Revista Colombiana de
Hematología y Oncología

Julio - Diciembre de 2024 • Volumen 11 - Número 2

ARTÍCULO ORIGINAL

Prediction of cardiotoxicity in breast cancer patients exposed to anthracyclines during trastuzumab treatment.

Predicción de cardiotoxicidad en pacientes con cáncer de mama expuestas a antraciclinas durante el tratamiento con trastuzumab.

» Ángel Medina Pabón[1]
» José Fidel Tatis Méndez[1]
» Luis Rodolfo Gómez Wolff [2]
» Nicolás Lopera Arrázola [3]
» Alexis del Carmen Llamas Jiménez [4]
» Nicolás Ignacio Jaramillo Gómez [4]

[1] Fundación Auna Ideas, Medellín, Colombia.
[2] Instituto de Cancerología las Américas, Grupo Auna, Medellín, Colombia.
[3] Universidad CES, Medellín, Colombia.
[4] Clínica Las Américas, Grupo Auna, Departamento y Coordinación de Cardiología, Medellín, Colombia

Recibido el 30 de abril de 2024; aceptado el 06 de noviembre de 2024

Doi: https//doi.org/10.51643/22562915.703

Abstract

Trastuzumab (TRZ) improves survival in women with HER-2-positive breast cancer but is associated with significant cardiotoxicity, especially when administered after anthracyclines (AC) and cyclophosphamide. **Methods:** We conducted an ambispective cohort study from an oncology center to evaluate the cardiac safety of trastuzumab combined with anthracyclines in women with stage I-III HER-2-positive breast cancer who received a regimen based on AC (doxorubicin and cyclophosphamide) followed by trastuzumab between January 2017 and December 2022. Cardiovascular risk factors such as left ventricular ejection fraction (LVEF), global longitudinal strain (GLS), and treatment discontinuation were collected. Cardiac events (CE) were defined according to the new European Society of Cardiology (ESC) 2022 criteria (including reduction in LVEF and GLS). In addition, Cox regression was used to predict associations with cardiotoxic development. **Results:** Of 205 women, median were 52 years old (IQR 42-59). Eighty-four presented with TRZ-induced cardiotoxicity, with a median treatment duration of 9 months (IQR 8-11) (LVEF reduction ≥ 10%) and 7 months (IQR 6-8) (GLS reduction ≥ 15%), respectively. Age older than 65 years (HR:1.67; 95% CI 0.98-2.8; P=0.05), history of coronary artery disease (HR:4.67; 95% CI 1.4-14; P=0.012), and adjuvant radiotherapy to the

*** Autor para correspondencia:** Ángel Medina. Médico Epidemiólogo, Máster en Economía de la Salud. Fundación Auna Ideas.
Correo electrónico: michael.medpa@gmail.com
https//doi.org/10.51643/22562915.703

left breast (HR:1.34; 95% CI 0.8-2.2 P=0.242) were associated with the development of early cardiotoxicity. **Conclusions:** The incidence of cardiotoxicity in breast cancer patients treated with AC associated with TRZ is high given the new ESC criteria with the performance of GLS as a diagnostic test. These findings suggest more intensive cardiac monitoring in patients with risk factors over 65 years of age with previous coronary artery disease, and exposed to radiotherapy in the left breast.

Keywords: cardiotoxicity; global longitudinal strain; stroke volume; anthracyclines; trastuzumab.

Resumen

El trastuzumab (TRZ) mejora la supervivencia en mujeres con cáncer de mama HER-2-positivo, pero se asocia a una cardiotoxicidad significativa, especialmente cuando se administra después de antraciclinas (AC) y ciclofosfamida. **M**étodo: Realizamos un estudio de cohortes ambispectivo desde un centro oncológico para evaluar la seguridad cardíaca de trastuzumab combinado con antraciclinas en mujeres con cáncer de mama HER-2 positivo en estadio I-III que recibieron un régimen basado en AC (doxorrubicina y ciclofosfamida) seguido de trastuzumab entre enero de 2017 y diciembre de 2022. Se recopilaron factores de riesgo cardiovascular como la fracción de eyección del ventrículo izquierdo (FEVI), la tensión longitudinal global (GLS) y la interrupción del tratamiento. Los eventos cardíacos (EC) se definieron según los nuevos criterios de la Sociedad Europea de Cardiología (ESC) 2022 (incluida la reducción de la FEVI y la TFL). Además, se utilizó la regresión de Cox para predecir las asociaciones con el desarrollo de cardiotoxicidad. **Resultados:** De 205 mujeres, la mediana fue 52 años (IQR 42-59). Ochenta y cuatro presentaron cardiotoxicidad inducida por TRZ, con una mediana de duración del tratamiento de 9 meses (IQR 8-11) (reducción de LVEF ≥ 10%) y 7 meses (IQR 6-8) (reducción de GLS ≥ 15%), respectivamente. La edad superior a 65 años (HR:1,67; IC 95% 0,98-2,8; P=0,05), los antecedentes de enfermedad coronaria (HR:4,67; IC 95% 1,4-14; P=0,012) y la radioterapia adyuvante en la mama izquierda (HR:1,34; IC 95% 0,8-2,2 P=0,242) se asociaron con el desarrollo de cardiotoxicidad precoz. **Conclusiones:** La incidencia de cardiotoxicidad en pacientes con cáncer de mama tratadas con AC asociada a TRZ es elevada debido a los nuevos criterios ESC y a la realización de GLS como prueba diagnóstica. Estos hallazgos sugieren una monitorización cardiaca más intensiva en pacientes con factores de riesgo mayores de 65 años con enfermedad coronaria previa y expuestas a radioterapia en la mama izquierda.

Palabras clave: cardiotoxicidad; tensión longitudinal global; volumen de ictus; antraciclinas; trastuzumab.

Introduction

Breast cancer is a common neoplasm that causes high levels of morbidity and mortality. Recent GLOBOCAN 2020 data produced by IARC (International Agency for Research on Cancer) in 185 countries reported 2.3 million new cases of breast cancer and a mortality rate of 6.9%[1]. In addition, systemic therapy will depend on the molecular subtype, the three main ones being: first, the presence of estrogen or progestin hormone receptor (70% of patients); second, the presence of human epidermal growth factor 2 (ERBB2; formerly HER2; 15-20%), and third, triple negative (tumors lacking the three standard molecular markers; 15%). Similarly, the primary oncologic treatment for patients with ERBB2-positive tumors is an antibody directed against ERBB2 (trastuzumab) combined with chemotherapy (taxanes and/or anthracyclines)[2].

Anthracyclines (AC) and humanized anti-HER-2 monoclonal antibodies such as trastuzumab (TRZ) are highly effective chemotherapeutic agents, but their use exposes survivors to the

risk of cardiotoxicity. Many studies have shown that multiple factors are involved in the acute cardiotoxicity induced by these drugs, including oxidative stress and cell death[3]. However, the most common manifestation of chemotherapy-induced cardiotoxicity is heart failure, which in some cases can be advanced and with high mortality, as occurs with the use of AC[4]. Studies have reported a mortality rate that is 3.5 times higher than that caused by idiopathic cardiomyopathies[5].

Nevertheless, the incidence of cardiotoxicity (CT) with this sequential treatment (AC and TRZ) is high: between 20% and 30% of patients develop asymptomatic left ventricular (LV) dysfunction and between 3% and 5% develop symptomatic heart failure[6,8]. Furthermore, the myocardial damage caused is reversible, allowing recovery of function and resumption of oncological treatment if indicated[9].

Early ultrasound detection using Global Longitudinal Strain (GLS) and Left Ventricular Ejection Fraction (LVEF) has been shown to influence the cardiologic prognosis of these patients through timely cardioprotective treatment of subclinical cardiotoxicity, allowing the oncologist to avoid drug withdrawal of chemotherapy[8]. Indeed, it is essential to know the factors associated with cardiotoxicity or cardiac event (CE) for greater follow-up and echocardiographic monitoring, especially in those patients at high risk.

In this study, the incidence of early symptomatic and asymptomatic cardiotoxicity due to trastuzumab with prior use of anthracyclines was determined in a reference oncology institution. Furthermore, the efficiency and cut-off points of echocardiographic diagnostic parameters (LVEF and GLS) to detect LV dysfunction were evaluated. Finally, factors associated with early cardiotoxicity during the first year of TRZ exposure were identified.

Materials and methods

All patients diagnosed with stage I-III HER-2-positive breast cancer, previously treated with AC and followed by one year of TRZ exposure during the period from January 2017 to December 2022, were retrospectively reviewed. These patients were monitored by serial transthoracic echocardiograms requested by the Las Americas Cancer Institute and performed by the Cardiology Unit of the Las Americas Clinic. Patients treated with AC had a mean duration of 1.5 ± 0.5 months. Subsequently, TRZ was initiated a median of 21 days (20 to 23 days) after completion of AC treatment and administered for 12 months (11 to 13 months). All patients underwent at least five echocardiograms: T-1 before treatment with AC, T0 shortly after completion of AC and before initiation of TRZ, T1 at three months (4-6 months) after initiation of TRZ, T2 at six months (6-8 months), T3 at nine months (9-10 months), and T4 at 12 months (12-13 months).

Data were collected directly from the electronic medical record by study co-investigators trained by the principal investigator, an oncologist, and a cardiologist, who clarified any concerns to avoid information bias. A standardized electronic form followed the protocol approved by the institution's ethics committee with minute number 175, October 11, 2021.

Echocardiographic acquisition was performed in the Americas Clinic Database in the Cardiology Department using transthoracic echocardiographic with commercially available equipment (iE33, Philips Medical Systems, Andover). Readers were blinded to the subjects' echocardiographic examination time points, medical history, and treatments. Only left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) were recorded.

According to the consensus of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (ASE/EACVI)[12,13], asymptomatic cardiotoxicity is defined as a ≥10% reduction in LVEF% to < 50%

without signs or symptoms. Heart failure or symptomatic cardiotoxicity is defined as any ≥ 5% reduction in LVEF% to < 50% with signs or symptoms of heart failure. The abnormal LVEF for our institution is < 55% by expert consensus.

However, in the most recent guidelines on cardio-oncology from the European Society of Cardiology[14], symptomatic cardiotoxicity was defined as a reduction in left ventricular ejection fraction (LVEF) associated with symptoms (dyspnea, ankle edema, or fatigue) or signs (elevated jugular venous pressure, pulmonary crackles, or peripheral edema) of heart failure, which was divided into four levels of management: Mild; symptoms that do not require intensive therapy. Moderate; requires intensive outpatient heart failure therapy. Severe: Requires hospitalization. Very severe: Requires ionotropic support and intensive care unit management. Patients who presented cardiotoxicity with CA followed by TRZ received cardioprotective treatment (ACE inhibitors and beta-blockers).

Asymptomatic cardiotoxicity (no signs or symptoms of heart failure) is also divided into three categories: Mild, when there is a reduction in GLS >15% and new LVEF ≥50% [10,11], or/and further elevation of cardiac biomarkers. Moderate, when the new LVEF is between 40-49% with a reduction of ≥10% of the initial LVEF, or when the LVEF reduction is <10% and presents with a decrease in GLS >15% or new elevation of cardiac biomarkers. Severe, when the new LVEF is <40%.

Continuous variables with normal distribution were presented as mean ± SD, those with non-normal distribution were summarized as median (interquartile range (25 to 75)), and categorical variables were presented as percentages. Differences in continuous data between patients with and without cardiotoxicity were compared using Student's t-test, t-test, or Wilcoxon rank for nonparametric variables. Categorical variables were compared using the chi-squared test. One-way ANOVA analysis for repeated measures was used to compare significant differences in continuous longitudinal echocardiographic parameters. To correlate continuous variables, differences and final values of LVEF and GLS with CS, scatter plots and ROC curves were used to correlate both diagnostic tests.

In addition, survival analysis for CT was performed using the Kaplan-Meier curve for patients with risk factors. The differences between the survival curves were considered statistically significant by the Long Rank test, with a p-value of less than 0.05. The dependent variables were the time and occurrence of CT observed during the first 12 months of TRZ treatment, for which associations were sought with Cox proportional hazards analysis. Analysis was performed using univariable and multivariable Cox regression models. Factors associated with CT were identified using variables with HR greater than one in the multivariate and p-values less than 0.05. Analyses were performed using the Jamovi Project 2022 statistical package, version 2.3.

Results

Patient characteristics and follow-up: Two hundred and five patients with newly diagnosed breast cancer treated with AC followed by TRZ and serial echocardiograms were followed for 12 months (11 to 13 months). Baseline clinical characteristics are summarized in Table 1. According to the American Society of Echocardiographic, forty-six patients (22%) developed CT (cardiotoxicity) with a median time of 9 months (8 to 11 months). Meanwhile, for the new European Society of Cardiology cardiotoxicity criteria, which include GLS changes, eighty-five patients (41%) developed CT at a median time of 7 months (6 to 8 months) after the start of TRZ chemotherapy. Of these, 46% were asymptomatic and 54% had symptoms of mild heart failure. Similarly, 72% were on cardioprotective management (ACEI and beta-blocker).

Table 1.
General characteristics of the population with and without the event.

Variable	without Cardiotoxicity n= 121	Cardiotoxicity n = 84	p
Age (years) * ll	51.3 (49-54)	52.4 (49-55)	0.54
BMI(kg/m²) † §	27 (24-30)	26 (23-29)	0.67
BSA (m²) † §	1.7 (1.6-1.8)	1.65 (1.6-1.8)	0.16
LVEF initial† ll	60 (60-62)	62 (60-65)	0.001
GLS initial † ll	-20.1 (-19; -22)	-21.6 (-20; -23)	0.002
LVEF final † ll	60 (60-64)	55 (53-60)	0.001
GLS final † ll	-20 (-19; -22)	-18 (-16; -19)	0.001
DIF LVEF † ll	0 (0; 5)	-10 (-8; -15)	0.001
DIF GLS † ll	0 (-5; 5)	-17 (-15; -22)	0.001
SAH ǂ	41 (64)	23 (36)	0.32
Type II DM ǂ	18 (72)	7 (28)	0.15
Dyslipidemia‡	31 (59)	22 (41)	0.93
Obesity (BMI >30) ǂ	33 (67)	16 (33)	0.17
Smoking‡	18 (56)	14 (44)	0.73
Alcohol drinker	7 (58)	5 (42)	0.96
PSHD ǂ	8 (44)	10 (56)	0.18
Previous arrhythmias‡	4 (50)	4 (50)	0.59
PCHD ǂ	1 (25)	3 (75)	0.16
COPD ǂ	4 (67)	2 (33)	0.69
CKD ǂ	0 (0)	1 (100)	0.22
Right breast CA ǂ	64 (63)	38 (37)	0.28
Left breast CA ǂ	57 (55)	46 (45)	0.28
Stage I	18 (47)	20 (53)	0.28
Stage II	61 (62)	37 (38)	0.28
Stage III	41 (59)	28 (41)	0.28
Radiotherapy BL	103 (50)	46 (45)	0.28
Radiotherapy + T Boost BL	22 (48)	24 (52)	0.08
Total anthracycline dose (mg/m²) † §	400 (382-440)	400 (376-432)	0.76
Total trastuzumab dose (mg/m²) * ll	7238 (6960-7516)	6722 (6342-7101)	0.98
Cardiotoxic asymptomatic moderate		4 (5)	
Cardiotoxic asymptomatic mild		35 (41)	
Cardiotoxic symptomatic mild		46 (54)	
Received cardioprotection		61 (72)	

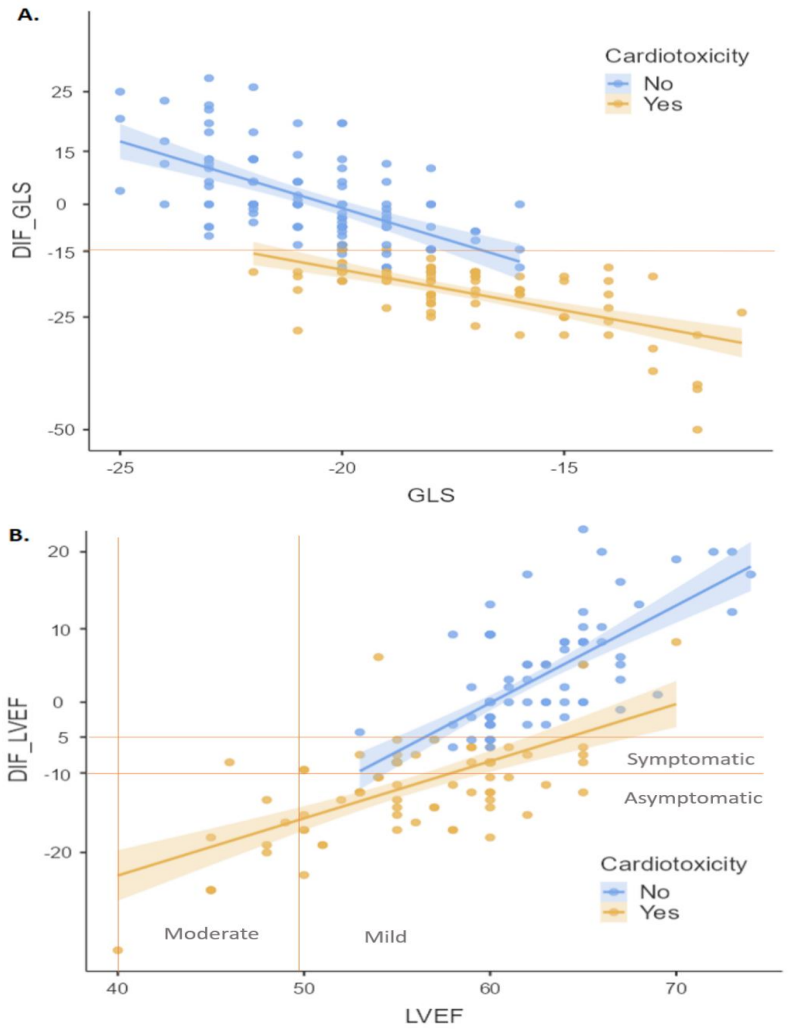
* Mean (confidence interval 95%); † Median (25th - 75th Percentile); ǂ N (%); BSA: Body Surface Area; BMI: Body Mass Index; HR: Heart Rate; EF: Ejection Fraction; GLS: Global Longitudinal Strain SAH: Systemic Arterial Hypertension; DM: Diabetes Mellitus; PSHD Previous structural heart disease; PCHD: Previous coronary heart disease; CA: Cancer; Chemo: Chemotherapy; bpm: beats per minute. Categorical variables were compared using the chi-square test ǂ, p-value ≤ 0.05. Continuous variables were compared using Mann Whitney U test § or Student t test ll, p-value ≤ 0.05.

According to echocardiographic parameters during follow-up, 75 patients had a difference of 15% or more from baseline LVEF compared to the control group, while 10 patients had a difference of 10%-14% from baseline LVEF with changes >5% in LVEF and symptoms such as dyspnea or fatigue. In addition, 46 patients had changes >10% and 36 patients had changes between 5% and 10% of LVEF, respectively. Eleven patients had changes in LVEF >10% after AC management without affecting the final EC results (HR: 0.8 95% CI:0.4-1.6 p:0.52).

The correlation of the values between the difference of GLS and LVEF with the final values of GLS and LVEF had an inversely proportional relationship; the greater the negative difference, the lower the absolute value of GLS or LVEF. The distribution and the difference between the groups with and without CT are shown in Figure 1. The lowest point of change in LVEF was 40%, while GLS decreased to -12%; this change was observed five months after the start of TRZ - none of the echocardiographic parameters returned to their pre-chemotherapy values.

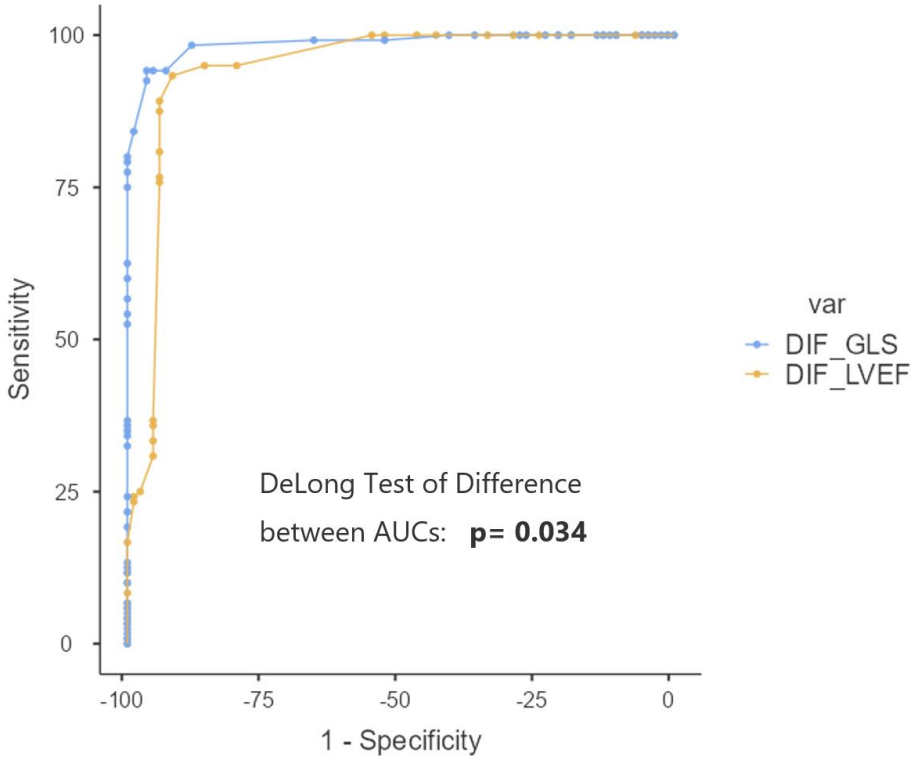
Figure 1.

Illustrating the difference between the groups with and without cardiotoxicity. **A.** percentage reduction in left ventricular global longitudinal strain (GLS) variation with standard error. **B.** percentage reduction in left ventricular ejection fraction (LVEF) variation with standard error. Symptomatic (patients with any of the following symptoms such as dyspnea, chest pain, fatigue).



When comparing the efficiency of diagnostic tests in predicting cardiotoxicity or CT, a larger area under the curve was observed for GLS (AUC: 0.987) at a cut-off of >15%; it had a sensitivity of 99% and a specificity of 66%. While LVEF (AUC: 0.945) with a cut-off point >10% showed a sensitivity of 100% and a specificity of 47%, being highly sensitive and not very specific, Figure 2.

Figure 2.
ROC Curve: Combined between LVEF AND GLS



Furthermore, the probability of not having the disease when the diagnostic test result is negative or negative predictive value (NPV) improves with the cut-off points established for diagnosis (reduction >15% GLS and >10% LVEF). In comparison, the probability of having the disease if the diagnostic test result is positive or positive predictive value (PPV) improves with lower cut-off points (reduction >13% GLS and >5% LVEF) associated with clinical symptoms of heart failure. Similarly, the Youden index (as a cutoff point determining the highest sensitivity and specificity together) was high in those with a higher PPV, with similar test performance for GLS and LVEF. However, the performance for GLS was higher in detecting those who were truly healthy or had a higher NPV. Table 2.

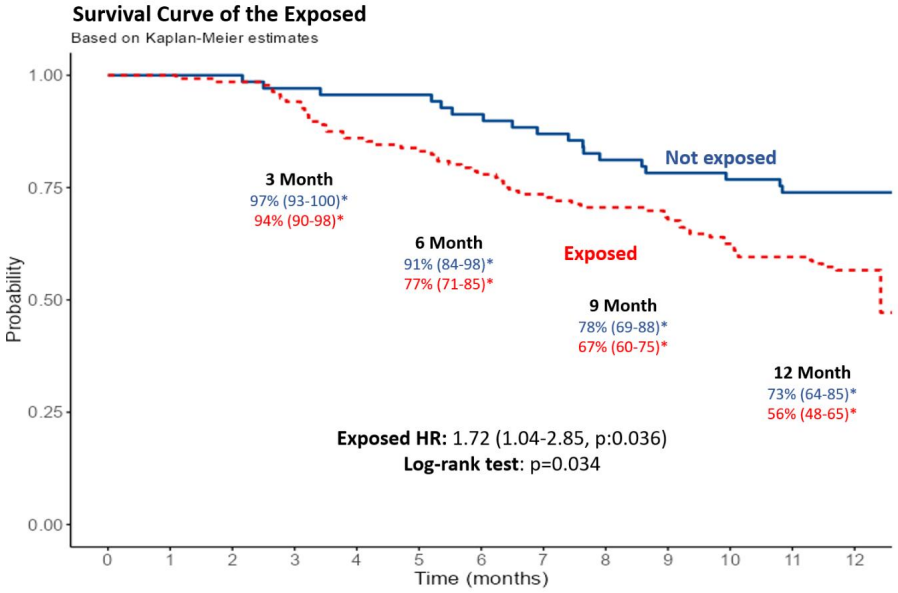
Table 2.
Comparison of validity, reliability and security between LVEF and GLS.

	Cut point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's index	AUC	Metric Score
DIF LVEF	-5	93	92	94	91	0.85	0.945	1.85
	-7	95	80	87	92	0.75	0.945	1.75
	-10	100	47	73	100	0.47	0.945	1.47
DIF GLS	-15	99	66	80	98	0.65	0.987	1.65
	-14	98	88	92	97	0.87	0.987	1.87
	-13	94	93	95	92	0.87	0.987	1.87

On the other hand, when performing the univariate analysis in the Cox regression, the variables over 65 years of age, radiation to the left breast plus boost therapy or boost therapy, history of arrhythmia, structural heart disease, smoking, alcoholism, dyslipidemia, behaved as risk factors without having statistical significance; except with previous coronary disease, finding a strong significant association HR: 3.3 (1.03-10.5; p:0.044). (See supplementary material).

Therefore, the Kaplan-Meier curve showed that patients exposed to one or more of the above factors were 1.7 times more likely to present with CT in the first year than those without such exposure. This was a statistically significant difference for a log-rank test p:0.034. It was also evident that approximately 23% of those exposed had CT at six months, while this increased to 44% at one year, a much lower figure in those not exposed, 9% and 27% respectively. Total events GLS: 85, of which 20 were for the non-exposed for the exposed and 65 for the exposed. * 95% confidence interval. GLS: Global Longitudinal Strain. Figure 3.

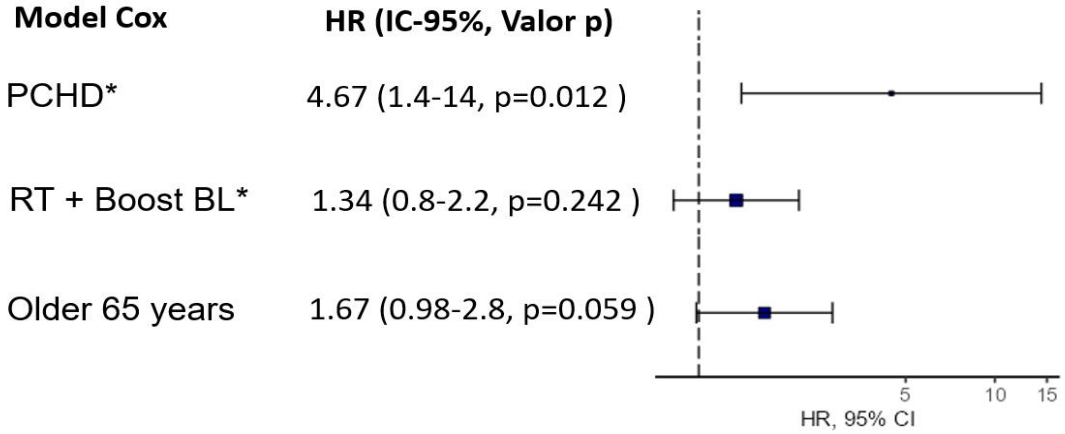
Figure 3.
Survival between groups exposed and not exposed to one or more of the risk factors for developing cardiotoxicity.



Note: Groups not exposed (n=69) and exposed (n=136).

Finally, when multivariate Cox regression was performed, a history of coronary artery disease increased the HR to 4.67 times when associated with women over 65 years of age (HR:1.67) and radiotherapy plus booster therapy to the left breast (HR:1.34). Statistically significant for coronary artery disease. Figure 4.

Figure 4.
Predictive variables of cardiotoxicity with Cox regression model.



Note: *PCHD: Previous coronary heart disease; RT + T Boost BL: Radiotherapy and therapy boost left breast.

Discussion

The present study analyzed the echocardiographic changes (LVEF and GLS) to determine the incidence of cardiotoxicity in women with breast cancer treated with AC followed by TRZ and found a higher incidence (41%) using the current criteria of the Cardio-Oncology Task Force of the European Society of Cardiology (ESC). Meanwhile, according to the American Echocardiographic Society criteria, the incidence was 22%. This is similar to other studies where the incidence increases with prior use of anthracycline and cyclophosphamide, which can be as high as 20-30%[6,9]. Likewise, the median occurrence of CT was analyzed, finding that the GLS is the echocardiographic parameter first changed before the LVEF is changed, seven months and nine months, respectively.

In addition, when evaluating the efficiency of both tests, in the ROC curve, a statistically significant difference was found in the area under the curve (AUC), which was 0.98 with an optimal cut-off point for GLS (≥-14%), revealing a superior performance due to its high sensivity: 98% and specificity: 88%. Meanwhile, for LVEF, AUC: 0.94 with a cut-off of (≥-10), a highly sensitive (100%) and not very specific (47%) test was found. Similarly, a cohort study in Egypt in 2019 found an AUC: 0.98 with an optimal cut-off point for GLS (-18%) with a sensitivity of 92.5% and specificity of 83%, with 30% trastuzumab-induced cardiotoxicity between 6-9 months diagnosed with a reduction in LVEF ≥10%[15].

The risk factors first analyzed in the Cox regression and grouped as exposure variables (history of coronary artery disease, structural heart disease, arrhythmia, smoking, age >65 years, and radiotherapy to the left breast) had a 1.7-fold risk of developing an event during the first year with TRZ; these factors are also described in the 2022 ESC guidelines and other similar studies[14, 18].

In addition, other risk factors such as dyslip-

idemia, smoking, alcohol, and previous structural heart disease had an HR greater than 1, as described in several studies[19]. In the multivariate analysis with Cox regression, we found that the risk of cardiotoxicity increased sevenfold in women older than 65 years, with a history of coronary artery disease and exposed to radiotherapy to the left breast plus booster therapy to the tumor bed, becoming a significant predictive factor for the clinician in the follow-up and monitoring of these patients exposed to AC followed by TRZ, especially in those with a low LVEF[19, 21]. It is important to emphasize that patients with significantly altered values of both parameters (GLS and LVEF) were not able to return to the initial values[8].

Overall, 72% of patients were receiving cardioprotective treatment. However, there is conflicting evidence that ACEIs/ARBs and beta-blockers provide substantial cardioprotection against decline in LVEF. One issue that limits the direct comparison of these studies is the differences in the definition of primary and secondary outcomes and the method of measurement. Other studies have used only echocardiography and have not relied on central laboratory assessments. This effect was modest, probably due to the unselected patient populations and the treatment of low-risk individuals[20].

On the other hand, this study has certain limitations. It is a study from a leading oncology center with a secondary source of clinical history in collaboration with oncologists and cardiologists, which may not reflect all oncology centers performing this treatment in the population with HER2-positive breast cancer. All patients were previously treated with four cycles of anthracyclines, and the follow-up was one year from the start of TRZ, so that conclusions can only be drawn for this population. In addition, we did not obtain data on troponin levels as a biomarker of heart disease in this study.

Conclusions

This study is one of the first to propose, based on COX models, the prediction of early cardiotoxicity in patients with HER-2 positive breast cancer in stages I-III, operated on with AC followed by TRZ, monitored with parameters echocardiographic tests (GLS and LVEF) for one year, in a reference oncology center in Colombia. Characteristically, patients over 65 years of age with previous coronary artery disease, exposed to radiotherapy in the left breast, have a higher risk of early cardiotoxicity than those who did not have these factors.

These models must be validated in the different institutions of the country, which would achieve valid national registries; in addition, we could advance aid and corrective measures to current health policies, strengthening the joint work between oncologists and cardiologists for early detection and the prevention of long-term catastrophic events.

Thanks

To the patients who agreed to participate in the study, our most fraternal gratitude to Las Americas Cancer Institute and Las Americas Clinic cardiology group for supporting this initiative.

Contributions

Contributors played a substantial role in conception, design, acquisition, analysis, interpretation, writing, and critical review of the manuscript. All authors approved the final content and accept responsibility for its accuracy and integrity.

Funding Sources

No funding or contributions were received to carry out this study.

Conflict of interests

Authors declare no conflict of interest in carrying out this study.

Author's Bio

Ángel Medina. Medico Epidemiólogo, Máster en Economía de la Salud Universidad CES, Medellín, Colombia.

José Fidel Tatis. Profesional en gerencia en sistemas de información en salud, Universidad de Antioquia, Medellín, Colombia.

Rodolfo Gómez. Médico y Cirujano. Especialización en Oncología Clínica.

Nicolás Lopera. Médico y Cirujano

Alexis Llamas. Médico y Cirujano. Especialización en Cardiología.

Nicolás Jaramillo. Médico y Cirujano. Especialización en Cardiología.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. [internet] 2021; 71(3):209-249. Available from: https://doi.org/10.3322/caac.21660
2. Waks AG, Winer EP. Breast Cancer Treatment: A Review. JAMA. [internet] 2019 22; 321(3):288-300. Available from: https://doi.org/10.1001/jama
3. Kong CY, Guo Z, Song P, Zhang X, Yuan YP, Teng T, Yan L, Tang QZ. Underlying the Mechanisms of Doxorubicin-Induced Acute Cardiotoxicity: Oxidative Stress and Cell Death. Int J Biol Sci. [internet] 2022;18(2):760-770. Available from: https://doi.org/10.7150/ijbs.65258
4. Keshavarzian E, Sadighpour T, Mortazavizadeh SM, Soltani M, Motevalipoor AF, et al. Prophylactic Agents for Preventing Cardiotoxicity Induced Following Anticancer Agents: A Systematic Review and Meta-Analysis of Clinical Trials. RevRecent Clin Trials. [internet] 2023; 18(2):112-122. Available from: https://doi.org/10.2174/1574887118666230118102252
5. Ruiz-Mori E, Ayala-Bustamante L, Burgos-Bustamante J, et al. Cardiotoxicidad por quimioterapia en el Instituto Nacional de Enfermedades Neoplásicas 2012-2016. HorizMéd Lima. [internet] 2017; 17(3):24-8. Available from: http://dx.doi.org/10.24265/horizmed.2017.v17n3.05
6. Jerusalem G, Lancellotti P, Kim SB. HER2+ breast cancer treatment and cardiotoxicity: monitoring and management. Breast Cancer Res Treat. [internet] 2019; 177(2):237-250. Available from: https://doi.org/10.1007/s10549-019-05303-y PMID: 31165940; PMCID: PMC6661020.
7. Tarantini L, Cioffi G, Gori S, Tuccia F, Boccardi L, Bovelli D, Lestuzzi C, Maurea N, Oliva S, Russo G, Faggiano P; Italian Cardio-Oncologic Network. Trastuzumab adjuvant chemotherapy and cardiotoxicity in real-world women with breast cancer. J Card Fail. [internet] 2012; 18(2):113-9. Available from: https://doi.org/10.1016/j.cardfail.2011.10.015. PMID: 22300778
8. Fei HW, Ali MT, Tan TC, Cheng KH, Salama L, Hua L, Zeng X, Halpern EF, Taghian A, MacDonald SM, Scherrer-Crosbie M. Left Ventricular Global Longitudinal Strain in HER-2 + Breast Cancer Patients Treated with Anthracyclines and Trastuzumab Who Develop Cardiotoxicity Is Associated with Subsequent Recovery of Left Ventricular Ejection Fraction. Echocardiographic. [internet] 2016; 33(4):519-26. Available from: https://doi.org/10.1111/echo.13168 Epub 2016 Mar 16. PMID: 26992012
9. Lax J, Piñeiro D. Consenso de diagnóstico, prevención y tratamiento de la cardiotoxicidad por tratamiento médico del cáncer. Versión resumida. Rev Argent Cardiol. [internet] 2013; 81(6):530-6. Available from:

http://dx.doi.org/10.7775/rac.es.v81.i6.3537

10. Iana JC, Galderisi M, Barac A, et al: Expert consensus formultimodality imaging evaluation of adult patients dur-ing and after cancer therapy: A report from the AmericanSociety of Echocardiographic and the European Associa-tion of Cardiovascular Imaging.J Am Soc Echocardiogr. [internet] 2014;27:911–939. Available from: https://doi.org/10.1016/j.echo.2014.07.012 PMID: 25172399
11. Sengupta PP, Northfelt DW, Gentile F, Zamorano JL, Khandheria BK. Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. MayoClin Proc. [internet] 2008; 83(2):197-203. Available from: https://doi.org/10.4065/83.2.197 PMID: 18241629.
12. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, Amir EA, Marwick TH, Gupta D, et al. Assessment of Prognostic Value of Left Ventricular Global Longitudinal Strain for Early Prediction of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis. JAMA Cardiol. [internet] 2019;4(10):1007-1018. Available from: https://doi.org/10.1001/jamacardio.2019.2952 PMID: 31433450; PMCID: PMC6705141.
13. Arciniegas Calle MC, Sandhu NP, Xia H, Cha SS, Pellikka PA, Ye Z, et al. Two-dimensional speckle tracking echocardiographic predicts early subclinical cardiotoxicity associated with anthracycline-trastuzumab chemotherapy in patients with breast cancer. BMC Cancer. [internet] 2018;18(1):1037. Available from: https://doi.org/10.1186/s12885-018-4935-z PMID: 30359235; PMCID: PMC6203211.
14. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). European Heart Journal, [internet] 2022; 43(41): 4229–4361. Available from: https://doi.org/10.1093/eurheartj/ehac244
15. El-Sherbeny WS, Sabry NM, Sharbay RM. Prediction of trastuzumab-induced cardiotoxicity in breast cancer patients receiving anthracycline-based chemotherapy. J Echocardiogr. [internet] 2019; 17(2):76-83. Available from: https://doi:10.1007/s12574-018-0394-4 Epub 2018 Aug 11. PMID: 30099714.
16. Abouegylah M, Braunstein LZ, Alm El-Din MA, et al. Evaluation of radiation-induced cardiac toxicity in breast cancer patients treated with trastuzumab-based chemotherapy. Breast Cancer Res Treat. [internet] 2019; 174:179–185. Available from: https://doi:10.1007/s10549-018-5053-y PMID: 30478787. PMCID: PMC8590794.
17. Cao L, Hu WG, Kirova YM, et al. Potential impact of cardiac dose-volume on acute cardiac toxicity following concurrent trastuzumab and radiotherapy. Cancer Radiother. [internet] 2014; 18:119–124. Available from: https://doi.org/10.1016/j.canrad.2014.01.001 PMID: 24642505.
18. Bergom C, Bradley JA, Ng AK, Samson P, Robinson C, Lopez-Mattei J, Mitchell JD. Past, Present, and Future of Radiation-Induced Cardiotoxicity: Refinements in Targeting, Surveillance, and Risk Stratification. JACC CardioOncol. [internet] 2021 21;3(3):343-359. Available from: https://doi:10.1016/j.jaccao.2021.06.007 PMID: 34604796; PMCID: PMC8463722.
19. Jawa Z, Perez RM, Garlie L, Singh M, Qamar R, Khandheria BK, Jahangir A, Shi Y. Risk factors of trastuzumab-induced cardiotoxicity in breast cancer: A meta-analysis. Medicine (Baltimore). [internet] 2016 Nov;95(44):e5195. Available from: https://doi:10.1097/MD.0000000000005195 PMID: 27858859; PMCID: PMC5591107.
20. Padegimas A, Clasen S, Ky B. Cardioprotective strategies to prevent breast cancer therapy-induced cardiotoxicity. Trends Cardiovasc Med. [internet] 2020 Jan;30(1):22-28. Available from: https://doi:10.1016/j.tcm.2019.01.006 PMID: 30745071; PMCID: PMC7287268.

21. Koulaouzidis G, Yung AE, Yung DE, Skoniec-zna-Żydecka K, Marlicz W, Koulaouz-idis A, Charisopoulou D. Conventional cardiac risk factors associated with tras-tuzumab-induced cardiotoxicity in breast cancer: Systematic review and meta-anal-ysis. CurrProblCancer. [internet] 2021 Oct;45(5):100723. Available from: https:// doi:10.1016/j.currproblcancer.2021.100723 PMID: 33726923.

Supplementary Material.

Variables associated with cardiotoxicity in the univariate analysis.

Variables	HR	(IC-95%)	p
Olderage 65 years	1.3	(0.75-2.2)	0.356
Radiotherapy BL	1.1	(0.73-1.75)	0.595
Radiotherapy + T Boost BL	1.3	(0.82-2.16)	0.244
PSHD*	1.9	(0.96-.3.64)	0.064
PCHD*	3.3	(1.03-10.5)	0.044
Cardiacarrhythmia	1.5	(0.56-4.2)	0.406
Smoking	1.3	(0.72-2.3)	0.387
Dyslipidemia	1.1	(0.7-1.87)	0.591
Alcohol drinker	1.2	(0.47-2.9)	0.736

Note: *PSHD Previous structural heart disease; PCHD: Previous coronary heart disease. Radiotherapy + T Boost BL: Radiotherapy and Therapy Boost Left breast.