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Original Article

Early detection of chemotherapy-induced cardiotoxicity in lymphoma patients: RT-3DE/2D-STI and predictive role of LAEFa/LASr

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Abstract: Objective: To evaluate the utility of real-time three-dimensional echocardiography (RT-3DE) and two-dimensional speckle tracking imaging (2D-STI) for early detection of chemotherapy-induced cardiotoxicity in lymphoma patients, and to identify independent predictors of cardiotoxicity using these imaging parameters. Methods: We conducted a single-center retrospective cohort study at The First People's Hospital of Changde City, enrolling 110 lymphoma patients who received anthracycline-based chemotherapy between January 2020 and January 2024. Echocardiographic assessments, including RT-3DE and 2D-STI, were performed before chemotherapy and within 72 hours after the 3rd and 6th cycles. Cardiotoxicity was defined as a ≥ 10% reduction in left ventricular ejection fraction (LVEF) or an LVEF < 50%. Results: Baseline clinical characteristics showed significant differences in gender and hypertension between the cardiotoxic and non-cardiotoxic groups (both $P < 0.05$). RT-3DE revealed time-dependent changes, with LAEFa higher and LAEFa/LAEFt lower in the cardiotoxic group at 3 and 6 weeks post-chemotherapy, respectively (all $P < 0.05$). 2D-STI showed significant differences in LASct and LASr at 3 and 6 weeks (all $P > 0.05$). GEE analysis indicated that changes in LAEFa, LAEFp, LAEFt, LASr, LASct, and LVEF were driven by the time × group interaction effect (all $P < 0.05$). Conclusion: RT-3DE and 2D-STI are sensitive for early detection of anthracycline-induced cardiotoxicity in lymphoma patients. LA functional indices (LAEFa, LAEFp, LAEFt) and LA strain indices (LASr, LASct) may detect cardiotoxicity earlier than LVEF, suggesting their potential role in optimizing cardio-oncology monitoring strategies.

Keywords: Real-time three-dimensional echocardiography, two-dimensional speckle tracking imaging, lymphoma, chemotherapy, early cardiotoxicity monitoring

Introduction

Lymphoma, a heterogeneous group of malignant tumors originating from the lymphohematopoietic system, ranks among the hematological malignancies with the highest incidence and mortality rates worldwide. It is also one of the most common malignancies in China [1]. According to the GLOBOCAN 2022 study, approximately 85,200 new cases of lymphoma were reported in China in 2022, with an incidence rate of 6.03 per 100,000 population. The number of deaths reached around 41,600, corresponding to a mortality rate of 2.95 per 100,000 population [2], reflecting an ongoing increase in the disease burden.

Chemotherapy is a standard treatment for lymphoma. Patients with early-stage Hodgkin lymphoma (HL) typically require 2-6 cycles of chemotherapy, while non-Hodgkin lymphoma (NHL) patients may undergo 6-8 cycles or more, depending on the lymphoma subtype and stage [3, 4]. Combined chemotherapy regimens centered on anthracyclines have significantly improved the prognosis of patients with various lymphoma subtypes. For early-stage HL patients treated with 2-6 cycles of the ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine), the 5-year progression-free survival (PFS) rate exceeds 85% [5]. For patients with intermediate-to-high-risk NHL requiring 6-8 cycles of the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine), the

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5-year overall survival (OS) rate reaches 88.5% [6].

Anthracycline-induced cardiotoxicity presents distinct time-dependent characteristics. According to the 2016 European Society of Cardiology Position Statement on Cancer Therapy and Cardiovascular Toxicity [7], acute toxicity typically occurs within hours to days after drug infusion, manifesting as transient pericarditis, QT interval prolongation, or arrhythmias, with favorable clinical outcomes. Early chronic toxicity, primarily characterized by occult left ventricular (LV) dysfunction, may be subclinical initially, with a decline in left ventricular ejection fraction (LVEF) of ≥ 10% from baseline or an LVEF < 50% as the disease progresses. Traditional LVEF monitoring has significant limitations: as a macro-indicator of global LV systolic function, LVEF decreases only after significant myocardial cell damage or functional impairment, typically delayed by 3-6 months compared to subclinical injury, and it cannot detect early myocardial strain abnormalities [8, 9]. However, early intervention during the subclinical phase can reverse cardiac function in 64-82% of patients with early-onset cardiotoxicity [10]. Therefore, developing sensitive and specific early monitoring technologies is critical for improving cardio-oncology management in lymphoma patients undergoing chemotherapy.

Real-time three-dimensional echocardiography (RT-3DE) and two-dimensional speckle tracking imaging (2D-STI) are advanced echocardiographic techniques that provide a new approach for early detection of cardiotoxicity. RT-3DE uses a volume probe to capture dynamic three-dimensional data of the entire heart, enabling direct quantification of left atrial (LA) parameters such as maximum volume (LAVmax), minimum volume (LAVmin), and functional indices (total function: LAEFt; conduit function: LAEFp; booster pump function: LAEFa). Compared to two-dimensional echocardiography, RT-3DE has lower measurement errors and is particularly useful for detecting subtle early LA remodeling during chemotherapy [11, 12]. On the other hand, 2D-STI calculates myocardial strain parameters (LA reservoir strain: LASr; LA conduit strain: LAScd; LA contractile strain: LASct) by tracking the movement of natural acoustic speckles in myocardial tissue. Its sensitivity to subtle myocardial systolic dysfunction is 2-3 times higher than that of traditional echocardiographic indicators, enabling the detection of subclinical myocardial injury even when LVEF remains normal [13].

Although there is evidence supporting the use of RT-3DE and 2D-STI for monitoring anthracycline-induced cardiotoxicity in breast cancer, most studies in lymphoma have focused on late-stage cardiotoxicity (≥ 1 year after treatment completion), with little attention to the dynamic changes in early LA function during chemotherapy. Furthermore, the diagnostic efficacy of combining RT-3DE and 2D-STI for early-onset cardiotoxicity in lymphoma patients, as well as the feasibility of using LA function/strain parameters as predictors of chemotherapy-induced cardiotoxicity, has not been fully explored. This study aims to analyze the dynamic changes in LA function and strain parameters in lymphoma patients before chemotherapy and after 3 and 6 cycles of anthracycline-based chemotherapy. Additionally, it seeks to identify independent predictors of early-onset cardiotoxicity, assess the clinical value of RT-3DE and 2D-STI for early diagnosis, and provide evidence-based support for optimizing cardio-oncology management strategies in lymphoma patients.

Materials and methods

Patient selection

Muñoz-Rossi et al. [14] reported a 13% incidence of anthracycline-related cardiotoxicity.

Statistical parameters: The following standard norms were set for moderate-effect-size studies: (1) Type I error rate (α) = 0.05 (two-sided); (2) Type II error rate (β) = 0.25 (statistical power = 75%, which is common in single-center retrospective studies with real-world data constraints); (3) Attrition rate = 8% (lower than 10% due to strict electronic medical record screening).

We adopted the two-independent-samples t-test formula for continuous parameters (such as LAEFa), which was more aligned with our study's primary comparison, instead of the single-proportion formula. This was verified using G*Power 3.1 software. The key formula is:

$$n = \frac{(z_{1-a} + z_{1-\beta})^2 \times (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2} \times (1 + \text{attrition rate})$$

z1-α/2 = 1.96 (α = 0.05), z1-β = 0.67 (β = 0.25, power = 75%);

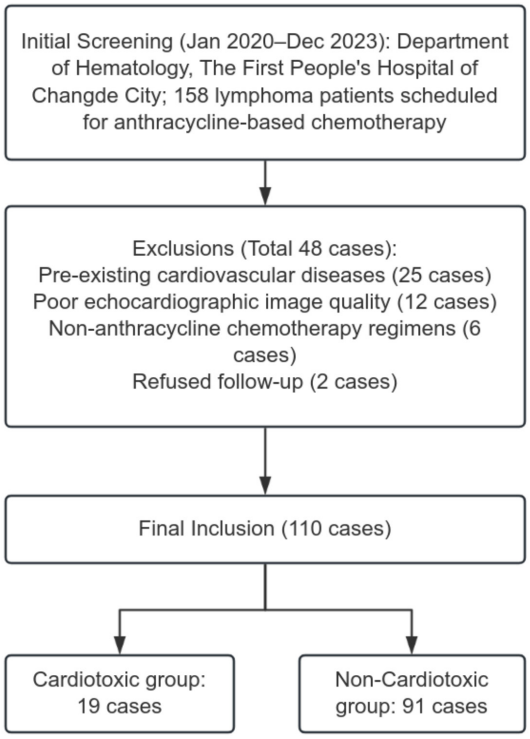

Figure 1. Patient enrollment flow diagram for lymphoma patients undergoing anthracycline-based chemotherapy.

$\sigma1 = \sigma2 = 4.5$ (SD of LAEFa in both groups, assumed equal for simplicity);

$\mu1-\mu2 = 6$ (predefined mean LAEFa difference between groups);

Attrition rate = 8%.

Considering the 1:7 group ratio (13% cardiotoxicity incidence: 1 cardiotoxic case for every 7 non-cardiotoxic cases), the minimum total sample size required to ensure sufficient cases in both groups is 90 cases (12 cardiotoxic, 78 non-cardiotoxic). Our study ultimately enrolled 110 patients (19 cardiotoxic, 91 non-cardiotoxic), exceeding the minimum required sample size.

A total of 110 chemotherapy patients treated at The First People's Hospital of Changde City from January 2020 to January 2024 were included.

The inclusion criteria were as follows: (1) Pathologically confirmed Hodgkin lymphoma or non-Hodgkin lymphoma. (2) Scheduled to receive anthracycline-based chemotherapy regimens. (3) Age ≥ 18 years. (4) Baseline left ventricular ejection fraction (LVEF) ≥ 50%. (5) Completed both RT-3DE and 2D-STI assessments before chemotherapy, and within 72 hours after the 3rd and 6th chemotherapy cycles.

The exclusion criteria were: (1) History of severe cardiovascular diseases (e.g., myocardial infarction, advanced heart failure, cardiomyopathy). (2) Uncontrolled comorbidities affecting cardiac function (hypertension, diabetes mellitus, thyroid dysfunction). (3) Recent treatment with therapies impacting cardiac function, including radiation therapy or cardiotoxic medications. (4) Severe hepatic or renal insufficiency.

Known allergy to echocardiographic contrast agents

This study was approved by the ethics committee of The First People's Hospital of Changde City. Details of the sample size screening process are shown in **Figure 1**.

Data extraction

Assessments were completed within 7 days prior to chemotherapy, including information such as age, gender, and Body Mass Index (BMI), as well as comorbidities like diabetes and hypertension. Comorbidities were assessed using standardized questionnaires and laboratory tests to confirm diabetes (fasting blood glucose ≥ 7.0 mmol/L or HbA1c ≥ 6.5%) and hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or on antihypertensive treatment). Patients received standard chemotherapy regimens containing anthracycline drugs (each cycle lasting 21 days). Pathological subtypes were confirmed according to the World Health Organization (WHO) classification, and disease staging was conducted using the Ann Arbor system. Patients underwent RT-3DE and 2D-STI examinations within 72 hours after the 3rd and 6th chemotherapy cycles.

Outcome measures

The primary outcomes included RT-3DE parameters after the 3rd and 6th chemotherapy cycles (LAEFt, LAEFp, LAEFa, LVEF) as well as 2D-STI parameters (LASr, LAScd, LASct).

Cardiotoxicity was determined by a decrease in LVEF of ≥ 10% from baseline or an LVEF < 50%, with or without related symptoms of heart fail-

ure. Patients were categorized into two groups: the cardiotoxic and non-cardiotoxic groups.

Equipment

The Philips EPIQ 7C ultrasound system (Philips Medical Systems, USA) was used for all examinations. Conventional two-dimensional echocardiography was performed using the S5-1 probe, while three-dimensional echocardiography utilized the X5-1 volume probe.

(1) Conventional echocardiography: Patients were examined in the left lateral decubitus position with electrocardiogram (ECG) monitoring in a resting state. Left ventricular structure and function were assessed, and parameters measured included: left ventricular end-diastolic diameter (LVEDd), interventricular septal thickness (IVS), left ventricular posterior wall thickness (LVPW), LVEF, relative wall thickness (RWT), and left ventricular mass index (LVMI).

(2) RT-3DE: The apical four-chamber view was selected to obtain clear endocardial images. During breath-holding, dynamic 3D images were recorded over four cardiac cycles. Offline analysis was conducted using QLAB 13.0 software in the 3DQA mode to generate time-volume curves for the left atrium. Parameters such as left atrial maximal volume (LAVmax), minimal volume (LAVmin), and pre-systolic volume (LAVpre) were recorded. These volume measurements were normalized to body surface area (BSA) to compute the left atrial volume index (LAVImax). Mechanical function parameters of the left atrium were also calculated, including LAEFt, LAEFp, and LAEFa.

(3) 2D-STI: The apical four-chamber and two-chamber views were selected. Image parameters were adjusted to obtain clear endocardial delineation of the left atrium. Offline analysis was conducted using QLAB 13.0 software with the AutoStrain LA technique, which automatically identifies and traces the endocardial border of the left atrium in 2D images. Strain values for different phases of the cardiac cycle were measured relative to the end-diastolic zero-strain reference point, including LA reservoir strain (LASr), conduit strain (LAScd), and contraction strain (LASct).

Statistical analysis

Statistical analysis was performed using R 4.4.1 software. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as counts and percentages. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Independent t-tests or Mann-Whitney U tests were used for continuous variables. For categorical variables, Pearson's chi-square test was used first; if there was an expected frequency of < 5 in any cell of the contingency table, Fisher's exact test was applied instead, and the two-tailed *P*-value of Fisher's exact test was used for statistical inference.

Generalized Estimating Equations (GEE) were used to analyze repeated measures data and assess changes in echocardiographic parameters over time, accounting for within-subject correlations. All statistical tests were conducted with a significance level (α) set at 0.05, and a $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of general characteristics

No significant differences were observed between the two groups in terms of age, body mass index, prevalence of diabetes, lymphoma type, or disease stage (all $P > 0.05$). However, significant differences were noted in gender and the distribution of hypertension (both $P < 0.05$), with a higher proportion of males and hypertensive patients in the cardiotoxic group, as shown in **Table 1**.

No significant differences were found in any of the echocardiographic parameters (all $P > 0.05$), including LVEDd, IVS, LVPW, RWT, LVM, and LVMI, as shown in **Table 2**.

Comparison of RT-3DE and 2D-STI parameters before chemotherapy, 3 and 6 cycles of chemotherapy

Regarding LAEF-related indices, significant differences were observed in post-3-cycle LAEFa and post-6-cycle LAEFa between groups (both $P < 0.001$). Specifically, the cardiotoxic group exhibited higher LAEFa after 3 cycles but lower LAEFa after 6 cycles. Among left atrial total function indices, post-6-cycle LAEFt ($P = 0.001$) was significantly reduced in the cardiotoxic group. For LVEF, only post-6-cycle LVEF showed a significant difference ($P < 0.001$), with a lower value in the cardiotoxic group (**Figure 2**).

Table 1. Comparison of clinical data between two groups

Characteristic		Non-cardiotoxic (N = 91)	Cardiotoxic (N = 19)	Z/χ^2	P
Age(year)		58.00 (56.00, 61.00)	58.00 (55.50, 60.50)	0.074	0.941
Gender	Male	51 (56%)	17 (89.5%)	7.442	0.006
	Female	40 (44%)	2 (10.5%)		
BMI (kg/m^2)		23.40 (21.50, 25.70)	22.10 (20.85, 23.30)	0.381	0.704
Diabetes		26 (28.6%)	2 (10.5%)	2.697	0.148[a]
Hypertension		18 (19.8%)	0 (0%)	4.494	0.038[a]
Type	Non-Hodgkin lymphoma	72 (79.1%)	14 (73.7%)	0.272	0.602
	Hodgkin lymphoma	19 (20.9%)	5 (26.3%)		
Stage	III-IV	57 (62.6%)	13 (68.4%)	0.227	0.634
	I-II	34 (37.4%)	6 (31.6%)		

Note: BMI: Body Mass Index. When conducting data analysis and calculation, the assignment of values for categorical data, Cardiotoxic = 1, Non-Cardiotoxic = 0; Gender: male = 1, female = 0; Hypertension: yes = 1, no = 0; Type: Non-Hodgkin lymphoma = 1, Hodgkin lymphoma = 2; Stage: III-IV = 2, I-II = 1. [a]*P* value was obtained using Fisher's exact test, and it represents a two-tailed result.

Table 2. Comparison of conventional echocardiographic parameters between two groups

Characteristic	Non-cardiotoxic (N = 91)	Cardiotoxic (N = 19)	t/Z	P
LVEDd (mm)	41.06 (40.00, 45.00)	43.00 (41.10, 45.45)	1.056	0.291
IVS (mm)	7.96 (6.83, 10.35)	7.47 (6.00, 8.72)	0.543	0.587
LVPW (mm)	9.34 (7.06, 12.00)	8.23 (6.95, 12.00)	0.539	0.590
RWT	0.41 ± 0.09	0.38 ± 0.08	0.678	0.500
LVM (g)	120.91 (104.53, 133.99)	117.20 (91.84, 129.38)	0.761	0.447
LVMI (g/m^2)	73.10 (66.60, 86.02)	76.36 (60.00, 82.58)	1.083	0.279

Note: LVEDd: Left Ventricular End-Diastolic Diameter; IVS: Interventricular Septal Thickness; LVPW: Left Ventricular Posterior Wall Thickness; RWT: Relative Wall Thickness; LVM: Left Ventricular Mass; LVMI: Left Ventricular Mass Index.

In the cardiotoxic group, post-3-cycle LASct (-15.00 vs. -18.00, P < 0.001), post-6-cycle LASct (-12.00 vs. -17.00, P < 0.001), and post-6-cycle LASr (13.00 vs. 14.00, P = 0.029) were significantly lower than those in the non-cardiotoxic group. No significant intergroup differences were observed for the remaining parameters (pre-chemo LAScd, post-3-cycle LAScd, post-6-cycle LAScd, pre-chemotherapy LASct, pre-chemotherapy LASr, post-3-cycle LASr) (all P > 0.05, **Figure 3**).

After 3 cycles of chemotherapy, significant differences in left atrial function were noted between the non-cardiotoxic and cardiotoxic groups. On RT-3DE (**Figure 4A**, **4B**): LAEFa and LAEFt in the non-cardiotoxic group remained within the normal range; the cardiotoxic group displayed "compensatory" features, including left atrial volume dilation and a significant increase in LAEFa - suggesting that the left atrium compensated for early myocardial injury by enhancing active contraction. On 2D-STI (**Figure 4C**, **4D**): LASr and LASct in the non-cardiotoxic group were normal; in the cardiotoxic group, LASr showed no significant change, while LASct was impaired - and this abnormality occurred earlier than that of the traditional LVEF indicator.

Results from GEE revealed that changes in LAEFa were primarily influenced by the interaction between chemotherapy time and cardiotoxicity status. At 6 weeks post-chemotherapy, LAEFa in the cardiotoxic group was significantly lower than that in the non-cardiotoxic group (P < 0.05). At 3 weeks post-chemotherapy, the non-cardiotoxic group showed a significant decrease in LAEFa (P < 0.05), whereas no significant change in LAEFa was observed in the cardiotoxic group (P > 0.05). These findings indicated significant differences in the dynamic change patterns of LAEFa between the two groups during chemotherapy, with the cardiotoxic group exhibiting significant functional decline in the late stage (6 weeks post-chemotherapy) (P < 0.05).

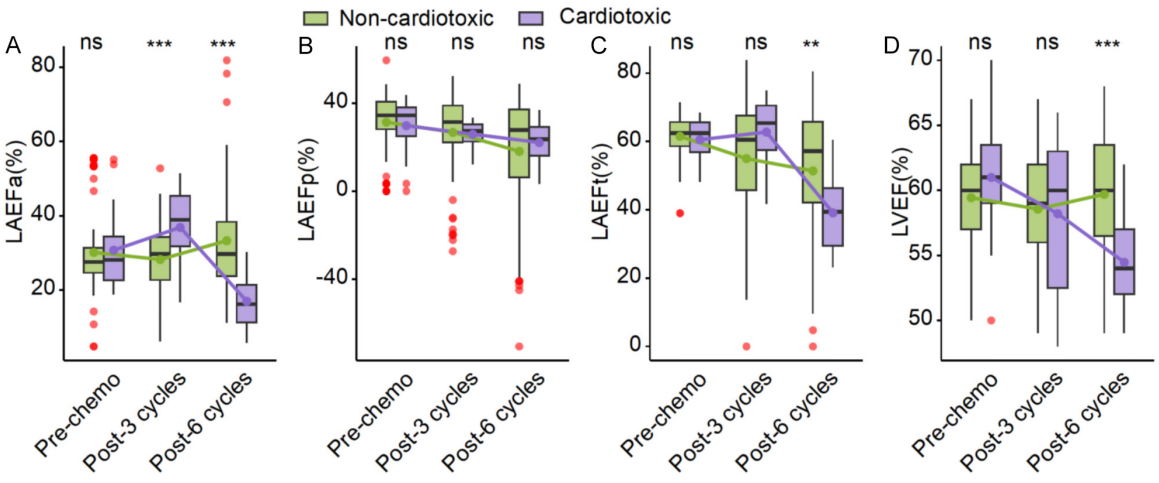

Figure 2. Comparison of RT-3DE parameters between two groups. A: Comparison of LAEFa between the two groups at pre-chemo, Post-3 cycles, and Post-6 cycles. B: Comparison of LAEFp between the two groups at the three time points. C: Comparison of LAEFt between the two groups at the three time points. D: Comparison of LVEF between the two groups at the three time points. Note: RT-3DE: Real-Time Three-Dimensional Echocardiography; LAEFa: Left Atrial Booster Pump Function Ejection Fraction; LAEFp: Left Atrial Conduit Function Ejection Fraction; LAEFt: Left Atrial Total Function Ejection Fraction; LVEF: Left Ventricular Ejection Fraction; ns: Non-significant ($P > 0.05$); **: $P < 0.01$; ***: $P < 0.001$.

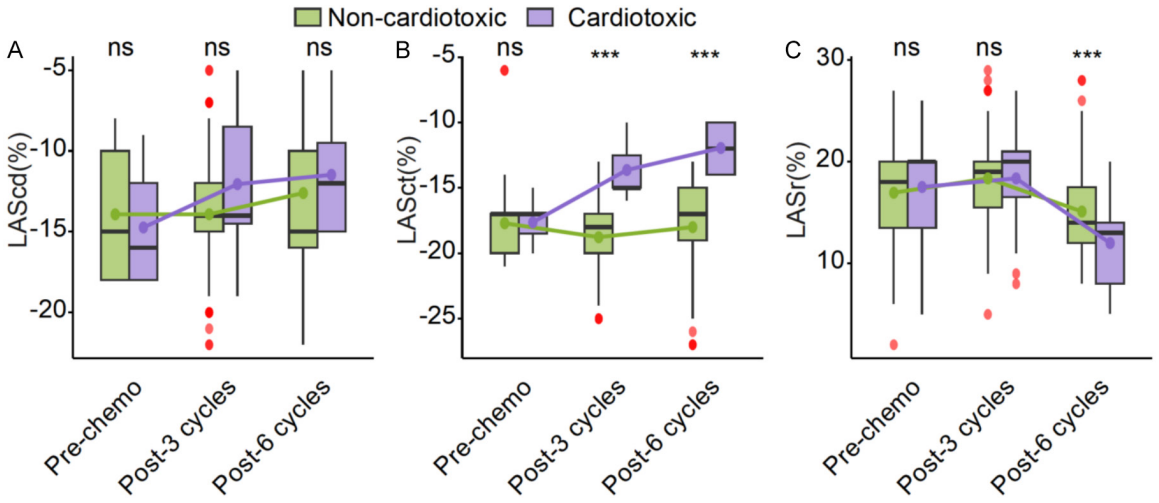

Figure 3. Comparison of 2D-STI parameters between two groups. A: Comparison of LAScd between the two groups at pre-chemo, Post-3 cycles, and Post-6 cycles. B: Comparison of LASct between the two groups at the three time points. C: Comparison of LASr between the two groups at the three time points. Note: 2D-STI: Two-Dimensional Speckle Tracking Imaging; LAScd: Left Atrial Conduit Strain; LASct: Left Atrial Contractile Strain; LASr: Left Atrial Reservoir Strain; ns: Non-significant ($P > 0.05$); ***: $P < 0.001$.

With pre-chemotherapy (time = 0) as the reference, LAEFp in the non-cardiotoxic group significantly increased at 3 weeks post-chemotherapy and maintained this significant increasing trend at 6 weeks post-chemotherapy (both $P < 0.05$) - reflecting the compensatory adjustment of LA conduit function in the non-cardiotoxic group. In contrast, the cardiotoxic group did not exhibit a similar significant compensatory increase in LAEFp at either 3 or 6 weeks post-chemotherapy (both $P > 0.05$), suggesting that cardiotoxicity may disrupt the normal compensatory process of LA conduit function.

Using pre-chemotherapy as the reference, LAEFt in the non-cardiotoxic group significantly increased at 3 weeks post-chemotherapy and remained at a significantly elevated level at 6

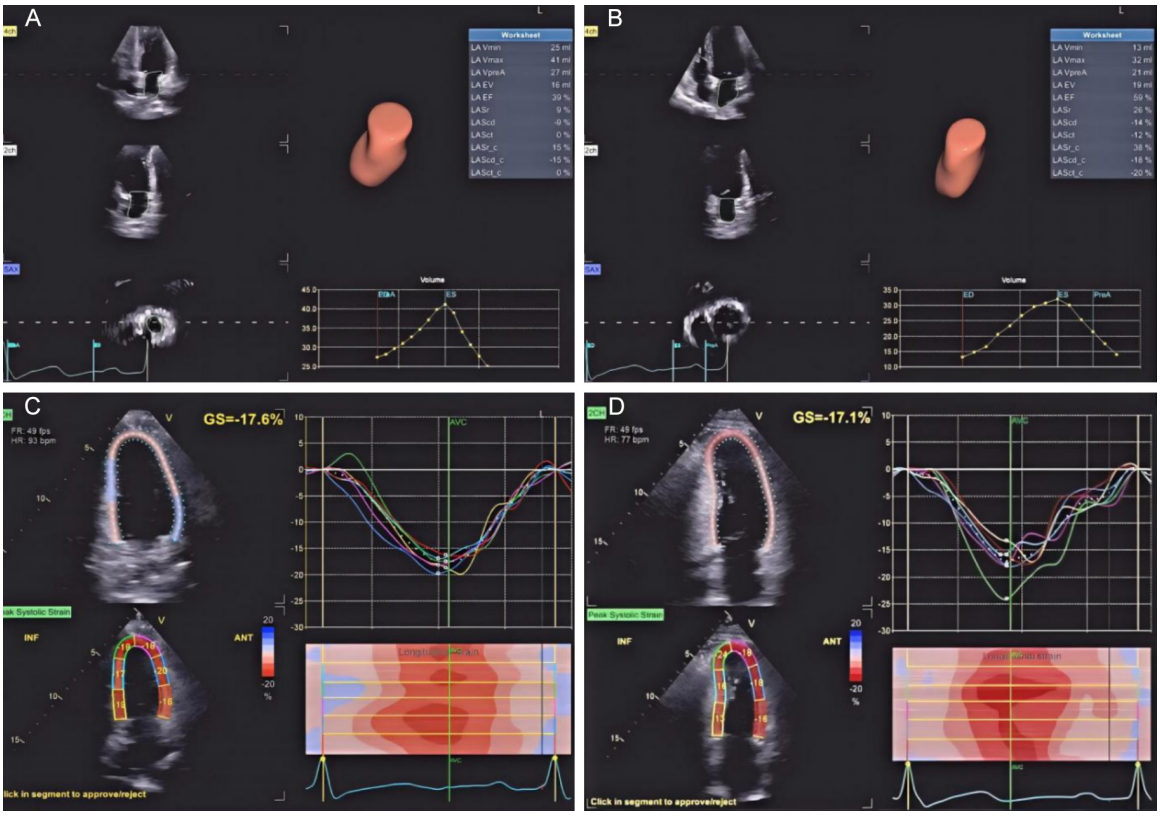

Figure 4. Representative images of RT-3DE and 2D-STI at 3 weeks after chemotherapy. A: Left atrial three-dimensional volume curve in Non-cardiotoxicity group. B: Left atrial three-dimensional volume curve in Cardiotoxicity group. C: Left ventricular strain curve in Non-cardiotoxicity group. D: Left ventricular strain curve in Cardiotoxicity group. Note: RT-3DE: Real-Time Three-Dimensional Echocardiography; 2D-STI: Two-Dimensional Speckle Tracking Imaging; LA Vmax: Left Atrial Maximum Volume; LA Vmin: Left Atrial Minimum Volume; LAEF: Left Atrial Ejection Fraction; LAEFa: Left Atrial Booster Pump Function Ejection Fraction; LAScd: Left Atrial Conduit Strain; LASct: Left Atrial Contractile Strain; LASr: Left Atrial Reservoir Strain; 4ch: Apical Four-Chamber View; 2ch: Apical Two-Chamber View; SAX: Short-Axis View; GS: Global Strain; HR: Heart Rate (bpm); FR: Frame Rate (fps).

weeks post-chemotherapy (both $P < 0.05$) - indicating dynamic compensatory adjustment of LA total function in the non-cardiotoxic group. Although LAEFt in the cardiotoxic group showed a tendency to increase at 3 weeks post-chemotherapy, this change was not statistically significant ($P > 0.05$), implying that cardiotoxicity may interfere with the normal compensatory progression of LA total function during chemotherapy.

Changes in LVEF were primarily affected by the interaction between chemotherapy time and cardiotoxicity status ($P < 0.05$), while neither the independent main effect of time nor that of group reached statistical significance (both $P > 0.05$). Notably, the time-group interaction effect was statistically significant ($P < 0.05$). With pre-chemotherapy as the reference, the dynamic change patterns of LVEF during chemotherapy differed between the non-cardiotoxic and cardiotoxic groups. At 3 weeks post-chemotherapy, no significant change in LVEF was observed in the non-cardiotoxic group ($P > 0.05$, **Table 3**).

After 6 cycles of chemotherapy, the functional differences between the two groups further widened (**Figure 5**). On RT-3DE (**Figure 5A**, **5B**): LAEFa and LAEFt in the non-cardiotoxic group remained stable; the cardiotoxic group showed more pronounced left atrial volume dilation, and both LAEFa and LAEFt were significantly decreased, indicating the loss of left atrial compensatory capacity and global functional decompensation. On 2D-STI (**Figure 5C**, **5D**): Left atrial strain indices in the non-cardiotoxic group remained normal; both LASr and LASct in the cardiotoxic group were significantly abnormal, with strain curves showing damage-related characteristics (a gentle upward trend during

Table 3. GEE analysis of RT-3DE parameters

Parameter		B	S.E.	Lower Limit of 95% CI	Upper Limit of 95% CI	Wald Chi-square	P	Exp(B)	Lower Limit of 95% CI of Exp(B)	Upper Limit of 95% CI of Exp(B)
LAEFa	Before chemotherapy was used as reference group.									
	Post-6 Cycles	-0.938	1.701	-4.272	2.396	0.304	0.581	0.391	0.014	10.978
	Post-3 Cycles	-1.358	1.602	-4.497	1.782	0.718	0.397	0.257	0.011	5.941
	Non-Cardiotoxicity was used as reference group.									
	Cardiotoxicity	-4.112	2.130	-8.286	0.063	3.727	0.054	0.016	0.000	1.065
	Post-6 Cycles * Cardiotoxicity * Gender	-10.348	2.092	-14.449	-6.248	24.47	0	3.20E-05	5.31E-07	0.002
	Post-6 Cycles * Non-Cardiotoxicity * Gender	-3.173	2.651	-8.369	2.024	1.432	0.231	0.042	0.000	7.567
	Post-3 Cycles * Cardiotoxicity * Gender	3.269	10.499	-17.308	23.846	0.097	0.755	26.297	3.04E-08	22718965208
	Post-3 Cycles * Non-Cardiotoxicity * Gender	-4.796	2.181	-9.07	-0.521	4.836	0.028	0.008	0.000	0.594
	Before chemotherapy * Cardiotoxicity * Gender	-4.355	2.857	-9.955	1.246	2.322	0.128	0.013	4.75E-05	3.476
	Before chemotherapy * Non-Cardiotoxicity * Gender	-6.733	2.041	-10.733	-2.732	10.882	0.001	0.001	2.18E-05	0.065
LAEFp	Before chemotherapy was used as reference group.									
	Post-6 Cycles	-14.375	2.392	-19.063	-9.687	36.112	0.000	5.72E-07	5.26E-09	6.21E-05
	Post-3 Cycles	-4.78	1.551	-7.819	-1.741	9.502	0.002	0.008	0.000	0.175
	Non-Cardiotoxicity was used as reference group.									
	Cardiotoxicity	5.700	3.418	-0.999	12.399	2.781	0.095	298.834	0.368	242523.971
	Post-6 Cycles * Cardiotoxicity * Gender	5.956	4.847	-3.543	15.455	1.51	0.219	386.007	0.029	5153385.621
	Post-6 Cycles * Non-Cardiotoxicity * Gender	16.258	4.672	7.101	25.415	12.11	0.001	11506891.43	1213.718	1.09093E+11
	Post-3 Cycles * Cardiotoxicity * Gender	-1.062	1.792	-4.574	2.45	0.351	0.553	0.346	0.010	11.589
	Post-3 Cycles * Non-Cardiotoxicity * Gender	11.7	3.414	5.009	18.39	11.747	0.001	120521.599	149.769	96985977.14
	Before chemotherapy * Cardiotoxicity * Gender	7.968	3.484	1.14	14.796	5.232	0.022	2887.962	3.128	2666258.981
	Before chemotherapy * Non-Cardiotoxicity * Gender	10.501	2.751	5.11	15.893	14.574	0	36365.674	165.647	7983636.224
LAEFt	Before chemotherapy was used as reference group.									
	Post-6 Cycles	-15.313	2.160	-19.546	-11.08	50.268	0	2.24E-07	3.25E-09	1.54E-05
	Post-3 Cycles	-6.138	2.030	-10.117	-2.158	9.139	0.003	0.002	4.04E-05	0.116
	Non-Cardiotoxicity was used as reference group.									
	Cardiotoxicity	1.588	2.386	-3.089	6.265	0.443	0.506	4.895	0.046	525.762
	Post-6 Cycles * Cardiotoxicity * Gender	-4.393	3.475	-11.204	2.419	1.597	0.206	0.012	1.36E-05	11.236
	Post-6 Cycles * Non-Cardiotoxicity * Gender	13.086	3.435	6.354	19.818	14.514	0	482120.304	574.638	404497918.4
	Post-3 Cycles * Cardiotoxicity * Gender	2.208	11.157	-19.659	24.074	0.039	0.843	9.093	2.90E-09	28520092394
	Post-3 Cycles * Non-Cardiotoxicity * Gender	6.904	3.165	0.701	13.107	4.759	0.029	996.111	2.016	492293.02
	Before chemotherapy * Cardiotoxicity * Gender	3.614	1.678	0.326	6.902	4.64	0.031	37.106	1.385	994.246
	Before chemotherapy * Non-Cardiotoxicity * Gender	3.769	1.423	0.98	6.557	7.017	0.008	43.322	2.665	704.235

LVEF	Before chemotherapy was used as reference group.								
	Post-6 Cycles	-1.132	0.430	-1.976	-0.289	6.928	0.008	0.322	0.139	0.749
	Post-3 Cycles	-1.456	0.663	-2.755	-0.157	4.826	0.028	0.233	0.064	0.855
	Non-Cardiotoxicity was used as reference group.									
	Cardiotoxicity	-1.052	1.037	-3.086	0.981	1.029	0.31	0.349	0.046	2.667
	Post-6 Cycles * Cardiotoxicity * Gender	1.172	1.278	-1.332	3.676	0.841	0.359	3.227	0.264	39.47
	Post-6 Cycles * Non-Cardiotoxicity * Gender	-0.606	0.883	-2.336	1.124	0.471	0.493	0.546	0.097	3.078
	Post-3 Cycles * Cardiotoxicity * Gender	-5.005	1.034	-7.032	-2.978	23.417	0	0.007	0.001	0.051
	Post-3 Cycles * Non-Cardiotoxicity * Gender	1.418	0.909	-0.364	3.2	2.431	0.119	4.128	0.695	24.534
	Before chemotherapy * Cardiotoxicity * Gender	-1.961	1.717	-5.327	1.405	1.304	0.254	0.141	0.005	4.076
	Before chemotherapy * Non-Cardiotoxicity * Gender	-0.238	0.715	-1.638	1.162	0.111	0.739	0.788	0.194	3.197

Note: GEE: Generalized Estimating Equations; RT-3DE: Real-Time Three-Dimensional Echocardiography; LAEFa: Left Atrial Booster Pump Function Ejection Fraction; LAEFp: Left Atrial Conduit Function Ejection Fraction; LAEFt: Left Atrial Total Function Ejection Fraction; LVEF: Left Ventricular Ejection Fraction; B: Regression Coefficient; S.E.: Standard Error; CI: Confidence Interval; Wald Chi-square: Wald; Exp(B): Odds Ratio.

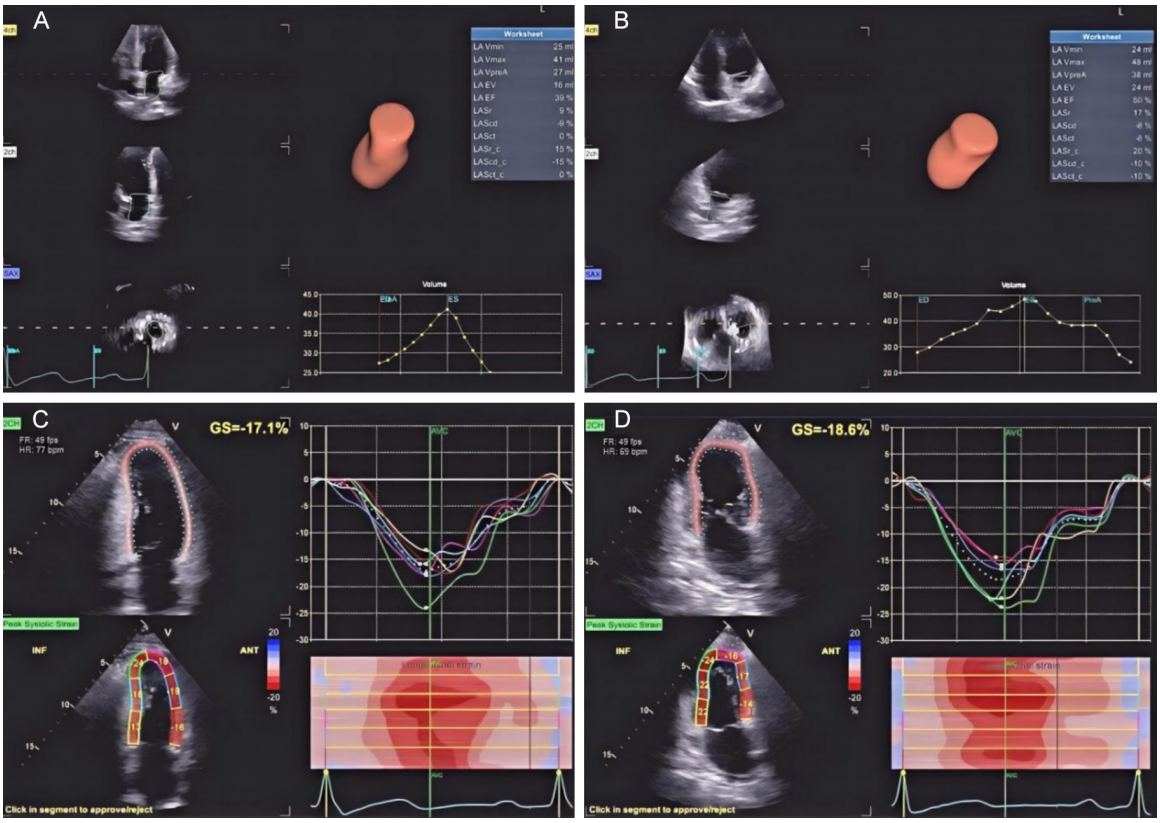

Figure 5. Representative images of RT-3DE and 2D-STI at 6 weeks after chemotherapy. A: Left atrial three-dimensional volume curve in Non-cardiotoxicity group. B: Left atrial three-dimensional volume curve in Cardiotoxicity group. C: Left ventricular strain curve in Non-cardiotoxicity group. D: Left ventricular strain curve in Cardiotoxicity group. Note: RT-3DE: Real-Time Three-Dimensional Echocardiography; 2D-STI: Two-Dimensional Speckle Tracking Imaging; LA Vmax: Left Atrial Maximum Volume; LA Vmin: Left Atrial Minimum Volume; LAEF: Left Atrial Ejection Fraction; LAEFa: Left Atrial Booster Pump Function Ejection Fraction; LAEFt: Left Atrial Total Function Ejection Fraction; LAScd: Left Atrial Conduit Strain; LASct: Left Atrial Contractile Strain; LASr: Left Atrial Reservoir Strain; 4ch: Apical Four-Chamber View; 2ch: Apical Two-Chamber View; SAX: Short-Axis View; GS: Global Strain; HR: Heart Rate (bpm); FR: Frame Rate (fps).

the reservoir phase and a shallow downward trend during the contraction phase). Meanwhile, LVEF in the cardiotoxic group only decreased significantly after 6 cycles, whereas abnormalities in left atrial strain indices emerged earlier - confirming the advantage of 2D-STI in the early detection of cardiotoxicity.

For LASr: The main effect of chemotherapy time was statistically significant ($P < 0.05$), indicating that LASr underwent a significant overall change throughout the chemotherapy course. The main effect of the cardiotoxicity group was not statistically significant ($P > 0.05$), while the time-group interaction effect was statistically significant ($P < 0.05$) - demonstrating that the change pattern of LASr varied by cardiotoxicity status. With pre-chemotherapy as the reference, the non-cardiotoxic group showed a tendency toward compensatory changes at 3 weeks post-chemotherapy. In contrast, the cardiotoxic group exhibited a significantly faster rate of LASr decline than the non-cardiotoxic group starting from 3 weeks post-chemotherapy; as chemotherapy progressed to 6 weeks, the numerical difference in LASr between the two groups further widened - suggesting that the cardiotoxic group experienced early abnormal impairment of left atrial reservoir function.

For LASct: The main effect of chemotherapy time was statistically significant ($P < 0.05$), indicating that LASct underwent an overall change over the course of chemotherapy. The main effect of the cardiotoxicity group was also statistically significant ($P < 0.05$), meaning there were differences in the baseline level or overall trend of LASct between the cardiotoxic and

non-cardiotoxic groups. At 3 weeks post-chemotherapy, LASct in the non-cardiotoxic group increased significantly - reflecting compensatory enhancement of global left atrial systolic function. In contrast, LASct in the cardiotoxic group decreased significantly at 3 weeks post-chemotherapy, suggesting early impairment of global left atrial systolic function in this group. By 6 weeks post-chemotherapy, LASct remained at a relatively high level in the non-cardiotoxic group, while it continued to decline in the cardiotoxic group - resulting in a statistically significant intergroup difference ($P < 0.05$).

For LAScd: Chemotherapy time, cardiotoxicity group, and their interaction all had significant effects on LAScd. With pre-chemotherapy as the reference, LAScd showed a significant overall change at 3 weeks post-chemotherapy. At the interaction effect level, the non-cardiotoxic group exhibited a significant difference in LAScd compared with the baseline at 6 weeks post-chemotherapy ($P < 0.05$) - reflecting the characteristic change of left atrial systolic function in the non-cardiotoxic group during chemotherapy. In contrast, the cardiotoxic group displayed a significantly different LAScd change pattern from the non-cardiotoxic group at 3 weeks post-chemotherapy ($P < 0.05$). This finding suggested that the cardiotoxic group experienced early abnormal impairment of left atrial systolic function as early as 3 weeks post-chemotherapy, with a change trajectory distinct from that of the non-cardiotoxic group (**Table 4**).

Discussion

Lymphoma, a common hematological malignancy, is frequently associated with the risk of cardiotoxicity during treatment, particularly when anthracycline drugs are used [15]. Acute cardiotoxicity typically manifests early in the treatment course, characterized by transient pericarditis, prolonged QT intervals, and acute arrhythmias, which generally resolve within two weeks after treatment initiation [16, 17]. In contrast, chronic cardiotoxicity may emerge during or after treatment, occasionally presenting as late as one year or more post-therapy. It is primarily characterized by irreversible cardiac dysfunction that can progress to heart failure [18, 19]. Long-term cardiac toxicity may contribute to mortality in approximately one-third of affected patients, with some developing severe heart failure in advanced stages, potentially leading to life-threatening sequelae [6, 14, 20]. Given the insidious onset and subtle initial manifestations of chronic cardiotoxicity, precise detection of chemotherapy-induced cardiac dysfunction before the development of overt heart failure is crucial. Current guidelines advocate for vigilant monitoring of left ventricular function before, during, and after chemotherapy to identify cardiotoxicity associated with antineoplastic therapy [21]. This study used 2D-STI and RT-3DE to assess early cardiotoxicity in anthracycline-treated lymphoma patients, focusing on left atrial indices to address gaps in traditional LVEF-centered monitoring.

The cardiotoxic group had a significantly higher proportion of male patients (89.5% vs 56% in the non-cardiotoxic group, $P = 0.006$), consistent with literature identifying male gender as a major risk factor for anthracycline-induced cardiotoxicity [22, 23]. Estrogens, abundant in female patients, mitigate anthracycline-induced oxidative stress by upregulating antioxidant enzymes such as superoxide dismutase and inhibit myocardial cell apoptosis via suppression of pro-apoptotic pathways, including caspase-3 activation. In contrast, male patients lack this hormonal protection, leading to increased accumulation of reactive oxygen species and greater myocyte damage [24]. A cohort study of 1,165 adolescent and young adult cancer survivors further confirmed this trend, reporting a 34% higher cumulative risk of cardiovascular toxicity in males compared to females after anthracycline treatment [25]. Notably, age modifies this gender effect: postmenopausal women exhibit cardiovascular disease risk similar to that of age-matched males, which may narrow the gap in susceptibility to anthracycline cardiotoxicity between elderly men and women [23]. The absence of an age-related association with cardiotoxicity in this study is likely attributable to the relatively concentrated age distribution of the study population, which lacked sufficient variability to detect age-related differences in toxicity risk.

Hypertension prevalence differed significantly between the two groups, with 0% of patients in the cardiotoxic group and 19.8% in the non-cardiotoxic group having hypertension ($P = 0.034$). This difference may be explained by the cardioprotective role of renin-angiotensin-aldo-

Table 4. GEE analysis of 2D-STI parameters

Parameter		B	S.E.	Lower Limit of 95% CI	Upper Limit of 95% CI	Wald Chi-square	P	Exp(B)	Lower Limit of 95% CI of Exp(B)	Upper Limit of 95% CI of Exp(B)
LASr	Before chemotherapy was used as reference group.									
	Post-6 Cycles	-3.015	0.666	-4.32	-1.709	20.49	0	0.049	0.013	0.181
	Post-3 Cycles	0.824	0.425	-0.009	1.656	3.761	0.052	2.279	0.991	5.238
	Non-Cardiotoxicity was used as reference group.									
	Cardiotoxicity	-0.235	1.171	-2.53	2.059	0.04	0.841	0.790	0.080	7.842
	Post-6 Cycles * Cardiotoxicity * Gender	-4.147	1.789	-7.653	-0.641	5.374	0.02	0.016	0.000	0.527
	Post-6 Cycles * Non-Cardiotoxicity * Gender	0.843	0.972	-1.062	2.747	0.752	0.386	2.323	0.346	15.593
	Post-3 Cycles * Cardiotoxicity * Gender	-3.985	4.379	-12.567	4.596	0.828	0.363	0.019	3.49E-06	99.12
	Post-3 Cycles * Non-Cardiotoxicity * Gender	0.704	0.882	-1.024	2.433	0.638	0.424	2.023	0.359	11.388
	Before chemotherapy * Cardiotoxicity * Gender	-5.162	5.074	-15.106	4.782	1.035	0.309	0.006	2.75E-07	119.357
	Before chemotherapy * Non-Cardiotoxicity * Gender	-0.572	1.001	-2.533	1.389	0.327	0.568	0.564	0.079	4.012
LASct	Before chemotherapy was used as reference group.									
	Post-6 Cycles	1.397	0.510	0.399	2.395	7.532	0.006	4.043	1.491	10.966
	Post-3 Cycles	0.294	0.425	-0.539	1.128	0.478	0.489	1.342	0.583	3.088
	Non-Cardiotoxicity was used as reference group.									
	Cardiotoxicity	3.654	0.354	2.959	4.348	106.306	0.000	38.613	19.28	77.333
	Post-6 Cycles * Cardiotoxicity * Gender	3.098	0.461	2.195	4.001	45.239	0.000	22.154	8.982	54.642
	Post-6 Cycles * Non-Cardiotoxicity * Gender	-1.073	0.689	-2.423	0.276	2.43	0.119	0.342	0.089	1.318
	Post-3 Cycles * Cardiotoxicity * Gender	-0.299	0.214	-0.718	0.12	1.96	0.161	0.742	0.488	1.127
	Post-3 Cycles * Non-Cardiotoxicity * Gender	-0.42	0.529	-1.458	0.617	0.631	0.427	0.657	0.233	1.853
	Before chemotherapy * Cardiotoxicity * Gender	-2.005	0.310	-2.613	-1.397	41.757	0.000	0.135	0.073	0.247
	Before chemotherapy * Non-Cardiotoxicity * Gender	0.999	0.515	-0.011	2.009	3.755	0.053	2.715	0.989	7.455
LAScd	Before chemotherapy was used as reference group.									
	Post-6 Cycles	2.074	0.306	1.474	2.673	45.954	0.000	7.953	4.367	14.484
	Post-3 Cycles	1.044	0.452	0.159	1.929	5.346	0.021	2.841	1.172	6.884
	Non-Cardiotoxicity was used as reference group.									
	Cardiotoxicity	0.797	0.9457	-1.056	2.651	0.711	0.399	2.22	0.348	14.166
	Post-6 Cycles * Cardiotoxicity * Gender	-3.201	0.916	-4.996	-1.406	12.219	0	0.041	0.007	0.245
	Post-6 Cycles * Non-Cardiotoxicity * Gender	-1.079	0.807	-2.661	0.504	1.785	0.182	0.34	0.07	1.655
	Post-3 Cycles * Cardiotoxicity * Gender	-4.172	1.979	-8.049	-0.294	4.445	0.035	0.015	0.000	0.745
	Post-3 Cycles * Non-Cardiotoxicity * Gender	-1.449	0.752	-2.922	0.024	3.717	0.054	0.235	0.054	1.024
	Before chemotherapy * Cardiotoxicity * Gender	-4.627	0.854	-6.301	-2.954	29.378	0.000	0.01	0.002	0.052
	Before chemotherapy * Non-Cardiotoxicity * Gender	0.145	0.752	-1.329	1.619	0.037	0.847	1.156	0.265	5.048

Note: GEE: Generalized Estimating Equations; 2D-STI: Two-Dimensional Speckle Tracking Imaging; LASr: Left Atrial Reservoir Strain; LASct: Left Atrial Contractile Strain; LAScd: Left Atrial Conduit Strain. B: Regression Coefficient; S.E.: Standard Error; CI: Confidence Interval; Wald Chi-square: Wald; Exp(B): Odds Ratio.

sterone system (RAAS) inhibitors, commonly prescribed for hypertension. RAAS inhibitors reduce anthracycline-induced myocardial fibrosis by inhibiting TGF-β/Smad signaling and attenuate oxidative stress via suppression of NADPH oxidase [26, 27]. Moey et al. [26] validated this cardioprotective effect in a study of breast cancer patients, reporting a 42% reduction in cardiotoxicity among those using RAAS inhibitors during trastuzumab treatment. Prior studies have shown that hypertensive patients exhibit LA strain and functional abnormalities - including higher LAVImax and lower LASr - that reflect early compensatory adaptation to hemodynamic stress [26, 28]. However, long-term hemodynamic load and chronic RAAS activation can still lead to myocardial fibrosis, which may exacerbate chemotherapy-induced cardiotoxicity [29, 30]. This dynamic was not fully captured in the short-term follow-up of this study. The lack of data on antihypertensive medication use limits direct confirmation of RAAS inhibitors' role in mitigating cardiotoxicity, but the significant difference in hypertension prevalence highlights the need to distinguish hypertension from its treatment in future risk stratification.

Diabetes prevalence showed no significant inter-group difference, with 28.6% of patients in the non-cardiotoxic group and 10.5% in the cardiotoxic group having diabetes. This finding contrasts with prior research linking diabetes to reduced LA reserve function - characterized by lower LASr, LAEFt, and LAEFp - via mechanisms such as microvascular disease, insulin resistance, lipid disorders, and myocardial energy deficiency [31-37]. Two factors may explain this discrepancy: first, the small sample size of the cardiotoxic group reduces statistical power to detect weak associations; second, unmeasured variability in glycemic control may have muted the signals. Salgado et al. [38] demonstrated that optimal glycemic control (HbA1c < 7%) reduces cardiotoxicity risk by 35%, and significant variation in diabetes management may have obscured potential associations in the current cohort.

The selection of cardiac function assessments at 3 and 6 cycles post-chemotherapy was guided by the well-documented cumulative dose-dependent toxicity of anthracyclines. Clinical evidence indicates that anthracycline-associated heart failure typically occurs at cumulative doses between 400 and 550 mg/m^2; at 550 mg/m^2, the incidence of heart failure rises to 7-26%, and at 700 mg/m^2, this rate increases to 48% [39-41]. A key finding of this study is that LA indices - including LAEFa (booster pump function), LAEFt (total function), and LASct (contractile strain) - exhibit dynamic, group-specific changes earlier than LVEF, highlighting the LA's role as a sensitive "hemodynamic buffer" for early myocardial injury.

At 3 cycles post-chemotherapy, LAEFa was significantly elevated in the cardiotoxic group relative to the non-cardiotoxic group. This elevation is interpreted as a compensatory response whereby the LA enhances its active contraction to offset subtle LV diastolic dysfunction that remains undetectable by LVEF. By 6 cycles, however, LAEFa and LAEFt declined sharply in the cardiotoxic group, signaling that atrial myocyte damage has exceeded the LA's adaptive reserve capacity [25, 26]. This trajectory - initial compensatory increase followed by maladaptive decrease - aligns with the biological mechanism of anthracycline toxicity: early myocardial stress triggers LA functional compensation, but prolonged exposure depletes this reserve, leading to irreversible myocyte damage [42-44]. GEE analysis confirmed that LAEFt exhibited this biphasic pattern, with abnormal changes detectable at 3 cycles - weeks earlier than the first significant decline in LVEF. LVEF, by contrast, showed a significant inter-group difference only at 6 cycles, reinforcing its inherent limitation as a delayed marker of overt LV dysfunction rather than subclinical injury.

The utility of 2D-STI-derived LASct as an early marker of cardiotoxicity was further validated by the study's results. LASct was significantly reduced in the cardiotoxic group as early as 3 cycles post-chemotherapy and remained significantly lower at 6 cycles. This observation aligns with findings from prior studies in breast cancer, where Mokadem et al. [45] and Emerson et al. [46] demonstrated that LA strain parameters detect anthracycline-induced myocardial injury earlier than LVEF. The current study extends this observation to lymphoma patients, with early reduction in LASct reflecting direct damage to LA myocytes driven by anthracycline-mediated disruption of mitochondrial oxidative phosphorylation and myofibrillar structure [40] - pathways that precede overt LV dysfunction.

This study is among the first to validate the combined use of RT-3DE and 2D-STI for quantitative monitoring of early anthracycline-induced cardiotoxicity in lymphoma patients. This approach addresses a critical gap in the literature, as most prior research on these advanced echocardiographic technologies has focused on breast cancer [47-50]. The two modalities offer complementary strengths that enhance early detection of cardiotoxicity.

RT-3DE reduces measurement error in LA volume quantification compared to conventional 2D echocardiography [51, 52], making it ideal for capturing subtle early LA remodeling during chemotherapy. By directly quantifying LA functional indices (LAEFa, LAEFp, LAEFt), RT-3DE enables precise assessment of compensatory reserve and early decompensation - key features that distinguish the cardiotoxic and non-cardiotoxic groups at 3 cycles.

2D-STI improves the sensitivity of strain assessment to microstructural myocardial damage [51, 53, 54], allowing the detection of LASct abnormalities at 3 cycles when LVEF remains normal. Its ability to quantify myocardial fiber deformation at the subclinical stage aligns with the study's goal of early cardiotoxicity detection.

Together, these technologies provide a comprehensive assessment of early cardiac dysfunction: RT-3DE quantifies LA functional reserve, while 2D-STI measures strain parameters that signal subclinical myocyte injury [53, 54]. This combination outperforms traditional LVEF-centered monitoring, as demonstrated by the finding that LA indices detect cardiotoxicity-related changes weeks earlier than LVEF.

This study has several limitations that should be considered. First, the population was restricted to patients with a baseline LVEF ≥ 50%, excluding those with pre-existing cardiac dysfunction. While this criterion ensured homogeneity, it limits the generalizability of the results to real-world patients with underlying heart disease. Future studies could include patients with a baseline LVEF of 45-50%, which represents a "gray zone" of subclinical dysfunction, to assess the utility of RT-3DE/2D-STI in higher-risk populations. Additionally, the cardiotoxic group was small, comprising only 19 patients, which reduces statistical power and limits the ability to validate associations between hypertension, diabetes, and cardiotoxicity. This also restricted subgroup analyses, such as those based on lymphoma subtype or anthracycline cumulative dose. The study also lacked long-term follow-up data, which is critical for linking early changes in LA functional and strain indices to long-term clinical endpoints like heart failure hospitalization or mortality. An important unanswered question is whether abnormalities in LAEFa or LASct predict the risk of cardiac events 1-5 years post-chemotherapy, which could be addressed in future studies with extended follow-up. Furthermore, the study did not collect data on anthracycline cumulative dose, RAAS inhibitor use, or glycemic control (HbA1c levels), leaving potential confounders unaccounted for. Finally, the absence of a control group of lymphoma patients who received non-anthracycline chemotherapy limits the ability to distinguish anthracycline-specific toxicity from general chemotherapy-related stress on cardiac function.

In conclusion, this study demonstrates that RT-3DE and 2D-STI are superior to traditional LVEF in the early detection of anthracycline-induced cardiotoxicity in lymphoma patients. These advanced imaging techniques can capture subtle, early changes in LA function and strain that precede overt LVEF abnormalities. LA functional indices (e.g., LAEFa) and LA strain parameters (e.g., LASct) emerge as key markers of early subclinical injury. Baseline clinical characteristics identify gender and hypertension as important correlates of cardiotoxicity risk, with male patients and those without hypertension exhibiting higher vulnerability. GEE analysis confirms that dynamic cardiac function trajectories differ significantly between the cardiotoxic and non-cardiotoxic groups, with the former showing early functional impairment progressing to decompensation. These findings validate the clinical utility of RT-3DE and 2D-STI in optimizing cardio-oncology monitoring for lymphoma patients receiving anthracycline-based chemotherapy.

Disclosure of conflict of interest

None.

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References

[1] Matasar MJ and Zelenetz AD. Overview of lymphoma diagnosis and management. Radiol Clin North Am 2008; 46: 175-198.

[2] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.

[3] Hoppe RT, Advani RH, Ai WZ, Ambinder RF, Armand P, Bello CM, Benitez CM, Bierman PJ, Boughan KM, Dabaja B, Gordon LI, Hernandez-Ilizaliturri FJ, Herrera AF, Hochberg EP, Huang J, Johnston PB, Kaminski MS, Kenkre VP, Khan N, Lynch RC, Maddocks K, McConathy J, McKinney M, Metzger M, Morgan D, Mulroney C, Rabinovitch R, Rosenspire KC, Seropian S, Tao R, Winter JN, Yahalom J, Burns JL and Ogba N. Hodgkin lymphoma, version 2.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2020; 18: 755-781.

[4] Horwitz SM, Ansell S, Ai WZ, Barnes J, Barta SK, Brammer J, Clemens MW, Dogan A, Foss F, Ghione P, Goodman AM, Guitart J, Halwani A, Haverkos BM, Hoppe RT, Jacobsen E, Jagadeesh D, Jones A, Kallam A, Kim YH, Kumar K, Mehta-Shah N, Olsen EA, Rajguru SA, Rozati S, Said J, Shaver A, Shea L, Shinohara MM, Sokol L, Torres-Cabala C, Wilcox R, Wu P, Zain J, Dwyer M and Sundar H. T-Cell lymphomas, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2022; 20: 285-308.

[5] Makiyama J, Imaizumi Y, Watanabe H, Fujioka M, Chiwata M, Kitanosono H, Nakashima J, Miyazaki Y and Yoshida S. Outcomes in patients with classic Hodgkin lymphoma treated with ABVD: a single-center retrospective study. Intern Med 2021; 60: 709-718.

[6] Fanale MA, Cheah CY, Rich A, Medeiros LJ, Lai CM, Oki Y, Romaguera JE, Fayad LE, Hagemeister FB, Samaniego F, Rodriguez MA, Neelapu SS, Lee HJ, Nastoupil L, Fowler NH, Turturro F, Westin JR, Wang ML, McLaughlin P, Pinnix CC, Milgrom SA, Dabaja B, Horowitz SB and Younes A. Encouraging activity for R-CHOP in advanced stage nodular lymphocyte-predominant Hodgkin lymphoma. Blood 2017 27; 130: 472-477.

[7] Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A and Suter TM; ESC Scientific Document Group. 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). Eur Heart J 2016; 37: 2768-2801.

[8] Maraldo MV, Levis M, Andreis A, Armenian S, Bates J, Brady J, Ghigo A, Lyon AR, Manisty C, Ricardi U, Aznar MC and Filippi AR. An integrated approach to cardioprotection in lymphomas. Lancet Haematol 2022; 9: e445-e454.

[9] Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A and Suter TM; ESC Scientific Document Group. 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). Eur Heart J 2016; 37: 2768-2801.

[10] Kundnani NR, Passini V, Stefania Carlogea I, Dumitrescu P, Meche V, Buzas R and Duda-Seiman DM. Overview of oncology: drug-induced cardiac toxicity. Medicina (Kaunas) 2025; 61: 709.

[11] Kwon SH and Gopal AS. 3D and 4D ultrasound: current progress and future perspectives. Curr Cardiovasc Imaging Rep 2017; 10: 43.

[12] Shi J, Guo Y, Cheng L, Song F and Shu X. Early change in left atrial function in patients treated with anthracyclines assessed by real-time three-dimensional echocardiography. Sci Rep 2016; 6: 25512.

[13] Ylanen K, Eerola A, Vettenranta K and Poutanen T. Speckle tracking echocardiography detects decreased cardiac longitudinal function in anthracycline-exposed survivors of childhood cancer. Eur J Pediatr 2016; 175: 1379-1386.

[14] Muñoz-Rossi FA, Cárdenas-Corredor S, Saldarriaga Osuna LF, Guerra Kunze DA, León-León P, Sánchez DA, Mejia Nates V, Franco Puente LF, Suarez Jaramillo PL and Reche Martinez AJ. Chemotherapy-associated cardiotoxicity: a silent threat evidenced in a retrospective cohort study. Cureus 2025; 17: e78905.

[15] Moreno-Arciniegas A, Cadiz L, Galan-Arriola C, Clemente-Moragon A and Ibanez B. Cardioprotection strategies for anthracycline cardiotoxicity. Basic Res Cardiol 2025; 120: 71-90.

[16] Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D and Cipolla CM. Cardiotoxicity of anticancer treatments: epidemiology, detection, and management. CA Cancer J Clin 2016; 66: 309-325.

[17] Kong CY, Guo Z, Song P, Zhang X, Yuan YP, Teng T, Yan L and Tang QZ. Underlying the mechanisms of doxorubicin-induced acute cardiotoxicity: oxidative stress and cell death. Int J Biol Sci 2022; 18: 760-770.
[18] Barbosa MF, Fusco DR, Gaiolla RD, Werys K, Tanni SE, Fernandes RA, Ribeiro SM and Szarf G. Characterization of subclinical diastolic dysfunction by cardiac magnetic resonance feature-tracking in adult survivors of non-Hodgkin lymphoma treated with anthracyclines. BMC Cardiovasc Disord 2021; 21: 170.
[19] Dozic S, Howden EJ, Bell JR, Mellor KM, Delbridge LMD and Weeks KL. Cellular mechanisms mediating exercise-induced protection against cardiotoxic anthracycline cancer therapy. Cells 2023; 12: 1312.
[20] Dempke WCM, Zielinski R, Winkler C, Silberman S, Reuther S and Priebe W. Anthracycline-induced cardiotoxicity - are we about to clear this hurdle? Eur J Cancer 2023; 185: 94-104.
[21] Mohsenizadeh SA, Rajaeinejad M, Khoshfetrat M, Arefizadeh R, Mousavi SH, Mosaed R, Kazemi-Galougahi MH, Jalaeikhoo H, Faridfar A, Nikandish M, Alavi-Moghadam S and Arjmand B. Anthracycline-induced cardiomyopathy in cancer survivors: management and long-term implications. Adv Exp Med Biol 2025; 1474: 179-199.
[22] Cadeddu Dessalvi C, Pepe A, Penna C, Gimelli A, Madonna R, Mele D, Monte I, Novo G, Nugara C, Zito C, Moslehi JJ, de Boer RA, Lyon AR, Tocchetti CG and Mercuro G. Sex differences in anthracycline-induced cardiotoxicity: the benefits of estrogens. Heart Fail Rev 2019; 24: 915-925.
[23] Meiners B, Shenoy C and Zordoky BN. Clinical and preclinical evidence of sex-related differences in anthracycline-induced cardiotoxicity. Biol Sex Differ 2018; 9: 38.
[24] Volkova M and Russell R 3rd. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev 2011; 7: 214-220.
[25] Wong-Siegel JR, Hayashi RJ, Foraker R and Mitchell JD. Cardiovascular toxicities after anthracycline and VEGF-targeted therapies in adolescent and young adult cancer survivors. Cardiooncology 2023; 9: 30.
[26] Moey MYY, Liles DK and Carabello BA. Concomitant use of renin-angiotensin-aldosterone system inhibitors prevent trastuzumab-induced cardiotoxicity in HER2+ breast cancer patients: an institutional retrospective study. Cardiooncology 2019; 5: 9.
[27] Bavishi C, Bangalore S and Messerli FH. Renin angiotensin aldosterone system inhibitors in hypertension: is there evidence for benefit independent of blood pressure reduction? Prog Cardiovasc Dis 2016; 59: 253-261.
[28] Li L, Chen X, Yin G, Yan W, Cui C, Cheng H, Lu M and Zhao S. Early detection of left atrial dysfunction assessed by CMR feature tracking in hypertensive patients. Eur Radiol 2020; 30: 702-711.
[29] Fung MJ, Thomas L and Leung DY. Left atrial function: correlation with left ventricular function and contractile reserve in patients with hypertension. Echocardiography 2018; 35: 1596-1605.
[30] Hirose K, Nakanishi K, Daimon M, Iwama K, Yoshida Y, Mukai Y, Yamamoto Y, Nakao T, Oshima T, Matsubara T, Shimizu Y, Oguri G, Kojima T, Hasumi E, Fujiu K, Morita H and Komuro I. Association of atrial fibrillation progression with left atrial functional reserve and its reversibility. J Am Heart Assoc 2024; 13: e32215.
[31] Zhang L, Jing H, Wang L, Tang S and Wang J. Clinical characteristics of elderly patients with diffuse large B-cell lymphoma and the risk factors affecting cardiotoxicity of anthracycline. Altern Ther Health Med 2023; 29: 358-363.
[32] Baech J, Severinsen MT, Ovlisen AK, Frederiksen H, Vestergaard P, Torp-Pedersen C, Jorgensen J, Clausen MR, Poulsen CB, Brown P, Gang AO, Pedersen RS, Ekström Smedby K, Eloranta S, Jakobsen LH and El-Galaly TC. Risk of diabetes and the impact on preexisting diabetes in patients with lymphoma treated with steroid-containing immunochemotherapy. Blood Adv 2022; 6: 4427-4435.
[33] Drozd-Sokolowska J, Zaucha JM, Biecek P, Giza A, Kobylinska K, Joks M, Wrobel T, Kumiega B, Knopinska-Posluszny W, Spychalowicz W, Romejko-Jarosinska J, Fischer J, Wiktor-Jedrzejczak W, Dlugosz-Danecka M, Giebel S and Jurczak W. Type 2 diabetes mellitus compromises the survival of diffuse large B-cell lymphoma patients treated with (R)-CHOP - the PLRG report. Sci Rep 2020; 10: 3517.
[34] Kosalka P, Johnson C, Turek M, Sulpher J, Law A, Botros J, Dent S and Aseyev O. Effect of obesity, dyslipidemia, and diabetes on trastuzumab-related cardiotoxicity in breast cancer. Curr Oncol 2019; 26: e314-e321.
[35] Ritchie RH and Abel ED. Basic mechanisms of diabetic heart disease. Circ Res 2020; 126: 1501-1525.
[36] Zhang C, Shi Y, Liu C, Sudesh SM, Hu Z, Li P, Liu Q, Ma Y, Shi A and Cai H. Therapeutic strategies targeting mechanisms of macrophages in diabetic heart disease. Cardiovasc Diabetol 2024; 23: 169.
[37] Shlomai G, Neel B, LeRoith D and Gallagher EJ. Type 2 diabetes mellitus and cancer: the role of pharmacotherapy. J Clin Oncol 2016; 34: 4261-4269.

[38] Salgado TM, Birari PB, Alshahawey M, Hickey Zacholski E, Mackler E, Buffington TM, Musselman KT, Irvin WJ Jr, Perkins JM, Le TN, Dixon DL, Farris KB, Sheppard VB and Jones RM. Optimal hyperglycemia thresholds in patients undergoing chemotherapy: a cross sectional study of oncologists' practices. Support Care Cancer 2024; 32: 563.

[39] Shouman M, Brabant M, Rehman N, Ahmed S and Shahid RK. Perioperative management of patients with diabetes and cancer: challenges and opportunities. Cancers (Basel) 2024; 16: 2821.

[40] Narezkina A, Narayan HK and Zemljic-Harpf AE. Molecular mechanisms of anthracycline cardiovascular toxicity. Clin Sci (Lond) 2021; 135: 1311-1332.

[41] McGowan JV, Chung R, Maulik A, Piotrowska I, Walker JM and Yellon DM. Anthracycline chemotherapy and cardiotoxicity. Cardiovasc Drugs Ther 2017; 31: 63-75.

[42] Johnson M, D K. Anthracycline Toxicity: StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK599501/.

[43] Rusali CA, Lupu IC, Rusali LM and Cojocaru L. Left atrial strain - current review of clinical applications. Diagnostics (Basel) 2025; 15: 1347.

[44] Florescu M, Cinteza M and Vinereanu D. Chemotherapy-induced Cardiotoxicity. Maedica (Bucur) 2013; 8: 59-67.

[45] Mokadem ME, Shaaban SM and Amin OA. Evaluation of left atrial strain changes in patients with breast cancer after anthracycline therapy. Egypt Heart J 2025; 77: 46.

[46] Emerson P, Stefani L, Boyd A, Richards D, Hui R, Altman M and Thomas L. Alterations in left atrial strain in breast cancer patients immediately post anthracycline exposure. Heart Lung Circ 2024; 33: 684-692.

[47] Kinoshita T, Yuzawa H, Natori K, Wada R, Yao S, Yano K, Akitsu K, Koike H, Shinohara M, Fujino T, Shimada H and Ikeda T. Early electrocardiographic indices for predicting chronic doxorubicin-induced cardiotoxicity. J Cardiol 2021; 77: 388-394.

[48] Yagi R, Goto S, Himeno Y, Katsumata Y, Hashimoto M, MacRae CA and Deo RC. Artificial intelligence-enabled prediction of chemotherapy-induced cardiotoxicity from baseline electrocardiograms. Nat Commun 2024; 15: 2536.

[49] Kinoshita T, Onda N, Ohno R, Ikeda T, Sugizaki Y, Ohara H, Nakagami T, Yuzawa H, Shimada H, Shimizu K and Ikeda T. Activation recovery interval as an electrocardiographic repolarization index to detect doxorubicin-induced cardiotoxicity. J Cardiol 2023; 82: 473-480.

[50] Jiang F, Chen Y, Wu L, Zhang Y, Liu J, Sun X, Li J, Mao M and Yang S. Left heart function evaluation of patients with essential hypertension and paroxysmal atrial fibrillation by two-dimensional speckle tracking imaging combined with real-time three-dimensional ultrasound imaging. J Thorac Dis 2021; 13: 322-333.

[51] Jia Y, Wu Q, Yang Z, Sun R, Zhang K, Guo X, Xu R and Guo Y. Mechanisms of myocardial toxicity of antitumor drugs and potential therapeutic strategies: a review of the literature. Curr Probl Cardiol 2024; 49: 102782.

[52] Zhu S, Sun W, Qiao W, Li M, Li Y, Liang B, Wang J, Dong N, Zhang L and Xie M. Real time three-dimensional echocardiographic quantification of left atrial volume in orthotopic heart transplant recipients: comparisons with cardiac magnetic resonance imaging. Echocardiography 2020; 37: 1243-1250.

[53] Morra S, Hossein A, Rabineau J, Gorlier D, Racape J, Migeotte PF and van de Borne P. Assessment of left ventricular twist by 3D ballistocardiography and seismocardiography compared with 2D STI echocardiography in a context of enhanced inotropism in healthy subjects. Sci Rep 2021; 11: 683.

[54] Charfeddine S, Abid D, Hammami R, Gargouri R, Abid L, Triki F and Kammoun S. Myocardial performance after coronary re-implantation in pediatric patients assessed with conventional echocardiographic and 2D-speckle tracking analysis: a case-control study. Pan Afr Med J 2021; 38: 29.