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Left Ventricular Ultrasound Diastolic Parameters in Postmenopausal Breast Cancer Patients Treated with Adjuvant Anthracycline and Trastuzumab

Tea Chitadze [a*], Nino Sharashidze [a], Nino Lomia [a] and Maia tsiklauri [a]

[a] Ivane Javakhishvili Tbilisi State University (TSU), Georgia.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Breast cancer remains the leading cause of cancer-related deaths among women of all ages. As age increases, so does the risk of both cancer and cardiovascular diseases, heightening the likelihood of short-term and long-term cardiovascular side effects. Therefore, strategies for early diagnosis and prevention of cardiotoxicity are crucial. he optimal use of conventional echocardiographic parameters is important, especially given the limited access to advanced echocardiography in developing countries.
Aims: To evaluate changes in left ventricular (LV) ultrasound parameters, including diastolic parameters, in postmenopausal women with breast cancer (BC), as a high-risk group receiving anthracycline-trastuzumab-containing regimens.

**Corresponding author: E-mail: tea.chitadze095@med.tsu.edu.ge;*

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Study Design: A prospective 24-month single-center study.
Place and Duration of Study: From December 2019 to March 2024 at the ultrasound laboratory of Tbilisi State University Medical Center, Tbilisi, Georgia
Methodology: Seventy-four postmenopausal patients with primary BC receiving anthracycline or anthracycline-trastuzumab were assessed for LV systolic and diastolic parameters before the anticancer therapy and at six subsequent visits. Cardio-protection was administered to high-risk patients preventively and to others when cardiotoxicity developed. Multiple regression was used to estimate relationships between various independent and dependent variables. Cardiotoxicity was assessed using survival analysis tools (Kaplan-Meier curves and Cox proportional model).
Results: The two-year CTRCD survival rate was 63.5%. During the 2-year follow-up, the mean E/e' increased across the entire cohort, but remained within the normal range. E/e' >15 was noted only in CTRCD patients at 6th month mark (4.1%, n=3, P=.056) within the high-risk group, peaking at 9th month (10.8%, n=8, P< .00). Multiple regression indicated a significant association of IVRT baseline value with late cardiotoxicity (adj. beta-coefficient= 0.32; t = 2.73, P=.008) and DT baseline value with early cardiotoxicity (adj. beta-coefficient = -0.25; t = -3.31, P=0.002). GLS demonstrated predictive value from the first month in 13.5% of the cohort and in 34.5% of patients with CTRCD (P< .00).
Conclusion: Our 2-year longitudinal prospective study of anthracycline–trastuzumab-containing regimens in postmenopausal women with early BC revealed that: 1) Predictive association of E/e' with cardiotoxicity was not detected. 2) A reliable association with late cardiotoxicity (T7) from the diastolic parameters was revealed only by IVRT baseline value 3) A reliable association with early cardiotoxicity (T4) from diastolic parameters was revealed only by DT baseline. 4)GLS is superior to E/e' in its prognostic value and diagnostic ability of cardiotoxicity .

Keywords: Breast cancer; cardiotoxicity; global longitudinal strain; ejection fraction; LV diastolic disfunction; E/e.

ABBREVIATIONS

LV : left Ventricular
BC : breast Cancer
CTRCD : Cancer Therapy-related Cardiac Dysfunction
E/e' : The Ratio of Early Diastolic Mitral Inflow Velocity to Early Diastolic Mitral Annulus Velocity
IVRT : Isovolumic Relaxation Time
DT : Deceleration Time
GLS : Global Longitudinal Strain
LVEF : Left Ventricular Ejection Fraction
HFPEF : Heart Failure with Preserved Ejection Fraction
TSU : Tbilisi State University
Her2 : Human Epidermal Growth Factor Receptor 2
HR variability : Heart Rate Variability
ECG : Electrocardiogram
2de-two : Dimensional Echocardioscopy
PW-TDI : Pulsed Wave Tissue Doppler
E' : Early Diastolic Myocardial Relaxation
E : Mitral Early Diastolic Peak Velocity
A : Late Diastolic Peak Velocity
E/A : The Ratio of Peak Velocity Blood Flow from Left Ventricular Relaxation in Early Diastole (the E wave) to Peak Velocity Flow in Late Diastole Caused by Atrial Contraction (the A wave).

1. INTRODUCTION

BC is the most frequently diagnosed cancer in women [1,2] and remains the leading cause of cancer-related deaths among women of all ages [3,4]. As age increases, so does the risk of both cancer and cardiovascular diseases [4,5], heightening the likelihood of short-term and long-term cardiovascular side effects from cancer therapy or CTRCD frequency [1]. Long-term cardiotoxicity may lead to death in approximately one-third of patients [6]. Therefore, strategies for early diagnosis and prevention of cardiotoxicity are crucial. The optimal use of conventional echocardiographic parameters is important, especially given the limited access to advanced echocardiography in developing countries.

Diastolic dysfunction plays a fundamental role in the diagnosis of HFpEF events in the general population [7]. Although diastolic dysfunction may precede changes in LVEF, it is not included in the current definition of cardiotoxicity [8]. Several studies, including a meta-analysis,

suggest that measures of diastolic function change during cancer treatment, and these changes may predict subsequent systolic dysfunction in patients receiving anthracyclines and/or trastuzumab [9,10]. Nevertheless, data from various studies on diastolic function in anthracycline-trastuzumab regimens are sparse and conflicting [11]. The range and timing of changes in diastolic function during cancer treatment, as well as their prognostic significance for cardiotoxicity and systolic dysfunction, are poorly understood. Studies on the effects of anthracyclines in a small cohort of patients with BC have shown an isolated decreases in LV diastolic function parameters [12].

The aim of our study was to evaluate changes in left ventricular (LV) ultrasound parameters, including diastolic parameters, over a 2-year follow-up in postmenopausal women with BC, who represent as a high-risk group undergoing treatment with anthracycline-trastuzumab containing regimens.

2. MATERIALS AND METHODS

Our prospective 24-month follow-up single-center study enrolled a cohort of 100 participants with newly diagnosed BC (100% female). The research data were collected from December 2019 to March 2024 at the ultrasound laboratory of TSU Medical Center, Tbilisi , Georgia. The study was approved by the Ethical Commission of the Faculty of Medicine of TSU. Participants were referred from various sources. Ultimately, 79 patients were recruited for the study; five patients dropped by personal decision. The results of the 24 -month study was further analyzed in 74 recruited women. All patients provided written informed consent [13].

Inclusion criteria included: primary BC, anticancer therapy with anthracycline-trastuzumab-containing regimens, and postmenopausal status. Patients had at least two risk factors for the development of cardiotoxicity, including antitumor therapy with a high potential for cardiotoxicity.

Exclusion criteria included: inability to provide informed consent, history of prior chemotherapy or radiotherapy, unsatisfactory ultrasound images, any medical history affecting LV function, reduced LVEF<50%, severe valvular disease, primarily cardiomyopathy, permanently implanted pacemakers, atrial fibrillation or pregnancy.

We defined cardiotoxicity as a EF a reduction in EF from the baseline of 10% and / or EF<50, According to GLS decrease in GLS from the baseline of 15% and/or GLS<16%.

The age range of the study patients was 46-76 years, the a mean age at baseline of 62.3 years (SD-8.6), and a median age of 64 years. All patients (n-74) received doxorubicin, and in the HER2-positive patients (n-15) doxorubicin was followed by trastuzumab.

Research parameters and their dynamics were also evaluated by CTRCD risk groups (high, medium and low), and by treatment (anthracycline and anthracycline plus trastuzumab). Analysis of the percentage distribution of patients in the groups indicates that no one group prevails over the others.

A complete medical history, including demographic data, CTRCD risk factors, was collected from all patients at baseline. CTRCD risk factors were assessed in accordance with the 2022 ESC Guidelines for Cardio-Oncology, developed in collaboration with EHA, ESTRO and IC-OS by ESC Working Group on Cardio-Oncology [14]. Our study sample included 13.5% (n-10) high-risk patients, 41.9% (n-31) intermediate-risk patients, and 44.6% (n-33) low-risk patients. CPT was initiated by the attending cardiologist for all patients at high risk of CTRCD from the beginning and in cases of deterioration of systolic parameters (GLS or LVEF) in dynamics.

A prospective serial evaluation was performed at baseline (before the initiation of anthracycline -T0) and at 1st (T1), 2nd (T2), 3rd (T3), 6th (T4), 9th (T5), 12th (T6) and 24th month (T7) after beginning anthracycline therapy. In HER2-positive BC patients T4 and 3 months after the first dose of trastuzumab were the same.

A commercially available PHILIPS EPIQ 7G with X5-1 transmitter was used. Two-dimensional echocardioscopy (2DE) examinations were performed under normotensy and normosystoly with optimal ECG signal. Echo images were acquired within minimal HR variability during four equal cardiac cycles. 2DE was conducted in accordance with the recommendations of the American Society of Echocardiography and the British Society of Echocardiography's minimal

set of practice guidelines [14,15].All standard views were consistently selected correctly, including the three apical views (A4C; A2C; A3C). A complete 2DE echocardiographic examination, including functional systolic and diastolic parameters, was performed. GLS was calculated according to the aforementioned echo guidelines, as well as LVEF [13,15].

Pulsed Wave Tissue Doppler (PW TDI) was used to calculate early diastolic myocardial relaxation (e'), in the A4ch view by placing a sample volume in the septal and lateral annular sites during end-systole, at the end of exhalation while breath-holding. The ultrasound beam was aligned parallel to the motion of the mitral annulus. Mean e' was calculated by averaging the septal and lateral values. PW Doppler was used to calculate mitral early diastolic peak velocity (E), late diastolic peak velocity (A), and the E-wave deceleration time (DT). In the A4C the sample volume was positioned directly between the tips of the mitral valve leaflets, 1-3mm from their ends. IVRT was also measured using PW Doppler from the apical five-chamber view (A5C), with the sample volume placed between the aortic valve and the mitral valve.

Statistics: The results of our study were statistically processed using SPSSv.23.0 software (IBM SPSS, Chicago, IL, USA). Numeric variables are represented as means ± standard deviations (SD). Comparisones between groups were conducted Fisher's exact and independent t-tests, with One-Way ANOVA applied in some cases. Follow-up and baseline data within groups were analyzed by paired t-test. Categorical variables are presented as percentages, and their comparison between groups was performed using Fisher's exact and Chi2-tests.

A multiple regression model was employed to predict outcomes (dependent variables) on various factors and cofactors (independent variables). Outcomes included the presence of Cardiotoxicity at Stage 7 (24 months after initiation of chemotherapy) and at Stage 4 (6 months after initiation of chemotherapy). Independent variables included: a) all studied and calculated baseline variables: Age, CTRCD risk (score), hypertension, Diabetes Mellitus type 2, Coronary Artery Disease, Smoking, Obesity,chemotherapy regimen, anti-HER2-therapy, ejection fraction (EF0), global longitudinal strain (GLS0), the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity (E/e'0),E/A0, DT0,IVRT0 et al; b) change of following parameters from baseline value after one month: EF (Delta_EF1), GLS (Delta_ GLS1), E/e' (Delta_ E/e'1), E/A (Delta_ E/A1), DT (Delta_ DT1), IVRT (Delta_ IVRT1) et al. To evaluate the set of cardiotoxicity,survival curves were generated using the Kaplan-Meier method, and the hazard function was estimated using the Cox model. The Hazard Ratio (HR) was calculated alongside 95% confidence intervals (95% CI) to quantify the strength of the association between the variables of interest and the risk of cardiotoxicity. The criterion $p<0.05$ was used to reject the null hypothesis and assess significant differences of studied variables.

3. RESULTS

We studied the dynamics of the development of cardiotoxicity and, respectively, survival from it during the 24-month follow-up. In our study cohort, the two-year CTRCD survival rate was 63.5% (see Fig. 1).

Fig. 2 shows Cardiotoxicity onset rates at each stage of the study in the low (n=33) and high-moderate (n=41) risk groups.

The hazard ratio estimated by the Cox proportionality model shows that the risk of cardiotoxicity in the high-moderate risk group is statistically significantly 9.24 times greater than the risk of cardiotoxicity in the low risk group (HR=9.24, 95% CI-6.55-13.06, P< .00).

During the 2-year follow-up, the mean E/e' increased in the entire cohort, although it remained within the normal range (see Table 1).

However, when the E/e' >15 value was analyzed during the 2-year follow-up study in groups divided by cardiotoxicity (patients who developed CTRCD and did not develop CTRCD), increase in E/e' was observed only in cardiotoxic patients at all stages. An increase in E/e' >15 was first detected at T4, that is, the effect of the first dose of trastuzumab (4.1%, n=3, P=.056), all three belonged to the high-risk group. The peak was noted at T5 (10.8%, n=8, p=0.000), of which 6 patients belonged to the high-risk group. At 1 year (T6) decreased (5.4%, n=4, P=.02), all 4 belonged to high risk group. There was no statistically significant increase at 2 years. (see Table 2).

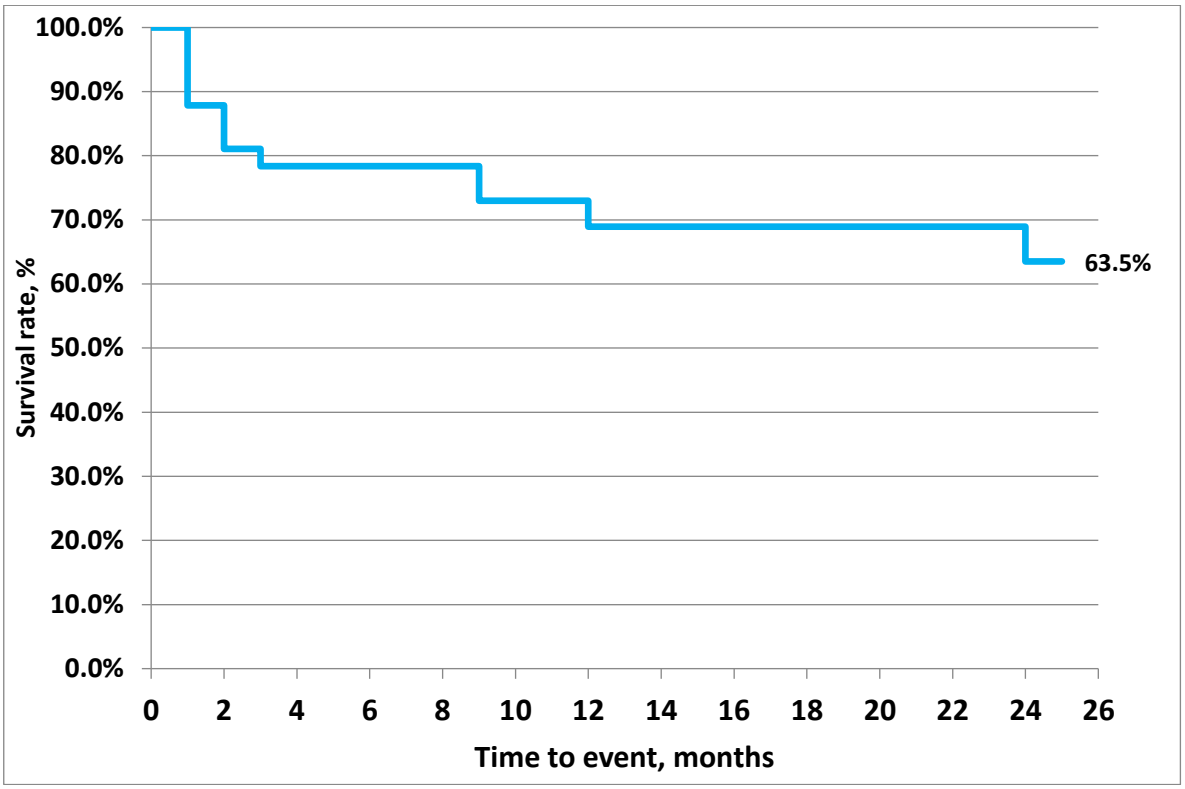

Fig. 1. Kaplan-Meier curve for Cardiotoxicity Survival (Total Group; n=74)

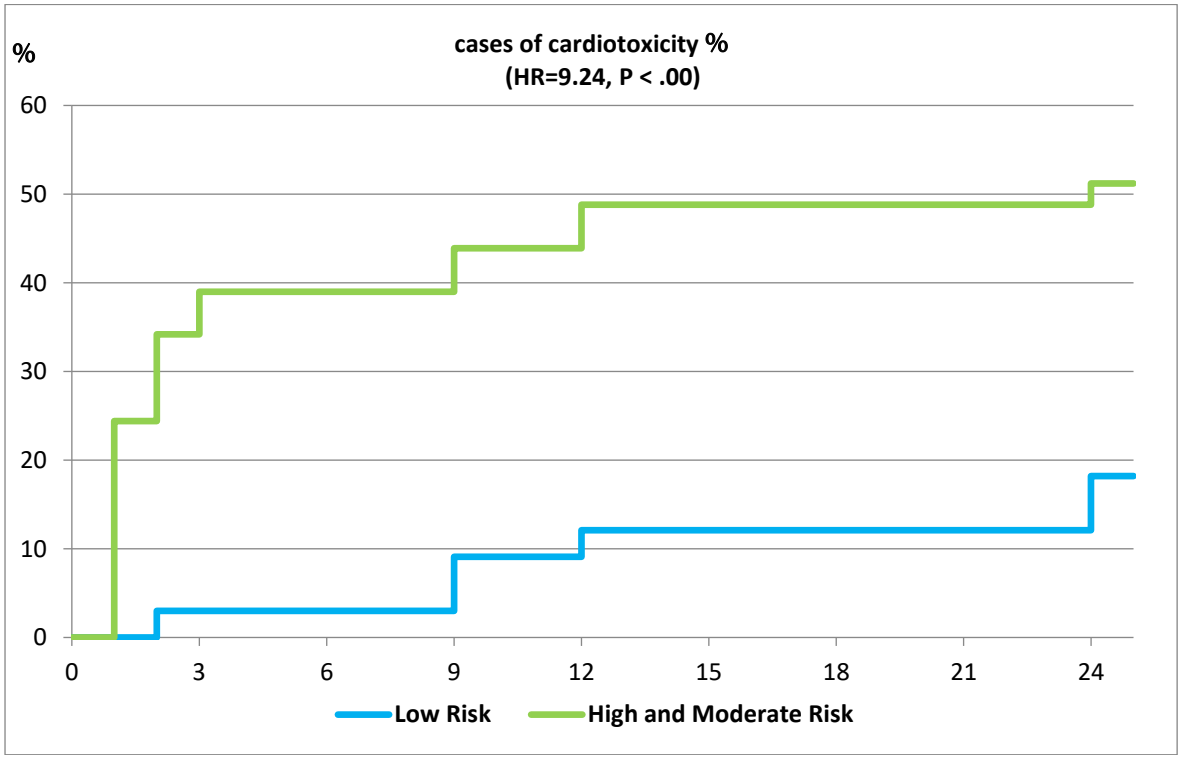

Fig. 2. Kaplan-Meier curves for Cardiotoxicity onset for the groups divided by risk: the group 1 (low risk; n=33) vs. the group 2 (high +moderate risk; n=41)

Table 1. E/e' mean during 2 years of observation

E/e’	T0	T1	T2	T3	T4	T5	T6	T7
CTRCD-Yes n=27								
mean	6.448	6.779	7.028	7.910	9.845	11.128	10.631	9.686
median	6.900	6.800	7.400	7.800	8.000	8.700	8.900	9.900
CTRCD-No n=64								
mean	6.304	6.553	6.778	7.016	7.313	7.489	7.653	7.613
median	6.000	6.700	6.800	7.000	7.400	7.500	7.700	7.700

Table 2. An increase in E/e' >15 during 2 years of observation

E/e’ elevated cases	1month	2months	3months	6months	9months	12months	24months
P				.056	.000	.021	.392
CTRCD cases							
n=	0	0	0	3	8	4	1
%	0.0	0.0	0.0	4.1	10.8	5.4	1.4
Non- CTRCD cases							
n=	0	0	0	0	0	0	0
%	0.0	0.0	0.0	0.0	0.0	0.0	0.0

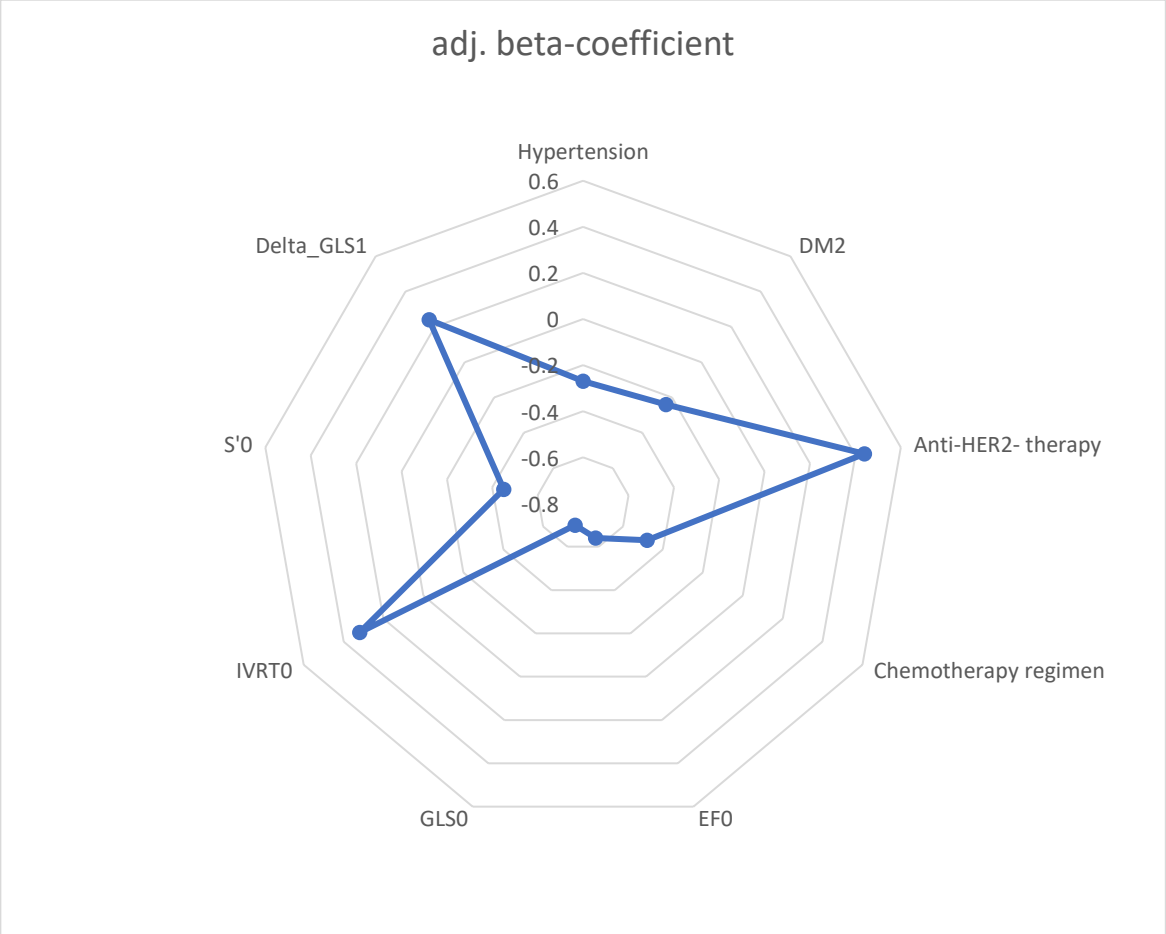

Fig. 3. Multiple Regression Analysis – Model 1

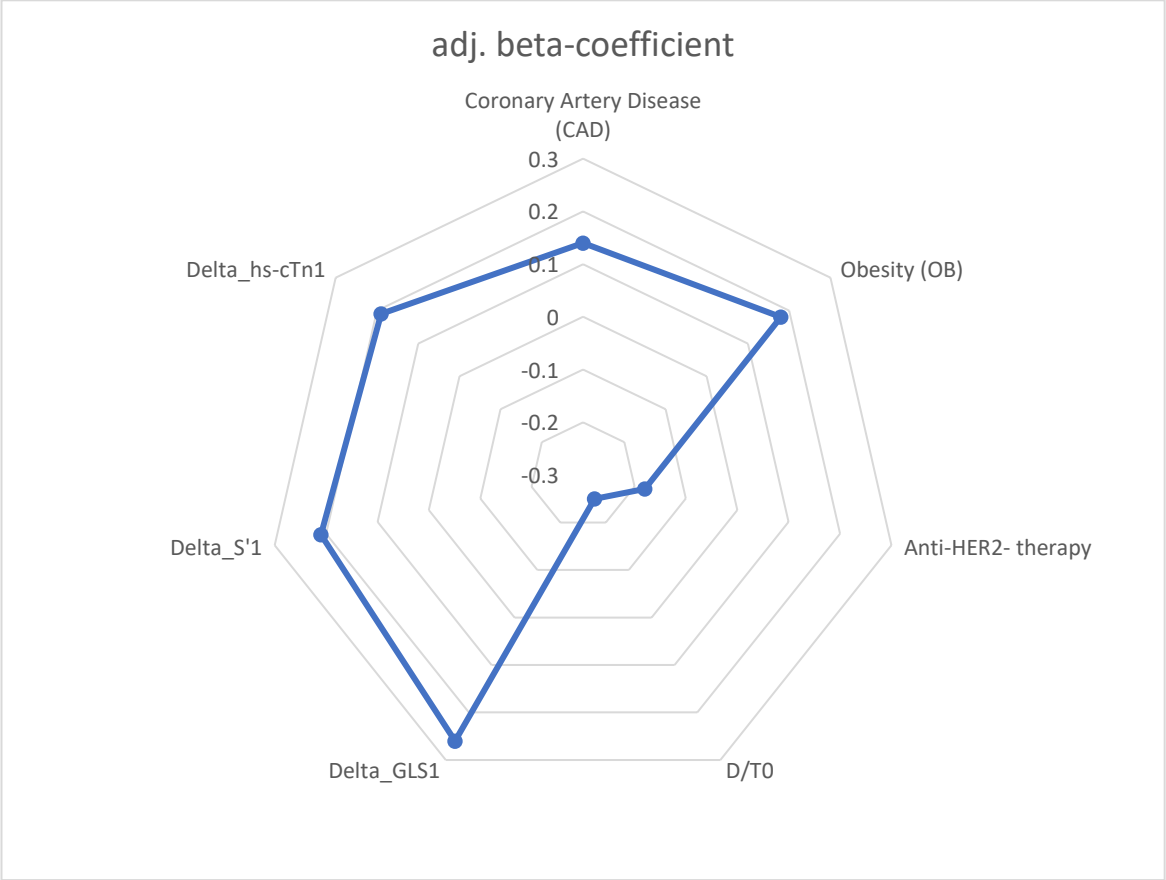

Fig. 4. Multiple Regression Analysis – Model 2

Among the diastolic functions studied by us (E/e', IVRT, DT, A/E) by multiple regression (Model 1) only baseline value of IVRT0 (adj. beta-coefficient= 0.32; t = 2.73, P=.01) showed a significant association with late cardiotoxicity (T7). Predictive association of E/e' with late cardiotoxicity was not revealed. (See Fig. 3).

Only baseline value of DT (multiple regression Model 2. adj. beta-coefficient = -0.25; t = -3.31, P=.002) revealed a reliable association with early cardiotoxicity (T4). Predictive association of E/e' with early CTRCD was not revealed. (see Fig. 4).

Ultrasound parameters were analyzed at T1 and T2 (groups divided according to cardiotoxicity detected at the end of the study). Of the parameters analyzed at T1 in the CTRCD cohort (13.5%, n=10), only GLS showed a statistically reliable reduction (60% of the CTRCD group at 24 months, n=6, p=0.000). At T2 in the CTRCD group (20.3%, n=15) with GLS, S' reduction was already noted (80.0% of the CTRCD cohort, n=12 and 33.3%, n=5 respectively. P=.00).

4. DISCUSSION

The two-year CTRCD survival incident in our study cohort was 63.5%. Throughout the study period, a total of 27 (36,5%) patients developed CTRCD. In different studies, these data are variable [16,17]. The hazard ratio estimated by the Cox proportional hazards model in our research shows that the risk of cardiotoxicity in the high-moderate risk group is statistically significantly 9.24 times greater than the risk of cardiotoxicity in the low-risk group. Sivisan Suntheralingam et al. also classified patients into CTRCD risk categories but had different risk estimates based on pretreatment characteristics. Patients in the highest risk category had a relative risk of CTRCD 1.7 to 2.4 times higher than those in the low-risk category (p = 0.010 and 0.005, respectively). The high absolute risk of CTRCD was 15.5–25.5% [18]. The higher risk in our population highly is likely related to older age.

During the 2 years of follow-up, the mean E/e' value in the entire cohort increased but remained

within the normal range, with a greater increase observed in patients with CTRCD. Studies by Wei Liu et al. and Ciro Santoro et al. indicated E/e' was also the only conventional echocardiographic parameter that had an increase, but remained within the normal range [19]. In contrast, E/e' ratio did not show significant differences during anthracycline treatment, according to Raluca I Mincu et al. study [20]. Additionally, in the first multicenter study of early diastolic dysfunction, Vito Calabrese et al. evaluated diastolic parameters, including E/e', at 1 week after chemotherapy, where E/e' abnormalities were not observed, although the difference in E/e' in our study was minimal at this early time point(E/e' baseline-6.448 vs. E/e' T1- 6.779) [21]. When we analyzed E/e' >15 rates during the 2 years of observation in groups divided by cardiotoxicity (patients who developed and did not develop it), an increase in E/e' was observed only in cardiotoxic patients at all stages. Ciro Santoro et al. also revealed value of the E/e' ratio in detecting cardiotoxicity [22].

Although within 2 years in our study E/e' the predictive ability with cardiotoxicity was not revealed by multiple regression. In our study, an increase in E/e' was observed with trastuzumab, and at all stages was reviled only in cardiotoxic patients, suggesting the usefulness of using E/e' as a surrogate indicator. A similar result was obtained by Kazunori Honda et al in a retrospective study of 129 BC HER2-positive women on a trastuzumab regimen. Through multiple regression analysis, they showed that E/e' at baseline or 3 months later was less likely to predict LVEF decline in patients; however, there was a potential chronological relationship between E/e' increase and MPGF decline [11]. We observed a considerable similarity between our study and Jenica Upshaw et al. [21] who conducted the largest 6.5-year prospective, strictly phenotypic longitudinal cohort study on 362 BC patients. Similar to our study, the patients were also on an anthracycline-trantuzumab-containing regimen and had risk factors for the development of CTRCD (overweight and one in three had hypertension or diabetes). In their study, Cox proportional hazards models over a median of 2.1 years showed steady deterioration in E/A ratio, lateral and septal e' velocities, and increasing E/e' ($p<0.01$). Doxorubicin-containing regimens were associated with a greater risk of E/e' > 14, evident at 6 months and persisting at 3 years, although this was not statistically significant.In our study, E/e' changes were observed at 6 months (T4), were statistically reliable, and lasted for 1 year, following by improvement .Diastolic dysfunction reversibilty was highly likly the result of optimal cardioprotection. In contrast to our study, in their study there were no significant changes in e' or E/e' ratio with trastuzumab monotherapy. In our study a peak of E/e' >15 was noted at T4 in our patients, who were on an anthracycline-trastuzumab regimen. Additionally, in their study, based on Kaplan-Meier analysis, the degree of abnormal diastolic function was 60% at 1 year, 70% at 2 years, and 80% at 3 years. A total of 5% (n-18) developed E/e' >14 during follow-up. However, at a maximum follow-up of 6.5 years, 71% of patients developed diastolic dysfunction, further suggesting the presence of transient diastolic dysfunction in some patients. In contrast to our study, in this study, the degree of diastolic dysfunction was associated with a subsequent decrease in LVEF, was also modestly associated with subsequent GLS decline, Moreover, worsening diastolic dysfunction was independently associated with a 2-fold increased risk of developing cardiotoxicity on follow-up echocardiography [23]. In our study, E/e' could not predict worsening of systolic parameters.

An E/e' increase >15 was first detected in the effect of T4 or the first dose of trastuzumab (4.1%, n=3, p=0.056), all three belonged to the high-risk group. The peak was noted at T5 and was 10.8% (n=8, p=0.000), an increase at the end of chemotherapy was not observed in our study. Unlike us, Vito Calabrese et al. in the first multicenter study of early diastolic dysfunction, where E/e' was evaluated 1 week after chemotherapy, 5% had E/e' >14, although they indicated a different value from our study, which probably became the reason for the difference [21].The peak of E/e' increase was noted at T5 (10.8%, n=8, p=0.000), of which 6 patients belonged to the high-risk group.

At 1 year (T6), positive dynamics were noted in some patients (5.4%, n=4, p=0.021), all of the remaining 4 participants belonged to the high-risk group. At 2 years, there was no statistically significant increase in E/e'. Predictive association of E/e' with cardiotoxicity was not revealed. A reliable association with late cardiotoxicity (T7) was revealed only in Basal value of IVRT0 .To determine which echo parameters showed earlier changes, we analyzed echo parameters at T1 and T2 in groups divided by cardiotoxicity detected at the

end of the study. At T1, in the CTRCD cohort (13.5%, n=10), only GLS showed changes-decrease and it was statistically significant , while at T2, in the CTRCD group together with GLS, S' decrease was already revealed. Similar to our study, by Zhang et al. there were no significant associations between post-anthracycline echocardiographic parameters and subsequent measures of E/e' [24]. 892 patients were analyzed from 13 studies by Raluca I Mincu et al., where E/e' did not show significant change at the end of anthracycline therapy, while LVEF and GLS were informative. Raluca I Mincu et al. Anthracycline had a modest early effect on the E/A ratio in BC patients without heart disease history, in contrast to our study EDT in this study also showed no change [20]. However, according to some studies, between standard echo-Doppler parameters, a decrease in E/A ratio and an increase in E/e' more than 2D LVEF can reveal early LV functional changes [22,25]. However, these are relatively old studies.

The effect of diastolic dysfunction on systolic dysfunction and mortality was studied prospectively (median time 243 days) in 190 patients with active cancer by Joshua H Arnold et al. Using multivariate analysis, they demonstrated a significant association of lateral E/e' and lateral e' with the development of systolic dysfunction and all-cause mortality (P = 0.015). Accordingly, they hypothesized that assessment of diastolic function in active cancer patients may be an early marker to predict the development of systolic dysfunction and all-cause mortality. However, this study was conducted in a relatively young group (58 ± 15 years), with only 78% being women, and the definition of heart failure was different, especially for GLS: LVEF absolute decrease >10% to a value below 53% or GLS relative decrease >10% between the first and third echocardiographic examinations [26].

5. CONCLUSION

Our 2-year longitudinal prospective study of anthracycline–trastuzumab-containing regimens in postmenopausal women with early BC revealed that: 1) Predictive association of E/e' with cardiotoxicity was not detected. 2) A reliable association with late cardiotoxicity (T7) from the diastolic parameters was revealed only by IVRT baseline value 3) A reliable association with early cardiotoxicity (T4) from diastolic parameters was revealed only by DT baseline. 4)GLS is superior to E/e' in its prognostic value and diagnostic ability of cardiotoxicity.

6. LIMITATIONS OF THE STUDY

The primary methodology limitations of the present study is the relatively small sample size. In our study, we also did not analyze in separate groups the different combinations of chemotherapeutic agents, as well as trastuzumab monotherapy regimen and patients who received radiotherapy in combination. Diastolic parameters were analyzed as secondary outcomes. These factors may affect the generalizability of our results and require further investigation in the future.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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