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Value of left atrial longitudinal strain as an early marker of cardiotoxicity in patients treated with anti-her2 therapy

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1. TITLE:

Value of left atrial longitudinal strain as an early marker of cardiotoxicity in patients treated with anti-her2 therapy.

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2. ABSTRACT

Background: While global left ventricular strain is the standard for detecting trastuzumab-induced cardiotoxicity in HER2-positive breast cancer, left atrial strain emerges as a promising tool for subclinical detection. This study evaluates the predictive value of 3-month left atrial strain and alternative echocardiographic parameters for early cardiotoxicity screening.

Methods: This prospective study included 37 women with HER2-positive breast cancer treated with trastuzumab. Follow-up was performed for 1 year with 4 measurements: baseline, 3, 6, and 12 months. Echocardiographic measures, such as PALS, Lacd, PACS and GLS, were assessed using speckle-tracking transthoracic echocardiography. Troponin I and proBNP levels were also extracted in each measurement. Diagnosis of cardiotoxicity followed established criteria. The analysis of the ROC curve evaluated the diagnostic accuracy of Lacd.

Results: Twenty seven percent of patients developed cardiotoxicity. ΔLAcd at 3 months proved to be an independent predictor of cardiotoxicity, in logistic regression models adjusted for both anthracyclines (OR 0.82, 95% CI 0.69–0.98; p=0.03), and age (OR 0.82, 95% CI 0.68–0.97; p=0.02). ROC analysis showed that 3-month ΔLAcd was significantly associated with cardiotoxicity (AUC: 0.76, 95% CI: 0.59–0.89, p=0.02), whereas ΔPALS showed only a trend (AUC: 0.70, p=0.08). A ΔLAcd cutoff of -2.45% yielded a sensitivity of 70.0%, specificity of 70.8%, PPV of 50.0%, and NPV of 85.0% for cardiotoxicity.

Conclusions: Our findings suggest that an early decline in left atrial conduit strain may identify a subgroup of trastuzumab-treated patients at increased risk of developing cardiotoxicity, with a reduction greater than 2.45% at 3 months showed a favorable sensitivity for detecting subsequent cardiotoxicity and may help identify patients who could benefit from closer cardiac surveillance.

KEY WORDS: Cardiotoxicity, trastuzumab, antiher2, strain, left atrium.

Clinical trial number: not applicable.

3. INTRODUCTION

Breast cancer is the leading cause of death among women aged 35-54, and the leading cause of cancer death among women in Spain (1). The HER2 positive subtype constitutes 25% of all breast cancers (2), being an aggressive breast cancer, with high-grade tumors, short disease-free periods, early systemic metastases, and reduced survival (3). Trastuzumab (recombinant antibody against HER2) is the standard treatment in these cases, and has been shown to increase survival in localized (4) (5) (6) and metastatic cancers (7). However, Cancer Therapy-Related Cardiac Dysfunction (CTRCD) is associated with it as the main side effect, appearing in 4% of monotherapy patients and in 27% of patients in combination with anthracyclines and cyclophosphamide (8). This is characterized by being potentially reversible and dose-independent. More specifically, focusing on the subclinical detection of cardiotoxicity, clinical practice guidelines currently describe it as a 15% drop in left ventricular global strain (GLS), but there are studies that advocate for left atrial strain as an even earlier marker of future cardiotoxicity (9)(10). Our objective is to determine whether left atrial strain is an early marker of cardiotoxicity at 3 months and whether there are echocardiographic parameters other than those already published for this purpose.

4. METHODS

4.1. Study population

Between June 2023 and August 2025, 37 women receiving transtuzumab in the adjuvant setting of HER-II-positive breast cancer were prospectively included. Exclusion criteria were presence of systolic dysfunction (LVEF<50%) at baseline evaluation, greater than mild valvular disease, presence of a valve prosthesis, permanent pacemaker implantation, persistent atrial fibrillation and congenital heart disease (with the exception of bicuspid aortic valve). Patients with inadequate acoustic window was also excluded. All patients underwent at least four echocardiographic examinations at our center (at baseline, 3, 6, and 12 months after starting transtuzumab therapy).

4.2. Study protocol

A complete past medical history, cardiac risk factors and medical treatment were recorded for all patients at baseline, with particular attention to prior chemotherapy and radiotherapy. Blood samples were collected at baseline and at 3, 6 and 12 months after inititation of transtuzumab therapy to assess troponin and NT-proBNP levels.

Each patient underwent a full cardiological assessment comprehensive of a complete echocardiogram at baseline before starting transtuzumab therapy, and then at 3,6, and 12 months

Cardiotoxicity was defined according to current guidelines as any of the following during follow-up: LVEF <50%, a 15% reduction in GLS, or hs-troponin levels above the 99th percentile.

4.2.1. Echocardiographic evaluation

All patients underwent complete transthoracic echocardiography using an EPIQ ultrasound system (Philips, Best, The Netherlands), equipped with an S5 or X5 transducer (1–5 MHz). Simpson's biplane method was used to assess indexed LV end diastolic (LVEDVI) and indexed LV end-systolic (LVESVI) volumes, LVEF and indexed left atrial volume (LAVI). Diastolic function was determined by measuring E/A ratio, E/E' ratio, deceleration time (DT), left atrial volume and maximum tricuspid

regurgitation (TR) velocity. Right chambers were evaluated by tricuspid annular plane systolic excursion (TAPSE), S' velocity at tissue doppler imaging (S'-TDI), and systolic pulmonary arterial pressure (sPAP).

LA and LV function were also assessed by STE and values of LA strain and GLS and reported as absolute values. For speckle-tracking echocardiographic analysis of LA and LV, 2D grayscale images were acquired at a frame rate of 40–80 frames per second and at least three consecutive cardiac cycles were recorded. The analysis of recordings was performed offline with a semi-automated acoustic tracking software.

Left ventricular strain was assessed from the apical 4, 3 and finally 2 chamber view and the mean GLS was additionally derived. Left atrial strain was obtained from the apical 4 chamber view and the value of PALS, Conduit (LACd) and Contraction (PACS) were then calculated tracking 3 points: medial mitral annulus, lateral mitral annulus and LA roof.

The standard right ventricular-focused apical four-chamber view calculates right ventricular free wall longitudinal strain (RVFWLS).

The region of interest was delineated by the Software and eventually optimized by manual adjustments when needed (figure 1).

4.3. Statistical Analysis

Continuous variables were evaluated for normality using the Shapiro–Wilk test and expressed as mean ± standard deviation (SD) if normally distributed. Categorical variables are presented as frequencies and percentages.

Baseline clinical and echocardiographic characteristics were compared between patients who developed cardiotoxicity and those who did not using the Student's t-test or Mann–Whitney U test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables, as appropriate.

Longitudinal changes in echocardiographic and biomarker parameters were assessed using repeated-measures analysis of variance (ANOVA), including the within-subject effect of time and the interaction between time and cardiotoxicity status (time × group interaction). Partial eta squared (η^2) was used as a measure of effect size.

Changes in echocardiographic parameters at 3 and 6 months were calculated as the difference between baseline and follow-up values and compared between groups using the Student's t-test or Mann–Whitney U test, as appropriate.

To identify independent predictors of cardiotoxicity, multivariable binary logistic regression analyses were performed. Given the limited number of cardiotoxicity events, regression models were intentionally restricted to avoid overfitting and included the 3-month change in left atrial conduit strain (ΔLAcd) adjusted separately for age and anthracycline exposure. Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

Receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminative performance of 3-month changes in left atrial conduit strain (ΔLAcd) and peak atrial longitudinal strain (ΔPALS) for predicting cardiotoxicity. The optimal cut-off value was determined using the Youden index. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated at the selected threshold.

A two-sided p-value <0.05 was considered statistically significant. Statistical analysis was performed by SPSS 25.0 software (SPSS, Inc., Chicago, IL, USA).

4.4. Use of artificial intelligence

Artificial intelligence has been used for image creation and bibliographic research.

5. RESULTS

A total of 45 female patients were initially enrolled in the study. Eight patients were excluded: five due to poor acoustic window, two because of atrial fibrillation, and one who declined participation. Therefore, the final study population consisted of 37 patients.

During follow-up, 10 patients (27%) developed cardiotoxicity. Among these, only one patient (2.7% of the total cohort) experienced moderate cardiotoxicity, defined as an asymptomatic left ventricular ejection fraction (LVEF) <50% during follow-up.

Regarding the timing of cardiotoxicity onset, only one patient (2.7%) developed cardiotoxicity at three months, six patients (16.2%) at 6 months, whereas the remaining three patients (8.1%) developed cardiotoxicity at 12 months of follow-up.

5.1. Baseline clinical and echocardiographic characteristics

Baseline clinical and echocardiographic characteristics are summarized in Tables 1 and 2.

The mean age of the population was 54.9 ± 12.3 years, with no significant baseline clinical or echocardiographic differences between groups. Overall, 15 patients (40.5%) received anthracyclines, and 10 (27%) underwent radiotherapy.

5.2. Echocardiographic evaluation during follow-up

Table 3 summarizes the longitudinal changes in echocardiographic and biomarker parameters according to cardiotoxicity status, as assessed by repeated-measures ANOVA. It showed a significant time × cardiotoxicity interaction only for LA conduit strain ($p=0.02$, partial $\eta^2=0.13$), indicating a different temporal evolution according to cardiotoxicity status. No significant interactions were observed for LVEF, left atrial volume, reservoir strain, contractile strain, or right ventricular free-wall longitudinal strain. A trend towards a differential temporal evolution was observed for NT-proBNP (interaction $p=0.09$; partial $\eta^2=0.12$) and hs-troponin (interaction $p=0.06$, partial $\eta^2=0.12$).

Early changes in echocardiographic parameters according to cardiotoxicity status are shown in Tables 4 and 5. At 3-month follow-up, patients who subsequently developed cardiotoxicity exhibited significantly greater changes in left atrial reservoir strain (PALS) and left atrial conduit strain (LAcd) compared with those who did not develop cardiotoxicity (p=0.03 and p=0.01, respectively). In contrast, no significant differences were observed for LVEF, GLS, left atrial volume, peak atrial contraction strain (PACS), or right ventricular free-wall longitudinal strain (RFWLS).

At 6 months, left atrial strain differences between groups remained evident. Patients with cardiotoxicity showed significantly greater changes in PACS (p=0.04), while changes in PALS and LAcd demonstrated borderline statistical significance (both p=0.05). No significant between-group differences were observed for LVEF, GLS, left atrial volume, or RFWLS.

5.3. ROC curves.

Receiver operating characteristic (ROC) analysis (Figure 2) demonstrated that 3-month changes in left atrial conduit strain (ΔLAcd) were significantly associated with the development of cardiotoxicity (AUC 0.76, CI 95% 0.59-0.89, p=0.02), whereas changes in peak atrial longitudinal strain (ΔPALS) showed only a trend toward significance (AUC 0.70, CI 95% 0.51-0.88, p=0.08). According to the Youden index, the optimal cut-off value for ΔLAcd was −2.45, yielding a sensitivity of 70.0%, specificity of 70.8%, positive predictive value of 50.0%, and negative predictive value of 85.0%.

5.4. Predictors of cardiotoxicity

Two multivariable logistic regression models were constructed to evaluate the association between early changes in left atrial conduit strain and the development of cardiotoxicity (Table 6). Given the limited number of cardiotoxicity events, models were intentionally restricted to avoid overfitting.

In the first model, adjusted for prior anthracycline exposure, 3-month ΔLAcd remained significantly associated with cardiotoxicity (OR 0.82, 95% CI 0.69–0.98; p=0.03), whereas anthracycline treatment itself was not associated with the outcome (p=0.44).Similarly, in the second model adjusted for age,

ΔLAcd remained an independent predictor of cardiotoxicity (OR 0.82, 95% CI 0.68–0.97; p=0.02), while age was not significantly associated with cardiotoxicity (p=0.50).

6. DISCUSSION

The major findings of our study were:

1) Cardiotoxicity occurred in 27% of patients receiving trastuzumab and was detected predominantly at the 6-month follow-up assessment
2) Alterations in left atrial strain parameters were observed earlier than conventional markers of cardiac dysfunction, with significant changes in left atrial reservoir and conduit strain already evident at 3 months, whereas left ventricular functional impairment became apparent later during follow-up
3) Early changes in left atrial conduit strain independently predicted the subsequent development of cardiotoxicity, suggesting that left atrial functional assessment may provide incremental value for the early identification of patients at risk.

Our findings regarding the incidence of cardiotoxicity are consistent with studies that share a multidimensional definition of this condition (with rates ranging from 20% (9) to 36%(10)) which explains why this percentage is higher than that reported in series restricting the diagnosis exclusively to a drop in LVEF (ranging from 9% (11) to 18,1% (12)).

In this context, the scientific evidence accumulated to date consistently demonstrates that alterations in left atrial strain (principally its reservoir and contraction phases) precede the deterioration of left ventricular ejection fraction and, in certain scenarios, occur simultaneously with or prematurely to GLS. For instance, Park et al. (12) demonstrated that the decline in PALS following chemotherapy possessed a superior predictive capacity for future cardiotoxicity compared to the decline in GLS in patients treated with trastuzumab (cutoff point: 11.79%; sensitivity: 76.9%; specificity: 81.4%); findings that are in close consonance with those reported by Narvasa et al. (10) and Bergamini et al. (11).

To the best of our knowledge this is the first study showing that early LA conduit strain decline is a predictor of cardiotoxicity, preceding fluctuation of GLS. Notably, some differences from the retrospective registry by Lassen et al. (9), who demonstrated a significant reduction in all left atrial strain parameters as early as 3 months after starting trastuzumab therapy. However, while Lassen et al.

observed a generalized decline in LA conduit strain even among patients who did not develop CTRCD (Δ: -2.2%), our prospective cohort revealed a more selective behavior. In our study, LA conduit strain remained stable in the non-cardiotoxicity group at 3 months (Δ LAcd: 0.73± 6.77%), contrasting with the reduction observed exclusively in the cardiotoxicity cohort (Δ LAcd: -5.99 ± 6.48%, p=0.01). This could point to the clinical potential of LAcd as a clinical parapotential marker of subclinical myocardial involvement.

The variation in reservoir strain also showed abnormal modifications; however, this finding was limited exclusively to the univariate analysis, a peculiarity that is probably subject to the sample size of the study.

6.1. Plausible pathophysiological mechanism

This finding could be explained by the pathophysiology of the atrial phases themselves. The reservoir phase depends closely on the longitudinal relaxation/contraction of the left ventricle (LV) and the compliance of the left atrium (LA). The conduit phase is highly influenced by LV relaxation and elastic recoil (e' wave, diastolic properties), and finally, the contraction phase depends on maintaining sinus rhythm (13).

Trastuzumab inhibits HER2/HER4 dimerization, blocking PI3K/Akt and MAPK pathways that maintain homeostasis, mitochondrial function, and calcium handling (14), which would progressively lead to increased myocardial stiffness and possible diastolic dysfunction (15).

In our study, at the start of treatment, before contractile strength was lost (which explains why ΔGLS and ΔLVEF at 3 months were normal, p=0.40 and p=0.42, respectively), the ventricular myocardium could become subtly stiffer. This loss of ventricular compliance could alter passive left atrial (LA) emptying, which would statistically translate into a decrease in LAcd.

6.2. Evolution of the different phases of atrial strain

In the initial part of treatment, at 3 months, damage to atrial distensibility predominates (decrease in ΔLAcd). At 6 months, the difference in ΔLAcd is subtly attenuated (p=0.05), but damage to contraction

strain emerges (ΔPACS p=0.04). These data are consistent with current evidence, in which LASr and LAcd are altered early (16). The contractile phase (LASct/PACS) may show an initial compensatory response (17) or deteriorate somewhat later, with a decrease as damage progresses and treatment accumulates (18), when atrial myopathy and/or diastolic dysfunction would be more advanced.

6.3. Anticipation of atrial strain to ventricular strain

The present study showed that LAcd significantly dropped after 3 months of follow-up only in the cardiotoxicity group, while a significant reduction in GLS was shown only after 6 months of treatment. Such findings are in line with those of Laufer-Perl et al (19). who showed a consistent reduction in LA strain values with no compatible change in GLS values in a population of patients undergoing anthracycline

6.4. ROC Curve Analysis

The analysis under the Curve shows us a cutoff point of reduction of -2.45% in the LAcd at 3 months, offering a sensitivity of 70% and a Negative Predictive Value (NPV) of 85%.

6.5. Model adjusted for anthracyclines and age

In our adjusted model, age and anthracycline exposure were selected as variables due to their established role as determinants of cardiotoxicity in the previous scientific literature (20) (21). Specifically, both age over 65 years (22) and the administration of high cumulative doses of anthracyclines (23) have been shown to independently increase myocardial vulnerability in this clinical setting.

In both models, this clinical variables were not significantly associated with the outcome, highlighting an independent prognostic value of early left atrial conduit dysfunction

6.6. Cardiac biomarkers

Regarding cardiac biomarkers, it is known that troponin I elevation, in particular, helps predict cardiotoxicity in patients treated with trastuzumab (24). However, the literature is not entirely consistent. In patients without prior anthracycline exposure, TnT and NT-proBNP showed rare elevations and little predictive utility in NeoALTTO (25). Consistently, another review concluded that troponin results in adjuvant trastuzumab therapy are conflicting, although overall they support a

possible early predictive role (26). In our study, troponin levels are generally elevated due to cancer treatment, but their longitudinal trajectory does not discriminate as accurately as conduit-phase atrial strain would in our case. Therefore, we could propose their measurement in combination with left atrial strain to maximize the negative predictive value.

6.7. Limitations

Our study has several limitations that should be acknowledged. First, the sample size is relatively small (n=37), and it reflects a single-center experience, which may limit the generalizability of our findings to broader or more diverse clinical settings. Second, due to the limited number of cardiotoxicity events recorded during follow-up (n=10), our multivariable binary logistic regression models were intentionally restricted to two variables to prevent overfitting. Consequently, we were unable to adjust simultaneously for all potential baseline clinical confounding factors within a single model. Third, although left atrial reservoir strain (ΔPALS) showed significant changes at 3 months in the univariate comparison, it did not achieve independent statistical significance in the ROC curve analysis (p=0.08) or the multivariable models, an aspect that was likely underpowered by our limited sample size. While all patients completed a 12-month echocardiographic follow-up, a longer observation period is needed to determine whether this early 3-month left atrial conduit dysfunction permanently correlates with long-term clinical heart failure or persistent left ventricular remodeling.

7. CONCLUSIONS

Our findings suggest that an early decline in left atrial conduit strain may identify a subgroup of trastuzumab-treated patients at increased risk of developing cardiotoxicity. In particular, a reduction greater than 2.45% at 3 months showed a favorable sensitivity for detecting subsequent cardiotoxicity and may help identify patients who could benefit from closer cardiac surveillance. These findings should be confirmed in larger prospective studies.

8. LIST OF ABBREVIATIONS

ACE-I: Angiotensin-Converting Enzyme Inhibitors

ANOVA: Analysis of Variance

ARBs: Angiotensin Receptor Blockers

AUC: Area Under the Curve

BMI: Body Mass Index

CI: Confidence Interval

CTRCD: Cancer Therapy-Related Cardiac Dysfunction

DT: Deceleration Time

E/A: Ratio of Early-to-Late Diastolic Transmitral Flow Velocities

E/e': Ratio of Transmitral Early Diastolic Velocity to Tissue Doppler Early Diastolic Mitral Annular Velocity

GLS: Global Longitudinal Strain

HER2 / HER-II: Human Epidermal Growth Factor Receptor 2

hs-troponin / Hs-Troponin: High-Sensitivity Troponin

LA: Left Atrium / Left Atrial

LAcd / ΔLAcd: Left Atrial Conduit Strain / Change in Left Atrial Conduit Strain

LASct: Left Atrial Contraction Strain

LASr: Left Atrial Reservoir Strain

LAVI: Indexed Left Atrial Volume

LV: Left Ventricle / Left Ventricular

LVEDVI: Indexed Left Ventricular End-Diastolic Volume

LVEF / ΔLVEF: Left Ventricular Ejection Fraction / Change in Left Ventricular Ejection Fraction

LVESVI: Indexed Left Ventricular End-Systolic Volume

LVM: Left Ventricular Mass

MAPK: Mitogen-Activated Protein Kinase

NPV: Negative Predictive Value

NT-proBNP / proBNP: N-Terminal pro-B-Type Natriuretic Peptide

OR / O.R.: Odds Ratio

PACS / ΔPACS: Peak Atrial Contraction Strain / Change in Peak Atrial Contraction Strain

PALS / ΔPALS: Peak Atrial Longitudinal Strain / Change in Peak Atrial Longitudinal Strain

PI3K/Akt: Phosphoinositide 3-Kinase / Protein Kinase B

PPV: Positive Predictive Value

RFWLS / RVFWLS / ΔRFWLS: Right Ventricular Free Wall Longitudinal Strain / Change in Right Ventricular Free Wall Longitudinal Strain

ROC: Receiver Operating Characteristic

S'-TDI: S' Velocity at Tissue Doppler Imaging

SD: Standard Deviation

sPAP: Systolic Pulmonary Arterial Pressure

STE: Speckle-Tracking Echocardiography

TAPSE: Tricuspid Annular Plane Systolic Excursion

TnT: Troponin T

TR: Tricuspid Regurgitation

9. DECLARATIONS

9.1. Ethics approval and consent to participate

The study was approved by the local Ethics Committee, and all patients provided written informed consent.

9.2. Consent for publication

Not applicable.

9.3. Availability of data and materials

The data underlying this article are available in the article.

9.4. Competing interests

The authors declare that they have no competing interests.

9.5. Funding

This work does not have external funding.

9.6. Authors' contributions

CAF: Conceptualization, methodology, data curation, formal analysis, writing – original draft preparatio, writing – review and editing.

SGC: Conceptualization, methodology, data acquisition (echocardiographic imaging), supervision, writing – review and editing.

RGG: Investigation and patient recruitment.

FMZC: Data acquisition (echocardiographic imaging).

EDDR: Data acquisition (echocardiographic imaging).

MEGC: Writing – review, editing and validation.

9.7. Acknowledgements

Not applicable.

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11. FIGURE LEGENDS

Figure 1. Example of LA strain analysis.

Figure 2. Receiver operating characteristic (ROC) curves of baseline-to-3-month changes in left atrial conduit strain (ΔLAcd) and peak atrial longitudinal strain (ΔPALS) for predicting cardiotoxicity.

12. TABLES

TABLE 1. Basal characteristics.

Variable	Global (n=37)	Cardiotoxicty (n=10)	No cardiotoxicity (n=27)	*p* value
Age (years)	54.9 ± 12.3	54.0 ± 8.0	55.2 ± 13.7	0.79
Hypertension	10 (27%)	2 (20%)	8 (30%)	0.69
Diabetes	4 (11%)	0 (0%)	4 (15%)	0.55
Dyslipemia	8 (22%)	1 (10%)	7 (26%)	0.40
Anthracycline	15 (40%)	5 (50%)	10 (37%)	0.71
BMI (kg/m^2)	26.9 ± 5.8	26.5 ± 4.6	27.0 ± 6.2	0.82
History of smoking	12 (32%)	4 (40%)	8 (30%)	0.70
ACE-I / ARBs	10 (27%)	2 (20%)	8 (30%)	0.69
Statins	6 (16%)	1 (10%)	5 (18%)	0.47
Beta-blockers	3 (8%)	1 (10%)	2 (7%)	0.80
Radiotherapy	10 (27%)	3 (30%)	7 (26%)	0.75

BMI: Body Mass Index; ACE-I: Angiotensin-Converting Enzyme Inhibitors; ARBs: Angiotensin Receptor Blockers.

TABLE 2. Baseline echocardiographic variables.

Variable	**Global (n=37)**	**Cardiotoxicity (n=10)**	**No cardiotoxicity (n=27)**	***p* value**
Indexed LVM (g/m2)	93.7 ± 28.9	87.4 ± 29.4	94.9 ± 31.9	0.57
LVEF (%)	63.6 ± 4.4	64.2 ± 4.3	63.4 ± 4.5	0.63
LA volume (ml/m^2)	27.9 ± 6.6	27.1 ± 4.4	28.2 ± 7.3	0.67
E wave (m/s)	0.77 ± 0.15	0.77 ± 0.14	0.77 ± 0.16	0.98
A wave (m/s)	0.83 ± 0.19	0.81 ±0.17	0.84 ± 0.19	0.68
E/e’	8.5 ± 3.2	8.5 ± 1.7	8.5 ± 3.6	0.94
TAPSE (mm)	22.4 ± 3.0	23.4 ± 3.5	22.0 ± 2.9	0.21
GLS (%)	-21.1 ± 2.5	-22.0 ± 2.0	-20.8 ± 2.6	0.20
RFWLS (%)	-25.2 ± 4.4	-26.3 ± 3.7	-24.8 ± 4.6	0.40
PALS (%)	35.6 ± 10.0	38.1 ± 10.2	34.6 ± 10.0	0.35
PACS (%)	-17.2 ± 5.8	-18.5 ± 5.7	-16.7 ± 5.9	0.42
LAcd (%)	-18.3 ± 7.5	-19.6 ± 7.4	-17.8 ± 7.7	0.52
HS-Troponin	2.2 ± 3.3	1.3 ± 0.5	2.5 ± 3.8	0.31
NT-proBNP	291 ± 98	65 ± 50	324 ± 101	0.40

LVM: Left Ventricular Mass; LVEF: Left Ventricular Ejection Fraction; LA: Left Atrial; TAPSE: Tricuspid Annular Plane Systolic Excursion; GLS: Global Longitudinal Strain; RFWLS: Right Free

Wall Longitudinal Strain; PALS: Peak Atrial Longitudinal Strain; PACS: Peak Atrial Contraction Strain; LAcd: Left Atrial Conduit Strain.

TABLE 3. Longitudinal changes in echocardiographic parameters according to cardiotoxicity status: repeated-measures ANOVA analysis.

Variable	**Time effect (p)**	**Group effect (p)**	**Group-time p**	**Partial η^2**
LVEF (%)	0.63	0.81	0.26	0.06
LA volume (ml)	0.78	0.72	0.37	0.04
LAcd (%)	0.42	0.85	0.02	0.13
PALS (%)	0.64	0.65	0.11	0.08
PACS (%)	0.92	0.60	0.31	0.05
RFWLS (%)	0.95	0.97	0.87	0.02
NT-proBNP	0.53	0.56	0.09	0.12
Hs-troponin	0.03	0.02	0.06	0.12

LVEF: Left Ventricular Ejection Fraction; LA: Left Atrial; RFWLS: Right Free Wall Longitudinal Strain; PALS: Peak Atrial Longitudinal Strain; PACS: Peak Atrial Contraction Strain; LAcd: Left Atrial Conduit Strain.

TABLE 4. Early changes in echocardiographic parameters at 3 months according to cardiotoxicity status.

Variable	**Cardiotoxicity**	**Non cardiotoxicity**	***p* value**
Δ LVEF	2.66 ± 8.07	0.90 ± 4.48	0.42

Δ GLS	1.34 ± 2.47	0.58 ± 2.31	0.40
Δ PALS	7.95 ± 10.92	-0.87 ± 10.00	0.03
Δ PACS	-1.95 ± 6.72	0.25 ± 5.22	0.31
Δ Lacd	-5.99 ± 6.48	0.73 ± 6.77	0.01
Δ RFWLS	1.36 ± 4.38	-0.12 ± 5.05	0.48
Δ LA volume (ml/m^2)	-0.99 ± 5.15	-0.39 ± 7.32	0.81

Δ values were calculated as baseline value minus follow-up value. LVEF: Left Ventricular Ejection Fraction; LA: Left Atrial; RFWLS: Right Free Wall Longitudinal Strain; PALS: Peak Atrial Longitudinal Strain; PACS: Peak Atrial Contraction Strain; LAcd: Left Atrial Conduit Strain.

TABLE 5. Changes in echocardiographic parameters at 6 months according to cardiotoxicity status.

Variable	**Cardiotoxicity**	**Non cardiotoxicity**	***p* value**
Δ LVEF	1.73 ± 7.67	2.54 ± 4.33	0.76
Δ GLS	2.88 ± 4.37	0.83 ± 2.80	0.14
Δ PALS	5.62 ± 7.26	-1.31 ± 9.04	0.05
Δ PACS	-3.05 ± 6.05	1.79 ± 5.37	0.04
Δ Lacd	-2.58 ± 4.50	-0.36 ± 6.66	0.05
Δ RFWLS	1.30 ± 3.01	0.28 ± 5.98	0.69
Δ LA volume (ml/m^2)	-1.34 ± 5.79	-1.20 ± 4.57	0.96

1 Δ values were calculated as baseline value minus follow-up value. LVEF: Left Ventricular Ejection
2 Fraction; LA: Left Atrial; RFWLS: Right Free Wall Longitudinal Strain; PALS: Peak Atrial
3 Longitudinal Strain; PACS: Peak Atrial Contraction Strain; LAcd: Left Atrial Conduit Strain.

4 TABLE 6. Logistic multivariable regression analysis for the prediction of cardiotoxicity.

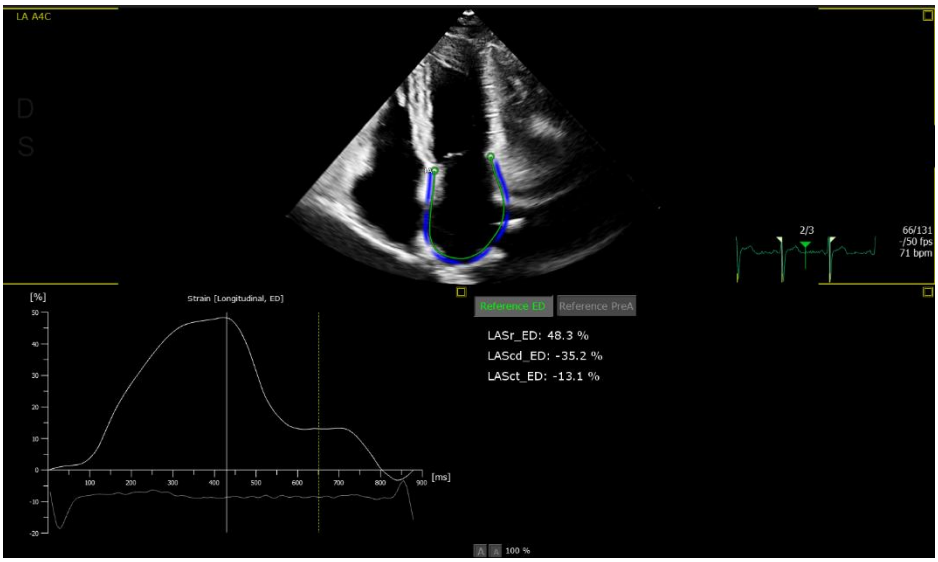
Variable	**O.R.**	**CI 95%**	***p* value**
Model 1			
Anthracyclines	0.51	0.09-2.87	0.44
ΔLAcd	0.82	0.69-0.98	0.03
Model 2			
Age (years)	1.02	0.95-1.10	0.50
ΔLAcd	0.82	0.68-0.97	0.02

5 O.R.:Odds Ratio; CI: Confidence Interval; ΔLAcd: Left Atrial Conduit Strain.

6

13. FIGURES

13.1. Figure 1



13.2. Figure 2

