International Journal of Cardiology Sciences

**ISSN Print:** 2664-9020
**ISSN Online:** 2664-9039
**Impact Factor:** RJIF 5.63
IJCS 2025; 7(2): 105-111
www.cardiologyjournals.net
Received: 14-07-2025
Accepted: 19-08-2025

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# Predictors of early subclinical left ventricular dysfunction in breast cancer patients treated with Trastuzumab

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**DOI:** https://www.doi.org/10.33545/26649020.2025.v7.i2b.125

**Abstract**
**Background:** Trastuzumab (TRZ) enhances survival outcomes in HER2-positive breast cancer however carries a substantial risk of cardiotoxicity that may not be detected by left ventricular ejection fraction (LVEF) alone.
**Objectives:** To identify early predictors of subclinical left ventricular dysfunction during TRZ therapy.
**Methods:** This prospective observational study involved 100 women starting TRZ with baseline LVEF > 55% and normal high-sensitivity troponin T (hs-TnT) who underwent assessments at baseline, 3, and 6 months. Testing included clinical evaluation, hs-TnT, LVEF, and global longitudinal strain (GLS).
**Results:** hs-TnT was elevated in 21% at 3 months and 22% at 6 months ($p$<0.001 across time). LVEF declined from 61.28±2.56% at baseline to 58.33±3.98% (3 months) and 55.18±6.90% (6 months) (both $p$<0.001). GLS worsened from −19.89±0.85% to −17.87±2.29% and −17.44±2.34% at 3 and 6 months (both $p$<0.001). A ≥15% GLS reduction occurred in 24% at 3 months and 27% at 6 months; overall cardiotoxicity occurred in 27%. On univariate analysis, 3-month hs-TnT, 6-month hs-TnT, ≥15% GLS drop at 3 months, and ≥15% GLS drop at 6 months predicted cardiotoxicity (all $p$<0.001). In multivariate analysis, only a ≥15% GLS fall at 6 months remained independently predictive (B = 9.080; 95% CI 3.829-15.497; p = 0.002).
**Conclusions:** Serial GLS and hs-TnT detect early myocardial injury during TRZ therapy. A ≥15% GLS decline particularly by 6 months independently predicts cardiotoxicity and may refine risk stratification beyond LVEF.

**Keywords:** Trastuzumab, cardiotoxicity, global longitudinal strain, high-sensitivity troponin, breast cancer

## Introduction
Breast cancer (BC) is the most frequently diagnosed malignancy in women, representing approximately one-third of all female cancers in the United States [1]. In patients with the more aggressive HER2-positive subtype, trastuzumab (TRZ) combined with anthracycline-based therapy has markedly improved both disease-free and overall survival [2]. Despite this therapeutic benefit, the risk of cardiotoxicity (CDT) remains significant, with 20-30% of individuals developing asymptomatic left ventricular (LV) dysfunction and 3-5% progressing to symptomatic heart failure [3]. Whereas anthracycline-induced cardiomyopathy has been extensively characterized and is considered largely irreversible [4], TRZ-related myocardial dysfunction is thought to be reversible in a substantial proportion of patients. Nevertheless, clinical predictors of such reversibility are not well established [5].
Accurate identification of patients at elevated risk of CDT during TRZ therapy is essential to initiate early intervention and mitigate progression to irreversible LV dysfunction. Conversely, recognizing patients with low risk of CDT may help avoid unnecessary intensive cardiac monitoring. Determining which cases of LV impairment are reversible is also of clinical value, as it may prevent unnecessary cardiovascular treatments or premature discontinuation of TRZ—a decision that could otherwise increase the likelihood of cancer recurrence [6]. Left ventricular ejection fraction (LVEF), routinely assessed by

echocardiography, carries prognostic importance but may lack the sensitivity to capture subtle myocardial damage [7].
Myocardial deformation imaging, particularly global longitudinal strain (GLS), has emerged as a sensitive tool for detecting subclinical LV dysfunction prior to overt LVEF reduction and for predicting cardiovascular outcomes in various cardiac disorders. Recent investigations have demonstrated that an early decline in GLS predicts subsequent LVEF deterioration in women with BC receiving TRZ [8].
Similarly, elevated plasma levels of high-sensitivity troponin I (hs-TnI) have been correlated with the risk of TRZ-induced CDT, suggesting that biomarker assessment may aid in prediction. However, robust echocardiographic or biochemical markers that reliably predict CDT are yet to be established [9].
In addition, one report suggested that factors such as cumulative chemotherapy dose, age, diabetes, hypertension, extremes of body weight, and severe comorbidities may contribute to the risk of chemotherapy-related CDT [10].
On this basis, the current study aimed to assess whether high-sensitivity troponin T (hs-TnT), GLS, and/or clinical characteristics could serve as predictors of TRZ-associated LV dysfunction.

## Patients and methods

### Design and population

This work tool place in Cardio-oncology unit at Cardiology Department, Tanta University and included 100 breast cancer patients planned to receive TRZ chemotherapy during the period from February 2023 to February 2025.
Written informed consent was obtained after a full explanation of potential benefits and risks; unanticipated risks were promptly disclosed to participants and the ethics committee, with strict protection of privacy and data confidentiality.

### Patient Selection

Eligible patients presented prior to therapy with an indication for TRZ, preserved LVEF > 55%, good right-ventricular function, and normal hs-TnT. Exclusions were baseline LVEF < 55% and/or right-ventricular dysfunction, elevated hs-TnT, moderate or severe aortic/mitral/tricuspid valve disease, poor echocardiographic image quality, unstable cardiac conditions (e.g., pericardial effusion or coronary artery disease), and congenital heart disease.

## Methods

### Baseline Assessment

At the first visit, all patients underwent detailed history and cardiovascular risk profiling, including age; hypertension (office BP ≥ 140/90 mmHg); diabetes mellitus (ADA criteria: HbA1c ≥ 6.5%, fasting glucose ≥ 126 mg/dL, or 2-h glucose ≥ 200 mg/dL); smoking (≥100 lifetime cigarettes and current smoking); obesity (BMI > 30 kg/m²); dyslipidemia (total cholesterol > 200 mg/dL, LDL-C > 130 mg/dL, triglycerides > 150 mg/dL, or lipid-lowering therapy); prior radiotherapy; and chest/thyroid disease.
A complete clinical examination, resting 12-lead ECG, laboratory testing including high-sensitivity troponin, and comprehensive two-dimensional transthoracic echocardiography (standard windows with ECG gating) were performed to document baseline structure and function.
GLS was measured by speckle-tracking echocardiography from apical 4-, 2-, and 3-chamber views; endocardial borders were traced on end-systolic frames, tracking was verified/adjusted, and GLS was reported as the average of segmental strains (normal ≥ −18%). A relative GLS reduction ≥ 15% from baseline was considered clinically significant [11].
Patients received individualized counseling on risk-factor control (diet, smoking cessation, exercise, weight management) and adherence to antihypertensive/antidiabetic therapy, were reassured regarding fitness for TRZ, and were educated about heart-failure symptoms and the scheduled follow-ups.

### Follow-Up Visits (3 and 6 Months)

At each follow-up, interval symptoms (especially heart-failure symptoms), cumulative TRZ dose, clinical examination, high-sensitivity troponin, ECG, and repeat echocardiography with GLS were obtained using the same protocols. TRZ -induced cardiotoxicity was defined as symptomatic LVEF < 40% or an asymptomatic LVEF drop > 10 points from baseline. When cardiotoxicity occurred, the oncology team was notified to consider alternative regimens; guideline-directed heart-failure therapy (ACE inhibitor/ARB and β-blocker as appropriate) was initiated, and echocardiography was performed before every planned TRZ dose [12]. If GLS fell by ≥ 15% without meeting cardiotoxicity criteria, cancer treatment was not stopped based on GLS alone, but the oncologist was informed of subclinical dysfunction [13].

### Statistical methods

Normality of distribution was tested with the Shapiro-Wilk test. Continuous variables were expressed as mean±SD, categorical variables as frequency and percentage. Comparisons across repeated non-parametric measures used the Friedman test; categorical associations employed chi-square analysis. Logistic regression (generalized linear models) was applied to determine predictors of CDT, with results presented as odds ratios (OR) and 95% confidence intervals (CI). OR = 1 denoted no effect, OR > 1 higher odds, and OR < 1 lower odds. The CI width reflected precision of the estimates. A two-sided $p<0.05$ was considered statistically significant.

## Results

Demographic data, medical history, risk factors, and vital signs in study cases were presented at Table 1.

**Table 1:** Demographic data, medical history, risk factors, and vital signs in study cases.

| Parameter | | Total cases (n=100) |
|---|---|---|
| Age (years) | | 36.81±6.29 |
| Weight (kg) | | 79.89±12.29 |
| Height (m) | | 1.66±0.04 |
| BMI (kg/m²) | | 29.12±4.75 |
| BSA (m²) | | 1.66±0.07 |
| HTN | No | 92 (92.0%) |
| | Yes | 8 (8.0%) |
| DM | No | 92 (92.0%) |
| | Yes | 8 (8.0%) |
| Dyslipidemia | No | 93 (93.0%) |
| | Yes | 7 (7.0%) |
| HR | | 85.67±9.54 |
| SBP | | 127.60±11.29 |
| DBP | | 74.96±10.86 |

Data were presented as mean ± SD or n (%).

According to tumor related data, 37% of the participants were classified as Grade I, 33% as Grade II, and 30% as Grade III. Regarding the tumor side, 75% of tumors were located on the left side, while 25% were on the right. In terms of radiotherapy, 75% of participants did not receive radiotherapy, whereas 25% underwent the treatment. Table 2

**Table 2:** Cancer-related characteristics in study cases.

| Parameter | Category | Total cases (n=100) |
|---|---|---|
| Tumor Grade | I | 37 (37.0%) |
| | II | 33 (33.0%) |
| | III | 30 (30.0%) |
| Tumor side | Left | 75 (75.0%) |
| | Right | 25 (25.0%) |
| Radiotherapy | No | 75 (75.0%) |
| | Yes | 25 (25.0%) |

According to the data, 100% of participants had normal baseline high sensitivity troponin levels. At 3 months, 79% maintained normal levels, and 21% showed elevated levels. At 6 months, 78% had normal troponin, while 22% exhibited elevated levels. The test result ($p$<0.001) shows a statistically significant change over time. Table 3

**Table 3: High sensitivity troponin in different follow up time points.**

| Parameter | Category | Baseline (n=100) | 3 month (n=100) | 6 month (n=100) | P value |
|---|---|---|---|---|---|
| **High sensitivity troponin** | No | 100 (100.0%) | 79 (79.0%) | 78 (78.0%) | p<0.001* |
| | Yes | 0 (0.0%) | 21 (21.0%) | 22 (22.0%) | |

* for significant p value (<0.05)

According to the data, the baseline EF had a mean of 61.28±2.56 and a median of 62.00. At 3 months, EF decreased to a mean of 58.33±3.98 and a median of 59.00. At 6 months, EF further declined to a mean of 55.18±6.90 and a median of 57.00. For GLS, the baseline mean was -19.89±0.85 and median -20.00. At 3 months, the mean dropped to -17.87±2.29 and median -19.00, and at 6 months, the mean was -17.44±2.34 and median -18.00. Both EF and GLS showed statistically significant changes over time (p < 0.001). Table 4

**Table 4:** Echocardiographic measurements in study cases.

| Parameter | Baseline (n=100) | 3 Month (n=100) | 6 Month (n=100) | P value |
|---|---|---|---|---|
| **EF** | 61.28±2.56 | 58.33±3.98 | 55.18±6.90 | p<0.001* |
| **GLS** | -19.89±0.85 | -17.87±2.29 | -17.44±2.34 | p<0.001* |

* for significant p value (<0.05).

According to outcome, 76% of participants had decline in GLS ≤ 15% at 3 months, while 24% exceeded this threshold. At 6 months, 73% had decline in GLS ≤ 15%, and 27% surpassed the 15% threshold. Regarding cardiac toxicity, 73% of participants did not experience toxicity, whereas 27% developed this condition. Table 5

**Table 5:** Outcome in study cases.

| Parameter | Category | Total cases (n=100) |
|---|---|---|
| GLS > 15% at 3 Months | No | 76 (76.0%) |
| | Yes | 24 (24.0%) |
| GLS > 15% at 6 Months | No | 73 (73.0%) |
| | Yes | 27 (27.0%) |
| Cardiac Toxicity | No | 73 (73.0%) |
| | Yes | 27 (27.0%) |

**GLS:** Global Longitudinal Strain.

According to the logistic regression analysis, univariate predictors of cardiac toxicity included 3-month high sensitivity troponin ($p$<0.001), 6-month high sensitivity troponin ($p$<0.001), decline in GLS > 15% at 3 months ($p$<0.001), and decline in GLS > 15% at 6 months ($p$<0.001). In multivariate analysis, decline in GLS > 15% at 6 months remained significant with a coefficient (B) of 9.080, 95% CI (3.829-15.497), and p=0.002. Table 6, Figure 1

**Table 6:** Logistic regression of predictors of cardiac toxicity in study cases.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| **Predictor** | **B [95% CI (lower-upper)]** | **P value** | **B [95% CI (lower-upper)]** | **P value** |
| Age (years) | 0.036 (-0.035-0.108) | 0.319 | | |
| Weight (kg) | -0.008 (-0.045-0.028) | 0.662 | | |
| Height (m) | 0.338 (-4.104-5.222) | 0.886 | | |
| BMI (kg/m²) | -0.025 (-0.120-0.065) | 0.600 | | |
| BSA (m²) | -0.251 (-4.124-3.489) | 0.896 | | |
| Residence | 0.502 (-0.395-1.430) | 0.274 | | |
| HTN | -1.389 (-4.446-0.699) | 0.283 | | |
| DM | -1.415 (-4.244-0.644) | 0.272 | | |
| Dyslipidemia | -0.087 (-2.025-1.616) | 0.927 | | |
| Tumor Grade | -0.019 (-0.546-0.516) | 0.943 | | |
| HR | -0.006 (-0.048-0.037) | 0.789 | | |
| SBP | -0.027 (-0.066-0.012) | 0.168 | | |
| DBP | -0.013 (-0.056-0.028) | 0.562 | | |
| 3 month High sensitivity troponin | 8.147 (4.664-13.565) | <0.001* | 1.902 (-6.107-10.803) | 0.660 |
| 6 month High sensitivity troponin | 8.328 (5.000-13.931) | <0.001* | 3.311 (-3.964-11.551) | 0.398 |
| GLS > 15 % at 3 month | 8.763 (5.419-14.129) | <0.001* | 3.460 (-3.031-10.747) | 0.322 |
| GLS > 15 % at 6 month | 10.808 (6.912-16.253) | <0.001* | 9.080 (3.829-15.497) | 0.002* |

**B:** Regression coefficient estimate, **CI_lower / CI_upper:** 95% Confidence Interval lower and upper bounds, * for significant p value (<0.05).

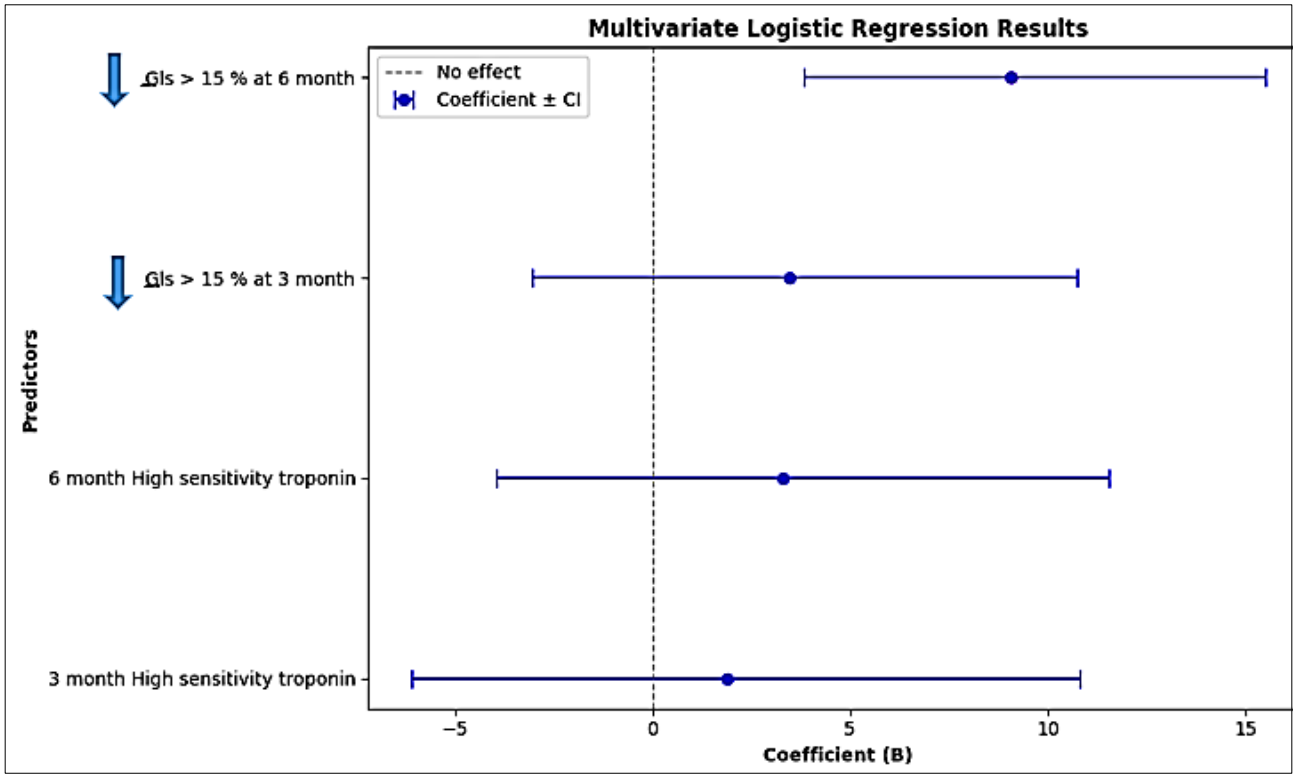


**Fig 1:** Multivariate logistic regression of predictors of cardiac toxicity in study cases.

## Discussion

TRZ improves outcomes in HER2-positive breast cancer but can cause cardiotoxicity often missed by LVEF alone [14]. Therefore, this prospective cohort of 100 women with preserved baseline LVEF initiating TRZ, we performed serial hs-TnT testing and echocardiography with GLS at baseline, 3, and 6 months to identify predictors of early myocardial injury.

In the current study, the age of the studied patients ranged from 26 to 49 years with a mean of 36.8±6.29 years. Kim *et al.* [15] retrospectively evaluated consecutive 787 patients who were treated with adjuvant TRZ for breast cancer. They found that their mean age was 49.9±9.5 years. Alizadehasl *et al.* [16], included 36 consecutive patients HER-2 positive breast cancer with asymptomatic mild LVSD. The mean age of the patients was 53.19 ± 12 years, with a minimum age of 30 years and a maximum of 84 years.

According to our study, the weight of the studied patients ranged from 59 to 100 kg with a mean of 79.89±12.29 kg, the height ranged from 1.59 to 1.72 m with a mean of 1.66±0.04m and the BMI ranged from 20.41 to 38.67 kg/m2 with a mean of 29.12±4.75 kg/m2. BSA ranged from 1.56 to 1.79 m2 with a mean of 1.66±0.07 m2. De Sanctis *et al.* [17], retrospectively reviewed data of 363 adult patients treated with adjuvant TRZ for HER2-positive breast cancer. They reported that the median weight of the studied patients was 62 (42-130) Kg, the height ranged from 1.37-1.78 m with median 1.60 m, BMI ranged from 15.77-50.15 kg/m2 with median 23.72 kg/m2. Ky *et al.* [18] measured 8 biomarkers in a multicenter cohort of 78 patients with breast cancer

undergoing doxorubicin and TRZ therapy. Their study noted that BMI ranged from 22.2-27.2 kg/m2 with median 25.1 kg/m2.

Regarding the risk factors, 8(8%) patients had HTN, 8 (8%) patients had DM and 7 (7%) patients had dyslipidemia. Consistency with our study, Bergamini *et al.* [19], enrolled one-hundred-twenty female patients affected by non-metastatic HER2 positive breast cancer. In overall cases, hypertension represented 23 (20.2%) and diabetes represented 6 (5.3%). Also, Alizadehasl *et al.* [16] found that 11.1% of the patients had diabetes, 19.4% had hypertension.

Regarding the tumor grade, 37 (37%) patients had grade 1, 33 (33%) patients had grade 2 and 30 (30%) patients had grade 3. 25 (25%) patients had right-sided tumor, and 75(75%) patients had left-sided tumor. Kim *et al.* [15] showed that in TRZ -related cardiac dysfunction (TRCD) patients, 21 (36.2%) had stage 1, 25 (43.1%) had stage 2 and 12 (20.7%) had stage 3. Ezaz *et al.* [20] identified women with breast cancer who received adjuvant TRZ. The sample consisted of 1664 older women (mean age 73.6 years) with 3-year HF/CM rate of 19.1%. They documented that the 26.8% of women had stage I cancer, 45.6% had stage II and 27.6% had stage III.

Based on our findings, HR ranged from 70 to 100 bpm with a mean of 85.67±9.54 bpm. SBP ranged from 100 to 165 mmHg with a mean of 127.6±11.29 mmHg and DBP ranged from 60 to 110 mmHg with a mean of 74.96±10.85 mmHg. In the same line with our study, Alizadehasl *et al.* [16] concluded that the mean heart rate was 86.3 ±11.2 bpm, the systolic BP was 121.4 ±15.9 and mean diastolic BP was 77.7 ±9.3.

Our study showed that among the studied patients, 25 (25%) had received radiotherapy. Ky *et al.* [18] reported that 46 (60%) of cases had radiotherapy. Also, Bergamini *et al.* [19], showed that 6 (5%) of patients underwent radiotherapy (RT).

In the present work, 100% of participants had normal baseline high sensitivity troponin levels. At 3 months, 79% maintained normal levels, and 21% showed elevated levels. At 6 months, 78% had normal troponin, while 22% exhibited elevated levels, with a statistically significant change over time ($p$<0.001). Comparable with our study, Ky *et al.* [18] revealed that levels of troponin increased significantly from baseline to visit 2 ($p$<0.001). However, Dores *et al.* [21] prospectively enrolled 51 consecutive patients treated with TRZ for advanced HER2-positive breast cancer. It was observed that Troponin was not statistically different at baseline and after three months of TZB therapy. The contradiction may be different sample size and the old age of their patients.

In the current study, the baseline EF had a mean of 61.28±2.56 and a median of 62.00. At 3 months, EF decreased to a mean of 58.33±3.98 and a median of 59.00. At 6 months, EF further declined to a mean of 55.18±6.90 and a median of 57.00. In the same line with our study, Mazzutti *et al.* [22] monitored BC patients using serial echocardiography at baseline prior to TRZ initiation (Exam 1) and subsequently at 3-month intervals during the first treatment year (Exams 2, 3, and 4). Their analysis demonstrated a significant reduction in LVEF between the initial and fourth assessments (Ex1: 64.1% ± 4.9 vs. Ex4: 60.9% ± 4.9, $p$ = 0.003).

In our study, the incidence of TRZ induced cardiotoxicity was 27 %. This agreed with Baron *et al.* [23], who evaluated LVEF in 76 women aged 36-73 years previously treated with TRZ and reported that 21 patients (28%) fulfilled the criteria for cardiotoxicity. Earlier clinical trials have also demonstrated higher rates of cardiac dysfunction following TRZ, particularly in individuals pre-exposed to anthracyclines, with incidences ranging from 20% to 27% [24]. By contrast, Nhat *et al.* [25] studied 110 BC patients with baseline cardiovascular risk factors and observed that 12 (10.9%) developed asymptomatic CTRCD during TRZ therapy. Differing from our results, Zhou *et al.* [26] analyzed a retrospective cohort of 51 patients referred for LV dysfunction after TRZ administration and reported that 80% developed permissive cardiotoxicity. This discrepancy may be attributable to their longer follow-up period, with a median duration of 3 years (range: 1.3-4 years), compared with our shorter observation window.

For GLS in our study, the baseline mean was -19.89±0.85 and median -20.00. At 3 months, the mean dropped to -17.87±2.29 and median -19.00, and at 6 months, the mean was -17.44±2.34 and median -18.00. Both EF and GLS showed statistically significant changes over time ($p$<0.001). According to outcome, 76% of participants had a decline in GLS ≤ 15% at 3 months, while 24% exceeded this threshold. At 6 months, 73% had a decline in GLS ≤ 15%, and 27% surpassed the 15% threshold. In the current work, GLS measurements after 3 and 6 months of treatment were significantly lower compared to baseline P value (<0.001). In alignment with our results, Nhat *et al.* [25] observed that in patients with moderate CTRCD, mean LV-GLS measured three weeks after completing TRZ was significantly reduced compared with baseline (−17.7±0.5% vs. −19.1±1.2%; P = 0.043). Similarly, Keramida *et al.* [27] evaluated LV and RV deformation parameters during TRZ therapy in BC patients and demonstrated that LV-GLS declined significantly at 3 months (−19.5±2.7 to −18.7±2.8; P = 0.0410) and further deteriorated at 6 months, reaching its lowest values (−17.9±6.1; P=0.002). Moreover, van der Linde *et al.* [28] confirmed a progressive decline in GLS over time (β = 2.7, 95% CI 0.8-4.6; $p$<0.001).

According to the logistic regression analysis, univariate predictors of cardiac toxicity included 3-month high sensitivity troponin, 6-month high sensitivity troponin, decline in GLS > 15% at 3 months, and decline in GLS > 15% at 6 months, all with p < 0.001. While, in multivariate analysis, decline in GLS > 15% at 6 months remained significant with a coefficient (B) of 9.080, 95% CI (3.829-15.497), and p = 0.002. Consistent with prior evidence, Nhat *et al.* [25] demonstrated that, among deformation indices of both ventricles, only LV-GLS showed a significant reduction in patients who developed CTRCD during TRZ therapy. GLS has therefore emerged as a sensitive tool for detecting subclinical myocardial impairment. An early relative decline of 10-15% during oncologic treatment appears to be a valuable threshold for anticipating subsequent cardiotoxicity. Indeed, previous studies indicated that early GLS deterioration could predict an ensuing decrease in LVEF approximately three months later [29]. Similarly, Kitayama *et al* [30] reported that hs-TnT was capable of identifying TRZ-related cardiotoxicity in BC patients, with either an increment above baseline or an integrated elevation over time proving more reliable than isolated absolute values. Katsurada *et al* [31] clearly showed that the continuous elevation of hs-TnT at 3 and 6 months

during TRZ therapy could predict the subsequent reduction of LVEF.

This single-center study with a small sample and short follow-up limits generalizability; moreover, cardiotoxicity attribution is confounded because most patients received TRZ after anthracyclines, raising cumulative toxicity concerns. Larger, longer, multicenter trials ideally assessing TRZ monotherapy are needed.

## Conclusions

hs-TnT elevation and decline in GLS by more than 15% threshold may be acts as predictors for the incidence of TRZ-induced LV dysfunction in patients with BC.

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**How to Cite This Article**
Fahmy AKE, Elsaied AM, Eldin SMS, Elshedoudy SA, Elhefnawy SB. Predictors of early subclinical left ventricular dysfunction in breast cancer patients treated with Trastuzumab. International Journal of Cardiology Sciences 2025; 7(2): 105-111.