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Advanced Echocardiography Findings of HER2-Positive Breast Cancer Patients Following Anthracycline-Based Chemotherapy

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ABSTRACT

Background: Cardiotoxicity, a common complication of chemotherapy, may have irreversible adverse effects on the heart. Anthracycline-based chemotherapy for breast cancer can lead to dilation-hypokinetic cardiomyopathy, eventuating in heart failure. As the primary diagnostic tool for cardiovascular toxicity, echocardiography may be essential in evaluating the heart function of such patients.

Objectives: This study aimed to identify the most important echocardiography findings for proper and timely diagnosis of cardiotoxicity in patients with HER2-positive breast cancer undergoing anthracycline-based chemotherapy.

Methods: Our final analysis included 132 female patients who were HER2-positive and had breast cancer. All of these patients had one pre-chemotherapy echocardiography and at least one echocardiography after three episodes of anthracycline-based chemotherapy. The patients' age, body mass index, and history of chemotherapy were recorded. Mean alterations from baseline echocardiography to echocardiography after three episodes of chemotherapy were calculated for all parameters evaluated. Data analysis was conducted using the Statistical Package for the Social Sciences v. 26.

Results: Significant changes were seen in three-dimensional left ventricular ejection fraction (LVEF 3D), two-dimensional left ventricular ejection fraction (LVEF 2D), left ventricular global circumferential strain (LVGCS), left ventricular global longitudinal strain (LVGLS), left ventricular end-diastolic volume (LVEDV), stroke volume (SV), left ventricular end-systolic volume (LVESV), right ventricular end-systolic dimension (RVESD) in patients with breast cancer ($P < 0.0001$). RVESD, LVESV, LVEDV, and SV significantly increased after three chemotherapy episodes, but LVEF (3D and 2D), absolute LVGCS, and absolute LVGLS fell significantly.

Conclusion: LVEF (3D and 2D), LVGCS, LVGLS, LVEDV, LVESV, SV, and RVESD are important echocardiography parameters in diagnosing cardiotoxicity in patients with HER2-positive breast cancer.

1. Introduction

Breast cancer (BC) is the most common cancer in women worldwide (1, 2). Approximately 1.7 million cases are diagnosed every year (3). The annual rate of breast cancer had a 3.1% increase from 1980 to 2010 (4). In parallel with this rise, advances in diagnosis and treatment led to increased survival rates (5). However, with increased life expectancy, chemotherapeutic agents' risk of cardiotoxicity also increased

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in breast cancer survivors (6). Cardiotoxicity, a common complication of chemotherapy, may leave irreversible adverse effects on the heart, such as subclinical myocardial infarction, heart failure, hypertension, vasospastic and thromboembolic ischemia, and rhythm disturbances (7, 8).

Anthracyclines, anti-HER2 agents, angiogenesis inhibitors, and anti-MET agents may cause cardiovascular (CV) toxicity via different mechanisms (9). Anthracyclines and trastuzumab are drugs used in combination to treat breast cancer that can lead to dilation-hypokinetic cardiomyopathy, eventuating in heart failure (10, 11). As the main diagnostic tool for cardiovascular toxicity, echocardiography is important in evaluating heart function in such patients (12, 13). A decrease in LVEF is considered an early stage of cardiotoxicity, but the guidelines' thresholds for medical judgments differ. Cardiotoxicity is defined as an LVEF fall by > 10% or an absolute EF < 53% by the American Society of Echocardiography and the European Association of Cardiovascular Imaging (14). A decrease of more than 5% in baseline LVEF to less than 55% in patients with symptomatic heart failure or more than 10% decline in LVEF to ≤ 55% in asymptomatic patients represents chemotherapy-induced cardiotoxicity in the European Society of Medical Oncology (ESMO) guideline (15).

LVEF, as the most common indicator of the systolic function of the heart, has low sensitivity and confounding variability for the diagnosis of cardiovascular toxicity (16-18). The most useful parameter for the prediction of cardiotoxicity is a 10–15% decrease in global longitudinal strain (GLS) in 2D speckle tracking echocardiography (STE) during chemotherapy (19). GLS and global circumferential strain (GCS), as diagnostic markers of early myocardial injury, can detect cardiotoxicity three months earlier than the LVEF drop (20-22).

2. Objectives

The current study aims to investigate the changes in the echocardiographic markers of cardiotoxicity in patients with breast cancer. This may help to reduce cardiovascular toxicity by early detection of myocardial injury. Establishing the proper and timely diagnosis of cardiotoxicity in patients with breast cancer can lead to a decrease in the mortality and morbidity of these patients.

3. Materials and Patients

3.1. Study Subjects and Study Design

This retrospective, cross-sectional study included the medical records of 132 female breast cancer patients over two years, from September 2019 to September 2021. The mean age was 51.14 ± 12.14 years in these patients. This research was approved by the institutional ethics committee. All study procedures were conducted as per the Declaration of Helsinki. Written informed consent about the data registration follow-up policy was obtained from all patients after explaining the purpose of the study. We ensured that the research and the participation of patients did not influence the diagnosis and therapeutic approaches.

The medical records of all patients newly diagnosed with breast cancer at the Cardio-Oncology Department of Rajaei Cardiovascular, Medical, and Research Center were studied. Any patients with a previous history of underlying heart disease, chemotherapy, and those who had refused follow-up visits or echocardiography were excluded. Also, patients who lacked appropriate echocardiographic views in their data were excluded. Ultimately, 132 breast cancer patients were included in the final analysis. All of these patients had one pre-chemotherapy echocardiography and at least one echocardiography after three episodes of chemotherapy. Patients included were HER2-positive and received anthracycline-based chemotherapy. The patients' age, body mass index (BMI), and history of chemotherapy were recorded.

3.2. Echocardiographic Acquisition

Transthoracic echocardiography was performed by skilled echocardiography fellows using a Phillips Epiq 7c ultrasound system. Left ventricular ejection fraction (LVEF) was measured with the modified Simpson's biplane method (18). GLS and GCS were calculated using data stored in the picture archiving and communication system (PACS) by an echocardiography fellow, confirmed by an expert cardiologist. TOMTEC-ARENA TTA2 software was used for 3D analysis. The descriptions of other echocardiography findings recorded and analyzed in our study are listed in Table 1.

3.3. Intra- and Inter-Observer Variability

For 15 indiscriminately selected patients, intra-observer variability and inter-observer variability were measured. For intra-observer variability, the same person re-measured the parameter ten days after the primary measurement. Inter-observer variability was measured by a second reviewer who was not informed about the clinical history and timing of echocardiography.

Table 1. Description of Echocardiographic Findings.

Echocardiographic Finding	Description
IVS	Inter-ventricular septum
RA area	Right atrium area
LA area	Left atrium area
E-velocity	Mitral inflow E velocity
A-velocity	Mitral inflow A velocity
RVsm	Right ventricular peak systolic myocardial velocity
TAPSE	Tricuspid annular plane systolic excursion
FAC	Fractional area change
TR gradient	Tricuspid regurgitant gradient
LVEF-3D	Left ventricular ejection fraction-three dimensional
LVEF-2D	Left ventricular ejection fraction-two dimensional
LVEDV	Left ventricular end-diastolic volume
LVESV	Left ventricular end-systolic volume
SV	Stroke volume
E-lateral	Myocardial early diastolic velocity (lateral)
E-septal	Myocardial early diastolic velocity (septal)
S-septal	Myocardial systolic velocity (septal)
RVEDD	Right ventricular end-diastolic dimension
LVGLS	Left ventricular global longitudinal strain
LVGCS	Left ventricular global circumferential strain
LVPWD	Left ventricular posterior wall end-diastolic dimension
RVESD	Right ventricular end-systolic dimension

3.4. Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA), version 26. Descriptive statistics, including mean and standard deviation, were calculated. The Wilcoxon signed-rank test was used to assess the difference in echocardiography findings between the first and second echocardiography of patients with breast cancer who underwent anthracycline-based chemotherapy. A P-value less than 0.05 was considered significant.

3.5. Ethical Approval

The study design and protocols were approved by the Ethics Committee of the Research Deputyship of Rajaie Cardiovascular, Medical, and Research Center (ID: IR.RHC.REC.1400.057).

3.6. Informed Consent

This was a retrospective study of medical records, and data on individual participants were not reported, so obtaining informed consent was not needed in light of the journal guidelines.

4. Results

A total of 132 women with breast cancer were enrolled in this study. The mean age was 51.14 ± 12.14 years, and the mean BMI was 26.95 ± 4.23 kg/m^2. The Wilcoxon signed-rank test was conducted to compare echocardiography findings in baseline echocardiography and echocardiography after three episodes of chemotherapy. Significant changes were seen in three-dimensional left ventricular ejection fraction (LVEF 3D), two-dimensional left ventricular ejection fraction (LVEF 2D), left ventricular global circumferential strain (LVGCS), left ventricular global longitudinal strain (LVGLS), left ventricular end-diastolic volume (LVEDV), stroke volume (SV), left ventricular end-systolic volume (LVESV), right ventricular end-systolic dimension (RVESD) in patients with breast cancer (P < 0.0001). RVESD, LVESV, LVEDV, and SV significantly increased after three chemotherapy episodes, but LVEF (3D and 2D), absolute LVGCS, and absolute LVGLS fell significantly.

Notable differences were not seen in other echocardiography findings (Table 2).

Demonstrate Categorized Echocardiographic Findings in Breast Cancer Patients before and after three episodes of chemotherapy (Figures 1-3.).

5. Discussion

In this study, we aimed to identify the most critical echocardiography findings for proper and timely diagnosis of cardiotoxicity in patients with HER2-positive breast cancer receiving anthracycline-based chemotherapy. In line with our hypothesis, chemotherapy had an adverse effect on the heart's right and left ventricular function. Based on the results of our study, it is essential to note that the absolute LVGLS, absolute LVGCS, and LVEF (3D and 2D) decreased as markers of LV function, while the RVESD, LVEDV, LVESV, and SV had increased significantly.

Table 2. A Summary of the Echocardiography Findings of Patients with Breast Cancer Who Received Anthracycline-Based Chemotherapy

Echocardiographic Finding	Mean at Baseline	Mean after Three Episodes of Chemotherapy	Z	P-value
IVS	7.93	8.03	-1.74	0.081
FAC	44.31	44.29	-1.50	0.132
E-velocity	73.17	72.49	-0.30	0.763
A-velocity	74.76	73.64	-0.94	0.343
RVsm	11.02	11.01	-0.82	0.410
TAPSE	20.56	20.53	-1.29	0.194
RA area	11.52	11.91	-0.015	0.987
LA area	15.98	16.21	-1.92	0.054
TR gradient	18.98	19.80	-1.06	0.289
LVEF-2D	54.20	50.81	-8.98	< 0.0001
LVEF-3D	55.08	52.04	-9.09	< 0.0001
LVPWD	7.658	7.933	-1.42	0.154
SV	35.65	40.15	-9.99	< 0.0001
LVESV	34.83	36.43	-9.48	< 0.0001
LVEDV	65.89	78.81	-9.98	< 0.0001
S-septal	8.05	8.03	-0.081	0.935
E-septal	8.50	8.43	-1.49	0.134
E-lateral	11.55	11.50	-1.71	0.086
LVGLS	-20.84	-17.13	-9.56	< 0.0001
LVGCS	-30.84	-21.44	-9.88	< 0.0001
RVEDD	30.14	30.18	-1.80	0.70
RVESD	24.06	26.62	-10.04	< 0.0001

Abbreviations: IVS: inter-ventricular septum; FAC: fractional area change, RVS: right ventricular peak systolic myocardial velocity; TAPSE: tricuspid annular plane systolic excursion; RA: right atrium; LA: left atrium; TR: tricuspid regurgitation; LVEF-2D: left ventricular ejection fraction-two dimensional; LVEF-3D: left ventricular ejection fraction-three dimensional; SV: stroke volume; LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume; E-velocity: mitral inflow E velocity; A-velocity: mitral inflow A velocity; S-septal: myocardial systolic velocity (septal); E-septal: myocardial early diastolic velocity (septal), E-lateral: myocardial early diastolic velocity (lateral); LVGLS: left ventricular global longitudinal strain; LVGCS: left ventricular global circumferential strain; LVPWD: left ventricular posterior wall end diastole dimension; RVESD: right ventricular end-systolic dimension; RVEDD: right ventricular end-diastolic dimension

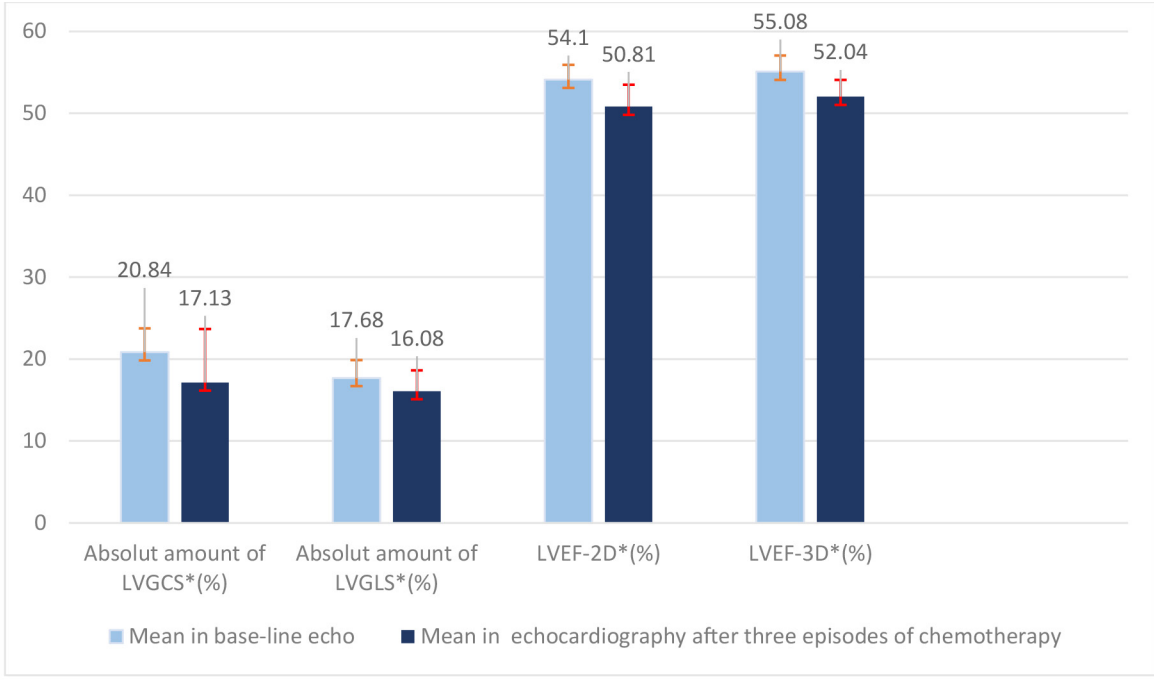

Figure 1. Important echocardiographic findings related to left ventricle function (*P value < 0.05)

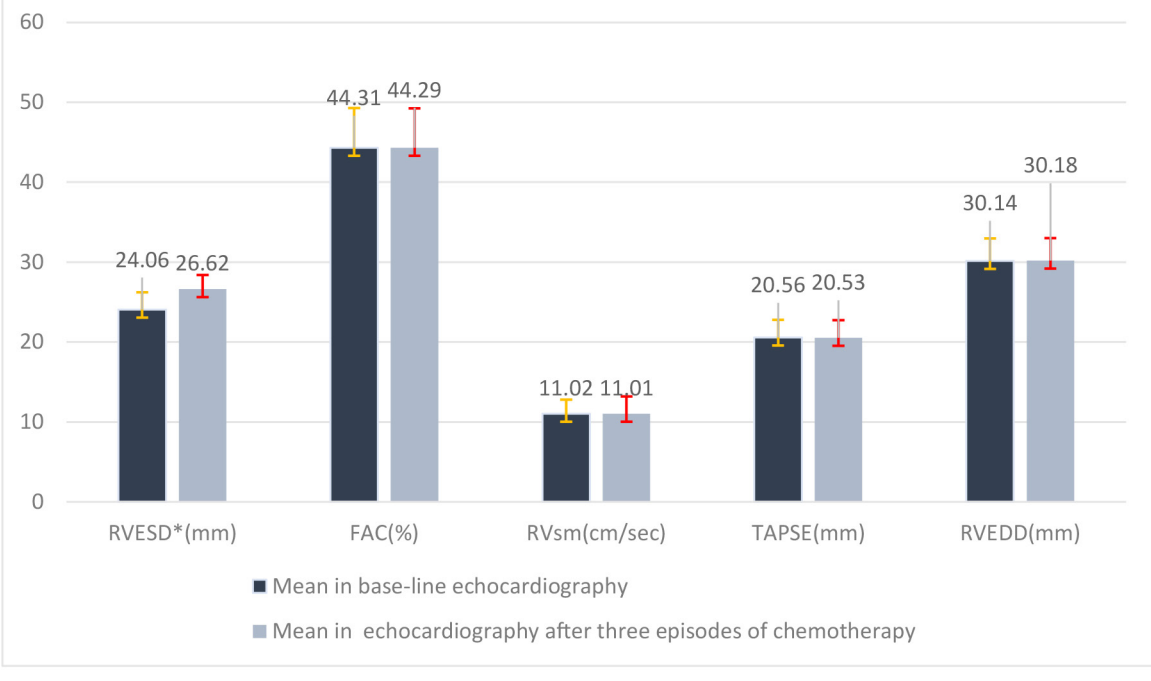

Figure 2. Important echocardiographic findings related to right ventricle function and size (*P value < 0.05)

Anthracycline-based chemotherapy causes cardiomyocyte injury and topoisomerase 2β inhibition, resulting in the activation of cell death pathways and inhibition of mitochondrial biogenesis, leading to left ventricular dysfunction (23). Also, reactive oxygen species production leads to lipoperoxidation of the cellular and nuclear membrane and deoxyribonucleic acid (DNA) damage (24).

A longitudinal prospective cohort study of 277 breast cancer participants receiving chemotherapy showed a significant LVEF decline (25). LVEF evaluation is recommended for the evaluation of cardiotoxicity in cancer patients, but the reported insensitivity of this diagnostic echocardiographic finding for myocardial injury in the early stages can not be neglected (8). Stage B heart failure, defined as early myocardial disease without heart failure symptoms, is the vital stage for cardio-oncologists to recognize and prevent progression to fatal and irreversible conditions such as heart failure (26). Therefore, it is important to use other echocardiographic findings to detect and diagnose cardiotoxicity in patients with cancer as soon as possible to decrease the mortality and morbidity of these patients.

In line with our results, the GLS, as an appropriate predictor of later reductions in EF, was meaningfully reduced in 24 patients with cardiotoxicity in the study of Negishi et al. (27).

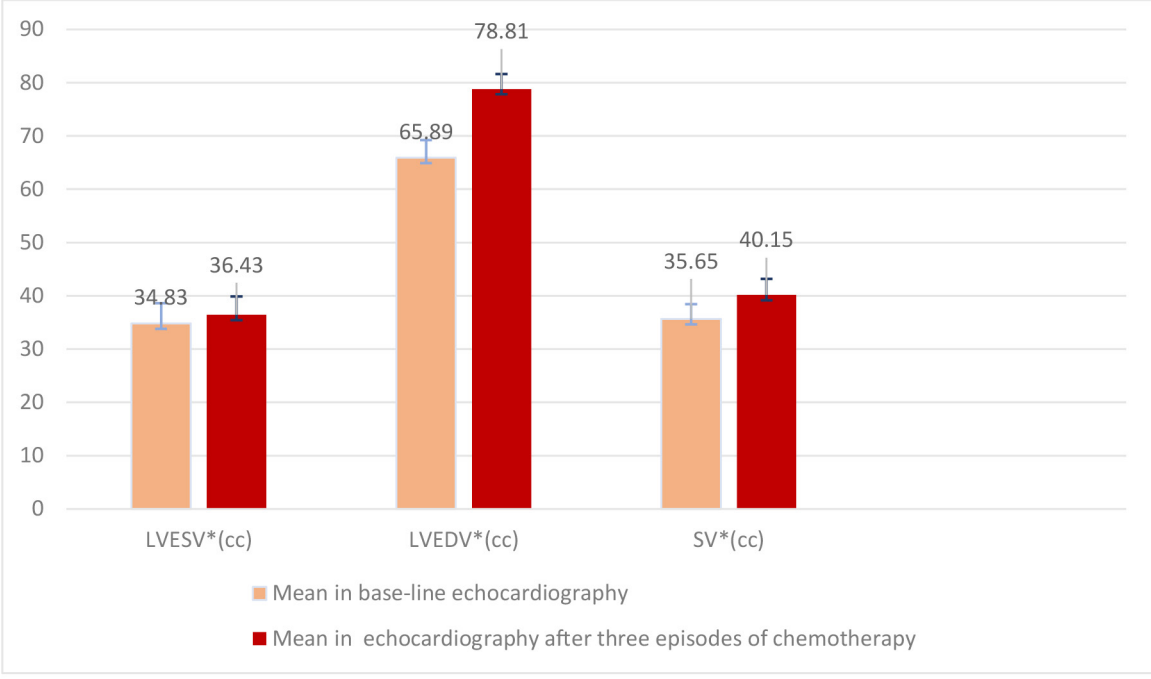

Figure 3. Important echocardiographic findings related to left ventricle volume (*P value < 0.05)

Also, in the prospective longitudinal sub-cohort study of Zhang et al., changes in 3D LVEF, GCS, and GLS were associated with concurrent and subsequent changes in systolic function (28). Also, recent studies have indicated that LVEF-2D and 3D decreased after anthracyline-based chemotherapy in patients with breast cancer (29, 30). It is noteworthy that although the SV increased significantly after chemotherapy, the greater rise in LVEDV caused a decrease in LVEF in our patients. Notably, LVEF-2D and 3D can be used as useful echocardiographic findings for detecting cardiotoxicity in patients with breast cancer.

In a systematic review of Evangelos K. Oikonomou et al., the prognostic value of LVGLS for early prediction of chemotherapy-induced cardiotoxicity was assessed, and it was concluded that measurement of GLS after initiation of potentially cardiotoxic chemotherapy with anthracyclines with or without trastuzumab had a good prognostic performance for subsequent cancer therapy-related cardiac dysfunction (31). Mornoş et al. found that the GCS and GLS fell by 12 weeks after the initiation of anthracycline chemotherapy, which is consistent with our results (32).

Recent studies demonstrate RV dysfunction in patients receiving anthracycline-based chemotherapy (33, 34). In a cross-sectional study by Esfahani et al., not only was there a significant decrease in RV systolic and diastolic function during chemotherapy but also, in line with our results, RVESD significantly increased after chemotherapy (35). Hence, anthracycline-based chemotherapy has a considerable adverse effect on the RV function of patients with breast cancer.

A longitudinal study by Barthur et al. in 2017 concluded that receiving trastuzumab can lead to a subtle but significant deleterious effect on RV structure and function (36). This is in good agreement with the results of our study, which show an increase in RVESD after anthracycline-based chemotherapy in patients with breast cancer. In the study of Keramida et al., 101 women with breast cancer who had trastuzumab chemotherapy were assessed. The researchers found that the deformation mechanics of both the left and right ventricles follow similar temporal patterns and degrees of impairment during trastuzumab therapy, confirming the global and uniform effect of trastuzumab on myocardial function (37). These findings support the results obtained from our analysis that chemotherapy can harm both LV and RV functions of the heart in breast cancer survivors.

It is crucial to note that the absolute LVGCS decreased in our study after the chemotherapy of patients. This finding correlates favorably with Kathleen W. Zhang et al., where a decrease in 3D-GCS was associated with concurrent and subsequent systolic and diastolic dysfunction (28). Also, in a cross-sectional study by Ciro Santoro et al., 100 patients with breast cancer who had anthracycline-based chemotherapy treatment were assessed, and LV-GCS was reduced significantly. This is also in accordance with the results of our study (38). Therefore, it is important to use LV-GCS as a diagnostic echocardiography finding for detecting cardiotoxicity in the early stages.

In our study, LVESV, LVEDV, and SV significantly increased after chemotherapy. Similarly, Díaz-Antón et al. found that LVEDV and LVESV significantly increased after chemotherapy in 72 patients with breast cancer (39). Also, in line with our results, other studies demonstrate an increase in LVESV and LVEDV as good predictors of cardiotoxicity in patients with breast cancer under anthracyline-based chemotherapy (40, 41). To sum up, LVESV and LVEDV can be used as important echocardiographic findings for detecting cardiotoxicity in breast cancer patients treated with anthracyline-based chemotherapy.

In conclusion, LVEF (3D and 2D), LVGCS, LVGLS, LVEDV, LVESV, SV, and RVESD are important echocardiography findings in the appropriate diagnosis of cardiotoxicity in patients with breast cancer.

5.1. Limitations

This study is not without limitations. First, due to the COVID-19 pandemic, some patients could not refer for a follow-up visit and were excluded from the study. In addition, some patients also received radiotherapy, and the inevitable cardiac effects of radiotherapy may interfere with our results. Another important limitation of this study was the lack of echocardiography in the chemotherapy course of patients to recognize which echocardiography findings reveal cardiotoxicity faster and sooner than others. Finally, our study was a single-center study, affecting the generalizability of the results.

5.2. Conclusion

Echocardiography appears to be a useful non-invasive method for achieving an early and proper diagnosis of cardiotoxicity. LVEF, LVGCS, LVGLS, LVEDV, LVESV, SV, and RVESD are important echocardiography findings in the appropriate diagnosis of cardiotoxicity in patients with HER2-positive breast cancer receiving anthracycline-based chemotherapy. These echocardiographic findings can use as proper and important diagnostic tools for preventing cardiotoxicity in patients with breast cancer who undergo anthracycline-based chemotherapy. Diagnosis of cardiotoxicity in patients with cancer at early stages can decrease mortality and morbidity in these patients.

5.3. Ethical Approval

The study design and protocols were approved by the Ethics Committee of the Research Deputyship of Rajaie Cardiovascular, Medical, and Research Center (ID: IR.RHC.REC.1400.057).

5.4. Informed Consent

All participants signed an informed consent form that explained all research details.

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Authors' Contribution

AA and MH conceived and designed the study and drafted the manuscript. MY participated in designing the study, performed parts of the statistical analysis, and helped draft the manuscript. HM, SE, SM, and MV reevaluated the clinical data, performed the statistical analysis, and revised the manuscript. PA, KM, RA, and PA collected the clinical data, interpreted them, and revised the manuscript. AA, MB, and FN re-analyzed the clinical and statistical data and revised the manuscript. All authors read and approved the final manuscript.

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Financial Disclosure

The authors declare that they have no competing interests.

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