


Redefining anthracycline-related subclinical cardiotoxicity: ‘Absolute’ and ‘relative’ change in longitudinal strain

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Abstract

Aims Anthracycline chemotherapy (AC) for breast cancer can cause cancer therapy-related cardiac dysfunction (CTRCD) with resultant heart failure, traditionally defined as a reduction in left ventricular (LV) ejection fraction on echocardiography. In recent years, global longitudinal systolic strain (GLS) has been used to identify subclinical cardiac dysfunction prior to development of overt CTRCD. Recent harmonized guidelines have incorporated GLS into definitions for CTRCD to identify cardiac dysfunction and inform decisions regarding cardioprotective strategies.

Methods and results We evaluated subclinical dysfunction in breast cancer patients treated with AC and determined the echocardiographic and patient factors associated with significant GLS changes. One hundred fourteen HER2 negative patients treated with AC were prospectively recruited and underwent serial echocardiograms (LVEF and LVGLS) at three time points (prior to AC, 3 months, and 1 year). CTRCD was defined as an asymptomatic reduction in LVEF of 10% or symptomatic drop of 5% to LVEF <53%. Subclinical LV dysfunction was defined as a reduction of $\geq 10\%$ in GLS compared with baseline, recognizing that this cut off identified an ‘at risk cohort’ rather than patients with established CTRCD. No participant demonstrated CTRCD by reduction in LVEF. Forty-three patients (38%) demonstrated a $\geq 10\%$ relative reduction in GLS at 12 months; 20/43 (47%) had a reduced absolute GLS to <16%, and were older, had hypertension, increased LV mass, lower baseline e’ velocity and GLS. GLS $\geq 20.5\%$ at baseline yielded a sensitivity of 79% and specificity of 87% for a normal GLS (i.e., $\geq 16\%$) at 1 year despite a $\geq 10\%$ reduction from baseline.

Conclusions We present a stepwise evaluation for subclinical LV dysfunction using both a relative reduction in GLS combined with an absolute reduction in GLS. We believe our findings may re-stratify patients with a high baseline GLS into a lower risk group despite transient relative GLS decrements $\geq 10\%$.

Keywords Anthracycline chemotherapy; Breast cancer; Global longitudinal systolic strain; Transthoracic echocardiography

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Introduction

With early cancer detection and the development of newer therapies, cancer survivorship has significantly improved over the last decade.^{1,2} Cardiotoxicity has demonstrated increased prevalence with improved survivorship in patients with cancer.³ Anthracycline chemotherapy (AC) is an essential

therapy to treat various cancers including breast cancer and has contributed to improved long-term patient survival.^{4,5} The effectiveness of AC is balanced against a significant risk of cancer therapy-related cardiac dysfunction (CTRCD) and future development of heart failure.⁶ There have been varying definitions for CTRCD with previous expert consensus statement from the European association of cardiovascular

imaging (EACVI) defining CTRCD as any reduction in left ventricular ejection fraction (LVEF) to <50% or a reduction of 10% to <53%.⁷ The American Society of Echocardiography (ASE) expert consensus statement defined cardiotoxicity as a symptomatic reduction in LVEF >5% or an asymptomatic reduction in LVEF >10% to <53%.⁸ The most contemporary guidelines have described mild asymptomatic CTRCD as a new relative decline in global longitudinal systolic strain (GLS) of $\geq 15\%$ from baseline.⁹ The CTRCD threshold for GLS was chosen in an effort to optimize specificity for interpreting relative GLS changes, with prior data reinforcing that a reduction in GLS between -8% and -15% may still identify patients at risk for CTRCD.^{8,10}

Transthoracic echocardiography (TTE) is widely used to assess cardiac function in breast cancer patients, although it has been historically under-utilized.¹¹ TTE is recommended at baseline prior to AC¹² and during therapy, based on expert opinion.^{4,10} TTE derived LVEF remains an important metric in assessing cardiac function, although an overt reduction in LVEF represents a late pathophysiological process whereby cardiac dysfunction may be permanent with resultant heart failure.¹³ Speckle tracking strain imaging has utilized GLS to identify subclinical cardiac dysfunction prior to development of clinically meaningful cardiac injury, expressed as a reduction in LVEF.^{7,13} Identifying subclinical cardiac dysfunction can inform decisions regarding cancer treatment including whether to avoid, interrupt or cease therapies and has demonstrated improved cardiac outcomes.¹¹

The incidence of cardiac dysfunction and consequent heart failure with AC is well recognized, and is often increased with other concomitant cardiotoxic therapies (eg trastuzumab).^{12,14} A meta-analysis of previous studies using GLS in the setting of chemotherapy has suggested the need for prospective studies with more clearly defined patient groups.¹⁰ This prospective study characterizes echocardiographic changes in LVEF and GLS in a clearly defined group of HER2 negative breast cancer patients who received only AC therapy. We evaluated patient demographic, clinical and echocardiographic characteristics at baseline prior to AC therapy that could be associated with subclinical LV dysfunction over 12 months.

Methods

Study population

This is prospective cohort study that recruited patients from multiple sites within the Western Sydney Local Health District. Serial transthoracic echocardiograms were performed at a single centre, at baseline, and at 3 and 12 months after AC. A total of 134 patients with histologically confirmed HER2 negative breast cancer were prospectively recruited.

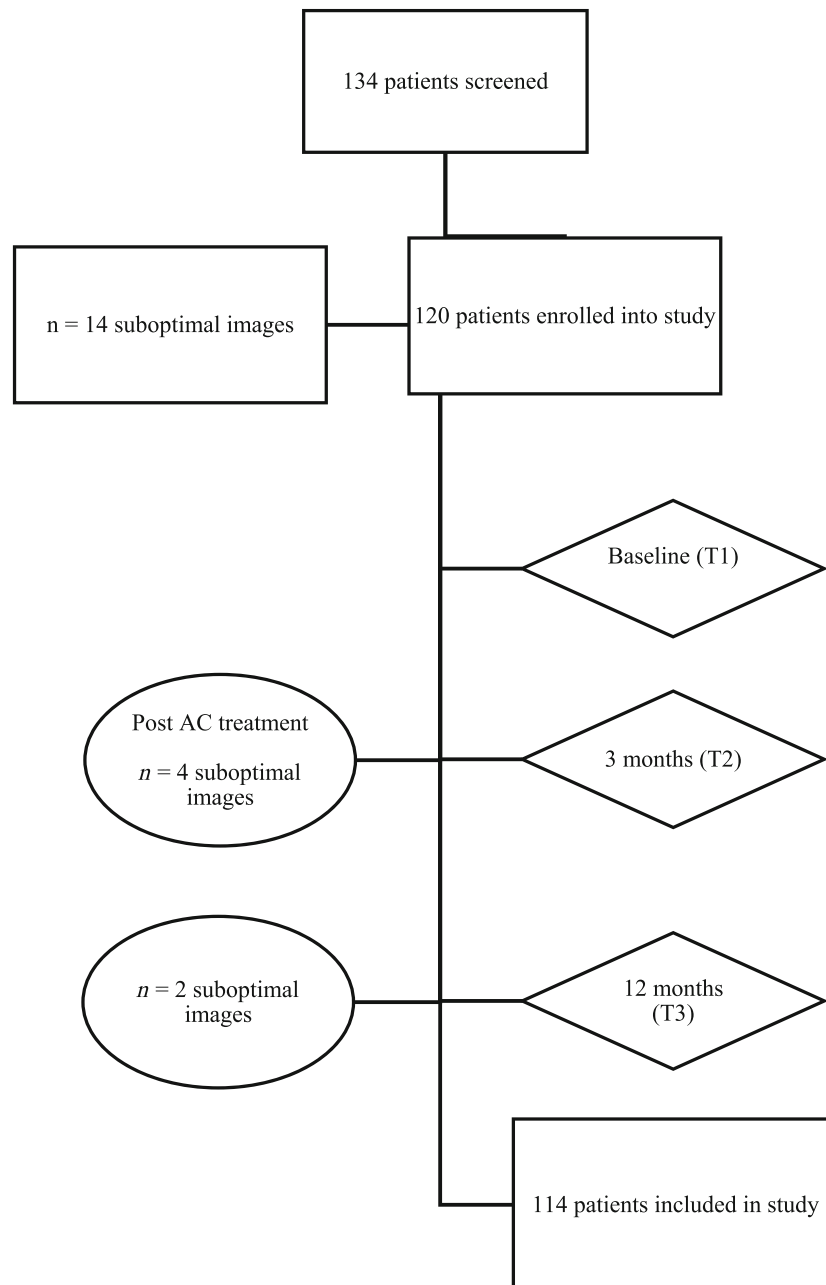
Anthracycline chemotherapy (doxorubicin or epirubicin) was administered (4 to 6 cycles) as per current protocols, determined by the treating oncologist. All patients underwent detailed baseline clinical evaluation; patients were not offered enrolment if there was significant valvular disease, a history of arrhythmia, prior cardiomyopathy, a history of coronary artery disease or revascularization, previous radiation or chemotherapy, previous cardiac surgery or implanted cardiac devices. The study ethics approval was obtained from the Human Research Ethics Committee of Western Sydney Local Health District.

Recruited participants underwent serial comprehensive transthoracic echocardiogram (TTE) with 2-dimensional, colour and Doppler images obtained from parasternal, apical, and subcostal views. *Figure 1* outlines the patient longitudinal follow up timeline during the study. Baseline echocardiograms (T1) were performed at least 1 week prior to the first cycle of AC chemotherapy. Fourteen patients were excluded at T1 due to inadequate image quality for offline strain analysis, often related to recent breast surgery. Serial echocardiograms were performed within a fortnight of anthracycline treatment completion (~ 3 months from baseline) (T2) and 12 months from baseline (T3). Four patients were excluded due to inadequate image quality at T2, with a further 2 excluded at T3. The remaining 114 patients with interpretable TTEs at all 3 time points were included in the analysis.

Two-dimensional echocardiography

Echocardiographic examinations were performed using commercially available ultrasound machines (Vivid E9 and Vivid 7, General Electric Healthcare, Horton, Norway). LV volumes were measured from apical 4- and 2-chamber views utilizing the Simpson's modified biplane method of disks and LVEF was calculated.¹⁵ Mitral inflow velocities to assess LV diastolic filling, were obtained with the pulsed-wave Doppler sample volume placed at the mitral leaflet tips. Pulsed wave Doppler tissue imaging was used to measure the septal and lateral peak velocities in systole (s') and early diastole (e') with sample volume placed at the septal and lateral mitral annulus, and mean annular velocities were calculated. GLS was measured offline (EchoPac version 203, General Electric-Vingmed) from the three apical LV focused views acquired at high frame rate (>60 fps). The endocardial border of the left ventricle was traced at end-systole and the region of interest was set to include the LV myocardium, with the software automatically subdividing each LV wall into three regions (basal, mid, and apical). Peak systolic strain was measured as the peak negative strain during systole. Longitudinal strain rate in systole (S-Sr), early diastole (E-Sr), and late diastole (A-Sr) were also measured. GLS was calculated as the average of the 18 segments from the 4-, 2-, and 3-chamber views. If two or more segments had uninterpretable longitudinal

Figure 1 Timeline for longitudinal follow up. Flow chart of timepoints of serial echocardiograms, prior to (T1), at 3 (T2), and 12 months (T3). Patients were excluded if suboptimal image quality. AC, anthracycline.

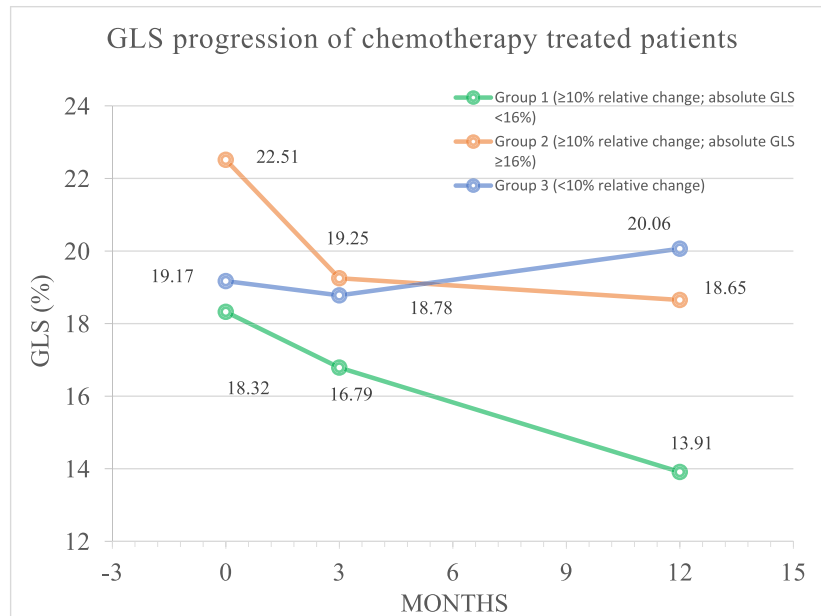


strain, it was excluded from analysis. GLS was collected from all three layers (endocardial, mid-myocardial, and epicardial). If not otherwise stated, GLS measurements represent mid-myocardial strain. Although LV GLS is a 'negative' value to represent myocardial shortening, for simplicity, the absolute values of GLS are reported in the results.

We defined CTRCD as a symptomatic reduction in LVEF of >5% or an asymptomatic reduction in LVEF of >10% from baseline to a value of $\leq 53\%$.⁸ We evaluated GLS to identify

subclinical cardiac dysfunction (rather than GLS CTRCD) and defined this as a relative reduction in GLS $\geq 10\%$ from baseline, as previously reported.^{16,17} There were 43 patients with $\geq 10\%$ reduction in GLS at T3. We further stratified this group with subclinical dysfunction based on patients with an absolute value of GLS <16% or GLS $\geq 16\%$ at T3 (Figure 2).¹⁸ Hence, three patient subgroups were identified at T3: Group 1 ($n = 15$): $\geq 10\%$ reduction in GLS compared with baseline, with GLS <16% at T3, Group 2 ($n = 28$): $\geq 10\%$ reduction in

Figure 2 Timeline of GLS alteration in the three groups. Line graph of alterations in LV GLS between groups prior to and at 3 and 12 months post-AC treatment. AC, anthracycline; GLS, global longitudinal strain; LV, left ventricular.



GLS compared with baseline, with GLS $\geq 16\%$ at T3, Group 3 ($n = 71$): $< 10\%$ reduction in GLS compared with baseline.

Inter-observer variability for LVEF and LV GLS was performed by 2 independent operators blinded to measurements in 20 randomly selected patients. Inter-observer variability was performed by the same operator in the same 20 patients at least 4 weeks after the initial measurements.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 26 (SPSS, Chicago, IL, USA), and differences were considered significant if $P < 0.05$. Continuous data are expressed as mean \pm standard deviation and categorical variables as a number (percentage). Baseline and follow-up data were compared by repeated measures analysis of variance (ANOVA) with least significant difference (LSD) post-hoc testing. Independent t -test was used to compare continuous variables in subgroup analysis. Chi-square test was used for analysis of categorical variables.

Logistic regression analysis was performed to identify univariate predictors for patients in Group 1 (i.e., individuals that would have a $\geq 10\%$ relative reduction to a GLS $< 16\%$ at T3). Significant univariate predictors were entered into a multivariable logistic regression model and examined by backwards binary multivariate regression analysis to determine independent predictors specifically for patients in group 1.

Inter-observer and intra-observer variability were assessed for LV GLS. Measurements were done using 20 randomly se-

lected subjects. Intra-class correlation coefficients (ICC) using a two-way random effects model was used to assess variability. Values between 0.75 and 0.9 represented good reliability and values ≥ 0.90 excellent reliability.¹⁹

Results

A 114 prospectively recruited breast cancer patients underwent serial echocardiograms over 12 months. Cardiovascular risk factors and cardioactive medications are listed in *Table 1* and *Table S1*. Eighty-six patients received radiation with 44 receiving left sided radiation. Thirty-eight patients (33%) had more than one cardiovascular risk factor. No participant reported any symptoms or had any signs of cardiac failure during the entirety of the 12 month follow up. Eighty-eight (77%) patients received doxorubicin (cumulative dose 343.6 ± 107.8 mg/m²), and 26 (23%) patients received epirubicin (cumulative dose 461.7 ± 142.2 mg/m²).

Clinical and echocardiographic parameters at each of the three visits are outlined in *Table 2*. The mean follow-up time at T2 and T3 was 92 and 372 days, respectively. Heart rate was significantly higher at T2, and then decreased at T3. Left ventricular end diastolic and end systolic volumes were significantly increased at T3 compared with T1 and T2. LVEF at T2 was significantly reduced, although within the normal clinical range. No patient developed CTRCD throughout the entirety of the study period (defined by alteration in LVEF).⁸ Average s' was significantly reduced at T3 compared with T1 and T2.

Table 1 Echo parameters of cohort T1–T3

	T1	T2	T3	ANOVA (<i>P</i> value)
Time to follow-up (days)	N/A	97 ± 23	372 ± 33	N/A
Height (cm)	160.1 ± 6.1	N/A	N/A	N/A
Weight (kg)	74.7 ± 15.8	74.4 ± 15.7	73.7 ± 15.4	0.177
BSA (m ²)	1.77 ± 0.17	1.77 ± 0.17	1.77 ± 0.18	0.501
BMI (kg/m ²)	29.17 ± 6.06	29.00 ± 5.99	28.58 ± 5.80	0.082
Heart rate (b.p.m.)	71.7 ± 11.5	77.5 ± 11.7 ^a	69.3 ± 9.9 ^{a,b}	<0.001
Systolic BP (mmHg)	118.0 ± 11.3	119.1 ± 12.9	120.9 ± 20.0	0.606
Diastolic BP (mmHg)	73.9 ± 8.7	74.7 ± 8.0	72.8 ± 8.6	0.478
LV mass (g/m ²)	75.73 ± 15.74	76.57 ± 15.06	75.36 ± 13.99	0.470
LVEDV (mL/m ²)	56.74 ± 10.31	57.21 ± 11.05	62.97 ± 11.48 ^{a,b}	<0.001
LVESV (mL/m ²)	22.31 ± 4.03	22.82 ± 4.27	24.81 ± 5.27 ^{a,b}	<0.001
Stroke volume (mL/m ²)	34.43 ± 6.61	34.39 ± 7.11	38.15 ± 6.62 ^{a,b}	<0.001
LVEF (%)	60.71 ± 2.39	60.01 ± 2.28 ^a	60.61 ± 2.08 ^b	0.008
Mean s' (cm/s)	7.98 ± 1.69	7.82 ± 1.39	7.20 ± 1.16 ^{a,b}	<0.001
E velocity (cm/s)	69.55 ± 13.24	63.56 ± 12.54 ^a	64.06 ± 12.79 ^a	<0.001
A velocity (cm/s)	67.75 ± 16.16	68.01 ± 16.07	65.65 ± 14.56 ^a	0.057
Mean e' (cm/s)	9.04 ± 3.98	8.06 ± 1.95 ^a	7.55 ± 1.89 ^{a,b}	<0.001
E/e'	8.44 ± 2.28	8.09 ± 2.46	8.92 ± 2.27 ^{a,b}	<0.001
GLS _{endo} (%)	22.19 ± 3.31	20.81 ± 3.55 ^a	21.08 ± 3.52 ^a	<0.001
GLS _{myo} (%)	19.88 ± 2.92	18.63 ± 3.20 ^a	18.91 ± 3.14 ^a	<0.001
GLS _{epi} (%)	17.94 ± 2.60	16.83 ± 2.89 ^a	17.09 ± 2.77 ^a	<0.001
S-Sr (1/s)	1.11 ± 0.21	1.08 ± 0.20 ^a	1.02 ± 0.18 ^{a,b}	<0.001
E-Sr (1/s)	1.33 ± 0.37	1.16 ± 0.34 ^a	1.18 ± 0.32 ^a	<0.001
A-Sr (1/s)	0.84 ± 0.23	0.86 ± 0.24	0.86 ± 0.23	0.232

Mean ± standard deviation for continuous variables.

BMI, body mass index; BP, blood pressure; BSA, body surface area; GLS, global longitudinal strain; LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; Sr, strain rate.

^a*P* < 0.05 when compared with T1.

^b*P* < 0.05 when compared with T2.

Table 2 Baseline parameter comparisons between groups

	Echo parameters at T1			<i>P</i> value
	Group 1 (<i>n</i> = 15)	Group 2 (<i>n</i> = 28)	Group 3 (<i>n</i> = 71)	
Age (years)	60.22 ± 9.72	50.65 ± 9.61 ^a	55.71 ± 8.68	0.005
Height (cm)	158.73 ± 5.66	160.07 ± 6.57	160.30 ± 6.10	0.663
Weight (kg)	76.97 ± 17.48	72.48 ± 17.48	74.88 ± 14.70	0.716
BSA (m ²)	1.78 ± 0.17	1.75 ± 0.21	1.78 ± 0.16	0.782
BMI (kg/m ²)	30.64 ± 7.00	28.22 ± 6.40	29.19 ± 5.73	0.495
Heart rate (b.p.m.)	71.00 ± 15.03	75.18 ± 10.80	70.44 ± 10.70	0.153
Systolic BP (mmHg)	129.53 ± 10.29	119.41 ± 12.47 ^a	122.12 ± 11.21	0.021
Diastolic BP (mmHg)	81.53 ± 4.26	74.85 ± 7.09 ^a	76.76 ± 8.94	0.031
Hypertension	9 (60.0)	5 (17.9) ^a	20 (28.2) ^a	0.014
Diabetes	2 (13.3)	1 (3.5)	3 (4.2)	0.321
Hypercholesterolaemia	7 (46.7)	4 (14.3) ^a	13 (18.3) ^a	0.046
LV mass (g/m ²)	83.84 ± 20.36	69.48 ± 13.71 ^a	76.17 ± 14.66	0.019
LVEDV (mL/m ²)	59.90 ± 10.25	55.23 ± 8.40	56.60 ± 11.04	0.393
LVESV (mL/m ²)	23.69 ± 3.84	21.64 ± 3.35	22.27 ± 4.29	0.289
LV stroke volume (mL/m ²)	36.21 ± 6.81	33.59 ± 5.50	34.33 ± 7.05	0.502
LVEF (%)	60.33 ± 2.53	60.93 ± 2.48	60.63 ± 2.33	0.549
Mean s' (cm/s)	6.99 ± 2.39	8.46 ± 1.68 ^a	8.10 ± 1.4	0.039
E velocity (cm/s)	66.22 ± 8.64	72.91 ± 12.60	6.88 ± 1.41	0.203
A velocity (cm/s)	74.82 ± 17.20	65.79 ± 14.93	6.63 ± 1.60	0.180
Mean e' (cm/s)	7.48 ± 1.96	9.46 ± 2.50	9.20 ± 4.60	0.288
E/e'	9.57 ± 2.85	8.07 ± 1.89	8.25 ± 2.13	0.126
GLS _{endo} (%)	20.48 ± 1.91	25.15 ± 2.26 ^a	21.33 ± 3.16 ^b	<0.001
GLS _{myo} (%)	18.32 ± 1.72	22.51 ± 1.97 ^a	19.13 ± 2.78 ^b	<0.001
GLS _{epi} (%)	16.54 ± 1.57	20.27 ± 1.80 ^a	17.29 ± 2.47 ^b	<0.001
S-Sr (1/s)	1.01 ± 0.19	1.24 ± 0.19 ^a	1.07 ± 0.21 ^b	<0.001
E-Sr (1/s)	1.04 ± 0.30	1.62 ± 0.37 ^a	1.28 ± 0.33 ^{a, b}	<0.001
A-Sr (1/s)	0.81 ± 0.27	0.91 ± 0.22	0.81 ± 0.22	0.082

Mean ± standard deviation for continuous variables.

BMI, body mass index; BP, blood pressure; BSA, body surface area; GLS, global longitudinal strain; LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; Sr, strain rate.

^a*P* < 0.05 when versus group 1.

^b*P* < 0.05 when versus group 2.

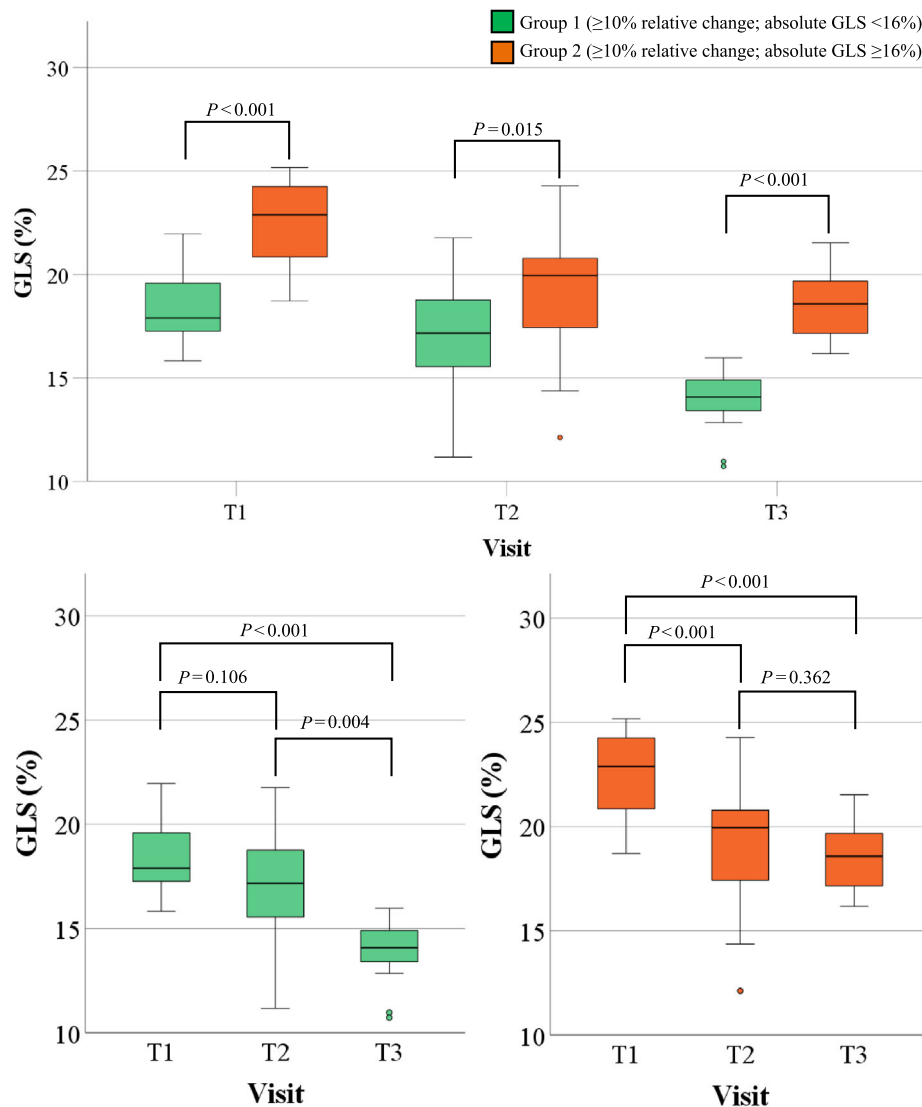
Similarly, GLS at T2 and T3 were significantly reduced compared with T1, with this being reflected in all three myocardial layers. S-Sr was significantly decreased at T2, and persisted at T3. Peak E, average e', and E-Sr were significantly reduced at T2 and T3 compared with T1, while E/e' only showed a significant difference between T2 and T3 (Table 2).

We identified patients with subclinical CTRCD defined as a $\geq 10\%$ decrease in GLS at T3 compared with baseline ($n = 43$), and further stratified this group into those with an absolute reduction in GLS $< 16\%$ (Group 1; $n = 15$) versus those with a preserved absolute GLS $\geq 16\%$ (Group 2; $n = 28$). Group 3 comprised patients who experienced $< 10\%$ decrease in GLS over the course of the study ($n = 71$). Figure 2 presents the GLS at the

three time points for each of these groups. Table S1 demonstrates the number of patients with GLS $< 16\%$ versus GLS $\geq 16\%$ in all 114 patients (with and without a relative change $\geq 10\%$) at T3. Of the patients with GLS $< 16\%$ at 12 months, 79% had a $\geq 10\%$ relative reduction in GLS compared with baseline. A total of 43 (37.7%) patients exhibited a $\geq 10\%$ relative reduction in GLS between T1 and T3, with only 15 (34.9%) of this group having a GLS $< 16\%$ at T3. Group 3 ($n = 71$) had a normal GLS throughout the census period without a $\geq 10\%$ relative change but did appear to have a trend towards a GLS recovery between 3 and 12 months.

Figure 3 presents box plots of the GLS measurements between groups 1 and 2 at 3 time points. GLS for group 1 patients was significantly lower at all time points compared

Figure 3 Comparison between the 2 groups at risk of LV subclinical dysfunction. Boxplots of groups with $\geq 10\%$ relative decrease in GLS at 12 months compared with baseline, stratified by an absolute GLS value of 16%. AC, anthracycline; GLS, global longitudinal strain; LV, left ventricular; T1, prior to AC treatment; T2, post-AC; T3, 12 months post-T1.



with group 2 (Figure 3). Group 1 exhibited significant reductions at T3 compared with T1 ($P < 0.001$) and T2 compared with T3 ($P = 0.002$), with no reduction between T1 and T2 ($P = 0.106$). Group 2 exhibited significant reductions at T2 and T3 compared with T1 ($P < 0.001$ for both), with no reduction in GLS between T2 and T3.

Table 2 compares baseline characteristics and echocardiographic parameters between groups 1 and 2. Group 1 patients were older ($P = 0.024$), with a higher prevalence of hypertension ($P = 0.004$), higher diastolic blood pressure and greater LV mass ($P = 0.009$ and $P = 0.012$, respectively). LV volumes were similar at T1; however, LVEF was significantly higher in group 2 at baseline ($P = 0.012$), albeit still within normal clinical range. GLS in all myocardial layers was significantly lower in group 1 compared with group 2 ($P < 0.001$).

Univariate clinical and echocardiographic predictors for patients in group 1 were age, presence of hypertension, hypercholesterolaemia, LV mass, average e' velocity and GLS. Backwards stepwise binary multivariate regression analysis (Table 3) was performed using nested analysis for demographic and clinical parameters (model 1), and for echocardiographic parameters (model 2), given the relatively small number of patients in group 1. In model 1, age, hypertension, and hypercholesterolaemia all showed modest univariate correlation to group 1 ($P = 0.003$, $P = 0.004$ and $P = 0.020$, respectively). Backwards binary regression analysis identified age as the only significant parameter, with an odds ratio of 0.905 ($P = 0.009$). In model 2, LV mass, average e' and LV GLS all demonstrated univariate correlation to group 1 ($P = 0.009$, $P = 0.013$ and $P < 0.001$, respectively). Backwards binary regression analysis identified only GLS as being significant, with an odds ratio of 0.354 ($P = 0.001$). A final analysis (model 3) was performed using the independent predictors for group 1 from models 1 and 2 (i.e., age and GLS). This demonstrated that only baseline GLS was a significant predictor of patients in group 1, with an odds ratio of 0.897 ($P = 0.002$).

We further examined the baseline GLS value that would identify patients in group 1 versus group 2. A cut-off value

for GLS was established by calculating the mean minus 1 standard deviation of the GLS at T1 for group 2 patients (GLS of 20.5%). Using this cut-off GLS of 20.5%, the sensitivity and specificity to identify patients in group 2 ($\geq 10\%$ reduction in GLS to $\geq 16\%$) from group 1 at timepoint T3 was 79% and 87%, respectively (Table S2).

Regarding intra-observer variability, the ICC for LV GLS was 0.989 (0.973–0.996). The inter-observer variability for LV GLS was 0.990 (0.976–0.996). The results here demonstrate excellent reproducibility for LV GLS.

Discussion

We present one of the largest prospective 'anthracycline only' breast cancer patient groups with comprehensive TTE assessment before, immediately after, and at 1 year following chemotherapy.

The key findings of our study are as follows (Figure 4):

- 1 43/114 (38%) patients demonstrated subclinical cardiac dysfunction with a $\geq 10\%$ reduction in LV GLS at 12 months after AC therapy.
- 2 Of the 43 patients with $\geq 10\%$ relative reduction in GLS compared with baseline, 15/43 (34.9%) had a reduction with an absolute GLS of $< 16\%$.
- 3 Baseline clinical and echocardiographic characteristics associated with $\geq 10\%$ GLS reduction with absolute GLS $< 16\%$ (group 1), were older age, hypertension, increased LV mass, lower e' velocity and GLS prior to AC therapy.
- 4 A baseline GLS $\geq 20.5\%$ had a sensitivity and specificity of 79% and 87% respectively, to maintain LV GLS at 'normal' levels ($\geq 16\%$), despite $\geq 10\%$ relative reduction from baseline GLS.

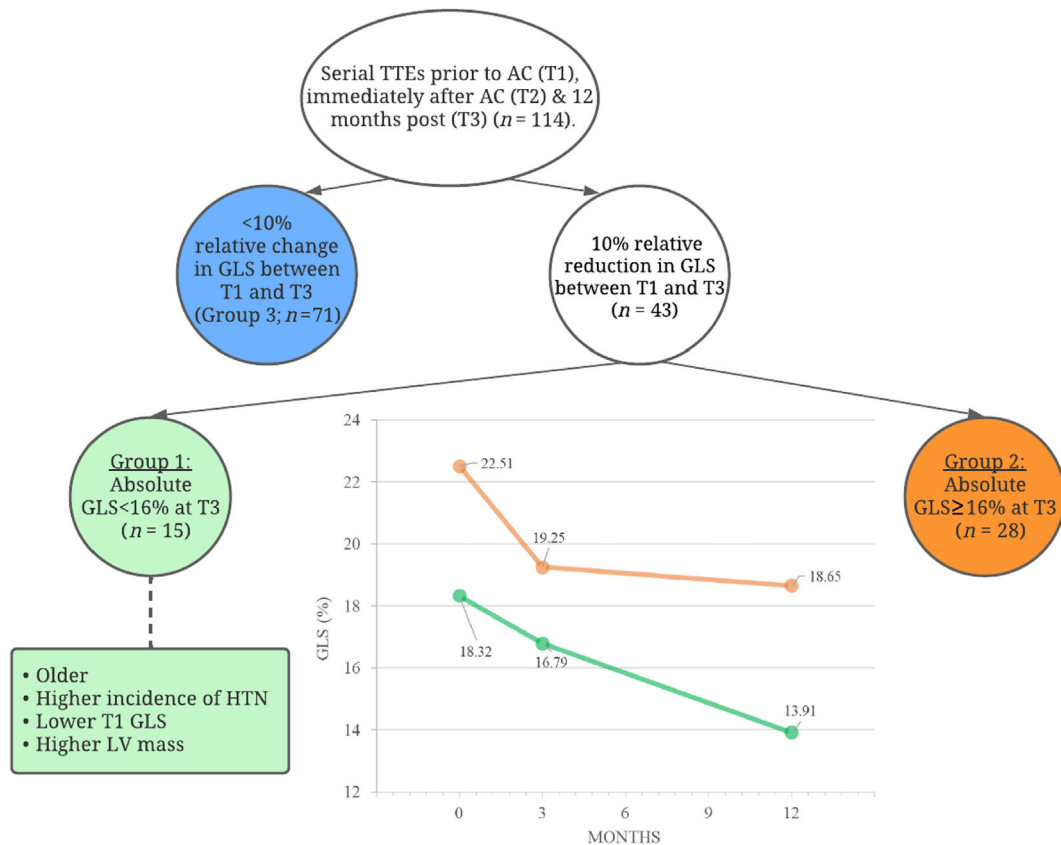
The study design included a strict enrolment protocol ensuring that recruited patients had no known cardiac

Table 3 Univariate and multivariate backward binary regression analysis of baseline parameters against designation to group 1 in at-risk groups

Parameters	Univariate		Multivariate	
	R	P value	OR (CI)	P value
Nested model 1: clinical variables				
Age	-0.436	0.003	0.905 (0.840–0.975)	0.009
Hypertension	-0.429	0.004	N/A	N/A
Hypercholesterolaemia	-0.354	0.020	N/A	N/A
Nested model 2: echocardiographic variables				
LV mass	-0.395	0.009	N/A	N/A
Average e'	-0.380	0.013	N/A	N/A
GLS	-0.734	< 0.001	0.354 (0.190–0.660)	0.001
Nested model 3: combined variables				
Age			0.335 (0.167–0.671)	0.091
GLS			0.897 (0.790–1.018)	0.002

BP, blood pressure; CI, confidence interval; GLS, global longitudinal strain; LV, left ventricular; OR, odds ratio.

Figure 4 Subclinical LV dysfunction in breast cancer patients 12 months post-AC. Relative and absolute LV GLS were used to identify patients developing subclinical LV dysfunction at 12 months. The stepwise process included (1) relative decrease in LV GLS $\geq 10\%$. (2) Absolute LV GLS $< 16\%$. In this cohort, patients who exhibited $\geq 10\%$ relative decrease in GLS to an absolute GLS $< 16\%$ were older, had a higher incidence of hypertension, a lower T1 LV GLS and higher LV mass compared with those with a GLS $\geq 16\%$. AC, anthracycline; GLS, global longitudinal strain; LV, Left ventricular; TTE, transthoracic echocardiogram.



pathology and with only one third of patients having more than one cardiac risk factor. Based on a recently developed cardiac risk assessment tool applicable to patients on AC, there was only 1 high risk patient in group 1 (6.7%) and group 2 (3.6%), while group 3 comprised 3 high risk patients (4.2%). There were 8 medium risk patients in group 1 (53.3%) and 6 medium risk patients in group 2 (21.4%) while group 3 included 22 medium risk patients (31%)—the remainder of the patients were all low risk (Table S3).²⁰ While the percentage of medium risk patients varies among the groups a Pearson Chi-square analysis was not significant. Our study was free of patients developing CTRCD defined by LVEF, which may reflect the small percentage of high risk patients in the study, improved contemporary cancer regimens as well as a medium term follow up of 12 months. Group 3 (n = 71) did not experience a relative GLS change of 10% and remained within the normal GLS range throughout therapy although there was a subtle downward trend of GLS between baseline and 3 months and a recovery of GLS between months 3 and 12 (Figure 2) suggesting that small initial rela-

tive GLS changes during AC are unlikely to correspond with significant change at 1 year. While no patients experienced overt CTRCD, 38% of our cohort experienced subclinical cardiac dysfunction with a reduction in GLS $\geq 10\%$ over 1 year. Among patients who experienced a $\geq 10\%$ drop in GLS, a pre-treatment GLS $\geq 20.5\%$ was protective against an absolute reduction in GLS (i.e., $< 16\%$) at 1 year. Our findings suggest the potential for a stepwise GLS guided model, whereby patients with a relative reduction in GLS of $> 10\%$ could be re-stratified as lower risk individuals based on a pre-treatment absolute GLS $> 20.5\%$. Such an approach once validated may enable fidelity to chemotherapeutic regimens and inform decisions regarding cardioprotective strategies. Relative changes in GLS changes can also provoke anxiety among patients and indecision among clinicians and once validated a high baseline GLS cut-off may serve to alleviate concerns.

TTE is the primary imaging modality used to determine CTRCD with AC therapy where even a mildly abnormal pre-treatment LVEF (i.e., 50–54%) has been identified as a significant risk factor for developing heart failure.⁷ While

AC-related cardiotoxicity can occur at variable periods after chemotherapy, previous research has demonstrated that most cases of AC cardiotoxicity occur within the first year after treatment, underscoring the importance of serial echocardiography.⁷ A reduction in LVEF is now appreciated as a late change reflecting a degree of irreversible myocardial damage^{6,7,13} with translation to poor patient outcomes.²¹ Previous studies of AC in breast cancer patients have yielded a 10–20% rate of CTRCD,¹⁰ although contemporary analyses suggest modern AC regimens are less likely to decrease LVEF,^{12,22} with a recent meta-analysis estimating the effect of AC in contemporary settings only decreases LVEF by ~5.4%.²² The LVEF in our cohort was within normal limits throughout the census period; however, a statistically significant reduction in LVEF between baseline and 3 months was noted with no persistence of this negative trend beyond 3 months. Peak systolic annular *s'* velocity was decreased at 3 months and demonstrated a small but significant reduction which persisted at 1 year, indicative of AC selectively affecting longitudinal function prior to a change in LVEF. Both end diastolic and end systolic LV volumes were also increased from baseline at 1 year, underscoring the development of LV remodelling with AC even when LVEF is preserved. Similar changes have been reported in studies using cardiac magnetic resonance imaging in breast cancer patients.²³

In recent years, GLS has been utilized to identify subclinical cardiac dysfunction in cardiovascular disease in general, and also related to cancer therapies. GLS is technically superior to LVEF, with relative angle independence of 2D speckle tracking strain and fewer geometric assumptions.^{12,24,25} The most recent ESC guidelines define GLS-CTRCD as a >15% relative change and this threshold was chosen to yield a high specificity to minimize overdiagnosis of CTRCD.⁹ While a 15% cut-off to define GLS-CTRCD is reasonable, there can be no doubt that relative GLS changes below this threshold may still be relevant and indicate subclinical dysfunction. Previous studies have suggested a relative drop in GLS of $\geq 10\%$ during chemotherapy represents subclinical dysfunction,^{16,26,27} and prior guidelines have supported cardiac specialist referral for such patients irrespective of symptoms to reduce development of heart failure.²⁸ Our study demonstrated a significant drop in relative GLS of $\geq 10\%$ in 43 patients (37.7%), underscoring the fact that subclinical myocardial changes occur even in a relatively healthy patient group following AC therapy. Moreover, changes in LV GLS independently predicts cardiac mortality and major adverse cardiac events, with a prognostic value superior to LVEF in non-cancer populations.²⁹

Prior data has suggested improved cardiac outcomes when GLS is monitored throughout cancer therapy.¹¹ Recently the SUCCOUR study sought to determine whether a GLS guided approach to cardioprotective therapies was superior to a traditional approach guided by changes in LVEF.¹³ The authors selected a relative GLS change of $\geq 12\%$ to guide the adminis-

tration of cardioprotective therapies.¹³ However, no difference in final LVEF among the two approaches was observed, although the GLS guided group received more cardioprotective therapies and had less of a drop in LVEF overall.¹³ Our data support the notion that absolute GLS value combined with relative GLS change may have a role in risk stratifying patients and therefore allow for a more nuanced GLS assessment, and potentially allow for better identification of patients with GLS CTRCD.

A recent classification of LV GLS has suggested that normal LV GLS is 18–20%, borderline LV GLS is 16–18%²⁵ while LV GLS <16% is considered reduced GLS²⁵ and has clinical relevance in the context of CTRCD. AC specific data has demonstrated a 4.7 fold increase in major adverse cardiac events in patients with a GLS of $\leq 16\%$.³⁰

In our study, patient characteristics associated with a relative reduction in GLS of >10% to an absolute value <16% included older age, presence of hypertension and a higher diastolic blood pressure, while baseline echocardiographic parameters included increased LV mass, reduced *e'* velocity and LV GLS. However, baseline LV GLS was the only independent determinant of subclinical LV dysfunction at 12 months, as GLS may represent the composite additive effects of increased age, hypertension, and increased LV mass, with a resultant lower GLS.

Although guidelines recommend a pre-chemotherapy baseline echocardiogram in breast cancer patients, associations between absolute pre-treatment GLS thresholds and CTRCD have been studied infrequently.^{14,31,32} A pretreatment GLS below 19.95% predicted CTRCD in a study of patients with haematological malignancies.³¹ Similarly, a retrospective analysis of breast cancer patients demonstrated a lower pre-treatment mean GLS of 19.4% among those who developed CTRCD while CTRCD-free patients demonstrated a higher baseline GLS of 23.1%.¹⁴ Our current study has added further merit to the concept of a 'protective' pre-treatment GLS (i.e., >20.5%) among breast cancer patients receiving AC.

AC is beneficial in the treatment of breast cancer although it nonetheless poses a risk of permanent irreversible myocardial dysfunction with development of heart failure.^{13,28} Conversely, interrupting essential cancer therapy may worsen outcomes or result in patient distress.²⁸ Our study suggests the consideration of a simple stepwise model where patients treated with AC who experience a drop in GLS of $\geq 10\%$ may be re-categorized as low risk if their baseline GLS is $\geq 20.5\%$. To our knowledge, this is the first study to suggest a simple and intuitive stepwise approach, which could potentially help alleviate patient anxiety, ensure completion of chemotherapy regimens and determine when to employ cardioprotective medications. However, further validation is required with a longer duration of follow up for adverse cardiovascular events. Our findings may not necessarily be applicable to other chemotherapeutic regimens but needs to be considered.

Study limitations and future directions

By virtue of recruitment of a low risk cohort, the patient subset did not experience significant CTRCD or adverse cardiac events within the follow up period. The persistence of GLS perturbation (as both a relative change and absolute GLS value), at 1 year suggests a future risk of cardiovascular morbidity. However, longer-term follow up for adverse cardiovascular events is not available in the current study cohort.

Cardiac biomarker abnormalities have been noted in prior AC studies^{6,16} but were not routinely performed in our study.

3D echocardiography was novel at the inception of our study but is now accepted as superior to standard 2D LVEF assessment reducing both inter-observer and test to test variability.⁷ In the current study, LVEF was well above the normal threshold with an average of 60%, making the probability of significant clinical reassignment (e.g., from normal range to abnormal LVEF) unlikely.

A high pre-treatment GLS may be protective against a subsequent reduced absolute GLS; however, the specific GLS cut off is unclear and a validation study is required to determine whether the proposed GLS $\geq 20.5\%$ may predict 'protection' even in patients with significant relative change in GLS (i.e., $>10\%$) with AC therapy.

Conclusion

This HER2 negative breast cancer cohort demonstrated no CTRCD by LVEF with AC therapy at 1 year, although 38% ($n = 43$) dropped GLS by $\geq 10\%$ with 15/43 patients demonstrating an absolute LV GLS $<16\%$ at 1 year. GLS at baseline was the single determinant of absolute GLS $<16\%$ at 1 year and was more commonly seen in older women with hypertension. Patients with GLS of $\geq 20.5\%$ before AC treatment

who experienced a $\geq 10\%$ relative drop in GLS, were more likely to have a normal absolute GLS at 1 year, suggesting that this group may be erroneously classified as subclinical CTRCD or in instances even commenced on cardioprotective therapy. Using absolute pre-treatment LV GLS along with relative LV GLS change may help to re-stratify a patient's risk for subclinical AC cardiotoxicity. Future validation studies with longer-term follow up are required to further confirm these preliminary findings.

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Conflict of interest

None declared.

Supporting information

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

Table S1. Patient characteristics and cardiovascular risk factors.

Table S2. Sensitivity and Specificity for Group 2 in the at-risk groups.

Table S3. Patient cardiotoxicity risk utilising the AC risk tool as proposed by Lyon AR et al. *Eur J Heart Fail.* 2020 Nov;22(11):1945-60.

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