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ORIGINAL ARTICLE

Early left ventricular ejection fraction trajectories according to CTox risk score in breast cancer patients treated with anthracycline and/or trastuzumab

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ABSTRACT

Aim To evaluate early within-patient changes in left ventricular ejection fraction (LVEF) and to describe these early LVEF trajectories according to CTox risk category

Methods This retrospective observational cohort study included 100 breast cancer patients treated at Adam Malik Hospital, from January to December 2024. CTox score was calculated prior to therapy initiation. Echocardiography was performed before the third cycle and after the fourth cycle of anthracycline- or trastuzumab-based therapy. The primary endpoint was early within-patient change in LVEF.

Results Based on CTox classification, 53% of patients were categorized as low-to-moderate risk and 47% as high-to-very high risk. Mean LVEF decreased from 62.64 ± 7.80% to 59.95 ± 7.46%, with a mean change of −2.69 ± 9.01% (p = 0.004). Early LVEF change did not differ between risk groups (between-group difference 0.54%; 95% CI, −2.97 to 4.05; p = 0.766). CTox score was not associated with early LVEF change when modelled as a continuous variable (β = 0.55; p = 0.453) or after adjustment for treatment regimen (β = 0.92; p = 0.212). Treatment type was independently associated with early LVEF change (p = 0.026).

Conclusion A modest early decline in LVEF was observed during initial therapy cycles. Early LVEF trajectory was not associated with CTox risk category but was influenced by treatment regimen. These findings should be interpreted as early imaging trajectory data rather than cardiotoxicity risk prediction.

Keywords: anthracyclines, cardiac function, drug-related side effects and adverse reactions, neoplasms, trastuzumab

INTRODUCTION

Breast cancer (BC) is one of the most common cancers in Indonesia with significant mortality, causing 20.4% deaths in 2020 (1). Its treatment is a complex process involving conventional treatment approaches such as surgery, chemotherapy, and radiotherapy. Even though significant progress has emerged in the field of cancer treatment and various new therapy options have emerged, chemotherapy is still considered the most effective and most widely used modality in treating cancer, especially in high risk and triple negative BC (2). For BC patients with positive human epidermal growth factor receptor-2 HER-2 (HER-2), targeted anti-HER-2 therapy is indicated. Trastuzumab directly targets the HER2 receptor and significantly reduces recurrence and mortality when combined with chemotherapy in HER2-positive early BC (3).

The benefits of these antineoplastic drugs are accompanied by potential cardiovascular adverse effects. One of the most used antineoplastic agents that can cause cardiotoxicity is anthracycline. Anthracycline interferes with deoxyribonucleic acid (DNA) replication and causes necrosis and apoptosis of cardiac myocytes followed by myocardial fibrosis and irreversible cardiotoxicity. Trastuzumab can also contribute to cardiotoxicity by inducing the production of reactive oxygen species (ROS), sarcomere disruption, and destabilization of myofibril structure (4).

Cardiotoxicity due to cancer therapy can manifest as a decrease in left ventricular ejection fraction (LVEF). According to

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the Cardiac Review and Evaluation Committee on trastuzumab-associated cardiotoxicity and the European Society for Medical Oncology (ESMO), cardiotoxicity is defined as a decrease in LVEF by 5% or to LVEF of less than 55% in the presence of symptoms of heart failure or an asymptomatic decrease in LVEF of 10% or more to an LVEF of less than 55% (5). While such definitions focus on clinically significant events, subclinical or early imaging changes may precede overt cardiotoxicity.

To improve risk stratification, several scoring systems have been developed to estimate the likelihood of cardiotoxicity during cancer therapy. One such tool is the cardiovascular toxicity (CTox) score developed by Trigo et al. in 2024, which incorporates serum creatinine, baseline LVEF, history of acute myeloid leukaemia, prior monoclonal antibody exposure, and radiotherapy history. Patients are classified into four categories: low (0–1), moderate (2), high (3–4), and very high (≥ 5) risk. The score demonstrated high specificity for identifying very high-risk patients (6).

Although CTox score was originally developed to estimate the likelihood of cardiotoxicity during cancer therapy, it remains unclear whether baseline CTox stratification is associated with early imaging-based changes in left ventricular function during the initial treatment cycles. Most available data focus on clinically significant cardiotoxicity events occurring later during cumulative exposure, whereas short-term functional shifts during early therapy remain less well characterized. Evaluating early LVEF trajectory across CTox risk categories may provide insight into whether these early functional changes reflect baseline risk burden or predominantly treatment-related effects.

The study aimed to evaluate early within-patient changes in LVEF during initial cycles of anthracycline- or trastuzumab-based therapy and to describe early LVEF trajectories according to CTox risk category.

MATERIAL AND METHODS

Subjects and study design

This is a retrospective observational cohort study at Adam Malik Hospital, Medan, Indonesia, between January and December 2024. One hundred eligible patients meeting inclusion criteria during the study period were included in the analysis using a consecutive sampling approach. Inclusion criteria encompassed adult patients (above 18 years old) with BC undergoing chemotherapy with anthracycline and/or trastuzumab who underwent echocardiography examination before the third cycle of chemotherapy and after the fourth cycle of chemotherapy. Patients with the following comorbidities: heart failure, cardiomyopathy, coronary artery disease, diabetes mellitus, hypertension, and history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) were excluded from the study. Flowchart of patients' selection in our study is shown in Figure 1.

The study protocol was reviewed and approved by the Institutional Review Board of Universitas Sumatera Utara (approval number: 927/KEPK/USU/2025). Due to the retrospective nature of the study and use of anonymized medical record data, the requirement for written informed consent was waived.

Methods

Data were collected from medical records of Adam Malik Hospital. Clinical history, vital signs, and laboratory results were

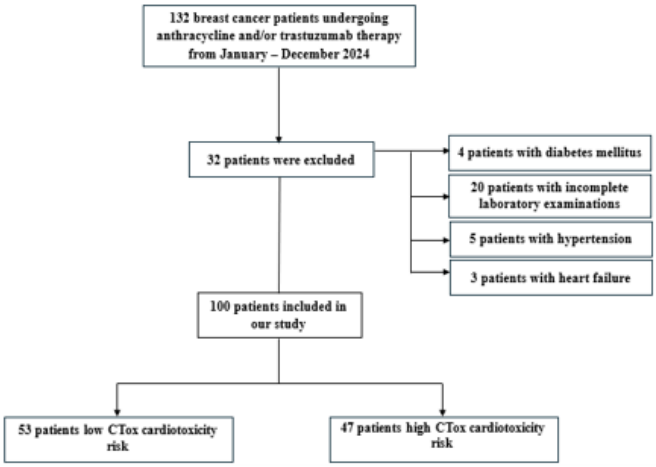


Figure 1. Flowchart of patient selection

Table 1. Cardiotoxicity (CTox) score

Predictive Factor	Scores
Previous radiotherapy	
No	0
Yes	2
Acute Myeloid Leukaemia	
No	0
Yes	2
History of monoclonal antibody	
No	0
Yes	1
LVEF	
≥64	0
54–63	2
≤53	3
Serum creatinine	
<0.82	0
0.82–1.30	1
1.31–1.70	2
≥1.71	3

LVEF, left ventricular ejection fraction.

extracted from the medical records and used to calculate CTox scoring risk. For the primary analysis, CTox was dichotomized into low-to-moderate (0–2) versus high-to-very high (≥ 3), consistent with the original CTox tier thresholds where scores ≥ 3 correspond to high-risk categories (Table 1). Dichotomization was used to preserve statistical power given limited sample size in some tiers. Sensitivity analyses were performed using the original CTox tiers and the continuous CTox score to assess robustness of the findings. CTox score calculation was performed independently from echocardiographic measurement.

Echocardiographic examinations were performed using a SonoSite ultrasound system (Fujifilm SonoSite Inc., Bothell, WA, USA) equipped with a phased-array transducer. LVEF was calculated using the biplane Simpson method from apical four- and two-chamber views in accordance with current echocardiographic recommendations. All examinations were performed using the same ultrasound system. Image acquisition and analysis were conducted by experienced cardiologists. Measurements were performed by more than one experienced cardiologist, reflecting routine clinical practice. CTox score calculation was performed independently from echocardiographic assessment,

and echocardiographers were not involved in CTox scoring. Formal blinding to CTox risk classification was not implemented.

In routine clinical practice at our institution, pre-treatment echocardiographic data were not consistently available for all patients. To ensure uniformity of measurement timing across the cohort and minimize missing data, baseline LVEF for this study was defined as the echocardiographic examination performed before the third chemotherapy cycle. Therefore, this measurement reflects early treatment-phase cardiac function rather than a true pre-treatment baseline value. Follow-up echocardiography was performed within the same treatment week following completion of the fourth cycle under clinically stable conditions. Blood pressure and clinical status were stable at the time of imaging, and both baseline and follow-up examinations were performed under comparable hemodynamic conditions using the same imaging protocol to minimize load-dependent variability of LVEF measurements. Because chemotherapy cycles were administered every 21 days according to institutional protocol, the interval between baseline and follow-up examinations was standardized across patients.

Baseline characteristics were presented descriptively. Standardized mean differences (SMD) were calculated to quantify imbalance between CTox groups instead of relying on hypothesis testing. The primary endpoint was the within-patient change in LVEF between baseline echocardiography (performed before the third cycle) and early follow-up echocardiography (performed after the fourth cycle). This change was interpreted as an early imaging monitoring signal rather than an event-based cardiotoxicity outcome. Secondary endpoints included between-group difference in mean LVEF at baseline and follow-up, and comparison of LVEF change across CTox categories.

Information regarding treatment regimen was collected from medical records and categorized as anthracycline-based therapy or trastuzumab-based therapy. No combination or sequential anthracycline–trastuzumab regimens were included in this cohort.

Anthracycline dosing was standardized at 50 mg/m² per cycle according to institutional protocol. Because follow-up echocardiography was performed after two additional cycles from baseline assessment, cumulative anthracycline exposure at the time of follow-up was uniform (100 mg/m²) among patients receiving anthracycline therapy.

Statistical analysis

Analysis was performed using the Statistical Package for Social Sciences software (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Numerical data will be tested for normality using the Kolmogorov-Smirnov test. Standardized mean differences (SMD) were used to describe imbalance between the groups. The primary analysis compared within-patient LVEF change over time (baseline vs follow-up) and assessed whether the change differed by CTox group (time × group interaction) using a two-way mixed ANOVA test with time (pre–post) as a within-subject factor and CTox risk group (low and high) as a between-subject factor.

To account for treatment heterogeneity, multivariable linear regression models were constructed with early LVEF change (ΔLVEF) as the dependent variable and CTox score and treatment regimen as independent variables. This approach was used to assess whether the association between CTox score and early LVEF trajectory persisted after adjustment for treatment type. Multivariable linear regression models were constructed to evaluate the association between CTox score and early LVEF change after adjustment for treatment regimen. The $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics according to CTox group are presented in Table 2. Variables embedded within the CTox score showed moderate-to-large imbalance (SMD > 0.5).

Table 2. Baseline characteristics of patients included in the study

Variable	Subjects (n=100)	CTox cardiotoxicity scores		SMD‡
		Low-to-moderate-risk (n=53)	High-to-very-high-risk (n=47)	
Age‡	52.41 ± 10.40	51.19 ± 9.26	53.79 ± 11.51	0.25
Pre-treatment LVEF*	62.64 ± 7.80	64.47 ± 7.64	60.57 ± 7.54	0.51
Post-treatment LVEF**	59.95 ± 7.46	62.03 ± 7.91	57.60 ± 6.20	0.62
Serum creatinine‡	0.82 ± 0.32	0.72 ± 0.25	0.94 ± 0.35	0.73
Pre-treatment systolic blood pressure*	118.18 ± 8.96	117.74 ± 8.22	118.68 ± 9.79	0.10
Pre-treatment diastolic blood pressure*	73.83 ± 6.54	73.66 ± 6.53	74.02 ± 6.61	0.05
Post treatment systolic blood pressure**	117.21 ± 8.79	117.45 ± 7.99	116.94 ± 9.69	0.06
Post treatment diastolic blood pressure**	75.17 ± 5.43	75.36 ± 5.54	74.96 ± 5.34	0.07
Haemoglobin‡	11.60 ± 1.41	11.77 ± 1.51	11.40 ± 1.28	0.26
Leukocyte ($10^3/\mu$L)	7.46 ± 2.15	7.69 ± 2.28	7.21 ± 1.99	0.22
Platelet ($10^3/\mu$L)	341.96 ± 135.41	344.75 ± 132.77	338.81 ± 140.22	0.78
History of radiotherapy				
Yes	9 (9%)	0 (0%)	9 (9%)	
No	91 (91%)	53 (53%)	38 (38%)	0.001†
History of monoclonal antibody usage				
Yes	11 (11%)	3 (3%)	8 (8%)	
No	89 (89%)	50 (50%)	39 (39%)	0.070†

* Before third cycle of chemotherapy and/or trastuzumab therapy; ** after fourth cycle of chemotherapy and/or trastuzumab therapy; ‡ unless otherwise stated; † p-value; LVEF, left ventricular ejection fraction.

Table 3. Results of two-way mixed ANOVA and analysis of within-subjects and between-subjects

Variable	F	p	η_p^2
Time (pre-post)	8.918	0.004	0.083
Risk group	12.751	0.001	0.115
Interaction (time and risk group)	0.089	0.766	0.001

According to original CTox classification, 24 patients (24%) were categorized as low risk (0–1), 29 (29%) as moderate risk (2), 43 (43%) as high risk (3–4), and 4 (4%) as very high risk (≥ 5). For primary analysis, low and moderate tiers were combined (53%), and high and very high tiers were combined (47%). When CTox score was modelled as a continuous variable in linear regression analysis, no significant association was observed between CTox score and early LVEF change (β = 0.55; p = 0.453). The overall model was not statistically significant (F = 0.568; p = 0.453), indicating that CTox score did not explain variability in short-term LVEF change.

The distribution of treatment regimen was as follows: 68 patients (68%) received anthracycline-based therapy, and 32 patients (32%) received trastuzumab-based therapy. After adjustment for treatment regimen, CTox score remained not significantly associated with ΔLVEF (β = 0.92; p = 0.212). Treatment regimen was independently associated with ΔLVEF (β = −4.40; p = 0.026).

Other baseline characteristics of the participants in our present study are described in Table 2. Overall mean LVEF decreased from 62.64±7.80% before the third cycle to 59.95±7.46% after the fourth cycle (mean change −2.69±9.01%; p = 0.004). Early LVEF change was −2.44% (95% CI, −5.09 to 0.21) in the low-to-moderate CTox group and −2.98% (95% CI, −5.29 to −0.67) in the high-to-very-high group. The between-group difference was 0.54% (95% CI, −2.97 to 4.05; p = 0.766). Time × group interaction was not statistically significant (F = 0.089; p = 0.766; η^2 = 0.001) (Table 3).

DISCUSSION

In this retrospective cohort of BC patients receiving anthracycline- or trastuzumab-based therapy, we observed a modest but statistically significant early decline in LVEF between the third and fourth chemotherapy cycles. This reduction did not meet established ESC/ESMO criteria for cancer therapy–related cardiac dysfunction and therefore should be interpreted as early imaging-based functional shifts rather than overt cardiotoxicity. Baseline differences in LVEF between CTox categories must be interpreted cautiously, as LVEF is incorporated into the CTox score calculation, and partly reflects score construction rather than independent myocardial impairment, a phenomenon consistent with incorporation bias in risk modelling (6,7). In addition, the use of LVEF measured after initiation of therapy as a component of the CTox score further limits its role as a true baseline predictor within the present study design. Therefore, CTox stratification in this study should be interpreted as reflecting early treatment-phase risk rather than a true pre-treatment predictive model.

Importantly, the time and risk group interaction were not statistically significant, indicating that CTox category did not predict differential early LVEF decline during the observed treatment period. Consistently, CTox score was not associated with early LVEF change when modelled as a continuous variable or after adjustment for treatment regimen. Within this short follow-up window, baseline CTox stratification was not associated with short-term differences in systolic function.

The limited interval between the third and fourth cycles is an important consideration. Anthracycline- and trastuzumab-related cardiotoxicity is known to be cumulative and progressive, and clinically meaningful differences in myocardial dysfunction may emerge only after longer exposure or higher cumulative doses. This is consistent with previous studies demonstrating that cardiotoxicity typically becomes apparent during later phases of treatment or follow-up rather than within the early treatment cycles (8,9).

Differences in early LVEF changes between treatment regimens may be explained by the distinct mechanisms and temporal patterns of cardiotoxicity associated with anthracyclines and trastuzumab. Anthracycline-related cardiotoxicity is typically dose-dependent and cumulative, often leading to irreversible myocardial injury, whereas trastuzumab-associated dysfunction is more commonly characterized by earlier, potentially reversible impairment of myocardial contractility (8,9).

From two-way mixed ANOVA analysis, a statistically significant within-patient reduction in mean LVEF was observed between the third and fourth cycles, with a moderate effect size. Early myocardial changes during initial exposure to cardiotoxic agents may reflect transient alterations in ventricular loading conditions, myocardial contractility, or early cellular injury mechanisms (10). However, the mean absolute reduction in LVEF (2.69 ± 9.01%) falls within the lower range of reported measurement variability for two-dimensional echocardiography and does not meet criteria for clinically defined cardiotoxicity (5). While such early changes may represent subclinical myocardial alterations, they should be interpreted cautiously in the absence of clinical endpoints. Nevertheless, these LVEF changes remain important because they can indicate subclinical changes in myocardial function that may still be asymptomatic. When a significant decrease in LVEF occurs, the patient is considered to have entered the end-stage of left ventricular systolic dysfunction (11). The European Society of Cardiology (ESC) recommends periodic LVEF measurements combined with cardiac biomarker tests to detect subclinical cardiac dysfunction due to anthracycline and/or trastuzumab therapy (8). Periodic LVEF measurements should also be performed every two cycles or every cumulative dose of doxorubicin ≥ 240 mg/m^2 (12).

Previous studies evaluating CTox and other risk stratification tools have primarily focused on clinically significant cancer therapy–related cardiac dysfunction occurring over longer follow-up periods (6,9). These studies demonstrated higher rates of cardiotoxic events among high-risk patients. In contrast, the present study evaluated early imaging-based changes within a short treatment window. The lack of differential early decline between CTox categories in our cohort does not necessarily contradict prior findings but may reflect the early timing of assessment and limited cumulative exposure. Notably, no significant difference in the magnitude of early LVEF change was observed between low- and high-risk groups. This suggests that early LVEF shifts during initial therapy exposure may reflect treatment-related effects common across risk strata rather than baseline risk stratification alone. Longer-term follow-up would be required to determine whether divergence between CTox categories becomes evident with cumulative exposure.

Measurement variability represents an additional consideration. LVEF assessment using the Simpson biplane method in

two-dimensional echocardiography is subject to interobserver and temporal variability, particularly when absolute changes are small (13). Although standardized institutional imaging protocols were applied, formal interobserver and interobserver variability analyses were not performed. Advanced techniques such as contrast-enhanced echocardiography, three-dimensional imaging, or global longitudinal strain (GLS) assessment may provide greater sensitivity for detecting early subclinical myocardial dysfunction (14).

Taken together, these findings suggest that early LVEF trajectory during initial cycles of cardiotoxic therapy may not be sufficiently discriminative to reflect CTox-based risk stratification within a short follow-up period. Future prospective studies with longer observation intervals and incorporation of event-based cardiotoxicity endpoints are required to determine the long-term prognostic utility of CTox score in clinical cardio-oncology practice.

This study has several limitations. The relatively short interval between the third and fourth chemotherapy cycles represents an important limitation. The cardiotoxic effects of anthracyclines and trastuzumab targeted therapy are cumulative and progressive, so the short duration of follow-up may have been unable to detect changes in LVEF. Therefore, the absence of a significant interaction effect in this study should be interpreted within the context of early follow-up timing rather than as definitive evidence of lack of predictive capacity. Furthermore, there is potential for interobserver and temporal bias in LVEF measurements using two-dimensional echocardiography, since echocardiographic measurements were not restricted to a single operator. The absence of uniformly available pre-treatment echocardiographic data represents an important limitation. As a result, baseline LVEF in this study reflects early treatment-phase assessment rather than true pre-therapy cardiac function. It is therefore possible that subtle functional changes may have already occurred prior to the defined baseline measurement. Formal blinding to CTox risk classification was not performed, which may introduce measurement variability.

CONCLUSION

In this cohort, early LVEF decline was observed during initial cycles of anthracycline- or trastuzumab-based therapy. However, early LVEF trajectory did not differ according to CTox risk category and was primarily associated with treatment regimen rather than baseline risk stratification. These findings support the interpretation of CTox within an early treatment-phase context rather than as a predictor of short-term myocardial change. Further studies with longer follow-up and event-based outcomes are needed to determine its prognostic value.

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CONFLICTS OF INTEREST

None to declare.

ETHICS STATEMENT

The study protocol was reviewed and approved by the Institutional Review Board of Universitas Sumatera Utara (approval number: 927/KEPK/USU/2025). Due to the retrospective nature of the study and use of anonymized medical record data, the requirement for written informed consent was waived.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS (CRediT)

Conceptualization: C.M., N.N.D., H.S.L.; **Data curation:** C.M.; **Formal analysis:** C.M., N.N.D., H.S.L., T.S., M.S.N.; **Funding acquisition:** C.M., N.N.D., H.S.L.; **Investigation:** C.M., N.N.D., H.S.L.; **Methodology:** C.M., N.N.D., H.S.L., T.S., M.S.N.; **Project administration:** C.M., N.N.D., H.S.L.; **Resources:** C.M., N.N.D., H.S.L.; **Software:** C.M.; **Supervision:** N.N.D., H.S.L., T.S., M.S.N.; **Validation:** C.M., N.N.D., H.S.L., T.S., M.S.N.; **Visualization:** C.M., N.N.D., H.S.L.; **Writing – original draft:** C.M., N.N.D., H.S.L.; **Writing – review & editing:** C.M., N.N.D., H.S.L., T.S., M.S.N. All authors have read and agreed to the published version of the manuscript.

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