Supplementary Online Content

Thavendiranathan P, Shalmon T, Fan CPS, et al. Comprehensive cardiovascular magnetic resonance tissue characterization and cardiotoxicity in women with breast cancer. *JAMA Cardiol*. Published online April 12, 2023. doi:10.1001/jamacardio.2023.0494

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

eMethods

CMR Acquisition: For assessment of left ventricular (LV) volumes, LV function, and LV strain, a stack of short axis and long axis (2-,3-,4-chamber) balanced steady state free precession (bSSFP) cine images were obtained. Parametric maps were acquired at basal, mid, and apical short axis slice locations. For assessment of edema, T2-mapping was performed using a T2-prepared single-shot multi-echo SSFP technique. For assessment of interstitial fibrosis and edema, T1-mapping was performed using a Modified Look-Locker Inversion Recovery (MOLLI) technique pre- and 15-minutes post-injection of 0.2mmol/kg body weight of gadobutrol (Gadovist, Bayer Healthcare, Berlin, Germany). Inline T1 and T2 maps were generated based on non-rigid motion correction. For assessment of hyperemia (a marker of inflammation) early gadolinium enhancement (EGE) was assessed using T1-weighted turbo spin echo (TSE) sequence pre- and 60-90 seconds post-contrast administration (using inbuilt body receiver coil) in a mid-ventricular short axis slice. For assessment of replacement fibrosis, late gadolinium enhancement (LGE) imaging was performed starting 10 minutes after contrast administration using a 2-dimensional phase sensitive inversion recovery gradient-recalled echo (PSIR GRE) sequence acquiring a short axis stack and 3 long-axis orientations matching the cine bSSFP slice locations.

CMR Analysis: CMR analysis was performed by fellowship trained radiologists blinded to all clinical data and using deidentified images. Assessment of LV volumes, function, and mass (T.S., C.U.), strain (C.P.H.), T1/T2 relaxation times (T.S., C.U.) and EGE/LGE (C.P.H) were performed using CVI[42] (5.13, Circle CVI, Calgary, Canada). LV volumes, function, and mass assessment was based on semi-automated smooth contouring of the endocardium and epicardium with inclusion of trabeculations and papillary muscles into the blood pool. All ventricular volumes and mass were indexed to patient's body surface area calculated using the Mosteller's formula. Myocardial peak

systolic LV global longitudinal and circumferential strains (GLS and GCS respectively) were measured on long- and short-axis bSSFP cine images respectively, using 2D-feature tracking (FT, version 5.9.3). GLS represents the average of the peak systolic strain from the three long-axis views while GCS reflects the average of the peak systolic strain from the entire short-axis stack. All strain data are reported as the percentage of shortening (positive values).

Both, magnitude and PSIR short- and long-axis LGE image data were evaluated visually and classified as LGE present/absent with verification of LGE presence by orthogonal views when possible and by a second reader (P.T.). In patients with LGE, the location and pattern were documented and the extent was quantified (C.P.H) using a threshold-based cutoff (4SD) above visually normal remote myocardium, expressed as percentage of total LV myocardial mass.

For EGE assessment epicardial and endocardial borders were carefully drawn on respective pre- and post-contrast T1-weighted TSE short axis images assessing mean myocardial signal intensities. In addition, a region-of-interest (RoI) was drawn in the dorsal skeletal muscle to assess skeletal muscle signal intensities. Relative enhancement was assessed as the signal intensity increase within the myocardium and skeletal muscle between pre- and post-contrast acquisitions. EGE ratio (EGEr) was calculated as the ratio of relative myocardial enhancement to relative skeletal muscle enhancement[1].

Analyses of T1/T2 maps were performed after carefully examining respective source images for artifacts (off-resonance or motion). Whole slices or segments with artifact were excluded from analysis. Both endo- and epicardial contours were carefully drawn to avoid blood pool and epicardial fat contamination with an additional 10% automated inbound off-set from both contours to further reduce risk of partial volume contamination. For calculation of ECV, large identical blood pool RoI's) were drawn on pre-/post-contrast T1 maps avoiding trabeculations. Myocardial extracellular volume fraction (ECV) was calculated as previously described incorporating same day hematocrit

$(HCT)^2$. Global values for T1, T2, and ECV were calculated as a pixel-weighted average of all 3 short axis slices. To better understand changes in ECV over time, the indexed extracellular volume (iECV) and intracellular volume (iICV) were calculated using the following equations (myocardial density: 1.05g/ml):

- iECV = (ECV% x indexed LV mass) / (myocardial density x 100)
- iICV = ((100%-ECV%) x indexed LV mass) / (myocardial density x 100)

The iECV is a measure of the absolute interstitial space (indexed to BSA) while the iICV is a measure the absolute intracellular space (indexed to BSA).

Serum Biomarkers: Both, high sensitive troponin I (HsTnI) and B-type natriuretic peptide (BNP) measurements were performed using manufacturer's reagents on the ARCHITECT i2000 immunoassay analyzer (Abbott Diagnostics, Abbott Park, IL, USA). The limit of detection for the troponin assay was 2pg/ml with coefficient-of variance (COV) of 5.6% at 46pg/ml and 4.3% at 1400pg/ml. The limit of detection for the BNP assay was 10pg/ml with COV of 8.8% at 67pg/mL and 8.2% at 300pg/ml.

Extended Statistical Analysis

Data visualization: Patient-specific profiles of clinical parameters, serum biomarkers, and CMR variables over follow-up were displayed using spaghetti plots. Given the serial nature of the measures, overall time trends were explored using natural cubic splines with four degrees of freedom in generalized estimating equation (GEE) with identity link functions. The 95% confidence intervals (CIs) were calculated based on robust sandwich estimators. The estimated overall time trends were evaluated using χ^2-tests against the intercept-only models. In addition, we assessed and displayed

patient-specific changes from baseline. The overall time trends of the changes were estimated using fixed-effect models and evaluated using *F*-tests.

eTable 1. Cancer Treatment Regimens and Doses Used in the Included Patients

Regimen	N	Sequence	Doses per administration
FEC-DH	126	3 cycles of FEC every 3 weeks; 3 cycles of docetaxel every 3 weeks; 17-18 cycles of trastuzumab every 3 weeks starting concurrently with docetaxel	5-fluorouracil (500mg/m^2), epirubicin (100mg/m^2), cyclophosphamide (500mg/m^2), docetaxel (100mg/m^2), trastuzumab (8mg/kg loading dose, then 6mg/kg maintenance)
ddAC-TH	7	4 cycles of AC every 2 weeks, followed by 4 cycles of paclitaxel every 2 weeks, 17-18 cycles of trastuzumab starting concurrent with paclitaxel every 2-3 weeks then every 3 weeks after completion of chemotherapy.	Doxorubicin (60mg/m^2), cyclophosphamide (600 mg/m^2), paclitaxel (175 mg/m^2), trastuzumab (8mg/kg loading dose, then 6mg/kg maintenance)
ACTH	4	4 cycles of AC every 3 weeks followed by 4 cycles of docetaxel every 3 weeks; 17-18 cycles of trastuzumab starting concurrently with docetaxel every 3 weeks.	Doxorubicin (60mg/m^2), cyclophosphamide (600 mg/m^2), docetaxel (100 mg/m^2), trastuzumab (8mg/kg loading dose, then 6mg/kg maintenance)

eTable 2. Typical CMR Imaging Parameters

Technique	CINE	EGE	T2-Mapping	T1-Mapping	LGE
Sequence	bSSFP	T1-weighted TSE	T2-prepared single-shot SSFP	MOLLI	PSIR GRE
Receiver Coil	24-Element Body Matrix	Body Coil	24-Element Body Matrix	24-Element Body Matrix	24-Element Body Matrix
Bandwidth	930 Hz/Px	310 Hz/Px	930 Hz/Px	1028 Hz/Px	140 Hz/Px
Breath-hold	Yes	Yes	Yes	Yes	Yes
Parallel Imaging	*GRAPPA; R*=2	*NONE*	*GRAPPA; R*=2	*GRAPPA; R*=2	*GRAPPA; R*=2
In-plane resolution (mm)	1.6 x 1.6	1.3 x 1.3	1.9 x 1.9	1.4 x 1.4	1.4 x 1.4
Slice thickness (mm)	8	10	8	8	8
TR / TE / (ms)	2.8/1.2	eff. TR=1RR/34	2.6/1.1	2.7/1.1	8.3/3.3
Flip angle (˚)	65	180	35	35	25
Miscellaneous	Temporal resolution: 36ms (13 lines/segment)	Turbofactor: 12; sup/inf saturation bands	eff. TR=3RR (4RR with HR>80bpm) T2 prep 0/24/55ms	Inversion Groups: 5(3)3 (pre-GBCA), 4(1)3(1)2 (post-GBCA) Min TI: 120ms; TI increment: 80ms	Manual TI optimization using TI scout

EGE, early gadolinium enhancement; LGE, late gadolinium enhancement; bSSFP, balanced steady state free precession; TSE, turbo spin echo; SSFP, steady state free precession; MOLLI, modified lock locker inversion recovery; PSIR, phase sensitive inversion recovery; sGRE, spoiled gradient recalled echo; Hz/Px, Herz/Pixel; GRAPPA, generalized autocalibrating partial parallel acquisition; TR, repetition time; TE, echo time; HR, heart rate; GBCA, gadolinium-based contrast agent; TI, inversion time.

eTable 3. Frequency of Measurements That Were Not Feasible or Available and Hence Imputed at the Various Time Points

This was mainly driven by patients not having a CMR due to their choice or inability to have CMR (e.g. implantation of MRI-unsafe breast expanders during cancer treatment). Furthermore, particularly for ECV and EGE measurements, additional missing data was due to patients refusing repeated GBCA administration at all or select visits. Final reason for missing data pertains to poor image quality or artifacts precluding accurate assessment (see **eTable 5**).Total sample size is 136 patients.

	Timepoint				
Variables	**1**	**2**	**3**	**4**	**6**
Native Global T1	0 (0.0%)	1 (0.7%)	8 (5.9%)	12 (8.8%)	3 (2.2%)
Global T2	0 (0.0%)	1 (0.7%)	8 (5.9%)	12 (8.8%)	3 (2.2%)
Global ECV	9 (6.6%)	12 (8.8%)	17 (12.5%)	19 (14.0%)	16 (11.8%)
EGEr	12 (8.8%)	16 (11.8%)	28 (20.6%)	27 (19.9%)	21 (15.4%)
LVEF	0 (0.0%)	1 (0.7%)	8 (5.9%)	9 (6.6%)	0 (0.0%)
LVEDV	0 (0.0%)	1 (0.7%)	8 (5.9%)	9 (6.6%)	0 (0.0%)
LVESV	0 (0.0%)	1 (0.7%)	8 (5.9%)	9 (6.6%)	0 (0.0%)
GLS	0 (0.0%)	1 (0.7%)	8 (5.9%)	9 (6.6%)	0 (0.0%)
GCS	1 (0.7%)	1 (0.7%)	8 (5.9%)	9 (6.6%)	0 (0.0%)

EGEr = early gadolinium enhancement ratio; ECV=extracellular volume fraction; LVEF=left ventricular ejection fraction; LVEDV=left ventricular end-diastolic volume; LVESV=left ventricular end-systolic volume; GLS=global longitudinal strain; GCS=global circumferential strain.

eTable 4. Cancer Treatment Summary

	Entire Cohort (N=136)	**No CTRCD (N=99)**	**CTRCD (N=37)**	***p***
Mean Doxorubicin equivalent dose (mg/m^2)*	204.9 ± 12.5	204.3 ± 12.8	203.0 ± 11.8	0.57
Doxorubicin, n (%)	10 (7%)	7 (7%)	3 (8%)	0.99
Epirubicin, n (%)	126 (93%)	92 (93%)	34 (92%)	
Pertuzumab, n (%)	21 (15%)	16 (16%)	5 (14%)	0.80
T-DM1, n (%)	2 (1%)	2 (2%)	0 (0%)	0.99
Adjuvant Radiation, n (%)	120 (88%)	86 (87%)	34 (92%)	0.54
Left : Right sided, n (%)	72:48	50:36	22:12	0.54
Mean heart radiation dose (cGy)*	170.8 ± 75.9	165.5 ± 75.2	184.0 ± 77.1	0.25

CTRCD, cancer therapy related cardiac dysfunction; T-DM1, trastuzumab emtansine; *reported as mean ± SD

eTable 5. Percentage of Segments Among Evaluable Segments That Were Excluded for the Various CMR Tissue Biomarker Measurements Due to Artifacts

Evaluable segments are calculated as total number of patients with the measurement obtained multipled by 16 segments per patient.

	Timepoint				
Variables	**1**	**2**	**3**	**4**	**6**
Native-T1	0.5%	0.5%	0.0%	2.6%	2.2%
T2	0.9%	0.6%	0.4%	2.4%	2.8%
ECV*	0.2%	1.4%	0.0%	0.0%	0.0%

ECV=extracellular volume fraction; *note: at some timepoints the proportion of unevaluable segments for ECV is reported as lower than native-T1despite T1 being a part of the ECV calculation. This is due to the fact that this table focuses on proportion of segments that were not evulable amongst evaluable segments (i.e, not measurable due to poor image quality). Some of our patients at certain time points refused contrast and hence an ECV map could not be generated. As a consequence this subset of patients did not have evaluable ECV segments while they would have had evaluable native-T1 segments. Therefore, the denominator is not the same for T1 and ECV. Out of 136 patients the number who refused contrast at each time point were 8, 7, 9, 10, 16 respectively. At timepoints 1, 3, 4, and 6 patients who refused contrast were different from those who had poor quality native T1 values that could not be analyzed.

eTable 6. CMR Tissue and Serum Biomarkers Over Follow-up Period for the Whole Cohort and Dichotomized by CTRCD Status
All values are reported as mean ± standard deviation.

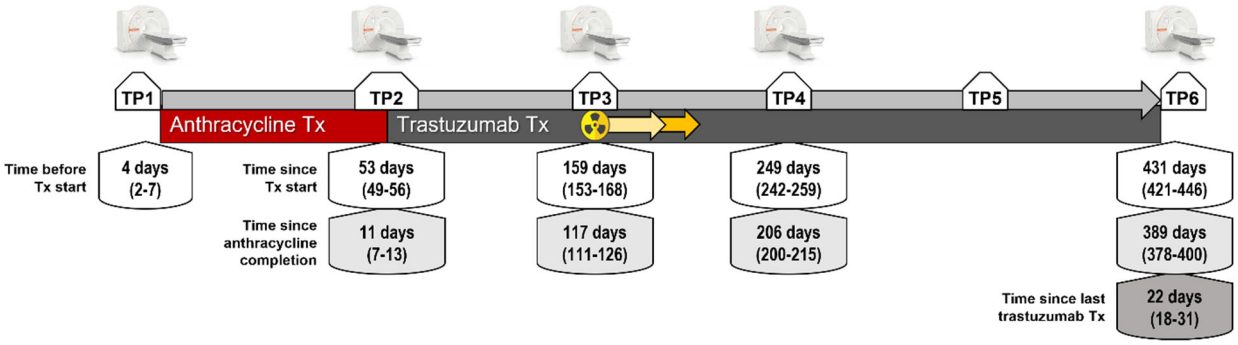
	CTRCD Status	Timepoint 1	Timepoint 2	Timepoint 3	Timepoint 4	Timepoint 6
Relative Myocardial Enhancement (%)	All	46.4 ± 16.9	56.3 ± 18.6	54.2 ± 15.9	46.5 ± 15.8	46.0 ± 16.8
	CTRCD	49.8 ± 18.3	61.7 ± 18.1	55.6 ± 18.7	49.9 ± 14.6	47.6 ± 16.6
	No CTRCD	45.0 ± 16.2	54.1 ± 18.5	53.7 ± 14.9	45.2 ± 16.1	45.4 ± 16.9
Relative Skeletal Muscle Enhancement (%)	All	24.2 ± 10.8	27.7 ± 10.6	29.5 ± 11.9	24.7 ± 10.0	22.8 ± 9.2
	CTRCD	25.4 ± 12.2	28.1 ± 11.7	28.4 ± 13.6	25.5 ± 9.7	23.5 ± 9.5
	No CTRCD	23.7 ± 10.2	27.5 ± 10.3	29.8 ± 11.3	24.4 ± 10.1	22.5 ± 9.2
Early Gadolinium Enhancement Ratio	All	2.2 ± 0.9	2.3 ± 0.9	2.1 ± 1.2	2.1 ± 1.3	2.3 ± 1.2
	CTRCD	2.3 ± 1.0	2.5 ± 1.1	2.2 ± 0.9	2.0 ± 0.8	2.3 ± 1.3
	No CTRCD	2.1 ± 0.9	2.2 ± 0.9	2.0 ± 1.3	2.2 ± 1.4	2.3 ± 1.2
T1 (ms)	All	1011.9 ± 26.4	1026.4 ± 29.0	1034.9 ± 28.3	1018.2 ± 27.6	1016.1 ± 30.9
	CTRCD	1009.0 ± 28.5	1023.5 ± 27.7	1037.7 ± 30.3	1018.5 ± 28.4	1019.4 ± 35.2
	No CTRCD	1013.0 ± 25.6	1027.5 ± 29.6	1033.9 ± 27.6	1018.1 ± 27.4	1014.8 ± 29.2
T2 (ms)	All	51.4 ± 2.2	52.5 ± 2.2	52.6 ± 2.2	51.5 ± 2.1	51.4 ± 2.2
	CTRCD	51.0 ± 2.3	52.0 ± 2.6	52.5 ± 2.2	51.0 ± 2.3	51.6 ± 2.3
	No CTRCD	51.5 ± 2.1	52.7 ± 2.1	52.7 ± 2.2	51.7 ± 1.9	51.3 ± 2.1
ECV (%)	All	25.3 ± 2.4	26.7 ± 2.7	26.8 ± 2.6	25.4 ± 2.5	25.3 ± 2.6
	CTRCD	24.9 ± 2.6	26.4 ± 3.0	26.3 ± 3.2	25.2 ± 2.9	25.5 ± 3.2
	No CTRCD	25.4 ± 2.4	26.8 ± 2.6	27.0 ± 2.4	25.5 ± 2.3	25.3 ± 2.4
iECV ml/m^2	All	8.7 ± 1.7	9.3 ± 1.9	9.6 ± 1.9	9.0 ± 1.8	8.8 ± 1.8
	CTRCD	8.4 ± 1.7	9.3 ± 1.7	9.6 ± 2.0	8.8 ± 2.0	9.0 ± 1.7
	No CTRCD	8.8 ± 1.7	9.3 ± 2.0	9.6 ± 1.8	9.0 ± 1.7	8.8 ± 1.9
iICV ml/m^2	All	25.6 ± 4.5	25.5 ± 3.8	26.3 ± 4.1	26.4 ± 4.8	26.1 ± 4.9
	CTRCD	25.2 ± 3.8	25.8 ± 3.9	26.7 ± 3.9	26.4 ± 5.5	26.5 ± 5.4
	No CTRCD	25.8 ± 4.7	25.4 ± 3.8	26.1 ± 4.2	26.5 ± 4.5	25.9 ± 4.6
HsTnI, ng/L	All	3 ± 4	10 ± 9	8 ± 14	5 ± 8	3 ± 6
	CTRCD	2 ± 1	11 ± 12	8 ± 18	4 ± 2	3 ± 1

	No CTRCD	4 ± 4	9 ± 8	8 ± 13	5 ± 9	4 ± 7
BNP pg/ml	All	21 ± 14	26 ± 25	18 ± 13	18 ± 16	20 ± 16
	CTRCD	21 ± 16	23 ± 20	19 ± 15	21 ± 24	24 ± 23
	No CTRCD	21 ± 13	27 ± 27	18 ± 13	17 ± 12	18 ± 12
LVmass index (g/m2)	All	35.9 ± 6.0	36.2 ± 5.6	37.6 ± 5.9	37.1 ± 6.6	36.4 ± 6.6
	CTRCD	35.2 ± 5.4	36.3 ± 5.5	37.9 ± 5.5	37.1 ± 7.3	37.1 ± 6.9
	No CTRCD	36.2 ± 6.2	36.2 ± 5.7	37.5 ± 6.1	37.1 ± 6.4	36.2 ± 6.5

CTRCD, cancer therapy related cardiac dysfunction; BNP, B-type natriuretic peptide; HsTnI, high sensitivity troponin I

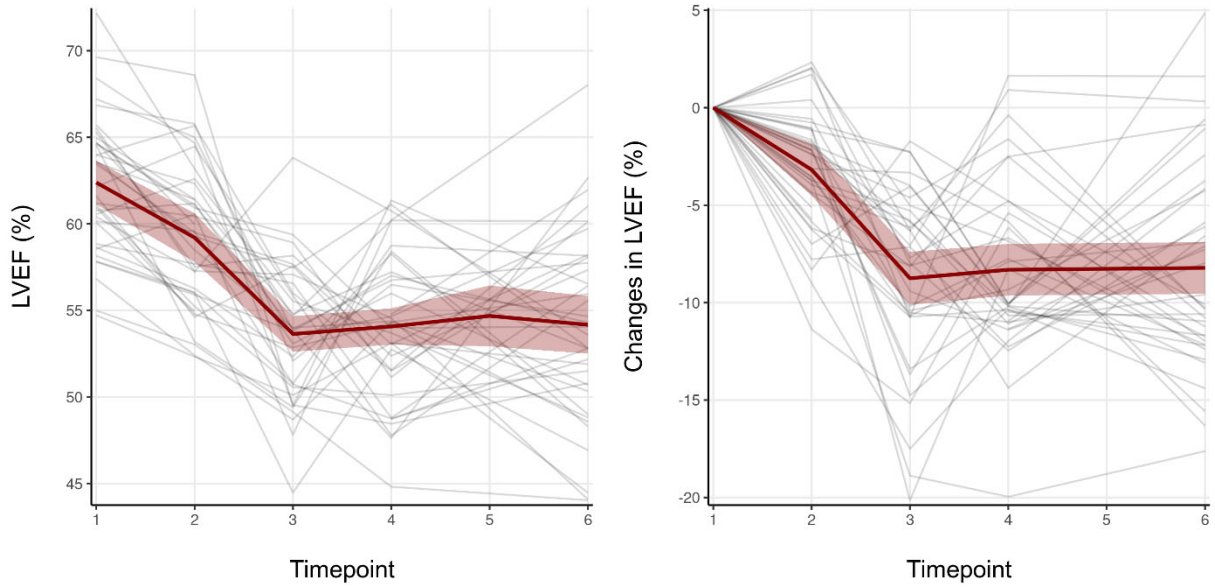
eFigure 1. CMR Imaging Time Points and Relationship to Cancer Treatment

The figure describes the sequential cancer treatment regimens and time (median [inter-quartile range] in days) of imaging in relationship to start and completion of anthracycline therapy and completion of trastuzumab therapy. Tx=treatment. TP=time point. TP1=pre-anthracycline, TP2=post anthracycline but pre-trastuzumab, TP3=3 months post-trastuzumab initiation, TP4=6 months post-post trastuzumab initiation, TP6=post-trastuzumab completion. TP5=9 months post-trastuzumab initiation but a CMR study was not performed at this time point.



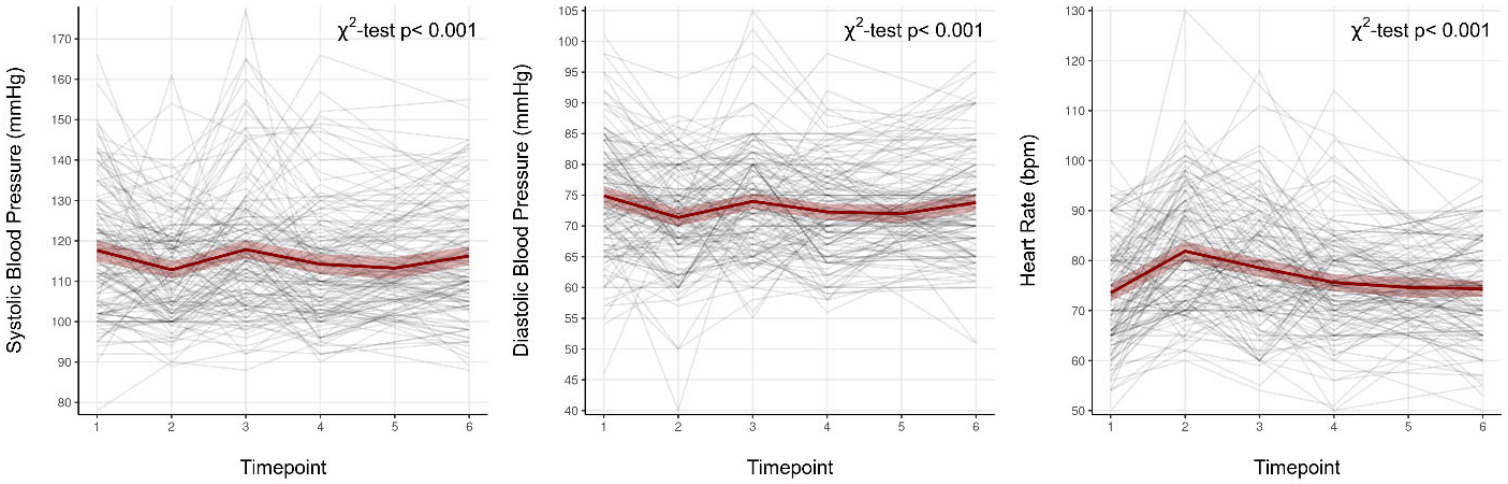
eFigure 2. Absolute Left Ventricular Ejection Fraction (LVEF) (left panel) and Its Change From Baseline (right panel) at Each Study Visit in the 37 Patients Who Developed CTRCD

Individual patient trajectories and the overall trajectories (red line) with corresponding 95% CI (red shade) are shown. See eFigure 1 for definition of the timepoints (x-axis).



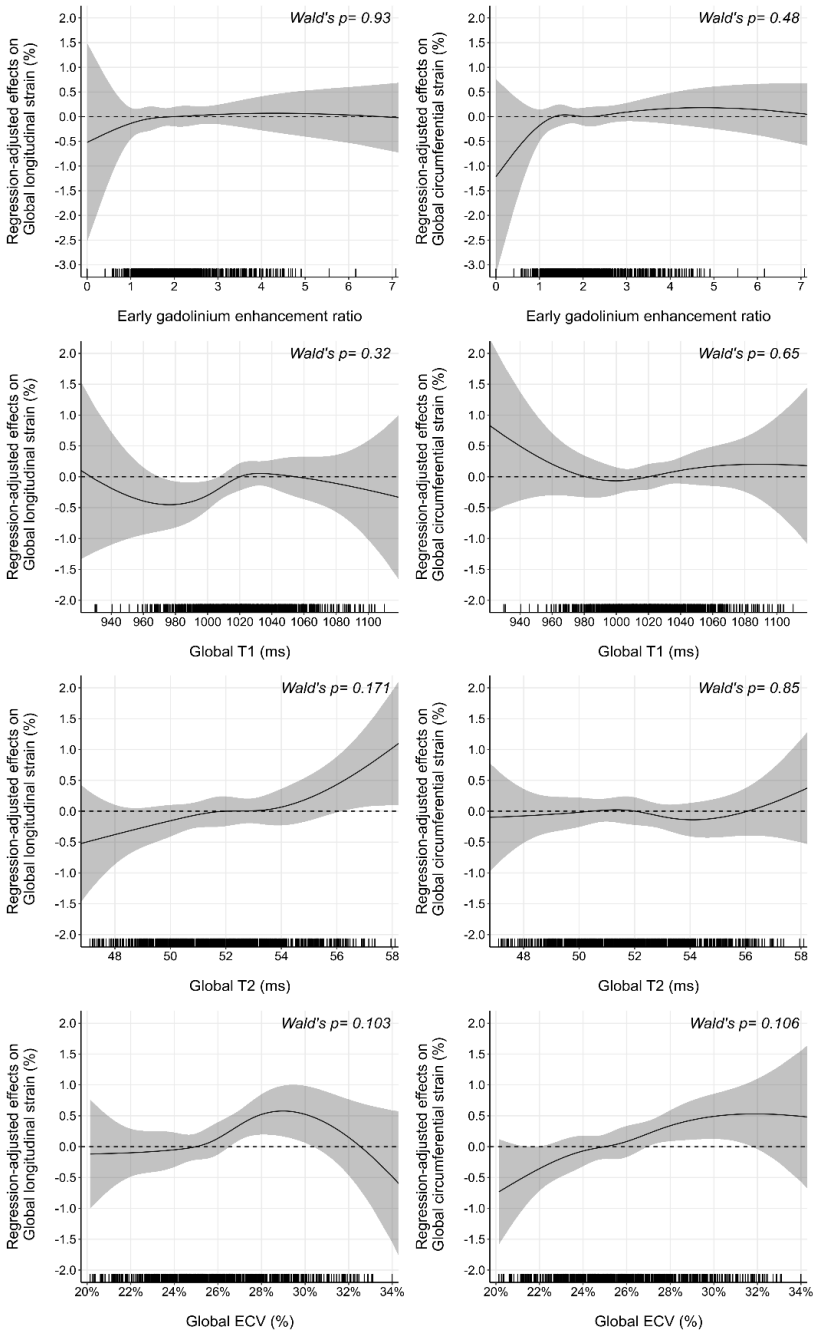
eFigure 3. Blood Pressure and Heart Rate at Each Study Visit

Individual patient trajectories and overall trajectories (red line) with corresponding 95% CI (red shade) are shown. The p-values assess if the estimated trajectory is different from a horizontal line (i.e., no changes from baseline). Post anthracycline there was a reduction in systolic and diastolic blood pressure and an increase in heart rate which then returned to baseline in follow-up. See **eFigure 1** for definition of the timepoints (x-axis).



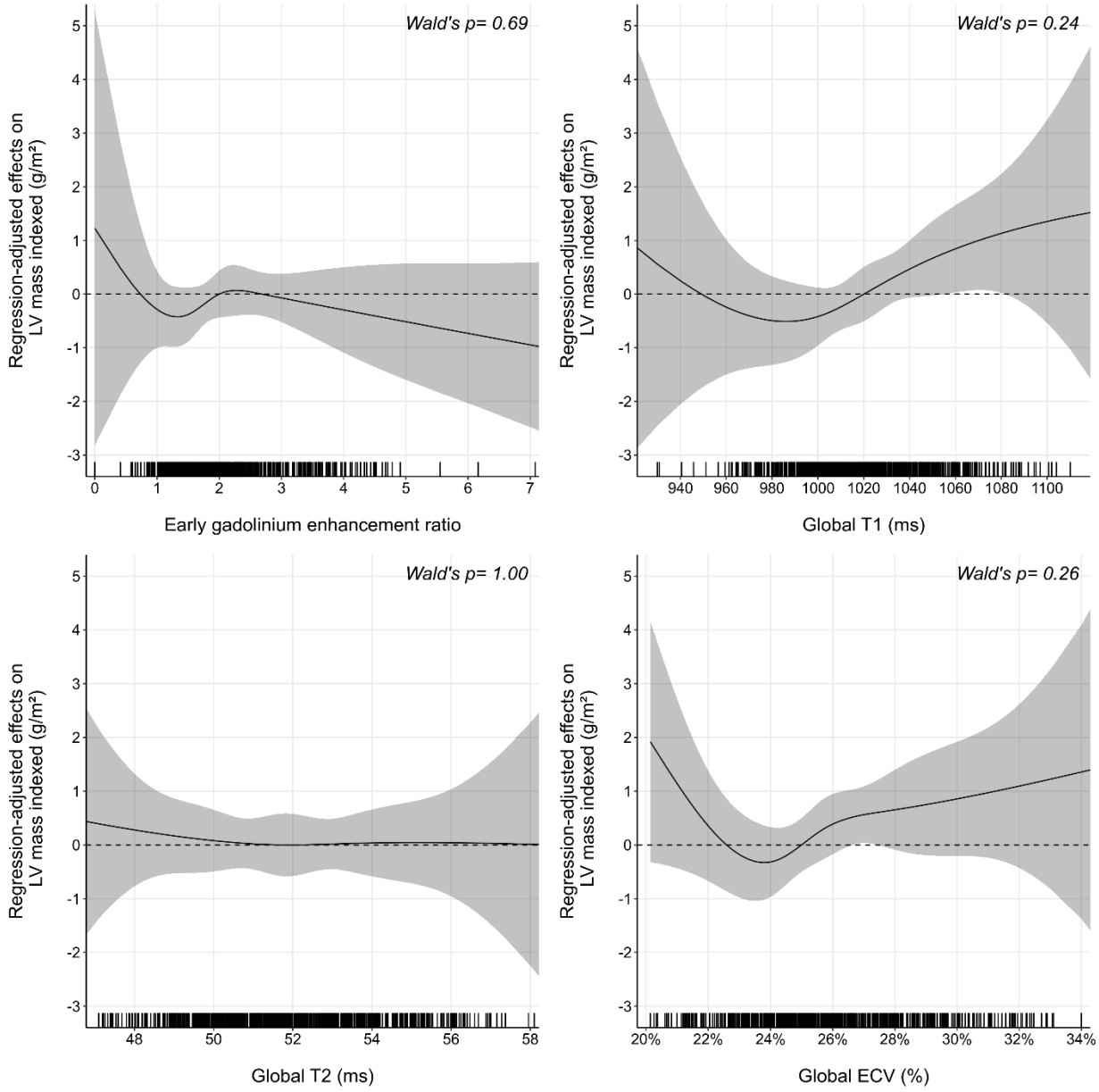
eFigure 4. Regression-Adjusted Nonlinear Concurrent Associations Between CMR Tissue Biomarkers and Myocardial Strain

The y-axes represent the regression-adjusted effects of the various tissue biomarkers (x-axes) on myocardial strain. See **Figure 3** (main manuscript) or **eFigure 5** for explanation of interpretation of the graphs. *P*-values <0.05 suggest statistically significant association. The black tick marks on the x-axis represent individual observed measurements. Note: Strain was considered as an absolute value.



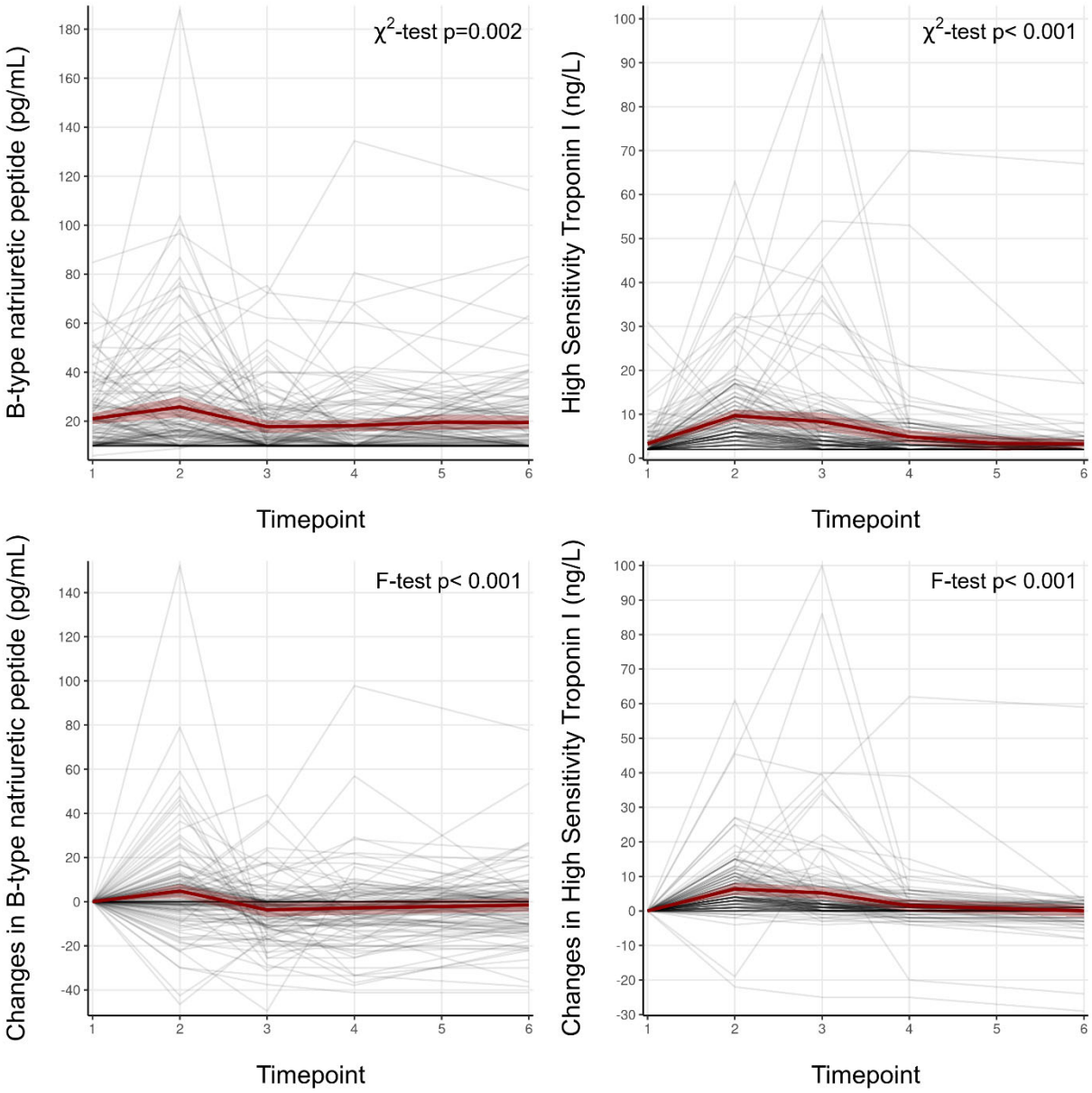
eFigure 5. Regression-Adjusted Nonlinear Concurrent Association Between CMR Tissue Biomarkers and LV Mass

The y-axes represent the regression-adjusted effects of the various tissue biomarkers (x-axis) on LV mass index (g/m^2). The gray shades represent the 95% CI. For example, an elevation of 100 ms in T1 from 1000 ms increased the LV mass on average by 1.486 (95% CI = [0.485, 2.486]) g/m^2. *P*-values <0.05 suggest statistically significant associations. The black tick marks on the x-axis represent individual observed measurements.



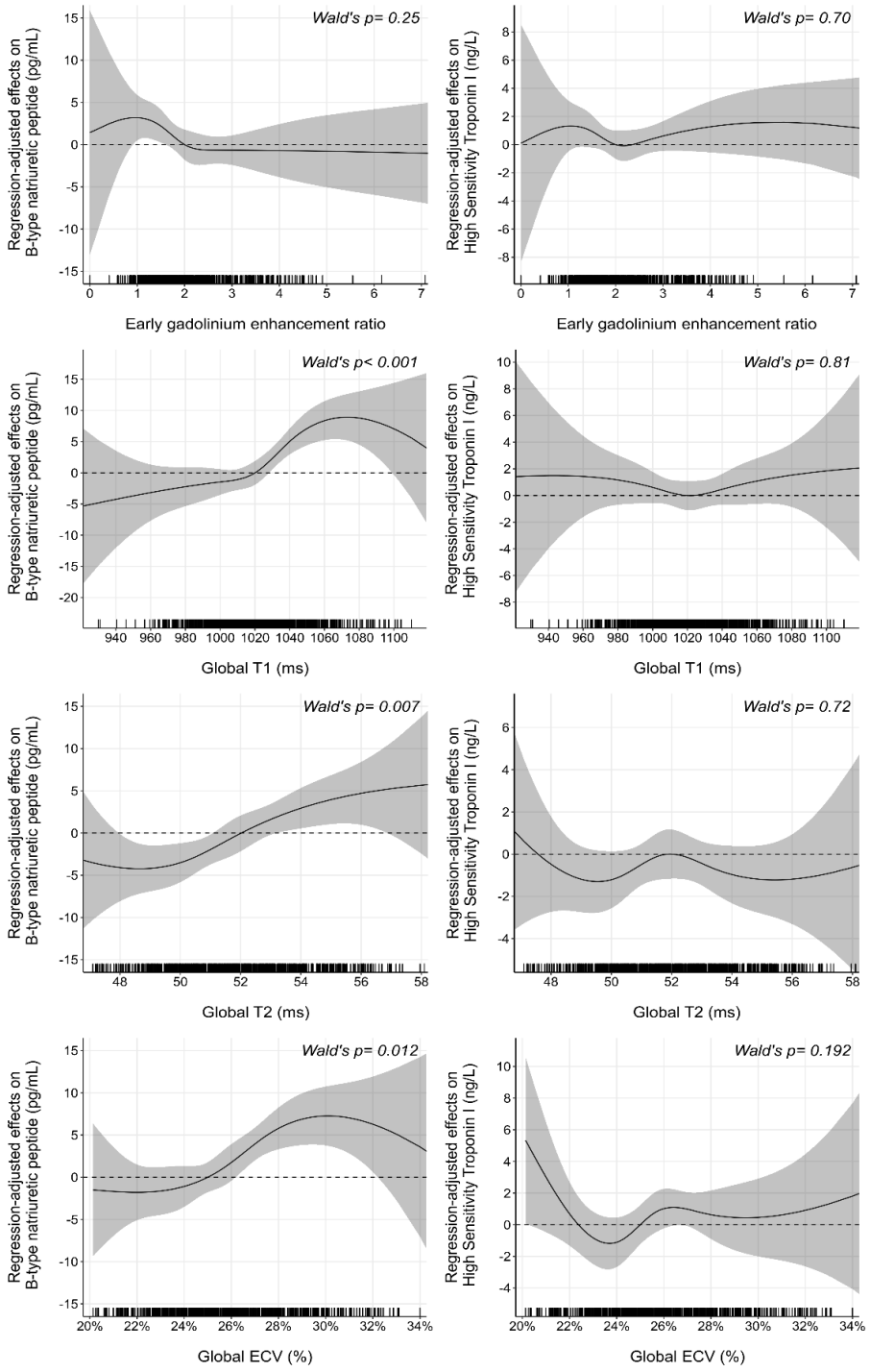
eFigure 6. Absolute BNP and Troponin at Each Study Visit (top two panels) and Changes Compared to Baseline (bottom two panels)

The estimated overall trajectory (red line) and its 95% CI (red shade) are shown with individual patient trajectories in the background. The p values assess if the estimated trajectory is different from a horizontal line (i.e., no changes from baseline). See **eFigure 1** for definition of the timepoints.



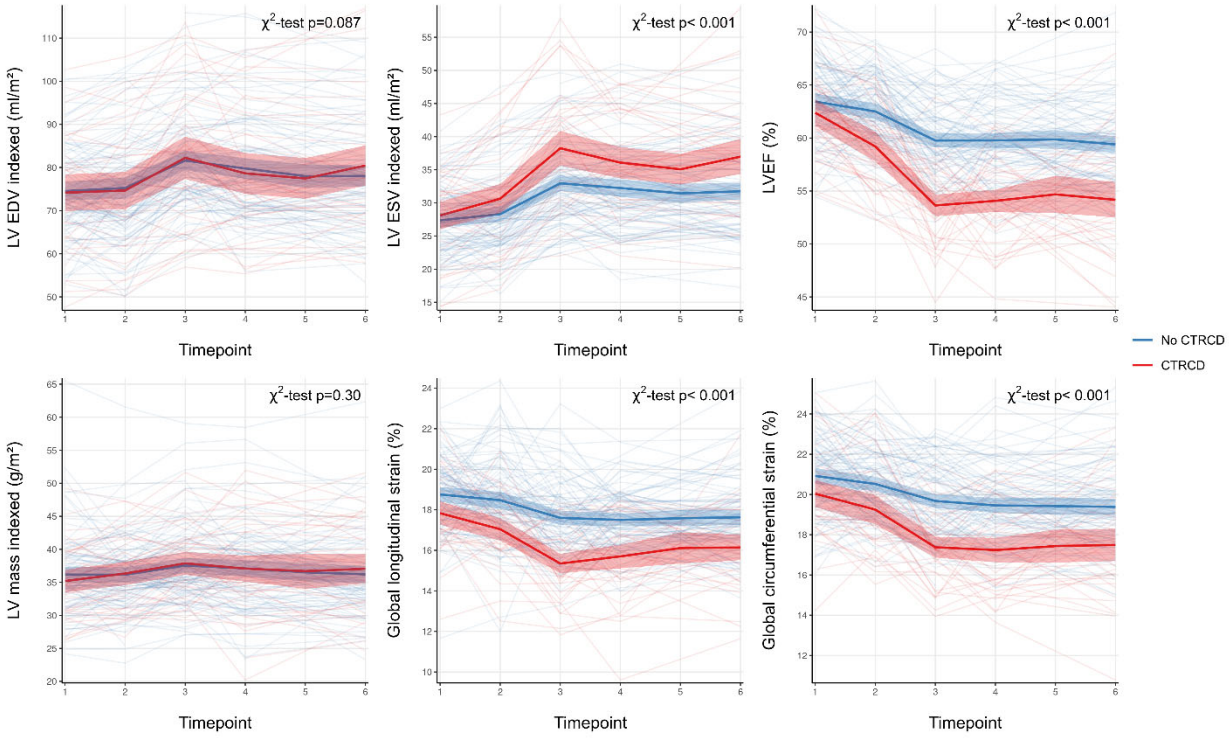
eFigure 7. Regression-Adjusted Nonlinear Concurrent Associations Between CMR Tissue Biomarkers and B-type Natriuretic Peptide (BNP) and High Sensitivity Troponin I

The y-axes represent the regression-adjusted effects of the various tissue biomarkers (x-axis) on B-type natriuretic peptides (left panels) or high sensitivity troponin I (right panels). The gray shades represent the 95% CI. *P*-values <0.05 suggest statistically significant associations. See **eFigure 5** for explanation of interpretation of the graphs.



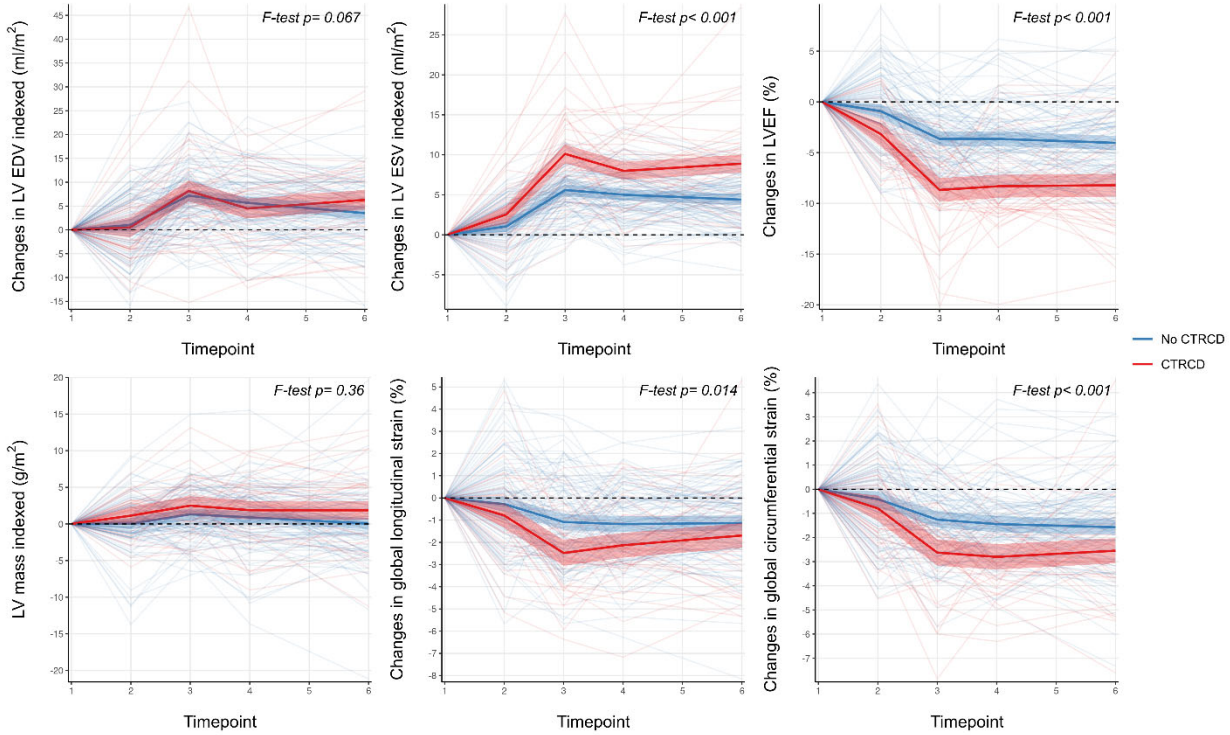
eFigure 8. CMR Left Ventricular Volumes, Mass, and Function at Each Study Visit by the Development of CTRCD During Follow-up

The estimated trajectory (red line for patients with CTRCD and blue line for patients without CTRCD) and its 95% CI (red and blue shades) are shown with individual patient trajectories in the background. P-values assess if the trajectories differ between patients with and without CTRCD. See **eFigure 1** for definition of the timepoints on the x-axis.



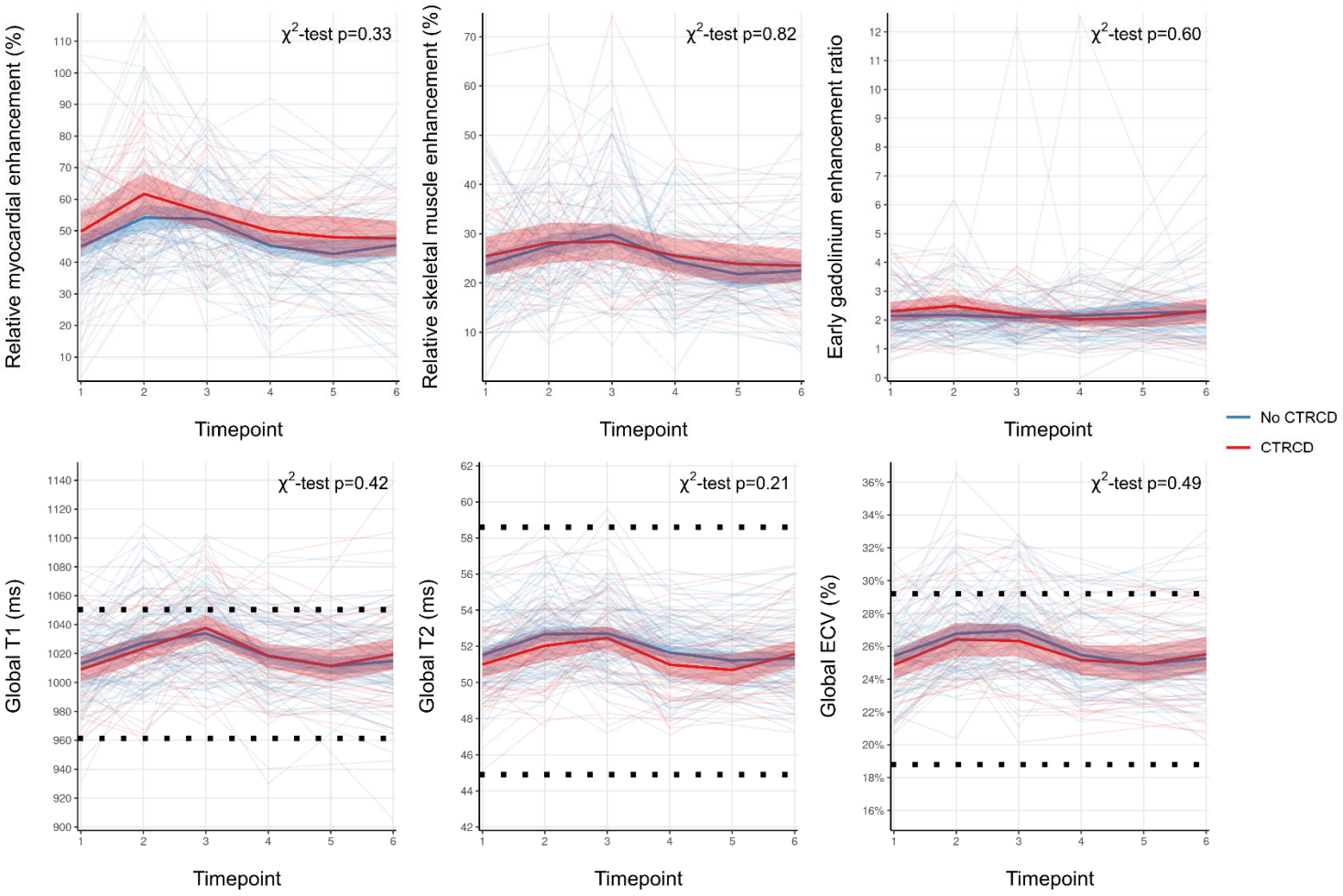
eFigure 9. Changes Compared to Baseline in Indexed LVEDV, LVESV, and LV Mass, LVEF, Global Longitudinal Strain and Global Circumferential Strain at Each Study Visit Grouped by the Development of CTRCD During Follow-up

The estimated trajectory (red line for patients with CTRCD and blue line for patients without CTRCD) and its 95% CI (red and blue shades) are shown with individual patient trajectories in the background. P-values assess if the trajectories of change differ between patients with and without CTRCD. See **eFigure 1** for definition of the timepoints on the x-axis.



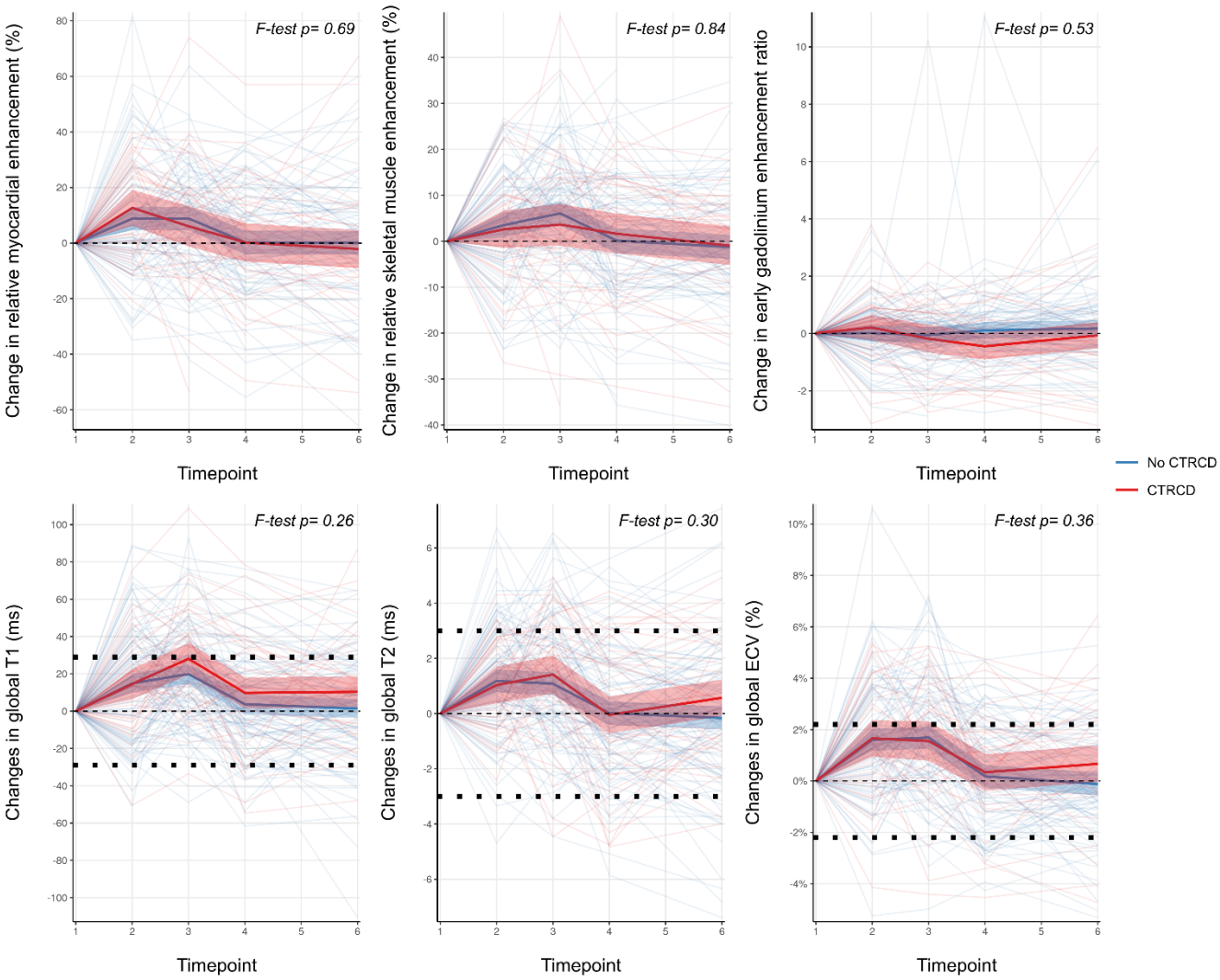
eFigure 10. CMR Tissue Biomarkers at Each Study Visit Grouped by the Development of CTRCD During Follow-up

The estimated trajectory (red line for patients with CTRCD and blue line for patients without CTRCD) and its 95% CI (red and blue shades) are shown with individual patient trajectories in the background. P-values assess if the trajectories differ between patients with and without CTRCD. Normal ranges for same CMR sequences and scanner from our prior publication[14] are provided as dashed lines for T1, T2, and ECV. See **eFigure 1** for definition of the timepoints on the x-axis.



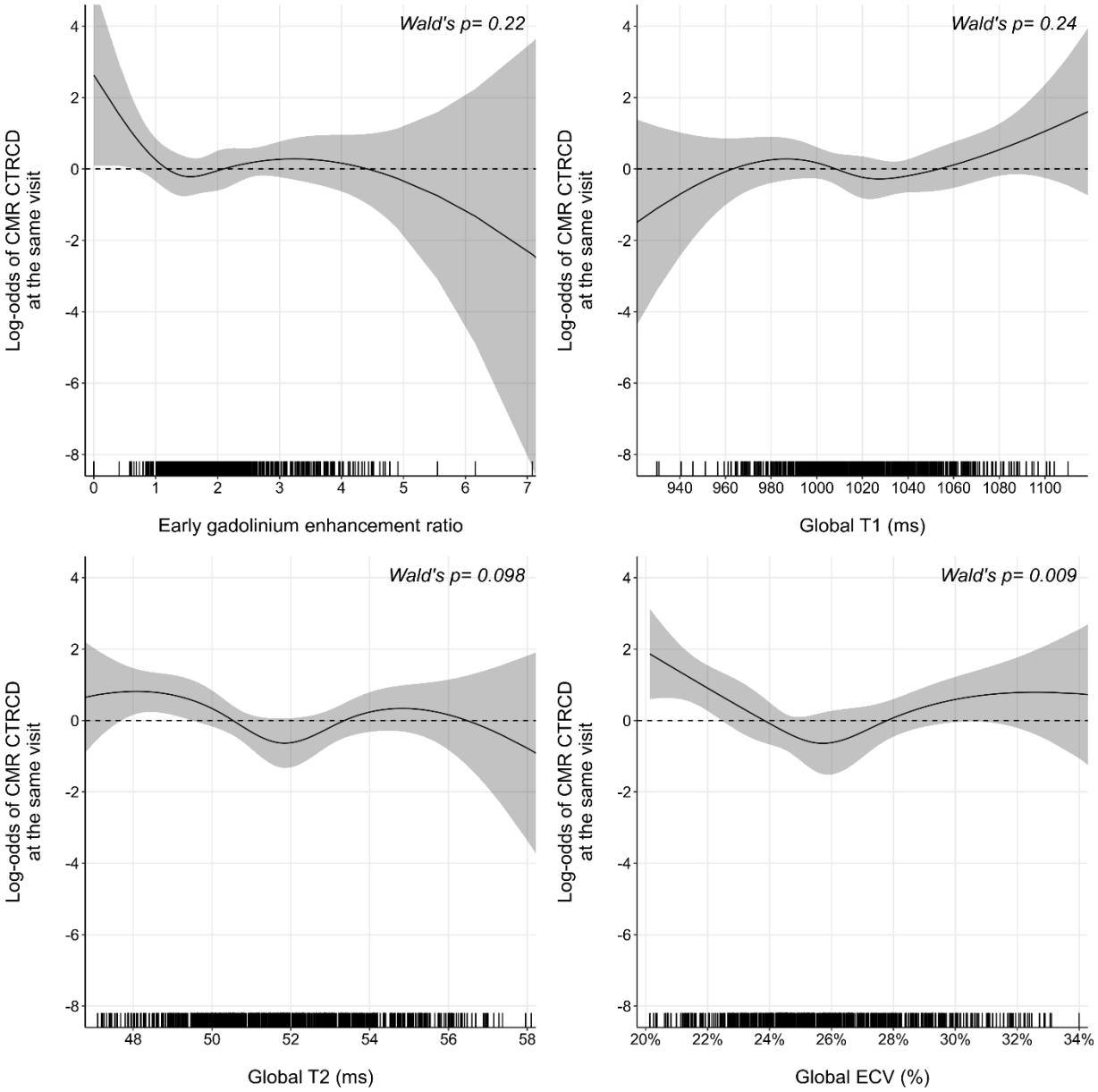
eFigure 11. Changes Compared to Baseline in EGE Measures, T1, T2, and ECV at Each Study Visit Grouped by the Development of CTRCD During Follow-up

The estimated trajectory (red line for patients with CTRCD and blue line for patients without CTRCD) and its 95% CI (red and blue shades) are shown with individual patient trajectories in the background. P-values assess if the trajectories of change differ between patients with and without CTRCD. Expected temporal variability for T1, T2, and ECV from the same CMR sequences and scanner from our prior publication[8] is provided as thick dashed lines. See **eFigure 1** for definition of the timepoints on the x-axis.



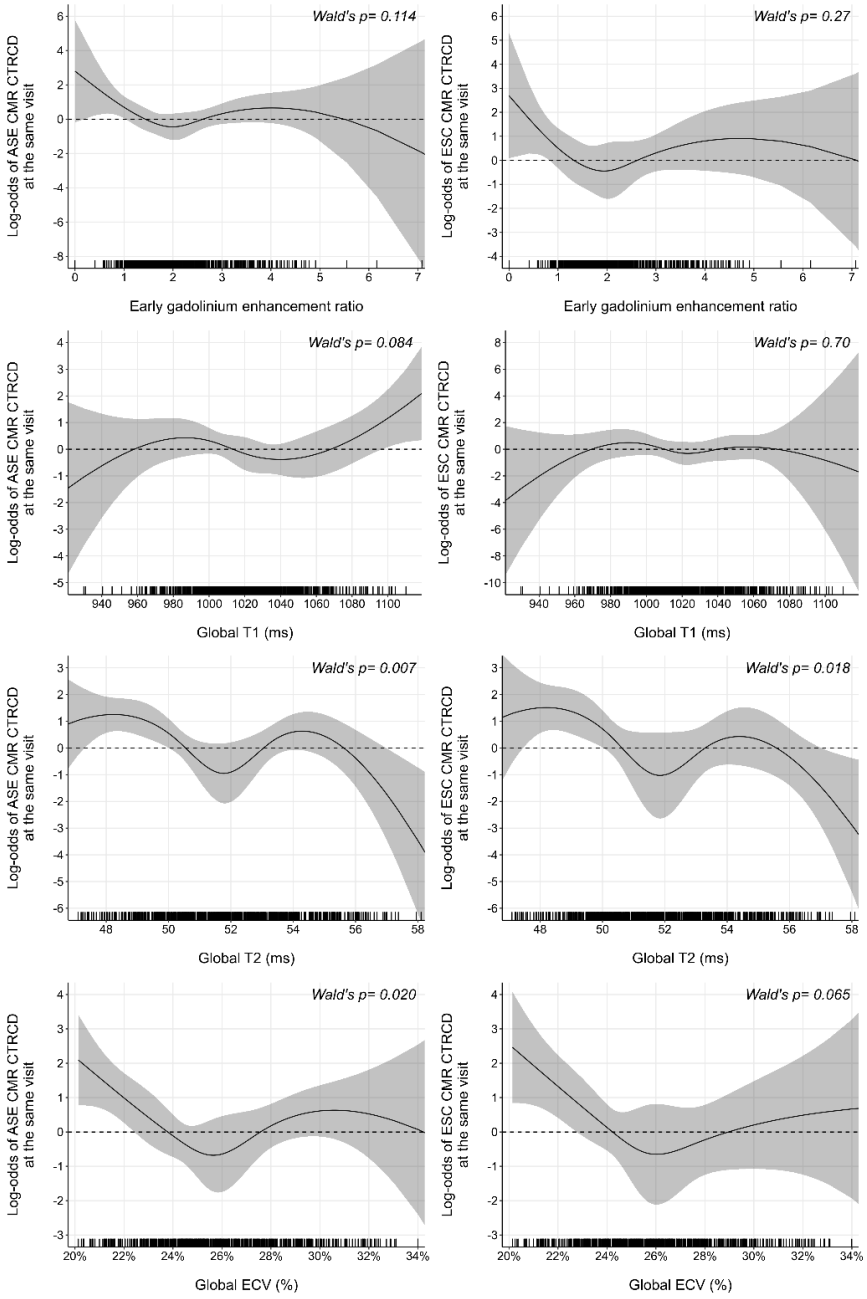
eFigure 12. Regression-Adjusted Nonlinear Concurrent Associations Between CMR Tissue Biomarkers and CTRCD in Terms of Log-Odds

The graphs show the log-odds of CTRCD (y-axis) associated with changes in CMR tissue biomarkers (x-axis). For example, a 100 ms increase from 1000 ms in T1 will increase the log-odds of CTRCD by 0.884 (95% CI = [-0.426, 2.194]), which translates to an OR of 2.421 ($=e^{0.884}$). In other words, a 100 ms increase from 1000 to 1100 ms in T1 will increase the likelihood of CTRCD by 142.1% at the same visit. The tick marks on the x-axis represent the individual observed measurements. The shaded region represents the 95% CI of the estimated association. P-values <0.05 suggest statistically significant associations.



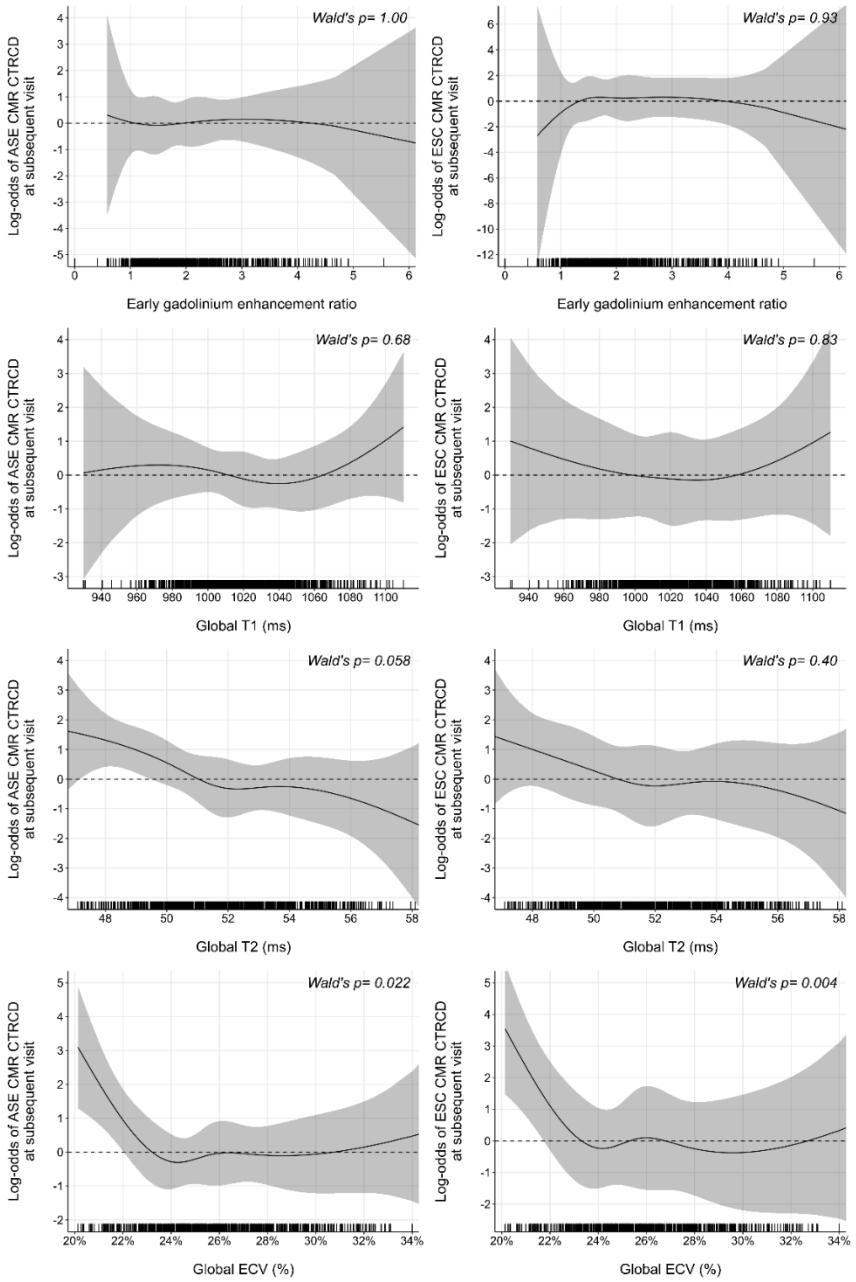
eFigure 13. Sensitivity Analysis Examining the Concurrent Association, in Terms of Log-Odds, Between Changes in CMR Tissue Biomarkers and CTRCD Using the ASE and ESC CTRCD Definitions

For example, a 100 ms increase in T1 from 1000 ms will increase the log-odds of ASE CTRCD by 0.845 (95% CI = [-0.236, 1.925]), which translates to an OR of 2.328 ($=e^{0.845}$). In other words, a 100 ms increase from 1000 to 1100 ms in T1 will increase the likelihood of ASE CTRCD by 132.8%. The minor tick marks on the x-axis represent the individual patient data points. The shaded region represents the 95% CI of the estimated association. P-values <0.05 suggest statistically significant associations.



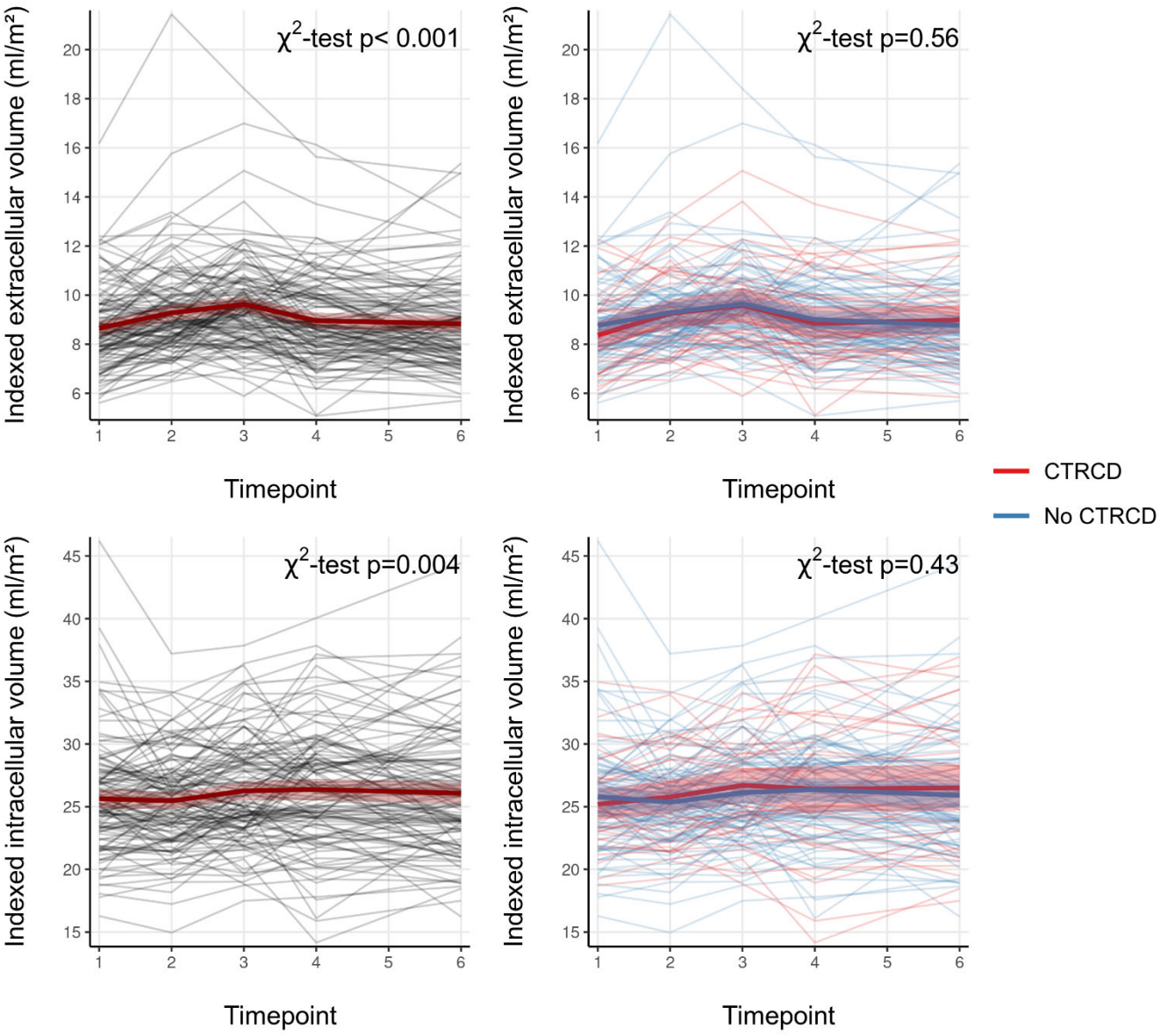
eFigure 14. Sensitivity Analysis Examining the Association, in Terms of Log-Odds, Between CMR Tissue Biomarkers and CTRCD at the Next Visit Using the ASE and ESC CTRCD Definitions

See **eFigures 12 and 13** for interpretation of the graphs. The tick marks on the x-axis represent the individual observed measurements. The shaded region represents the 95% CI of the estimated association. P-values <0.05 suggest statistically significant associations.



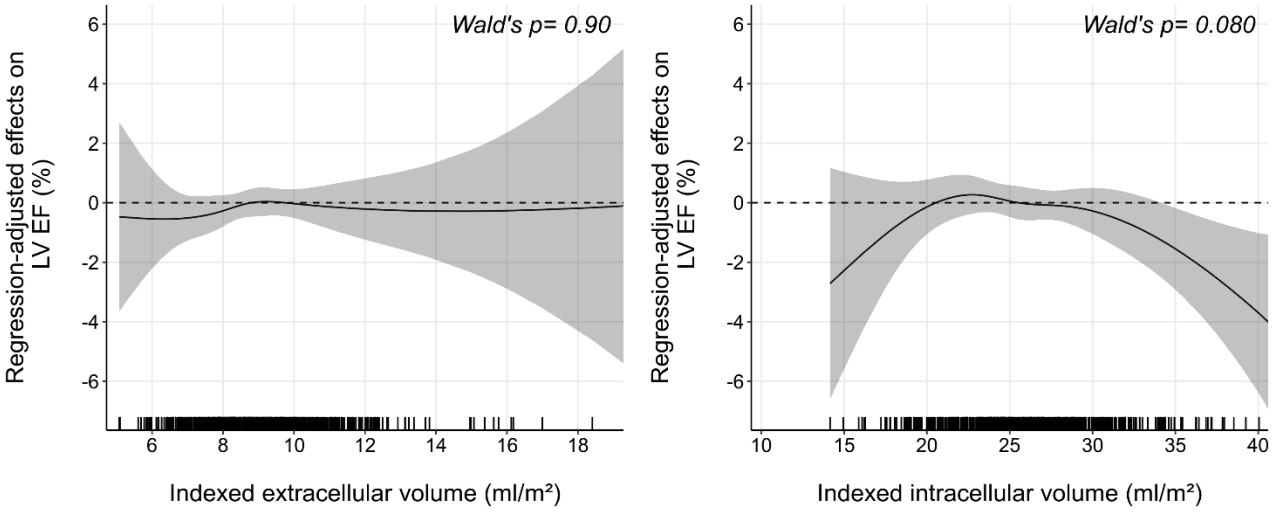
eFigure 15. Indexed Extracellular (iECV) and Intracellular (iECV) Volumes at Each Visit

Left panels: The estimated overall trajectory (red line) and its 95% CI (red shade) for the entire cohort are shown with individual patient trajectories in the background. The p-values assess if the estimated trajectory is different from a horizontal line. **Right panels**: The estimated trajectory (red line for patients with CTRCD and blue line for patients without CTRCD) and its 95% CI (red and blue shades) with individual patient trajectories in the background. P-values assess if the trajectories differ between patients with and without CTRCD. See **eFigure 1** for definition of the timepoints on the x-axis.



eFigure 16. Regression-Adjusted Nonlinear Concurrent Associations Between Indexed Extracellular and Intracellular Volume and Left Ventricular Ejection Fraction (LVEF)

The graphs show expected changes in LVEF (y-axis) associated with changes in CMR tissue biomarkers (x-axis). See **eFigure 5** for explanation of interpretation of the graphs. The shaded region represents the 95% CI of the estimated association. P-values <0.05 suggest statistically



significant association.

eReferences

1. Wassmuth R, Lentzsch S, Erdbruegger U, et al. Subclinical cardiotoxic effects of anthracyclines as assessed by magnetic resonance imaging-a pilot study. Evaluation Studies. *Am Heart J*. Jun 2001;141(6):1007-13. doi:10.1067/mhj.2001.115436
2. Arheden H, Saeed M, Higgins CB, et al. Measurement of the distribution volume of gadopentetate dimeglumine at echo-planar MR imaging to quantify myocardial infarction: comparison with 99mTc-DTPA autoradiography in rats. *Radiology*. Jun 1999;211(3):698-708.
3. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol*. Mar 1 2002;20(5):1215-21.
4. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. Sep 2014;27(9):911-39. doi:10.1016/j.echo.2014.07.012
5. Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *European heart journal*. Sep 21 2016;37(36):2768-2801. doi:10.1093/eurheartj/ehw211
6. Fitzmaurice GM, Laird NM, Ware JH. *Applied longitudinal analysis, 2nd Edition*. vol Chapter 9. John Wiley & Sons; 2012.
7. Diggle P, Haegerty P, Liang K, Zeger S. *The analysis of longitudinal data*. vol Chapter 12. Oxford University Press; 2002.
8. Altaha MA, Nolan M, Marwick TH, et al. Can Quantitative CMR Tissue Characterization Adequately Identify Cardiotoxicity During Chemotherapy?: Impact of Temporal and Observer Variability. *JACC Cardiovasc Imaging*. Apr 2020;13(4):951-962. doi:10.1016/j.jcmg.2019.10.016