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Echocardiographic Follow-Up in HER2 Positive and Negative Breast Cancer Patients: Is There a Sustained Decline in Left Ventricular Function Parameters Following Chemotherapy?

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ABSTRACT

Background: Breast cancer, as the most common malignancy among females, is a great concern for global health. Early diagnosis and advanced chemotherapy regimens have improved patients' survival, while increasing morbidities caused by chemotherapy in the long run. Chemotherapy regimens have caused a decrease in myocardial functional, which can be detected by echocardiography.

Objectives: The present study aimed to assess the decline curve in the left ventricular function parameters following chemotherapy and to compare the results among patients based on their Human Epidermal Growth Factor Receptor-2 (HER2) status.

Methods: This study was conducted on 427 consecutive female patients with breast cancer referred to the Cardio-Oncology Department of Rajaie Cardiovascular, Medical, and Research Center for pre-chemotherapy assessment between January 2019 and December 2020. The patients were divided into two groups based on the HER2 status. All the patients had at least one baseline (pre-chemotherapy) transthoracic echocardiography and were scheduled for four follow-up sessions: early post-anthracycline therapy and 3, 6, and 12 months following chemotherapy. Each echocardiography examination included the assessment of 2D Left Ventricular Ejection Fraction (LVEF), 3D LVEF, Global Longitudinal Strain (GLS), and Global Circumferential Strain (GCS). Linear mixed-effects models were utilized and the results were compared within and between the study groups. The R Project for Statistical Computing was used for data analysis.

Results: The results revealed significant changes in the means of 2D LVEF, 3D LVEF, GLS, and GCS during the 12 months of follow-up ($t = -27.04, -37.15, -33.3$, and -21.5, respectively; $P < 0.001$). Besides, the decline was more prominent in the HER2 positive patients ($t = -19.86, -15.35, -10.8$, and -9.6, respectively; $P < 0.001$).

Conclusions: The study results revealed a significant decline in the LV function parameters including 2D LVEF, 3D LVEF, GLS, and GCS following chemotherapy with anthracycline. This decline was more prominent in the HER2 positive patients who underwent Herceptin treatment. These results showed that the use of cardioprotective agents might lower the rate of decline in LV function parameters.

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1. Background

Breast cancer is the most common malignant neoplasm amongst females all over the world. Nowadays, with significant advances in early diagnosis and management

of breast cancer, patients' survival has markedly improved. However, the increased life span and the use of cardiotoxic chemotherapeutic agents have led to the increased incidence of cardiovascular disorders and the subsequent cardiac morbidity and mortality (1, 2).

Cardiotoxicity has been found following the administration of several chemotherapy regimens including anthracyclines and trastuzumab (Herceptin). This entity has been defined as a notable decline in Left Ventricular Ejection Fraction (LVEF). The rate of decline in LVEF has been controversial in different studies and guidelines (3). In 2013, Mor-Avi and Lang stated that a decrease of more than 5% in baseline LVEF to less than 55% while having symptomatic heart failure or more than 10% decline in LVEF to ≤ 55% in asymptomatic patients represented chemotherapy-induced cardiotoxicity (4). In 2014, the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) described a reduction of more than 10% in LVEF to less than 53% as the reference value for cardiotoxicity (3, 5).

Human Epidermal Growth Factor Receptor-2 (HER2) is a well-known gene that plays a critical role in the development of breast cancer. Anthracyclines are anti-neoplastic agents with the ability to cause significant oxidative stress and, subsequently, dose-dependent cardiovascular toxicity (6, 7). Trastuzumab is a monoclonal antibody that interferes with ErB2 (HER2/neu) signaling. It has been nominated as the second most cardiotoxic agent since the receptor signaling plays a key role in myocardial repair and cardiovascular hemostasis (7-9). This agent is usually prescribed in combination with anthracyclines for patients with aggressive HER2 positive breast cancer. This adjuvant therapy has markedly increased the cancer-free survival rate, while having synergistic effects on increasing the risk of cardiotoxicity. The incidence has been reported to be about 20 - 30% in patients with asymptomatic Left Ventricular (LV) failure and 3-5% in those with symptomatic LV dysfunction (6, 8, 10).

To date, echocardiographic evaluation of LVEF is the recommended modality to screen and monitor cardiotoxicity in cancer patients. However, LVEF has been reported to be insensitive in detection of myocardial injury, especially in early stages (2, 3, 10). Early myocardial disease without heart failure symptoms (stage B heart failure) has been considered a crucial phase for cardio-oncologists since timely detection and management can improve patients' morbidity/mortality and decrease the chance of progress to overt heart failure (6, 8, 10, 11).

In the literature, 2D Speckle Tracking Echocardiography (STE) including Global Longitudinal Strain (GLS) and Global Circumferential Strain (GCS) has been introduced as the marker of early myocardial injury. These modalities have been claimed to be able to detect cardiotoxicity three months earlier than LVEF decline, providing physicians with sufficient time to start cardio-protective therapies and proper interventions (6, 10-12). In 2017, Lorenzini et al. stated that 2D LVEF assessment was not reproducible and might differ by even about 10% among different studies on the same patient. Thus, they suggested the superiority of 3D LVEF assessment in the detection of cardiotoxicity in patients with breast cancer (3).

2. Objectives

The current study aims to investigate the changes in the echocardiographic markers of cardiotoxicity (2D LVEF, 3D LVEF, GLS, and GCS) in patients with HER2 positive and negative breast cancer during a one-year follow-up. Establishing the decline curve for LV function parameters in these patients may help determine the appropriate follow-up duration, optimal time for prescribing cardio-protective medications, and reduce costs for patients as well as for healthcare systems by decreasing unnecessary imaging. It will also help determine the difference in the baseline LVEF amongst HER2 positive and negative patients, which has not been studied yet to the best of our knowledge.

3. Patients and Methods

This study was approved by the Institutional Ethics Committee. Informed consent was also obtained from the patients prior to enrollment into the research.

3.1. Data Collection

In this study, 450 records of consecutive female patients with breast cancer referred to the Cardio-oncology Department of Rajaie Cardiovascular, Medical, and Research Center from January 2019 to December 2020 for pre-chemotherapy assessment were reviewed. Among these patients, those with a previous history of any malignancies, those with underlying heart disease, and patients who refused to refer for follow-up visits or echocardiography were excluded. Finally, 427 patients diagnosed with breast cancer who were scheduled to receive chemotherapy were enrolled into the study. All the patients had at least one baseline (pre-chemotherapy) transthoracic echocardiography. Subsequent echocardiographies were scheduled in four follow-up sessions: early post-anthracycline therapy and 3, 6, and 12 months following chemotherapy. The patients' age, Body Mass Index (BMI), HER2 status (positive vs. negative), and history of chemotherapy were recorded. During the regular follow-up sessions, the patients with a significant reduction in LVEF (to less than 45%) and those who failed or refused to refer for further follow-ups were excluded from the study.

3.2. Image Analysis

Transthoracic echocardiographic examinations were performed by trained echocardiography fellows via a Phillips Epiq 7c ultrasound system. The stored studies in the Picture Archiving and Communication System (PACS) were then used to obtain GLS and GCS in an offline manner. 3D analysis was performed via the offline TOMTEC-ARENA TTA2 software. All STE assessments and 3D analyses were conducted by a co-investigator (cardiologist, echocardiography fellowship) and were confirmed by another co-investigator (cardio-oncologist, echocardiography fellowship).

3.3. Data Analysis

The patients' data and echocardiography findings were divided into two groups of HER2 positive and HER2 negative. Each group was divided into five subgroups

analyzed regarding the time of follow-up (baseline, early post-anthracycline therapy, and follow-up at 3, 6, and 12 months).

3.4. Statistical Analysis

2D LVEF, 3D LVEF, GCS, and GLS variables based on the HER2 status were reported as mean ± SD. Box plots of these variables were also drawn for further descriptions. HER2 status was the independent variable, while the rest were considered dependent variables. During the follow-up, there were several missing cases (Figure 1). Consequently, repeated measures ANOVA would not be appropriate for data analysis despite the repeated nature of the data. To discard the effects of missing patients, the linear mixed effects models were utilized to assess the relationship between 2D LVEF, 3D LVEF, GLS, and GCS and the HER2 status. All analyses were conducted using lmer function in R 4.0.4 software.

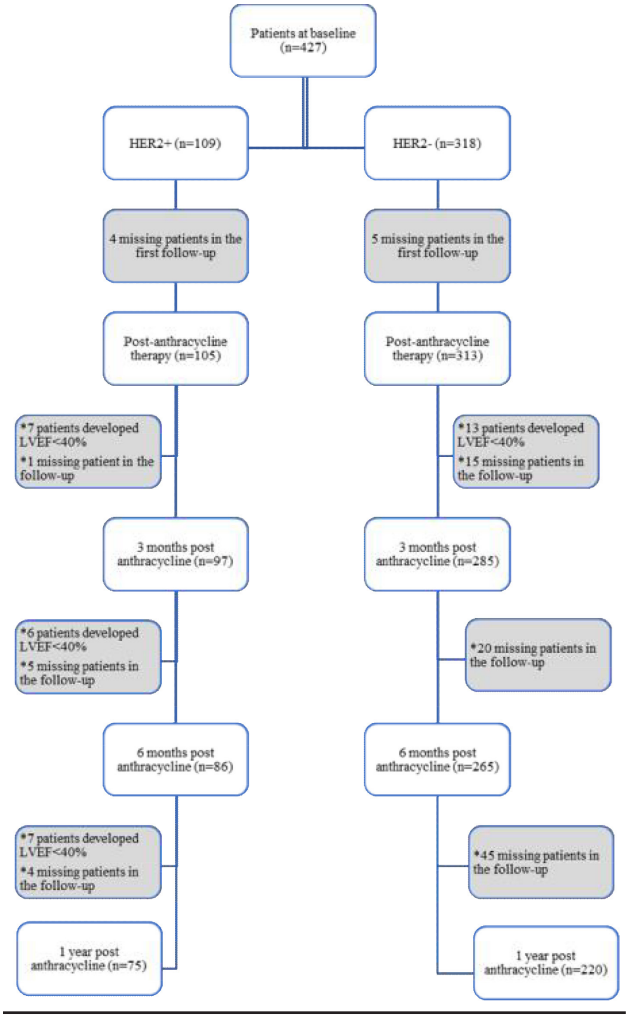
4. Results

This study was conducted on 427 female patients with breast cancer referred to a tertiary center from January 2019 to December 2020. The patients were divided into HER2 positive (n = 109, 25.5%) and HER2 negative (n = 318, 74.5%) groups. The number of patients involved in every follow-up session has been presented in Figure 1.

The study groups were compared in terms of age and BMI at baseline. The mean age of the patients was 47.4 ± 8.2 years in the HER2 positive group and 48.4 ± 8.7 years in the HER2 negative group, and the difference was not statistically significant (P = 0.28). Additionally, the mean BMI was 27.3 ± 4.7 kg/m2 in the HER2 positive group and 27.7 ± 5.0 kg/m2 in the HER2 negative group, and the difference was not statistically significant (P = 0.48).

At baseline, LV function measurements were performed for all the patients. The mean of 2D LVEF was 55.7 ± 1.3% in the HER2 positive patients and 56.1 ± 1.2% in the HER2 negative ones. Besides, the mean of 3D LVEF measured by TOMTEC analysis was 56.4 ± 1.9% and 57.6 ± 1.7% in the HER2 positive and negative patients, respectively. GLS was also assessed at baseline. The mean of GLS was -20.2 ± 0.8% in the HER2 positive group and -20.7 ± 1.7% in the HER2 negative patients. Moreover, the mean of GCS was -29.2 ± 1.6% and -31.0 ± 0.9% in the HER2 positive and negative patients, respectively. The parameters of LV function were measured in each session during the follow-up (Table 1). To compare the results, the follow-up sessions were numbered from 1 to 5. The R Project for Statistical Computing was utilized to compare the HER2 positive and negative patients at each follow-up session and to assess the significance of changes in the LV parameters during the follow-up.

Figure 1. The Number of Patients Enrolled into the Study



The number of patients in each follow-up session has been depicted in details. Missing patients in follow-up stands for the patients who failed or refused to attend the follow-up visits.

4.1. Left Ventricular Ejection Fraction by Two-Dimensional Assessment

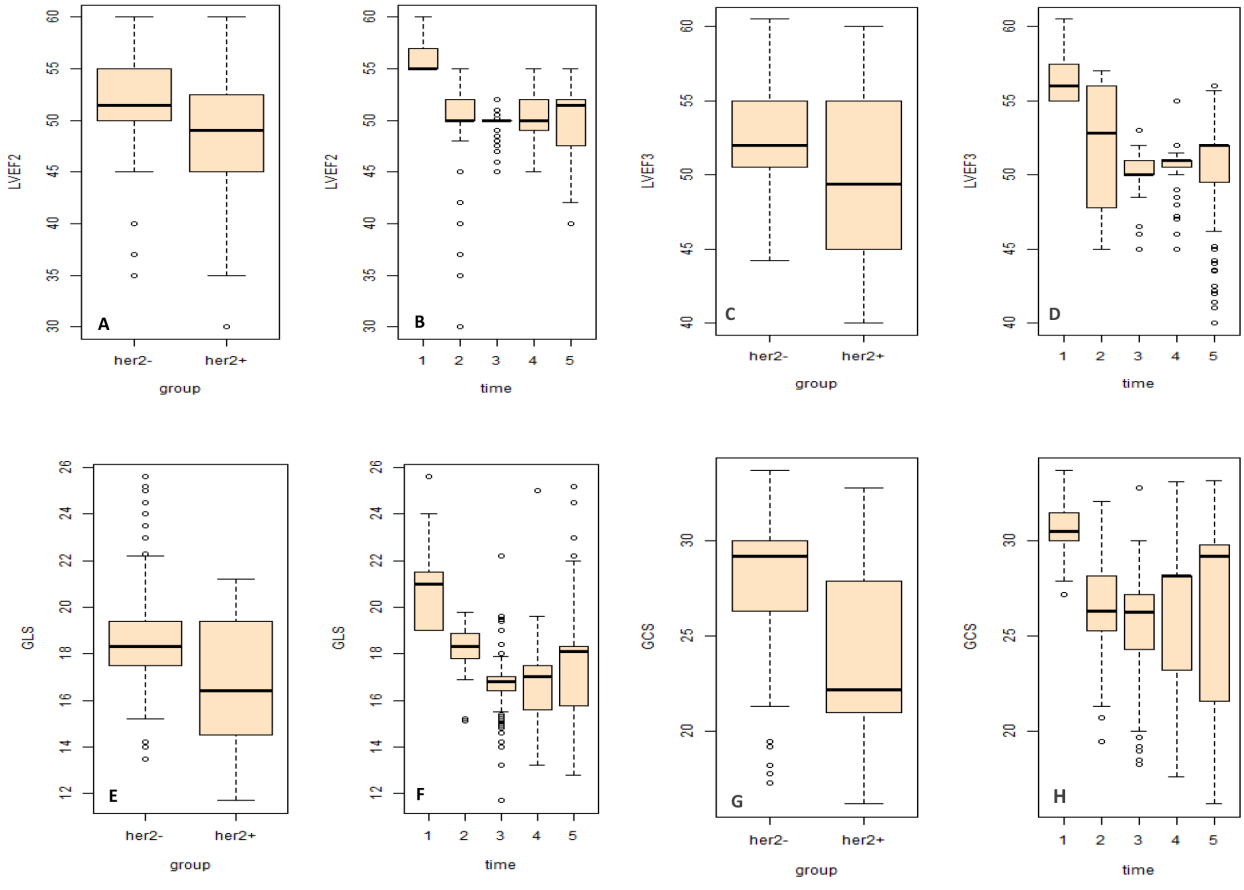
The results revealed a decrease in 2D LVEF among all the patients during the follow-up (t = -27.04; P < 0.001) (Figure 2B). Nonetheless, the decline in 2D LVEF was more

Table 1. Parameters of LV Function Measured in the HER2 Positive and Negative Patients during Each Follow-up Session

	At Baseline		Post-Anthracycline Therapy		3 Months Post-Anthracycline		6 Months Post-Anthracycline		12 Months Post-Anthracycline	
	HER2+ (n = 109)	*HER2- (n = 318)*	*HER2+ (n = 105)*	*HER2- (n = 313)*	*HER2+ (n = 97)*	*HER2- (n = 285)*	*HER2+ (n = 86)*	*HER2- (n = 265)*	*HER2+ (n = 75)*	*HER2- (n = 220)*
LVEF (2D) - %	55.7 ± 1.3	56.1 ± 1.2	49.4 ± 3.8	50.8 ± 3.6	46.9 ± 1.5	50.0 ± 0.8	45.8 ± 1.6	51.0 ± 1.8	44.7 ± 2.2	52.1 ± 1.5
LVEF (3D) - %	56.4 ± 1.9	57.6 ± 1.7	51.3 ± 2.9	52.1 ± 3.7	47.7 ± 2.8	50.5 ± 0.9	45.9 ± 1.7	51.2 ± 0.8	44.5 ± 2.3	52.0 ± 1.2
GLS- %	-20.2 ± 0.8	-20.7 ± 1.7	-18.2 ± 0.8	-18.5 ± 0.7	-15.1 ± 1.1	-17.4 ± 1.1	-15.0 ±0.8	-17.7 ± 1.1	-14.4 ± 1.2	-18.6 ± 1.3
GCS- %	-29.2 ± 1.6	-31.0 ± 0.9	-25.5 ± 2.0	-26.7 ± 1.8	-21.7 ± 1.5	-27.2 ± 1.8	-20.9 ± 1.1	-28.0 ± 1.1	-18.3 ± 1.4	-29.0 ± 2.1

Abbreviations: LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GCS, global circumferential strain; HER2+, HER2 positive; HER2-, HER2 negative

Figure 2. The Means of Changes in 2D LVEF (A, B), 3D LVEF (C, D), GLS (E, F), and GCS (G, H) among the Study Population based on the HER2 Status and Number of Follow-up Sessions



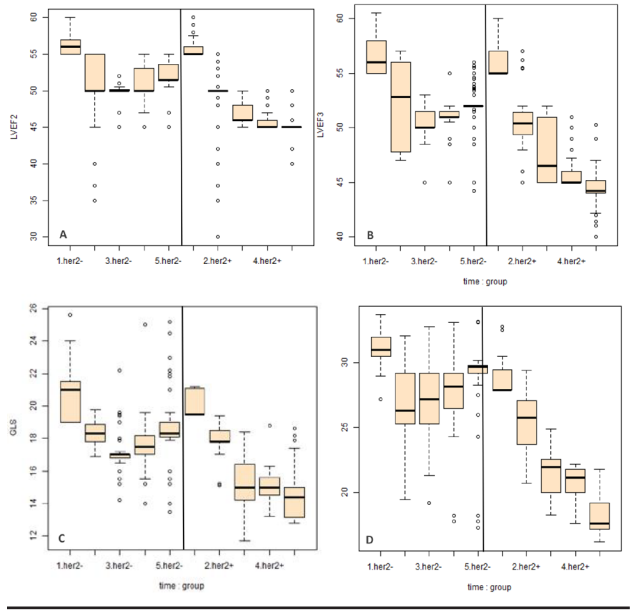
According to Figures A, C, E, and G, the decline was significant in the HER2 positive patients in comparison to the HER2 negative ones. According to Figures B, D, F, and H, the decrease was significant during the follow-up.
Abbreviations: LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GCS, global circumferential strain

prominent in the HER2 positive patients (t = -19.86; P < 0.001) (Figure 2A). The means of changes in 2D LVEF in HER 2 positive (right panel) and HER2 negative (left panel) patients in each follow-up session have been depicted in Figure 3. The session-by-session changes in 2D LVEF were also compared in HER2 positive (Figure 4A) and negative (Figure 4B) patients. The more each item was far from zero, the more significant the change in 2D LVEF would be. According to the results, the difference in 2D LVEF in the first and fifth echocardiography sessions was most prominent in the HER2 positive patients. In the HER2 negative patients, however, the most prominent change in 2D LVEF was detected between the first and third echocardiography sessions. On the other hand, no significant change was observed in 2D LVEF amongst HER2 negative patients between the second and fourth echocardiography sessions.

4.2. Left Ventricular Ejection Fraction by Three-Dimensional Assessment

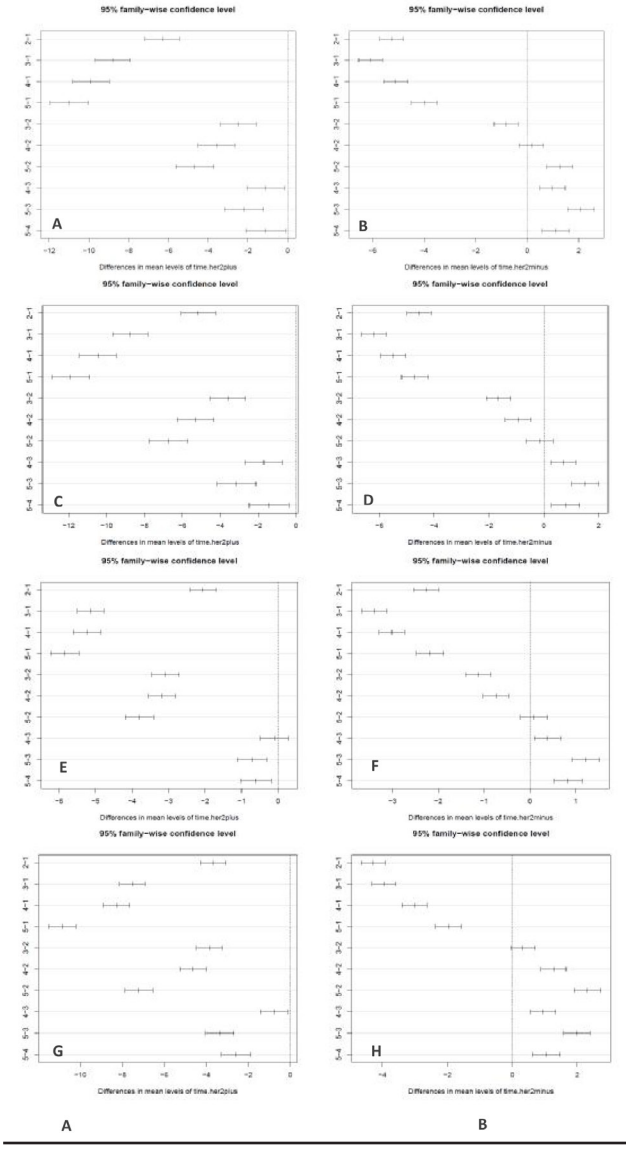
The changes in 3D LVEF were evaluated based on the HER2 status and time of follow-up (Figure 2). The results revealed a significant decline in 3D LVEF among all the patients during the follow-up (t = -37.15; P < 0.001). Yet, the decrease in 3D LVEF was more prominent among the

Figure 3. The Means of Changes in 2D LVEF (A), 3D LVEF (B), GLS (C), and GCS (D) in Each Follow-up Session in the HER 2 Positive (Right Panels) and HER2 Negative (Left Panels) Patients



Abbreviations: LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GCS, global circumferential strain

Figure 4. The Changes in 2D left ventricular ejection fraction (LVEF) Compared Session by Session in HER2 Positive (A) and Negative (B) Patients



The more each item is far from zero, the more prominent the change detected in 2D LVEF would be.

HER2 positive patients (t = -15.35; P < 0.001).

The means of changes in 3D LVEF in each follow-up session have been shown in Figure 3B where the right and left panels represent the HER2 positive and negative patients, respectively. As the figure depicts, the change in 3D LVEF was the most prominent between the first and fifth echocardiography sessions in the HER2 positive patients and between the first and third sessions among the HER2 negative ones. These results were the same as those of the 2D LVEF measurements (Figure 4). Based on the results presented in Figure 4D, there was no significant change in 3D LVEF among the HER2 negative patients between the second and fourth echocardiography sessions.

4.3. Global Longitudinal Strain

The results indicated a significant decline in the mean of GLS during the follow-up (t = -33.3; P < 0.001). Additionally, the GLS decline was more prominent in the HER2 positive patients (t = -10.8; P < 0.001). The means of changes in GLS based on the HER2 status and follow-up session have been presented in Figures 2E, 2F, and 3C. Accordingly, the decrease in the GLS was most notable between the first and fifth echocardiography sessions in the HER2 positive patients and between the first and third sessions among the HER2 negative ones (Figure 4). This was in line with the observations in LVEF analysis. Based on the results presented in Figure 4E, the change in GLS was not significant between the third and fourth echocardiography sessions among the HER2 positive patients. In the HER2 negative patients, however, this finding was noted between the second and fifth sessions (Figure 4F).

4.4. Global Circumferential Strain

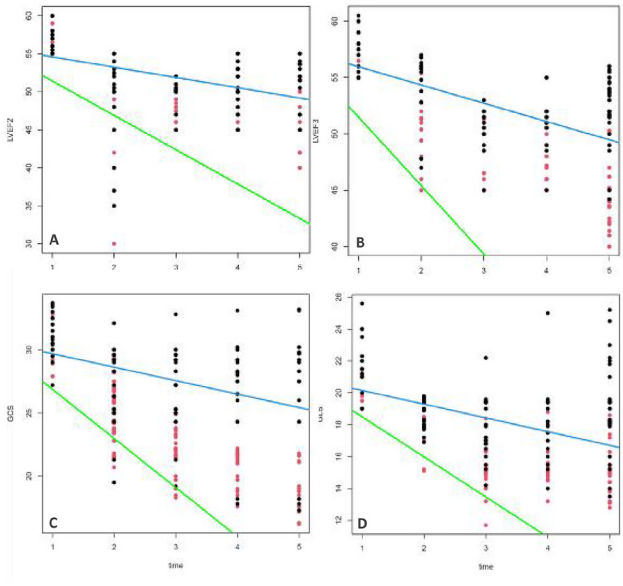
The results of GCS analysis showed a significant decrease in the circumferential strain during the 12 months of follow-up (t = -21.5; P < 0.001). The decline was more prominent in the HER2 positive patients, but the difference was less prominent compared to the decline in GLS (t = -9.6; P < 0.001). The means of changes in GCS based on the HER2 status and the follow-up times have been shown in in Figures 2G, 2H, and 3D. Similar to other LV function parameters, the decline in GCS was most prominent between the first and fifth echocardiography sessions in the HER2 positive patients. In HER2 negative patients, however, the difference in GCS was more prominent between the first and second follow-ups (Figure 4). According to Figure 4H, the change in GCS between the second and third echocardiography sessions was not significant.

5. Discussion

This study aimed to evaluate the effect of time on LV function in patients with breast cancer who had received anthracycline therapy during follow-up. The effect of HER2 status and the subsequent Herceptin (trastuzumab) therapy on LV function was assessed, as well. The findings revealed a significant decline in all LV function parameters; i.e., 2D LVEF, 3D LVEF, GLS, and GCS during the follow-up after anthracycline therapy. The results also suggested a significant decrease in all the aforementioned parameters in the HER2 positive patients in comparison to the HER2 negative ones.

The study findings showed that the mean of 2D LVEF was lower in the HER2 positive patients during the follow-up. The decline in 2D LVEF was also more prominent in this group during the follow-up. Moreover, measurements based on the echocardiography sessions demonstrated that in the HER2 positive patients, the change was more prominent between the first and fifth echocardiography sessions; i.e., the time when both anthracyclines and Herceptin had affected the LV myocardium. In the HER2 negative patients, the difference was more prominent between the first and third sessions, which indicated that the effects of cardiotoxicity could be mostly detected after three months of anthracycline treatment. However, no significant difference was observed in the HER2 negative patients between the second and fourth sessions of echocardiography. The prescription of cardio-protective medications might have reversed some of the adverse effects of anthracyclines, which were most notable

Figure 5. The Mean LVEF and the Decline Range of 2D LVEF (A), 3D LVEF (B), GLS (C), and GCS (D).



The blue lines represent the HER2 negative patients and the green lines represent the HER2 positive ones. The black and red dots show the spectrum of LVEF in the patients during the follow-up. Abbreviations: LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; GCS, global circumferential strain

in the third echocardiography session. This was not detected in the HER2 positive patients, which could be attributed to the fact that cardio-protective medications might be less effective in case of the simultaneous administration of anthracycline and Herceptin. Similar findings were achieved in 3D LVEF analysis, which indicated the good correlation of these two means of LVEF measurement when taking quantification standards into account (Figure 5). Generally, anthracyclines like doxorubicin and epirubicin are prescribed for the treatment of breast cancer. Cardiac effects including a decline in LVEF have been recognized throughout the cardio-oncology literature. In this context, several cardioprotective agents such as Angiotensin-Converting Enzyme (ACE) inhibitors, beta-blockers, statins, spironolactone, and N-acetyl cysteine have been suggested in studies. These medications have been found to decrease the LVEF decline in patients with breast cancer. However, there is no accepted universal consensus in this regard (13-17).

The results of the present research indicated a significant reduction in the mean of GLS during the follow-up, which was more prominent in the HER2 positive patients. Additionally, the GLS decline among the HER2 positive patients was more prominent between the first and fifth echocardiography sessions. Among the HER2 negative patients, however, the most prominent decrease in GLS was observed between the first and third sessions. As presumed for LVEF, the combination of anthracycline and Herceptin affected the longitudinal strain over time. In the patients who had not received Herceptin (i.e., HER2 negative patients), the most profound toxic effect on the longitudinal strain occurred three months after the anthracycline treatment. In the HER2 positive patients, there was no significant decline in GLS at three- and six-month follow-ups, which implied that cardioprotective drugs might control the sustained decline in the longitudinal strain. On the other hand, the lack of a significant GLS decline in HER2 negative patients between the early post-anthracycline echocardiography and one-year follow-up indicated that in the absence of Herceptin treatment, the recovery of GLS might occur by means of careful treatment within a year (Figure 5C).

Although the results of GCS analysis were somehow the same as those of GLS, the GCS decline was sustained amongst the HER2 positive patients throughout the follow-up period (Figure 5D). In the HER2 negative patients, however, the GCS decline was not significant in the early post-chemotherapy and three-month follow-up sessions. It was thus hypothesized that in the absence of Herceptin, GCS decline might occur more slowly compared to GLS decline. Global 2D strain has been considered a tool for detecting myocardial dysfunction when the conventional measures are within the normal ranges (18, 19). In this context, GLS is an independent predictor of decrease in LV function as well as a predictor of chemotherapy-induced cardiotoxicity (20). The threshold for cardiotoxicity prediction in GLS is a 10 - 15% decline from the baseline value (21). Jolly et al. disclosed that LV circumferential strain from cine white blood balanced Steady State Free Precession (bSSFP) in Cardiac Magnetic Resonance (CMR) imaging could be associated with changes in LVEF during the early stages of chemotherapy (i.e., three months). The reproducibility and acquisition in offline manner were mentioned as the great advantages of this method (22-24). Even though no comprehensive study has been conducted regarding STE-derived GCS, the results of the abovementioned study were consistent with those of the present investigation (25, 26).

The present study had several limitations. Firstly, this study was based on the regular follow-up of the patients and their willingness to attend the echocardiography sessions. Some patients refused to be visited and were excluded from the study. Secondly, due to the beginning of the COVID-19 pandemic and the subsequent restrictions, follow-up visits were only scheduled for specific patients who required to be followed up in their management plans. Therefore, some other patients were missed in the third or fourth follow-up session. Finally, some patients underwent radiotherapy during the course of follow-up. Hence, the inseparable effect of radiation on cardiac function could affect the study results.

In conclusion, the present study results revealed a significant decrease in the LV function parameters including 2D LVEF, 3D LVEF, GLS, and GCS following chemotherapy with anthracycline. This decline was more prominent in the HER2 positive patients who underwent Herceptin treatment. Overall, the results showed that the administration of cardioprotective agents could decrease the rate of decline in the LV function parameters, which was more notable in the HER2 positive patients.

5.1. Ethical Considerations

The study design and protocols were approved by the Ethics Committee of the Research Deputyship in Rajaie Cardiovascular, Medical, and Research Center

(ID: IR.RHC.REC.1399.037). Informed consents were obtained from all the patients before beginning the study.

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Authors' Contribution

Study concept and design: A.A. and M.H.; acquisition of data: S.H.K., S.A.M., K.R., and M.V.; analysis and interpretation of data: S.A. and A.B.; drafting of the manuscript: S.H.K.; critical revision of the manuscript for important intellectual content: F.N. and F.R.; statistical analysis: S.A. and A.B.

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