher exact test for categorical variables, as appropriate. For longitudinal trajectory analyses, patients were grouped according to CTRCD occurrence during follow-up because both early and late events were of interest for serial imaging patterns. Serial changes in CMR parameters were evaluated using linear mixed-effects models with time, CTRCD group, and their interaction as fixed effects and patient ID as a random intercept. For the main longitudinal analysis, patients were grouped according to the occurrence of CTRCD during follow-up. The primary association analysis evaluated the relationship between early LA changes from baseline to 3 months and 3-month CTRCD using Firth-penalized logistic regression. Each LA parameter was entered into a separate model adjusted for age and baseline CMR-derived LVEF. Odds ratios were reported per 1-SD change. The secondary association analysis used CTRCD occurring at either 3 or 12 months as the outcome. False discovery rate-adjusted P values were calculated using the Benjamini-Hochberg method. Analyses were performed using R software, version 4.5.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value < 0.05 was considered statistically significant.

Results

Study Population

The final study cohort consisted of 68 patients with breast cancer who completed serial CMR examinations during anthracycline-based chemotherapy and/or HER2 therapy. Among 95 screened patients between January 2022 and September 2025, 27 were excluded, leaving 68 patients in the final longitudinal cohort (Fig. 1). All patients completed baseline and 3-month CMR examinations, and 38 patients underwent additional 12-month CMR follow-up.

Baseline clinical and CMR characteristics were broadly comparable between patients with and without CTRCD. As shown in Table 1, the two groups had similar age, body mass index, body surface area, heart rate, cardiovascular risk factors, baseline LVEF, GLS, LA volume indices, LA emptying fractions, and LA strain parameters. Patients with and without 12-month CMR follow-up also showed comparable baseline clinical characteristics and similar rates of 3-month CTRCD; baseline GLS was lower in patients without 12-month follow-up, whereas baseline LVEF, maximum LAVI, LA reservoir strain, and 3-month CMR parameters did not differ significantly between groups (Table S1).

Table 1
Baseline Clinical and CMR Characteristics According to CTRCD Occurrence

Variable	CTRCD (n = 15)	No CTRCD (n = 53)	P value
Clinical characteristics			
Age, years	48.53 ± 7.33	52.25 ± 11.53	0.166
BMI at presentation, kg/m^2	25.31 ± 5.09	24.78 ± 3.70	0.976
BSA at presentation, m^2	1.65 ± 0.17	1.65 ± 0.15	0.877
Heart rate, bpm	74.40 ± 12.25	74.45 ± 10.79	0.970
Hypertension, n (%)	5 (33.3%)	19 (35.8%)	>0.999
Hyperlipidemia, n (%)	2 (13.3%)	3 (5.7%)	0.303
Diabetes, n (%)	3 (20.0%)	5 (9.4%)	0.361
Baseline CMR			
LVEF, %	64.15 ± 4.66	63.26 ± 4.32	0.451
GLS, %	-17.57 ± 2.00	-17.69 ± 1.31	0.818
$LAVI_{max}$, ml/m^2	29.96 ± 5.39	30.06 ± 6.39	0.988
$LAVI_{pre}$, ml/m^2	20.52 ± 4.33	20.17 ± 4.44	0.912
$LAVI_{min}$, ml/m^2	12.17 ± 2.93	12.16 ± 3.08	0.900
LA reservoir strain, %	30.66 ± 4.69	29.16 ± 5.46	0.225
LA conduit strain, %	20.31 ± 2.78	19.41 ± 2.87	0.231
LA booster strain, %	10.35 ± 3.11	9.75 ± 3.35	0.657
LAEF, %	59.39 ± 6.44	59.53 ± 6.01	0.971

Note: Data are presented as mean ± standard deviation, median (interquartile range), or n (%) as appropriate. CTRCD was defined according to the 2022 ESC cardio-oncology guidelines.

Abbreviations: BMI, body mass index; BSA, body surface area; CTRCD, cancer therapy-related cardiac dysfunction; GLS, global longitudinal strain; LA, left atrial; LAEF, left atrial emptying fraction; $LAVI_{max}$, maximum left atrial volume index; $LAVI_{pre}$, pre-atrial contraction left atrial volume index; $LAVI_{min}$, minimum left atrial volume index; LVEF, left ventricular ejection fraction.

CTRCD During Follow-up

CTRCD occurred in approximately one-fifth of the cohort during longitudinal follow-up. Overall, 15 of 68 patients (22.0%) developed CTRCD, including 11 patients with mild CTRCD and 4 patients with moderate CTRCD; no severe CTRCD was observed. With respect to timing, CTRCD was first detected at 3 months in 11 patients and at 12 months in 4 patients. Persistent CTRCD was observed in 2 patients (Table 2). Eleven patients developed CTRCD at 3 months, which constituted the primary outcome for association analyses.

Table 2
Clinical Characteristics of CTRCD Events During Follow-Up

Characteristic	Value
Overall CTRCD incidence, n (%)	15/68(22.0%)
Mild CTRCD, n (%)	11(73.3%)
Moderate CTRCD, n (%)	4(26.7%)
Severe CTRCD, n (%)	0(0.0%)
Onset at 3 months, n (%)	11(73.3%)
Onset at 12 months, n (%)	4(26.7%)
Persistent CTRCD, n (%)	2(13.3%)
With pre-existing hypertension, n (%)	5(33.3%)

Note: Percentages for severity, time of onset, and hypertension status are calculated based on the total number of CTRCD patients (n = 15). CTRCD was defined and graded according to the 2022 ESC cardio-oncology guidelines: mild CTRCD as new LVEF ≥ 50% with a relative decline in GLS > 15% from baseline; moderate CTRCD as new LVEF of 40–49%; and severe CTRCD as new LVEF < 40%. For the patients with persistent CTRCD, only the first event was included in primary analyses.

Abbreviations: CTRCD, cancer therapy-related cardiac dysfunction.

Serial Changes in CMR Parameters According to CTRCD During Follow-up

Left ventricular systolic function changed after treatment, but LVEF and GLS showed different longitudinal patterns according to CTRCD occurrence. LVEF decreased from baseline to 3 months in both patients with and without CTRCD, without a significant time-by-group interaction (P interaction = 0.238). In contrast, GLS showed a significant time-by-group interaction (P interaction < 0.001), indicating a greater longitudinal change in patients who developed CTRCD (Table 3, Fig. 3).

Table 3
Longitudinal Changes in CMR-Derived Ventricular and Left Atrial Parameters According to CTRCD Occurrence

CMR parameter	No observed CTRCD			Any CTRCD			P interaction
	Baseline(n = 53)	3 months(n = 53)	12 months(n = 28)	Baseline(n = 15)	3 months(n = 15)	12months(n = 10)	
LVEF, %	63.3 ± 4.3	59.9 ± 5.5	60.4 ± 5.3	64.1 ± 4.7	58.5 ± 7.4	60.6 ± 6.8	0.238
GLS, %	-17.7 ± 1.3	-16.2 ± 1.4	-16.3 ± 1.5	-17.6 ± 2.0	-14.5 ± 2.3	-14.2 ± 3.1	< 0.001
$LAVI_{max}$, ml/m^2	30.1 ± 6.4	29.8 ± 6.4	29.2 ± 7.2	30.0 ± 5.4	33.9 ± 5.6	32.6 ± 5.5	0.016
$LAVI_{pre}$, ml/m^2	20.2 ± 4.4	20.5 ± 5.1	19.9 ± 4.9	20.5 ± 4.3	21.9 ± 4.5	21.4 ± 4.9	0.597
$LAVI_{min}$, ml/m^2	12.2 ± 3.1	12.7 ± 3.3	13.1 ± 3.8	12.2 ± 2.9	14.5 ± 2.8	14.4 ± 2.6	0.051
Total LAEF, %	59.5 ± 6.0	57.2 ± 6.9	54.9 ± 8.11	59.4 ± 6.4	56.7 ± 6.4	55.2 ± 7.1	0.978
Passive LAEF, %	39.1 ± 11.9	36.9 ± 12.0	33.4 ± 14.2	40.6 ± 8.5	33.2 ± 8.3	31.3 ± 8.0	0.368
Active LAEF, %	20.5 ± 9.2	20.3 ± 9.6	21.5 ± 11.9	18.8 ± 10.5	23.5 ± 8.7	23.9 ± 8.9	0.206
reservoir strain, %	29.2 ± 5.5	27.2 ± 5.6	25.9 ± 5.1	30.7 ± 4.7	26.1 ± 5.9	25.6 ± 6.0	0.119
conduit strain, %	19.4 ± 2.9	18.1 ± 2.8	17.2 ± 3.3	20.3 ± 2.8	17.7 ± 3.4	17.0 ± 3.1	0.295
booster strain, %	9.8 ± 3.4	9.1 ± 3.5	8.7 ± 2.4	10.4 ± 3.1	8.3 ± 3.4	8.6 ± 3.3	0.259

Note: Values are mean ± SD (n). Patients were categorized according to the occurrence of CTRCD at either 3 months or 12 months. The Any CTRCD group included early transient CTRCD, persistent CTRCD, and late-onset CTRCD. P values for time-by-group interaction were derived from linear mixed-effects models including time, CTRCD group, and their interaction, with patient ID as a random intercept. Because 12-month CMR was available in a subset of patients, the number of observations at each time point is shown.

Abbreviations: CTRCD, cancer therapy-related cardiac dysfunction; GLS, global longitudinal strain; LA, left atrial; $LAVI_{max}$, maximum left atrial volume index; $LAVI_{pre}$, pre-atrial contraction left atrial volume index; $LAVI_{min}$, minimum left atrial volume index; LAEF, left atrial emptying fraction; LVEF, left ventricular ejection fraction.

Left atrial remodeling during follow-up was characterized by a combination of volume enlargement and functional decline. In the overall cohort, minimum LAVI increased significantly over time (P for time = 0.002), whereas maximum LAVI and pre-atrial contraction LAVI remained stable. In parallel, total LAEF, passive LAEF, LA reservoir strain, LA conduit strain, and LA booster strain decreased significantly during follow-up, while active LAEF showed no significant longitudinal change.

Maximum LAVI showed the clearest differential longitudinal trajectory among LA parameters. In patients who developed CTRCD, maximum LAVI increased from 30.0 ± 5.4 mL/m² at baseline to 33.9 ± 5.6 mL/m² at 3 months; in contrast, maximum LAVI remained stable in patients without CTRCD. The time-by-group interaction was significant for maximum LAVI (P interaction = 0.016), whereas minimum LAVI showed a borderline interaction (P interaction = 0.051). No significant time-by-group interactions were observed for pre-atrial contraction LAVI, total LAEF, passive LAEF, active LAEF, LA reservoir strain, LA conduit strain, or LA booster strain. Early LA volume and strain changes according to CTRCD trajectory are shown descriptively in Figure S1.

Primary Analysis: Early LA Remodeling and 3-Month CTRCD

In the primary association analysis, early LA volume enlargement and LA strain deterioration from baseline to 3 months were evaluated in relation to CTRCD occurring at 3 months. Early LA volume enlargement was associated with 3-month CTRCD, particularly for maximum LAVI. In Firth-penalized logistic regression models adjusted for age and baseline CMR-derived LVEF, an increase in maximum LAVI was significantly associated with 3-month CTRCD after false discovery rate correction (adjusted OR per 1-SD increase, 2.40; 95% CI: 1.16, 5.71; P = 0.018; FDR-adjusted P = 0.036). An increase in minimum LAVI was also associated with 3-month CTRCD before correction for multiple testing, but this association did not remain significant after false discovery rate correction (adjusted OR, 2.04; 95% CI: 1.02, 4.54; P = 0.044; FDR-adjusted P = 0.070) (Fig. 4, Table 4).

Table 4
Early CMR-Derived Left Atrial Remodeling Associated With 3-Month CTRCD

Parameter	N	Events	Adjusted OR (95%CI)	P value	FDR-adjusted P value
Increase in maximum LAVI	68	11	2.40 (1.16–5.71)	0.018	0.036
Increase in minimum LAVI	68	11	2.04 (1.02–4.54)	0.044	0.070
Decrease in total LAEF	68	11	0.89 (0.40–1.82)	0.755	0.755
Decrease in passive LAEF	68	11	1.25 (0.64–2.40)	0.511	0.584
Decrease in active LAEF	68	11	0.74 (0.37–1.40)	0.362	0.482
Adverse change in LA reservoir strain	68	11	4.78 (1.88–17.09)	< 0.001	0.002
Adverse change in LA conduit strain	68	11	3.23 (1.52–8.58)	0.001	0.005
Adverse change in LA booster strain	68	11	2.54 (1.25-6.00)	0.009	0.023

Note: Models used Firth penalized logistic regression and were adjusted for age and baseline CMR-derived LVEF. The outcome was CTRCD occurring at 3 months. Each atrial parameter was entered into a separate model. Odds ratios are reported per 1-SD specified change from baseline to 3 months. FDR-adjusted P values were calculated using the Benjamini-Hochberg method.

Abbreviations: CTRCD, cancer therapy-related cardiac dysfunction; FDR, false discovery rate; LA, left atrial; LAEF, left atrial emptying fraction; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; OR, odds ratio.

Changes in LA emptying fractions were not significantly associated with 3-month CTRCD. The adjusted ORs were 0.89 for total LAEF (95% CI: 0.40, 1.82; P = 0.755), 1.25 for passive LAEF (95% CI: 0.64, 2.40; P = 0.511), and 0.74

for active LAEF (95% CI: 0.37, 1.40; P = 0.362). Thus, none of the LA emptying fraction parameters showed a significant association with early CTRCD in the adjusted models.

Early adverse changes in all three LA strain components were significantly associated with 3-month CTRCD. After adjustment for age and baseline CMR-derived LVEF, the adjusted OR was 4.78 for LA reservoir strain (95% CI: 1.88, 17.09; P < 0.001; FDR-adjusted P = 0.002), 3.23 for LA conduit strain (95% CI: 1.52, 8.58; P = 0.001; FDR-adjusted P = 0.005), and 2.54 for LA booster strain (95% CI: 1.25, 6.00; P = 0.009; FDR -adjusted P = 0.023). Among these parameters, LA reservoir strain showed the largest effect estimate, followed by LA conduit strain and LA booster strain.

Secondary Analysis: Early LA Remodeling and CTRCD During Follow-up

In the secondary analysis using CTRCD detected at either 3 or 12 months as the outcome, the associations between early LA remodeling and CTRCD during the entire follow-up period were weaker than those observed for 3-month CTRCD. In adjusted models using CTRCD at either 3 or 12 months as the outcome, early increases in maximum LAVI and minimum LAVI and worsening of LA reservoir strain were associated with CTRCD before false discovery rate correction. However, after correction for multiple testing, no LA parameter remained significantly associated with CTRCD during the entire follow-up period (Table S2).

Discussion

In this prospective longitudinal CMR study of patients with breast cancer receiving anthracycline-based chemotherapy and/or HER2 therapy, LA remodeling was evident during treatment and was associated with early CTRCD. The principal findings were as follows: first, in the overall cohort, LA remodeling was characterized by increased minimum LAVI and reductions in total LAEF, passive LAEF, and LA reservoir, conduit, and booster strain during follow-up; second, GLS and maximum LAVI showed significant differential longitudinal trajectories according to CTRCD occurrence, whereas LVEF did not; third, early increases in maximum LAVI and decreases in LA reservoir, conduit, and booster strain were associated with 3-month CTRCD after false discovery rate correction. These findings suggest that CMR-derived LA remodeling, particularly maximum LAVI, together with GLS, may provide complementary information for characterizing early treatment-related cardiac changes beyond conventional LVEF assessment.

The present findings are consistent with the increasing recognition that ejection fraction is an incomplete marker of early cardiotoxicity. In this cohort, ejection fraction decreased after treatment but did not distinguish longitudinal patterns according to dysfunction occurrence, whereas global longitudinal strain showed a significant differential trajectory. This supports the value of myocardial deformation for early functional assessment during breast cancer therapy [21,5]. The additional finding that maximum left atrial volume index also showed a differential trajectory extends this concept from ventricular mechanics to atrial remodeling. Because left atrial volume and strain can be derived from standard cine cardiac MRI without additional image acquisition, they may be incorporated into routine image interpretation when serial cardiac MRI is performed for cardio-oncology surveillance.

Left atrial strain appeared to provide information that was not captured by left atrial emptying fractions. In the adjusted association analyses, early worsening of reservoir, conduit, and booster strain was associated with 3-month dysfunction, whereas left atrial emptying fractions were not significantly associated with the outcome. This

difference may reflect the greater sensitivity of deformation-based measures to early functional impairment compared with volume-derived emptying indices. The association across all three atrial strain components also suggests that early treatment-related dysfunction is accompanied by global impairment of atrial phasic function rather than an isolated change in one atrial phase. Therefore, left atrial strain may serve as a complementary imaging marker when ejection fraction remains preserved or changes are modest.

The weaker findings in the secondary analysis using dysfunction at either 3 or 12 months as the outcome should be interpreted cautiously. Most dysfunction events occurred at 3 months, whereas late-onset events were few and 12-month cardiac MRI was available only in a subset of patients. In addition, early transient, persistent, and late-onset dysfunction may represent different clinical trajectories. These factors likely reduced the ability of early left atrial changes to characterize dysfunction across the entire follow-up period. Accordingly, the present results should be interpreted as evidence of an association between early left atrial remodeling and early treatment-related dysfunction, rather than as proof of late risk prediction.

Our study adds to growing evidence that CMR surveillance in cardio-oncology should not be restricted to LVEF. Previous CMR studies have emphasized ventricular strain, myocardial edema, extracellular volume expansion, or late gadolinium enhancement as markers of treatment-related myocardial injury[21–23]. These approaches provide important information on ventricular mechanics and tissue characterization. Our findings add a chamber-level functional perspective by showing that LA volume and deformation can be quantified from routine cine CMR and may detect early remodeling during breast cancer therapy. This is particularly relevant for radiology practice because LA volumetric and feature-tracking strain analysis can be performed without additional image acquisition. Incorporating LA assessment into routine CMR interpretation may therefore improve the phenotyping of early cardiotoxicity, especially in patients whose LVEF remains within the preserved range.

Limitations

This study has several limitations. First, this was a single-center study with a modest sample size and a limited number of CTRCD events, which may restrict statistical power and generalizability. To mitigate small-sample bias, we used Firth penalized logistic regression and adjusted the models for age and baseline CMR-derived LVEF; however, the findings should be validated in larger multicenter cohorts. Second, cardiac biomarkers were not systematically available, and the definition of dysfunction relied on cardiac MRI-derived ejection fraction and global longitudinal strain criteria. Finally, 12-month CMR follow-up was available only in a subset of patients. We compared patients with and without 12-month follow-up and found broadly similar clinical and imaging characteristics, but incomplete long-term follow-up may still have limited the assessment of late-onset and persistent CTRCD.

Conclusion

Early CMR-derived LA volume expansion and phasic strain impairment were associated with 3-month CTRCD during breast cancer therapy. LA measures may complement ventricular assessment when cine CMR is performed, but larger multicenter studies must establish reproducibility, incremental value, and clinically actionable thresholds before these measures are used for risk prediction or treatment decisions.

Ethics Statement

The research reported in this paper adhered to the principles of the Declaration of Helsinki. The study protocol was approved by the institutional ethics committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences (IRB No. NCC2020C-508).

Clinical trial number

Not applicable.

Patient Consent Statement

Written informed consent was obtained from all participants in this study.

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Declarations

Consent for publication

Not Applicable.

Disclosures

None.

Author Contribution

M.D. and S.C. contributed equally to this work and share first authorship. M.D. contributed to data collection, image analysis, statistical analysis, interpretation of the results, and drafted the original manuscript. S.C. contributed to study conceptualization, methodology, supervision, funding acquisition, and manuscript revision. J.L., W.S., J.C., Sh.C., and F.L. contributed to patient recruitment, clinical data collection, and data curation. J.W. supervised the study, provided academic guidance, and critically reviewed and revised the manuscript. All authors reviewed and approved the final manuscript.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy and ethical restrictions but may be made available from the corresponding author upon reasonable request and subject to institutional approval.

References

1. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J Nov. 2022;1(41):4229–361. 10.1093/eurheartj/ehac244.
2. Thavendiranathan P, Negishi T, Somerset E, et al. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. J Am Coll Cardiol. Feb 2021;2(4):392–401. 10.1016/j.jacc.2020.11.020.
3. Huang F, Rankin K, Sooriyakanthan M, et al. Phenotypes of Myocardial Dysfunction on Serial Echocardiography and CMR in Women With Early-Stage Breast Cancer. JACC Cardiovasc Imaging May. 2025;18(5):540–53. 10.1016/j.jcmg.2024.12.010.
4. Thavendiranathan P, Shalmon T, Fan CS, et al. Comprehensive Cardiovascular Magnetic Resonance Tissue Characterization and Cardiotoxicity in Women With Breast Cancer. JAMA Cardiol Jun. 2023;1(6):524–34. 10.1001/jamacardio.2023.0494.
5. Marwick TH, Dewar E, Nolan M, et al. Strain surveillance during chemotherapy to improve cardiovascular outcomes: the SUCCOUR-MRI trial. Eur Heart J Nov. 2024;7(41):4414–24. 10.1093/eurheartj/ehae574.
6. Bana A, Li R, Mehmood Z, et al. CMR Left Ventricular Filling Pressure Exhibits Strong Haemodynamic Relevance and Outperforms Echocardiography in Multimodal Heart Failure Assessment. J Cardiovasc Dev Dis Jun. 2025;27(7). 10.3390/jcdd12070250.
7. Pradella M, Elbaz MSM, Lee DC, et al. A comprehensive evaluation of the left atrium using cardiovascular magnetic resonance. J Cardiovasc Magn Reson Summer. 2025;27(1):101852. 10.1016/j.jocmr.2025.101852.
8. Tahir E, Azar M, Shihada S, et al. Myocardial injury detected by T1 and T2 mapping on CMR predicts subsequent cancer therapy-related cardiac dysfunction in patients with breast cancer treated by epirubicin-based chemotherapy or left-sided RT. Eur Radiol Mar. 2022;32(3):1853–65. 10.1007/s00330-021-08260-7.
9. Liu J, Cao Y, Zhu K, et al. Early evaluation of subclinical cardiotoxicity in patients with lung cancer receiving immune checkpoint inhibitors by cardiovascular magnetic resonance: a prospective observational study. Quant Imaging Med Surg Oct. 2022;12(10):4771–85. 10.21037/qims-22-41.
10. Kouwenberg TW, Grotenhuis HB, Kremer LCM, et al. Early Detection of Acute and Early-Onset Cancer Therapy-Related Cardiac Dysfunction in Children With Cancer Using a Multiparametric Approach: Methodological Aspects of the EARLY Study. Cancer Med. May 2026;15(5):e71904. 10.1002/cam4.71904.
11. Yu C, Peikari M, Labib D, et al. Machine Learning Model Using Pre-Cancer Therapy Cardiac Magnetic Resonance Images to Predict Cancer Therapy-Related Cardiac Dysfunction. JACC Cardiovasc Imaging May. 2026;28. 10.1016/j.jcmg.2026.04.007.
12. Smiseth OA, Baron T, Marino PN, Marwick TH, Flachskampf FA. Imaging of the left atrium: pathophysiology insights and clinical utility. Eur Heart J Cardiovasc Imaging Dec. 2021;18(1):2–13. 10.1093/ehjci/jeab191.
13. Krittayaphong R, Jirataiporn K, Yindeengam A, Songsangjinda T. Cardiac Magnetic Resonance Left Atrial Strain in the Prediction of Death, Ischemic Stroke, and Heart Failure. J Am Heart Assoc. Sep 2024;3(17):e034336. 10.1161/jaha.124.034336.
14. Inoue K, Khan FH, Remme EW, et al. Determinants of left atrial reservoir and pump strain and use of atrial strain for evaluation of left ventricular filling pressure. Eur Heart J Cardiovasc Imaging Dec. 2021;18(1):61–70. 10.1093/ehjci/jeaa415.
15. Wu J, Xiang J, Gu X, et al. Left Atrial Minimum Volume Index at Cardiac MRI Predicts Adverse Outcomes after Acute Myocardial Infarction. Radiology Sep. 2025;316(3):e250078. 10.1148/radiol.250078.

16. Faggiano A, Casas G, Gonzalez-Santorum F, et al. Cardiac magnetic resonance-derived left atrial strain restratifies patients with hypertrophic cardiomyopathy at low-risk of sudden cardiac death. Eur Heart J Cardiovasc Imaging Jun. 2026;1(6):1268–80. 10.1093/ehjci/jeag049.
17. Winkler NE, Anwer S, Rumpf PM, et al. Left atrial pump strain predicts long-term survival after transcatheter aortic valve implantation. Int J Cardiol Jan. 2024;15:395:131403. 10.1016/j.ijcard.2023.131403.
18. Raafs AG, Vos JL, Henkens M, et al. Left Atrial Strain Has Superior Prognostic Value to Ventricular Function and Delayed-Enhancement in Dilated Cardiomyopathy. JACC Cardiovasc Imaging Jun. 2022;15(6):1015–26. 10.1016/j.jcmg.2022.01.016.
19. Aydemir DG, Molwitz I, Beitzen-Heineke A, et al. Right ventricular and biatrial CMR strain analysis detects myocardial functional impairment after breast cancer therapy. Eur Radiol May. 2026;36(5):4037–48. 10.1007/s00330-025-12257-x.
20. Bergamini C, Niro L, Springhetti P, et al. Role of Early Left Atrial Functional Decline in Predicting Cardiotoxicity in HER2 Positive Breast Cancer Patients Treated With Trastuzumab. Cardiovasc Toxicol Jun. 2024;24(6):550–62. 10.1007/s12012-024-09861-6.
21. Lamy J, Spoor DS, Langendijk JA, et al. Cardiac MRI-based Subclinical Cardiac Dysfunction during 2 Years after Breast Cancer Irradiation: The MEDIRAD EARLY-HEART Study. Radiol Cardiothorac Imaging Apr. 2025;7(2):e240231. 10.1148/ryct.240231.
22. Cadour F, Cautela J, Rapacchi S, et al. Cardiac MRI Features and Prognostic Value in Immune Checkpoint Inhibitor-induced Myocarditis. Radiology Jun. 2022;303(3):512–21. 10.1148/radiol.211765.
23. Juhasz V, Quinaglia T, Drobni ZD, et al. Atorvastatin and Myocardial Extracellular Volume Expansion During Anthracycline-Based Chemotherapy. JACC CardioOncol Feb. 2025;7(2):125–37. 10.1016/j.jaccao.2024.11.008.

Figures

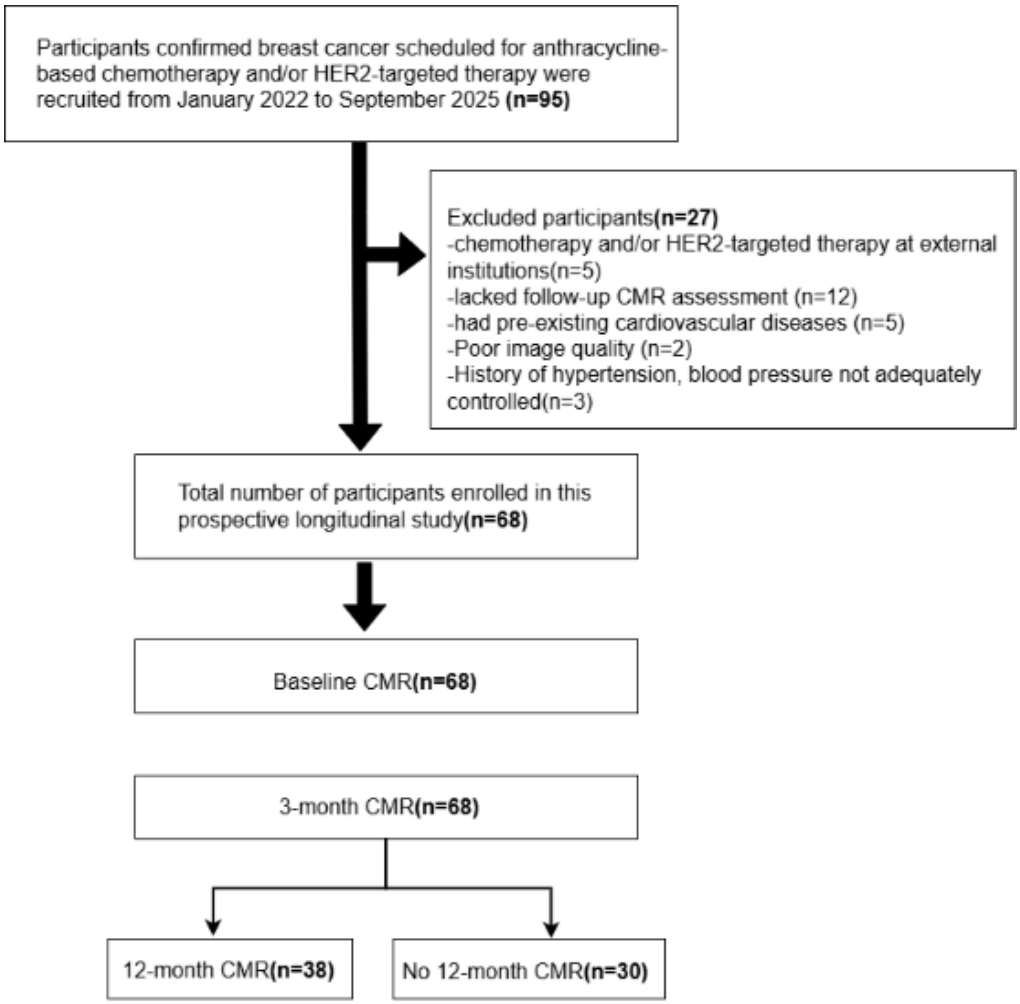

Figure 1

Study flow diagram. Flow diagram showing participant screening, exclusion, and final enrollment in the prospective longitudinal CMR cohort. A total of 95 patients with confirmed breast cancer scheduled to receive anthracycline-based chemotherapy and/or Her2 therapy were screened between January 2022 and September 2025. After excluding 27 participants, 68 patients were enrolled in the final longitudinal cohort and followed with serial CMR examinations.

Abbreviations: CMR, cardiovascular magnetic resonance; HER2, human epidermal growth factor receptor 2.

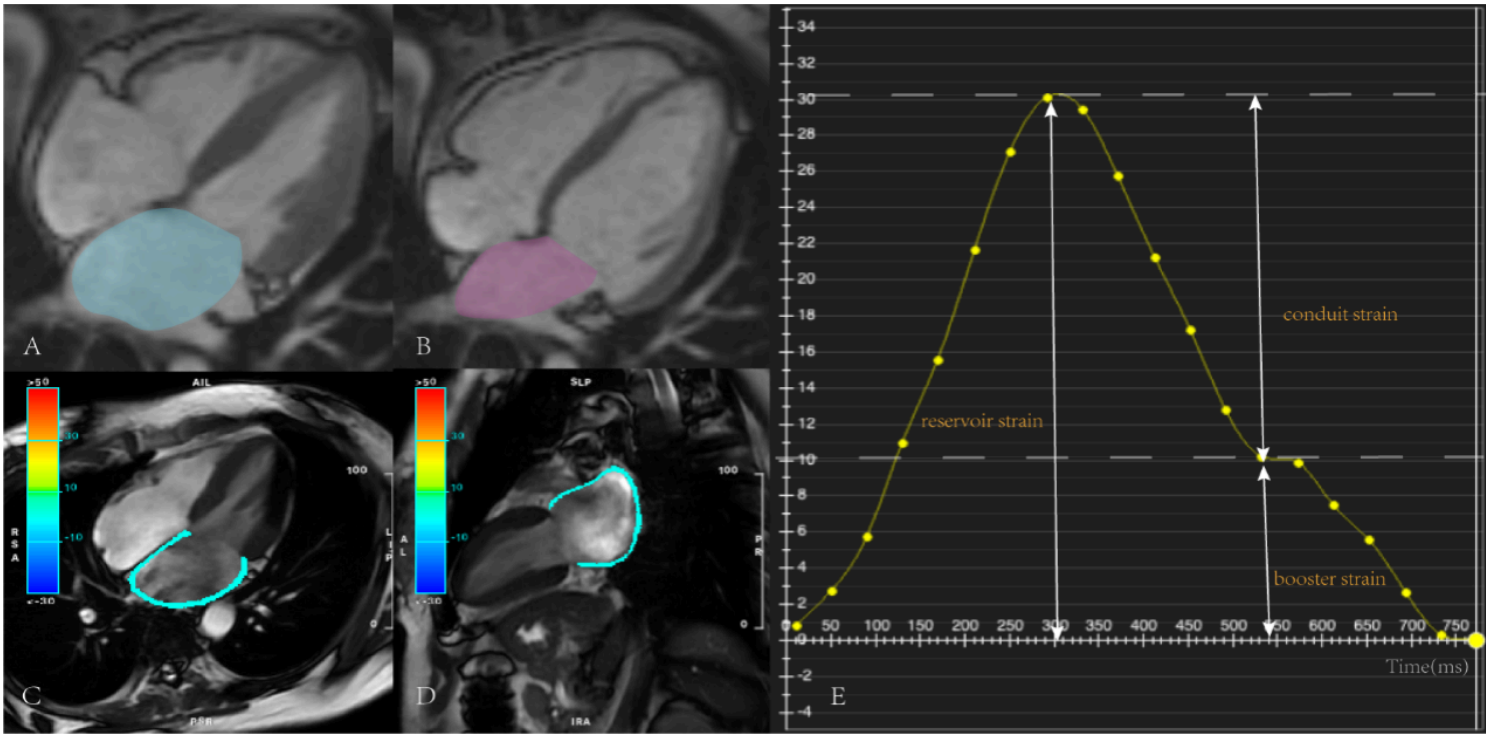

Figure 2

Representative cine cardiovascular magnetic resonance images illustrating left atrial volumetric and deformation analysis. Maximum left atrial volume was measured at the phase of largest atrial size and indexed to body surface area as LAVImax (A). Minimum left atrial volume was measured at the phase of smallest atrial size and indexed as LAVImin (B). Left atrial feature-tracking analysis was performed using standard 4-chamber (C) and 2-chamber (D) long-axis cine views. The left atrial strain curve was used to derive reservoir, conduit, and booster strain components (E). Reservoir strain was defined as peak positive left atrial strain during ventricular systole; conduit strain represented early passive emptying; and booster strain represented active atrial contraction.

Abbreviations: LA, left atrial; LAVImax, maximum left atrial volume index; LAVImin, minimum left atrial volume index.

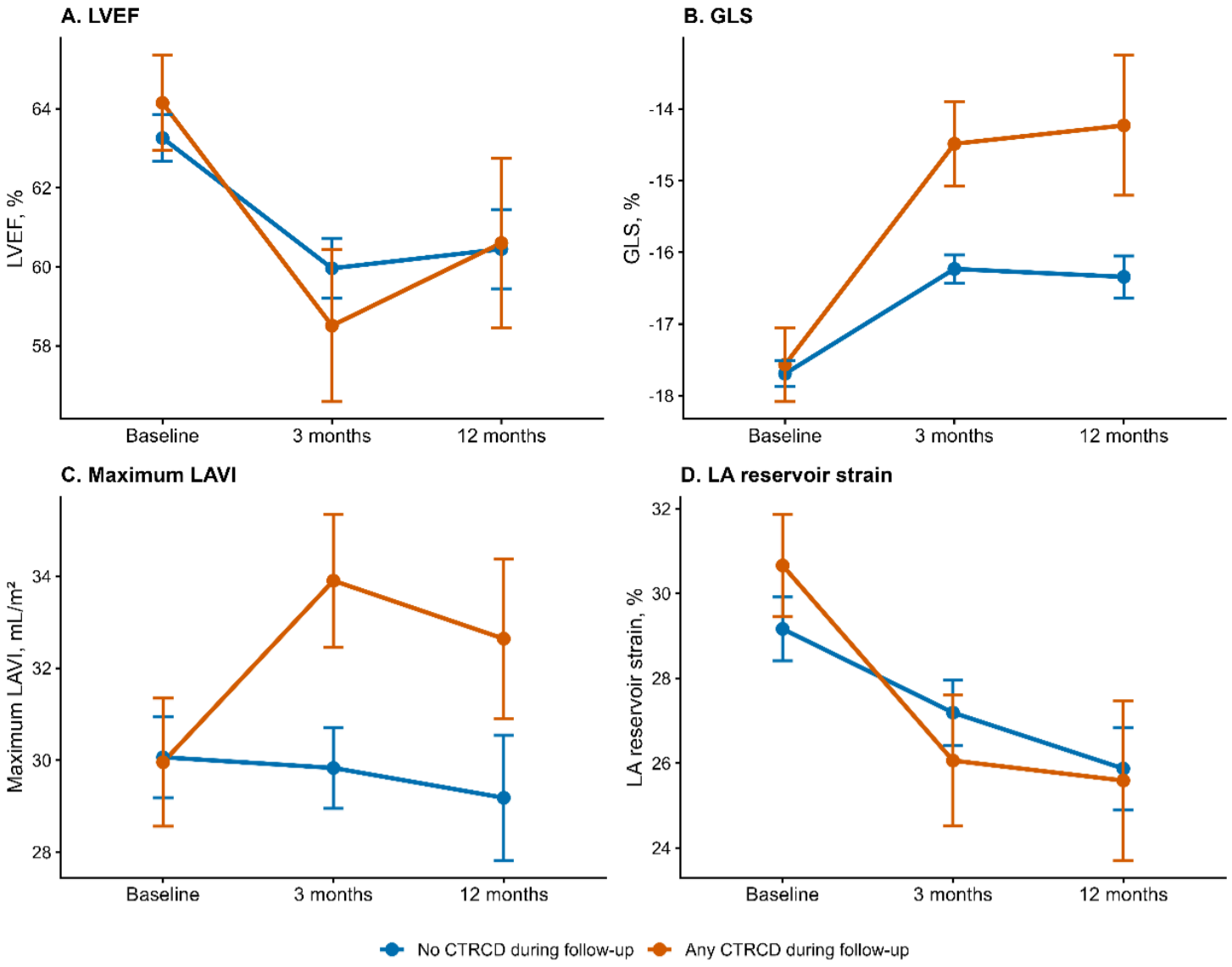

Figure 3

Longitudinal changes in ventricular and atrial CMR parameters according to CTRCD occurrence during follow-up Serial changes in CMR-derived LVEF (A), GLS (B), maximum LAVI (C), and LA reservoir strain (D) are shown from baseline to 3 months and 12 months. Patients were categorized according to whether CTRCD occurred at either 3 or 12 months. Points represent group means, and error bars represent standard errors. Compared with patients without observed CTRCD, patients with any CTRCD during follow-up showed more pronounced worsening in GLS and distinct longitudinal changes in maximum LAVI, with numerically greater early decreases in LA reservoir strain.

Abbreviations: CTRCD, cancer therapy-related cardiac dysfunction; GLS, global longitudinal strain; LA, left atrial; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction.

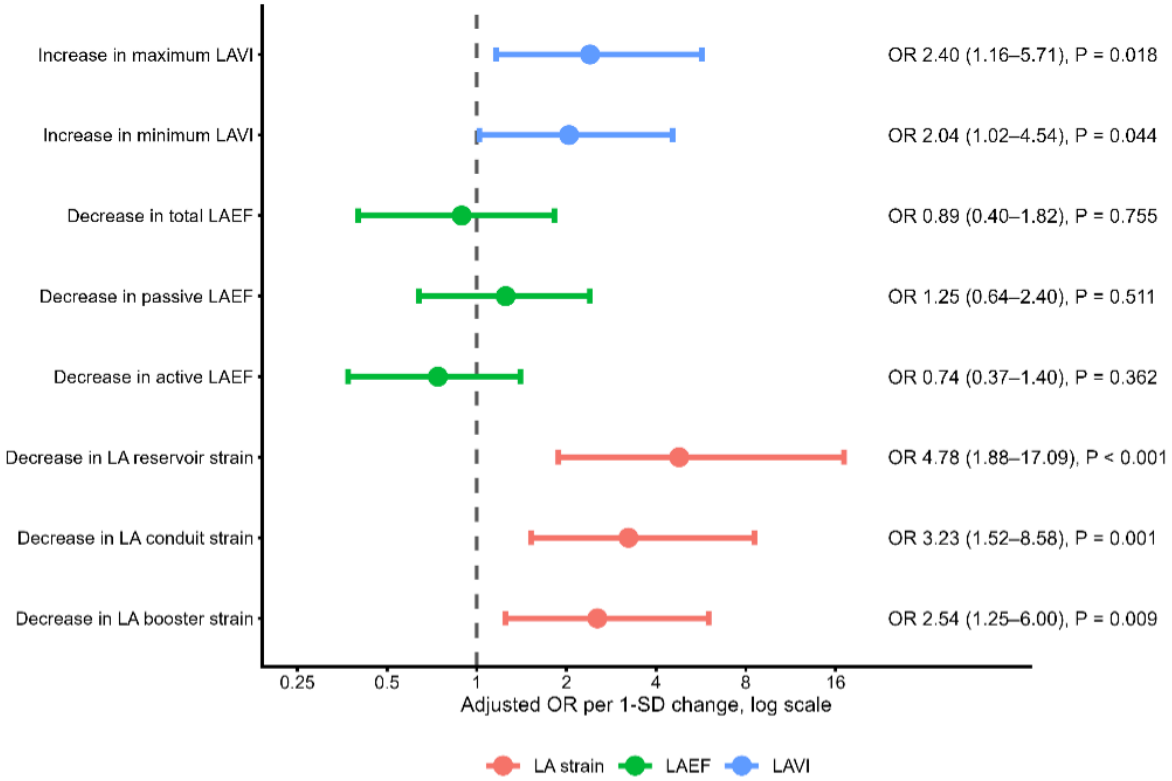

Figure 4

Forest plot of early atrial remodeling markers associated with 3-month CTRCD. Forest plot showed adjusted odds ratios and 95% confidence intervals for the association between changes in left atrial parameters from baseline to 3 months and CTRCD occurring at 3 months. Models used Firth penalized logistic regression and were adjusted for age and baseline CMR-derived LVEF. Odds ratios are reported per 1-SD prespecified adverse change. For LAVI parameters, adverse change was defined as an increase from baseline to 3 months. For LAEF parameters, adverse change was defined as a decrease from baseline to 3 months. For LA strain parameters, adverse change was defined as a decrease in absolute strain magnitude. The x-axis is displayed on a logarithmic scale.

Abbreviations: CTRCD, cancer therapy-related cardiac dysfunction; FDR, false discovery rate; LA, left atrial; LAEF, left atrial emptying fraction; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; OR, odds ratio.

Supplementary Files

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- SupplementaryMaterial.docx