

Factors associated with reduced left ventricular ejection fraction as a manifestation of Trastuzumab-induced cardiotoxicity in breast cancer patients

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Abstract

BACKGROUND: Breast cancer is the most common malignancy in women, with 15–20% being HER2-positive, an aggressive subtype treated with Trastuzumab. Despite its survival benefits, Trastuzumab may cause cardiotoxicity, typically monitored by left ventricular ejection fraction (LVEF). This study assessed Trastuzumab's impact on LVEF and related factors among women with breast cancer in Baghdad.

METHODS: This retrospective observational cohort study included 60 women with stage I–III HER2-positive breast cancer treated at Al-Amal National Oncology Hospital between January 2023 and May 2024. Baseline demographic, clinical, and echocardiographic parameters were collected, with follow-up assessments every three weeks during therapy and after the final cycle. Data were analyzed using SPSS version 27.

RESULTS: A P-value <0.05 was considered statistically significant. Mean LVEF declined significantly from $64.98\% \pm 5.50$ to $62.02\% \pm 6.91$ post-treatment ($P < 0.001$). The proportion of patients with impaired left ventricular diastolic function increased from 11.7% to 26.7% ($P = 0.003$). An LVEF decline of $\geq 10\%$ was considered clinically meaningful. Traditional risk factors were not associated with LVEF decline, whereas baseline LVDF (OR 10.80; 95% CI: 2.21–17.42; $P = 0.007$) and post-treatment LVDF (OR 8.20; 95% CI: 1.74–13.58; $P = 0.008$) were significantly linked to LVEF decline.

CONCLUSION: Trastuzumab can cause early cardiac function decline, which is not always detected by LVEF alone. Assessment of left ventricular diastolic function at baseline and during therapy can identify high-risk patients, enabling timely monitoring and management to balance anticancer benefits with cardiotoxic risk.

Keywords: Cardiovascular; Echocardiography; Physiology; Breast Cancer

Introduction

Breast cancer remains the most common malignancy and a leading cause of cancer-related mortality among women worldwide¹. Genetic mutations, particularly in the breast cancer susceptibility genes (BRCA1 and BRCA2), are strongly associated with increased risk². This heterogeneous disease is classified into four molecular subtypes: estrogen receptor-positive (ER+), progesterone receptor-positive (PR+), human epidermal growth factor receptor 2-positive (HER2+), and triple-negative breast cancer (TNBC)³. Among these, HER2-positive tumors, representing 15–20% of cases, are generally more aggressive and associated with poorer outcomes^{4–6}.

The introduction of Trastuzumab, a monoclonal antibody targeting HER2, revolutionized treatment and became the standard of care^{7,8}. Its mechanisms include inhibition of HER2 dimerization and downstream proliferative signaling^{9,10}, as well as immune-mediated effects such as antibody-dependent cellular phagocytosis¹¹. However, Trastuzumab-induced cardiotoxicity (TIC) remains a significant limitation¹², caused by inhibition of HER2 signaling in cardiomyocytes¹³. Early recognition of TIC is critical, as cardioprotective agents such as β -blockers and angiotensin-converting enzyme (ACE) inhibitors can prevent adverse outcomes^{14,15}.

A decline in left ventricular ejection fraction (LVEF) is the most common indicator of TIC¹⁶, though it often reflects late myocardial injury. Other parameters, including left ventricular end-diastolic dimension (LVEDD) and left atrial (LA) enlargement, may detect earlier dysfunction^{17–24}. Most of the current knowledge in this area derives from Western cohorts, whereas data from Asian and Middle Eastern populations remain scarce, despite breast cancer incidence in Asia rising by 3–6% annually. Currently, Asian women account for nearly 40% of global cases, are often younger at diagnosis, premenopausal, and have fewer conventional cardiovascular risk factors^{25–27}.

Although LVEF is a well-known manifestation

of TIC, it is considered a late marker of cardiac damage in breast cancer patients, highlighting the need to evaluate factors related to and predictive of LVEF decline. In light of the limited regional evidence, the present study was conducted in Baghdad to assess the effect of Trastuzumab on LVEF and its associated factors in women with breast cancer.

Methods

Study design and Population

The present study is a retrospective observational cohort study. The study population consisted of all female breast cancer patients treated with adjuvant Trastuzumab after completion of chemotherapy at the Al-Amal National Oncology Hospital in Baghdad, Iraq, from January 2023 to May 2024.

Inclusion and exclusion criteria

Eligible participants were women aged 18 years and older with histologically confirmed breast cancer, stage I to III (non-metastatic). All patients underwent complete or partial tumor resection surgery and followed institutional guidelines for adjuvant Trastuzumab therapy. Patients were excluded if they had a prior history of breast cancer, congenital heart disease, radiation exposure to the chest, incomplete medical records, or non-adherence to the treatment protocol.

Sixty-eight patients met the eligibility criteria; however, eight were excluded due to non-adherence, leaving 60 patients for final analysis.

Data collection

Baseline demographic and clinical data were recorded, including age, body mass index (BMI), past medical history (PMH), heart rate (HR), side of cancer involvement (right, left, bilateral), and disease stage. Echocardiographic findings—including LVEF, LVED, LA volume, and LVDF were collected both before and after Trastuzumab therapy.

Trastuzumab was prescribed by a specialist oncologist. Treatment began with an intravenous loading dose of 8 mg/kg, followed by 6 mg/kg

every three weeks over a one-year course²⁸.

A comprehensive transthoracic two-dimensional echocardiographic assessment was performed for all patients in the left lateral decubitus position. LV volumes and LVEF were measured using the biplane Simpson method. LA volume was determined at end-systole from the apical four-chamber view using the modified Simpson's rule. LVED was obtained from the parasternal long-axis view. LVDF was assessed using standard Doppler and tissue Doppler parameters and categorized as normal or impaired according to the recommendations of the European Association of Cardiovascular Imaging (EACVI)²⁹.

Baseline scans were performed prior to Trastuzumab initiation, with follow-up assessments every three weeks and after the final treatment cycle (median 8 weeks, range 3–14 weeks) to monitor cardiac performance. The final assessments were considered for analysis. A $\geq 10\%$ reduction in LVEF was defined as clinically significant.

Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of the College of Medicine, Ashur University, Baghdad. All participants were informed about the study objectives and procedures, and written informed consent was obtained prior to enrolment.

Statistical analysis

The collected data were entered into SPSS software (version 27). Categorical data are presented as n (%), and continuous data are expressed as mean \pm standard deviation (SD).

For inferential statistics, a paired samples t-test was used to compare the mean of quantitative variables post-trastuzumab intervention compared to before the intervention. The McNemar test was applied to compare the frequency percentages of categorical variables before and after the intervention. Furthermore, logistic regression analysis was employed to assess factors associated with the occurrence of LVEF

reduction, and odds ratios (OR) values are reported. For all analyses, a P-value of less than 0.05 was considered statistically significant.

Result

This study was conducted on 60 female breast cancer patients, with a mean age of 50.34 ± 9.22 years and a mean BMI of 23.36 ± 4.46 kg/m². Their PMH included ischemic heart disease (IHD) in 6.7%, hypertension (HTN) in 25%, tachycardia in 3.3%, and diabetes mellitus (DM) in 6.7%. Baseline and clinical characteristics of these patients are presented in [Table 1](#).

The LVEF of patients post-trastuzumab intervention showed a significant reduction, with a mean of $62.02\% \pm 6.91$, compared to a mean of $64.98\% \pm 5.50$ before treatment (P value < 0.001). Concomitantly, the LA volume post-trastuzumab intervention demonstrated a significant increase, with a mean of 33.83 ± 7.41 ml, compared to a mean of 32.24 ± 5.60 ml before treatment (P value = 0.004). In contrast, the LVED did not exhibit any significant changes (P value = 0.422). Furthermore, the distribution of LVDF pre- and post-trastuzumab intervention was as follows: it was normal in 88.3% and 73.3% of patients, and impaired in 11.7% and 26.7% of patients, respectively (P value = 0.003) ([Table 2](#)).

It should be noted that 9 of these patients had a $\geq 10\%$ decrease in LVEF post-trastuzumab intervention. Logistic regression analysis revealed that while older age, HTN, higher HR, LA volume, and increased LVED were associated with the increased odds of LVEF reduction, these associations were not statistically significant (P value > 0.05). In contrast, impaired LVDF at baseline (OR: 10.80; 95% CI: 2.21-17.42; P value = 0.007) and post-treatment (OR: 8.20; 95% CI: 1.74-13.58; P value = 0.008) significantly increased the odds of LVEF reduction ([Table 3](#)).

Discussion

Following Trastuzumab therapy, patients exhibited a significant reduction in LVEF compared with baseline values. A notable increase in LA volume accompanied this decline, while LVED remained unchanged. Additionally,

Table 1. Baseline and clinical characteristics of breast cancer patients

Variables		Total (n=60) Mean±SD N (%)
Age; year	< 40 yrs.	50.34±9.22 9(15%)
	40-50 yrs.	20(33.3%)
	>50 yrs.	31(51.7%)
BMI; kg/m ²	≤ 25 kg/m ²	23.36±4.46 37(61.7%)
	> 25 kg/m ²	23(38.3%)
PMH	IHD	4(6.7%)
	HTN	15(25.0%)
	Tachycardia	2(3.3%)
	DM	4(6.7%)
HR; bpm		84.98±13.11
Cancer side	Right	23(38.3%)
	Left	34(56.7%)
	Bilateral	3(5.0%)
Disease stage	I	10(16.7%)
	II	35(58.3%)
	III	15(25%)

Data shown n(%) or mean± standard deviation (SD)

HTN: Hypertension, IHD: Ischemic Heart disease; DM: Diabetes Mellitus, BMI: Body mass index, HR: Heart rate

Table 2. Comparison of echocardiographic factors before and after trastuzumab treatment in breast cancer patients

Parameters	Baseline Mean± SD	After treatment Mean± SD	P value
LVEF; %	64.98±5.50	62.02±6.91	<0.001*
LVED; cm	4.947±0.53	4.930±0.55	0.422
LA Volume; mL	32.24±5.60	33.83±7.41	0.004*
LVDF	Normal	53(88.3%)	0.003*
	Impaired	7(11.7%)	

LVEF: Left Ventricular Ejection Fraction; LVED: Left Ventricular End-Diastolic Diameter; LA: Left Atrium; LVDF: Left Ventricular Diastolic Function
A paired t-test was used to compare the mean values of quantitative variables after the intervention with those before the intervention, and to compare the frequency percentages of categorical variables before and after the intervention, the McNemar test was applied.

Table 3. Factors associated with LVEF reduction after trastuzumab treatment in breast cancer patients

Variables	Non-Reduce LVEF (n=51)	Reduce LVEF (n=9)	OR (95% CI)	P value	
Age; year	49.47±9.45	55.22±5.14	1.08(0.99-1.18)	0.088	
BMI; kg/m ²	23.39±4.49	23.19±4.54	0.99(0.84-1.16)	0.902	
	IHD	4(7.8%)	0(0.0%)	0.92(0.85-1.00)	1.00
PMH	HTN	12(23.5%)	3(33.3%)	1.62(0.35-7.50)	0.678
	Tachycardia	2(3.9%)	0(0.0%)	0.96(0.91-1.02)	1.00
	DM	4(7.8%)	0(0.0%)	0.92(0.85-1.00)	1.00
HR; bpm	82.85±12.40	96.33±11.22	1.09(1.02-1.16)	0.010*	
Cancer side	Right	20(39.2%)	3(33.3%)	0.77(0.17-3.46)	0.523
	Left	28(54.9%)	6(66.7%)	1.64(0.37-7.30)	0.719
	Bilateral	3(5.9%)	0(0.0%)	0.94(0.88-1.01)	1.00
LVED	Baseline	4.91±0.51	5.18±0.57	2.89(0.66-12.60)	0.159
	After treatment	4.88±0.51	5.23±0.68	3.55(.86-14.72)	0.081
LA volume	Baseline	32.76±5.62	29.29±4.76	0.87(0.74-1.02)	0.095
	After treatment	34.16±7.33	31.96±7.99	0.96(0.87-1.06)	0.410
LVDF	Normal	48(94.1%)	5(55.6%)	Ref.	0.007*
	Impaired	3(5.9%)	4(44.4%)	10.80(2.21-17.42)	
LVDF – After treatment	Normal	41(80.4%)	3(33.3%)	Ref.	0.008*
	Impaired	10(19.6%)	6(66.7%)	8.20(1.74-13.58)	

LVEF: Left Ventricular Ejection Fraction; BMI: Body Mass Index; PMH: Past Medical History; IHD: Ischemic Heart Disease, HTN: Hypertension; DM: Diabetes Mellitus; HR: Heart Rate; LVED: Left Ventricular End-Diastolic Diameter; LA: Left Atrium; LVDF: Left Ventricular Diastolic Function

the proportion of patients with diastolic dysfunction increased significantly after treatment, indicating a deterioration in diastolic performance associated with Trastuzumab exposure. Notably, traditional cardiovascular risk factors were not associated with LVEF decline, whereas baseline and post-treatment LVDF emerged as independent predictors.

As a decline in LVEF is a well-known manifestation of TIC¹⁶, our study confirmed this finding in a sample of Middle Eastern women, although we did not discuss it further due to its established nature. Importantly, our results suggest that both baseline and post-treatment impaired LVDF are associated with LVEF decline in breast cancer patients receiving adjuvant therapy. Several observational and imaging studies have similarly reported early diastolic changes, particularly when Trastuzumab is combined with anthracyclines or radiation^{30,31}. Cochet et al. also found that baseline impaired LVDF was a predictive factor for Trastuzumab-mediated cardiotoxicity after adjuvant anthracycline therapy in breast cancer patients³².

In our study, no significant association was observed between LVEF decline, as an indicator of TIC, and baseline clinical factors such as BMI, age, HTN, IHD, or DM. A study from Iraq evaluating early cardiac changes in HER2-positive breast cancer patients receiving adjuvant Trastuzumab reported similar findings, with no significant associations between cardiotoxicity and baseline factors such as age, BMI, hypertension, or DM, underscoring the greater predictive value of echocardiographic parameters over traditional risk factors³³.

Additionally, a retrospective Saudi study of 105 patients with HER2-positive early breast cancer treated with Trastuzumab reported no association between cardiotoxicity and HTN or DM; however, in contrast to our findings, they identified BMI as a significant predictor of LVEF decline³⁴. Our results were also partially consistent with a retrospective Italian cohort of 179 patients, which found that conventional cardiac risk factors (HTN, hypercholesterolemia,

DM, smoking, IHD, and prior chest radiotherapy) as well as cardioprotective medications (β -blockers, ACE inhibitors, and angiotensin receptor blockers) did not significantly influence TIC risk³⁵. Differences in cohort size, concurrent use of anthracyclines, and statistical modeling approaches may explain the discrepancies observed between studies.

Our analysis also found no significant relationship between LVEF decline and whether breast cancer was unilateral or bilateral. A retrospective study conducted between 2011 and 2015 in patients with HER2-positive early breast cancer similarly reported no association between tumor laterality and TIC, which is consistent with our findings³⁴. In contrast, another retrospective study from Saudi Arabia found that a unilateral tumor site was significantly associated with an increased incidence of TIC (present in 62.5% of cardiotoxic cases, $p = 0.0269$), suggesting tumor laterality as a potential risk factor³⁶. Collectively, these results indicate that tumor laterality cannot currently be considered a reliable predictor of TIC; larger prospective studies with standardized methodologies are warranted to clarify its clinical relevance.

Conclusion

Although LVEF is commonly used to monitor cardiac function, it may miss early subclinical myocardial injury. Our findings underscore the value of comprehensive LVDF assessment at baseline and during follow-up in breast cancer patients receiving Trastuzumab. Careful treatment decisions, made through close collaboration between oncologists and cardiologists, are essential to balance the therapeutic benefits of Trastuzumab with its potential cardiotoxic risk, especially in patients with impaired LVDF.

Strengths

A major strength of this study is its focus on a Middle Eastern population, where data on Trastuzumab-induced cardiotoxicity remain limited. Most existing evidence comes from

Western cohorts, despite Asian and Middle Eastern populations accounting for a large proportion of global breast cancer cases and often presenting distinct clinical characteristics, including younger age at diagnosis, higher premenopausal prevalence, and fewer conventional cardiovascular risk factors. By evaluating the effect of Trastuzumab on LVEF and its associated factors in women with breast cancer in Baghdad, this study provides valuable regional insight.

Limitations

This study has several limitations. Its retrospective design and relatively small sample size limit generalizability. Long-term outcomes such as overall cardiac status and survival were not assessed, and other echocardiographic parameters were not examined. The limited sample also prevented adjustment for the number of Trastuzumab cycles in regression analyses, although prior studies suggest TIC is generally not dose-dependent³⁷.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: SKS; MJJ; MR; AKS

Data Acquisition: SKS; MJJ; AKS

Data Analysis or Interpretation: SKS; MJJ; MR

Manuscript Drafting: SKS; MJJ; UP

Critical Manuscript Revision: SKS; MJJ; UP

All authors have approved the final manuscript and are responsible for all aspects of the work.

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