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Research Article

Predictors of Chemotherapy-Induced Cardiotoxicity in Breast Cancer: A Real-World Cohort Study

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Abstract

Chemotherapy-induced cardiotoxicity is a major complication in breast cancer patients treated with anthracycline- and trastuzumab-based regimens. Most prediction models come from North American or Western European cohorts. We aimed to develop and internally validate a 12-month cardiotoxicity model in Albanian breast cancer patients and to assess the added value of global longitudinal strain (GLS). It has been performed a retrospective cohort study of 314 consecutive female breast cancer patients treated with anthracycline- and/or trastuzumab-based regimens at the University Hospital Center "Mother Teresa" in Tirana between 2015 and 2022. All underwent baseline and follow-up echocardiography with left ventricular ejection fraction (LVEF) and GLS. Cardiotoxicity at 12 months, defined by contemporary cardio-oncology criteria, was the primary outcome. Multivariable logistic and Cox models were built and internally validated with 1,000-sample bootstrapping. Cardiotoxicity occurred in 63 of 314 patients (20.1%). Age and BMI were similar between groups, whereas patients with cardiotoxicity more often received combined anthracycline–trastuzumab therapy and had worse baseline GLS. A clinical model including age, BMI, hypertension, diabetes, dyslipidemia, previous cardiovascular disease, anthracycline and trastuzumab exposure, and left-sided radiotherapy achieved an AUC of about 0.72. Adding GLS increased the AUC to about 0.79 and improved overall performance. In Cox models, combined anthracycline–trastuzumab therapy and baseline GLS remained independently associated with time-to-cardiotoxicity. In this Albanian cohort, one in five breast cancer patients developed cardiotoxicity within 12 months. A GLS-augmented clinical model showed good performance and may support individualized risk stratification and surveillance in South-Eastern European cardio-oncology practice.

Keywords: Breast Neoplasms; Anthracyclines; Trastuzumab; Cardiotoxicity; Echocardiography; Global Longitudinal Strain; Risk Assessment.

INTRODUCTION

The use of modern cancer treatments has established chemotherapy-induced cardiotoxicity as a known side effect which mainly affects breast cancer patients who receive anthracyclines and HER2-targeted medications. The survival benefits of these treatments have led to higher rates of cardiovascular diseases among European and Balkan cancer survivors who live beyond their initial diagnosis [1–3]. The mechanism of anthracycline-induced myocardial damage depends on dose accumulation because these drugs create oxidative stress and block topoisomerase IIβ enzyme activity. The mechanism of trastuzumab-induced cardiac damage occurs through its interference with HER2-dependent cardiomyocyte repair processes which results in temporary or permanent cardiac dysfunction [4–8].

The improvement of breast cancer survival rates in South-Eastern Europe makes it essential to detect cardiotoxicity early while preventing its development in areas that lack fully developed cardio-oncology services [5,9]. Echocardiography functions as the primary cardiac monitoring tool while global longitudinal strain (GLS) serves as a sensitive method to detect early heart function changes before left ventricular ejection fraction (LVEF) shows significant alterations [10–15]. The availability of GLS-capable echocardiography equipment remains limited in Balkan and middle-income countries while biomarkers function as standard cardiac monitoring tools [16, 17].

The regional environment of Albania presents identical problems because it lacks standardized strain imaging technology and uses different follow-up methods and lacks research about metabolic risk factor interactions with treatment exposures and echocardiographic parameters that predict cardiotoxicity. The current medical practice in Albanian oncology lacks studies which assess GLS and combined clinical predictors for cardiotoxicity assessment [18-21]. The 2022 ESC baseline risk categories and Abdel-Qadir score and North American and Western European registry-based tools have not received validation for South-Eastern European populations [22-24]. The models used for cardiotoxicity risk assessment in other regions fail to apply to Balkan areas because of distinct patterns of comorbidities and treatment approaches and limited healthcare resources.

The research adds three distinct value points to the existing body of knowledge.

1. The research evaluates established cardiotoxicity predictors through regional assessment. The study investigates how clinical indicators and metabolic markers and treatment variables perform in Albanian patients who have not been studied in previous validation research.
2. The research investigates how GLS performs as a diagnostic tool when healthcare resources are limited. The recommended left ventricular dysfunction detection method GLS has not received any reports about its effectiveness in Albania or South-Eastern European countries.
3. The research creates essential baseline information which will help scientists validate risk models for future use. The research results create essential information which

enables healthcare professionals to modify or enhance current prediction models for their local practice.

Multiple clinical risk-prediction models exist to predict chemotherapy-related cardiotoxicity but most of them were developed from North American and Western European patient data. The Abdel-Qadir 7-factor score [24] uses seven variables to predict cardiotoxicity including age and hypertension and baseline cardiovascular disease and anthracycline dose and trastuzumab exposure. The ESC 2022 baseline risk categories [1] use clinical comorbidities and treatment exposures to divide patients into three risk groups from low to high. The Ezaz model [25] and Henriksen model [26] use registry data to predict cardiotoxicity but their performance varies between 0.75 and 0.85 AUC because they depend on anthracycline dose and cardiac disease history and trastuzumab treatment length which are not always recorded in low-resource settings.

The models demonstrate strong methodological qualities but they lack validation for South-Eastern Europe because obesity rates and hypertension prevalence and radiotherapy techniques and strain imaging availability differ from Western countries. The current prediction tools fail to account for regional limitations which include restricted GLS availability and different patient follow-up protocols. The algorithms show unknown effectiveness when used in Balkan healthcare systems. The lack of regional validation studies reveals an obvious deficiency in current research. The current models lack validation for Albania and its surrounding countries because no studies have evaluated their performance with local clinical and metabolic and therapeutic data from lower-resource cardio-oncology settings. The current research gap serves as the scientific basis for this study which investigates established risk factors in Albanian patients and develops initial findings for future regional validation of cardiotoxicity prediction models.

Rationale

The region of South-Eastern Europe shows limited research on cardio-oncology despite worldwide advancements in this field while its hospitals differ significantly in their ability to perform advanced echocardiographic tests [16, 21, 24]. The research investigates chemotherapy-induced cardiotoxicity risk factors in breast cancer patients at the University Hospital Center “Mother Teresa” in Tirana to generate data that will help local healthcare providers make better decisions.

The research investigates chemotherapy-related heart damage through a South-Eastern European patient population for the first time. The international scientific community has developed various prediction models but researchers have not studied these models in settings with limited resources. The study uses standardized echocardiographic tests to measure heart function while tracking total chemotherapy dose and studying local clinical risk factors which will help modify existing risk assessment models for South-Eastern European medical practice.

Research Gap and Study Hypotheses

Multiple research gaps exist regarding chemotherapy-related cardiotoxicity despite worldwide scientific studies about this topic in South-Eastern Europe. The ESC 2022 baseline risk categories and Abdel-Qadir score and large registry-based algorithms lack validation for Balkan populations as they do not work in these populations. The Western-derived risk tools face challenges in regional application because of different cardiovascular risk patterns and obesity rates and radiotherapy methods and restricted access to strain imaging technology. The performance of BMI and hypertension and anthracycline exposure and trastuzumab therapy and GLS as predictors for cardiotoxicity remains untested in an actual Albanian patient population. The region lacks research that assesses how combining clinical data with metabolic information and echocardiographic results enhances cardiotoxicity risk assessment.

Based on these gaps, the present study tested the following hypotheses:

- **H1.** Higher baseline cardiovascular risk (including hypertension, elevated BMI, and dyslipidemia) is associated with an increased likelihood of developing chemotherapy-induced cardiotoxicity.
- **H2**. Treatment-related factors specifically the type of anthracycline- and trastuzumab-based regimens and their combinations are independent predictors of cardiotoxicity in this population.
- **H3.** Baseline GLS provides incremental predictive value for early detection of cardiotoxicity beyond traditional clinical and metabolic risk factors.
- **H4.** A combined multivariable model integrating clinical, metabolic, and echocardiographic variables demonstrates superior discrimination compared with individual predictors alone.

These hypotheses guided the study design and the analytical framework used to evaluate cardiotoxicity risk in the Albanian breast cancer population.

MATERIALS AND METHODS

Study Design and Setting

This retrospective cohort study was conducted at the University Hospital Center "Mother Teresa" (UHCT) in Tirana, Albania, with data extraction and analysis performed at the University of Medicine, Tirana, between January 2023 and December 2024. Clinical, echocardiographic and treatment information was obtained from electronic medical records and anonymized prior to analysis. The study protocol was approved by the Institutional Ethics Committee of the University of Medicine, Tirana, and complied with the principles of the Declaration of Helsinki.

Study Population

A total of 350 consecutive breast cancer patients treated between 2015–2022 were screened. After applying predefined exclusion criteria—pre-existing left ventricular dysfunction (LVEF < 50%), significant valvular disease, prior myocardial infarction, congenital heart disease, incomplete clinical data, and loss to follow-up—314 patients formed the final analytic cohort. Among these, 63 (20.1%) developed cardiotoxicity and 251 (79.9%) did not.

A schematic patient flowchart is presented in Figure 1.

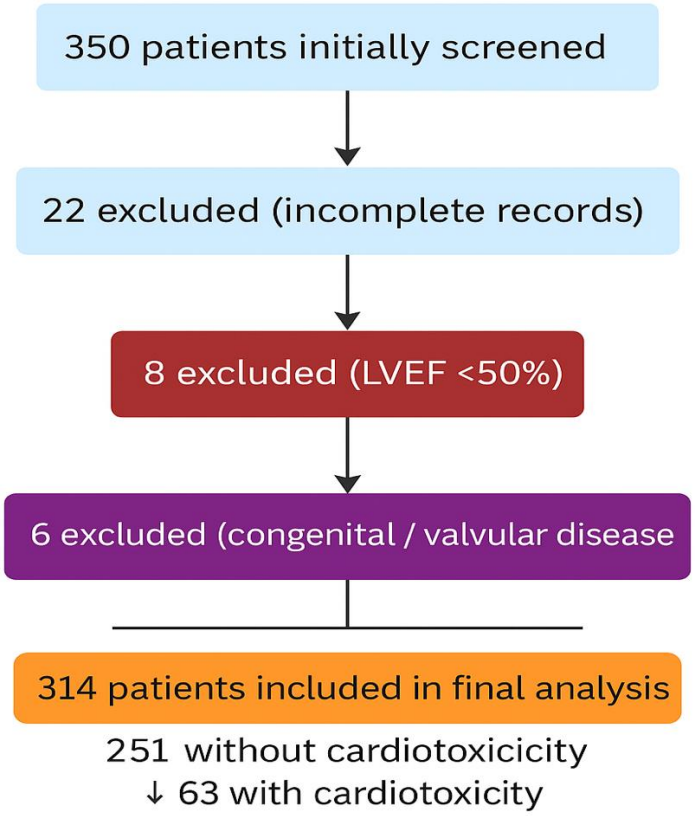

Figure 1. Flowchart of patient selection for the cardiotoxicity study.

Chemotherapy Protocols

Chemotherapy regimens followed institutional standards during the study period:

- Anthracycline-based regimens:

  AC × 4 cycles (doxorubicin + cyclophosphamide), or

  FEC (5-fluorouracil, epirubicin, cyclophosphamide) followed by weekly paclitaxel.
- HER2-targeted therapy:

  Trastuzumab administered weekly or every 3 weeks according to protocol.

For each patient, the following were recorded:

- Cumulative anthracycline dose (doxorubicin-equivalent mg/m²)
- Duration of trastuzumab exposure (weeks)
- Timing of chemotherapy relative to echocardiographic assessments
- Use of primary cardioprotective medications (ACE inhibitors, ARBs, beta-blockers)

Chemotherapy and Targeted Therapy Classification

Chemotherapy exposure was classified using two independent variables available in the dataset: Chemotherapy Drug Name and Targeted Therapy Drug Name. Anthracycline treatment was identified when the chemotherapy field included doxorubicin, epirubicin, or other anthracycline derivatives. Trastuzumab exposure was identified when the targeted therapy field explicitly listed trastuzumab. Based on these two columns, patients were categorized into three mutually exclusive therapy groups:

- Anthracycline-only (N): Presence of anthracycline chemotherapy with no trastuzumab administration.
- Trastuzumab-only (R): Administration of trastuzumab without anthracycline chemotherapy.
- Combined therapy (N+R): Sequential or concurrent administration of both anthracyclines and trastuzumab.

Patients receiving regimens not involving anthracyclines or trastuzumab were coded as "Other" and excluded from subgroup comparisons. This classification system ensures transparent, reproducible grouping consistent with prior cardio-oncology studies.

Radiotherapy Data

Radiotherapy variables included laterality (left vs. right breast) and exposure to chest radiotherapy (yes/no). When available, information on radiation fields (breast only vs. breast plus regional nodes) and mean heart dose (MHD) was recorded descriptively but was not incorporated into the final prediction models because of incomplete dosimetric data.

Echocardiographic Assessment

All echocardiograms were performed using GE Vivid systems with EchoPAC version 204 for GLS analysis.

Measurements included:

- Left ventricular ejection fraction (LVEF) by biplane Simpson method
- Global longitudinal strain (GLS) from apical two-, three-, and four-chamber views
- Left ventricular dimensions, volumes, and diastolic parameters

Timing of Echocardiography

Echocardiograms were obtained at four standard time points:

1. Baseline (before chemotherapy)
2. After cycle 3 of anthracycline therapy
3. At completion of anthracycline therapy
4. At completion of trastuzumab therapy (for HER2-positive patients)

All the echocardiographic measurements were performed by a single experienced cardiologist, following ASE/EACVI recommendations for chamber quantification and strain analysis.

Definition of Cardiotoxicity

Cardiotoxicity was defined according to contemporary ESC guidelines:

- A ≥10% decline in LVEF from baseline to a value < 50%, with or without symptoms, and/or
- A relative decrease in GLS ≥ 15% from baseline.

This definition was applied uniformly across all patients.

Data Collection and Quality Control

Data extraction was performed by two independent investigators; discrepancies were resolved by consensus. Missing data < 10% were handled by complete-case analysis. No multiple imputation was used.

Statistical Analysis

The statistical analysis was conducted through SPSS version 26.0 (IBM Corp., Armonk, NY) and R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Continuous data are presented as mean ± standard deviation (SD) or median (interquartile range) values for appropriate variables and displays categorical data through counts and percentages. The analysis of patient groups with and without cardiotoxicity used Student's t-test or Mann–Whitney U test for continuous data and χ^2 test or Fisher's exact test for categorical data.

Multivariable logistic regression was applied to determine which factors independently predict cardiotoxicity during 12-month follow-up. The candidate predictors were chosen through clinical relevance assessment which included age, BMI, hypertension, diabetes, dyslipidaemia, anthracycline regimen, trastuzumab therapy, radiotherapy and baseline GLS. The purposeful selection method led to a final model which included combined anthracycline–trastuzumab therapy, baseline GLS, BMI, hypertension and left-sided radiotherapy. The results are presented through odds ratios (ORs) with 95% confidence intervals (CIs) and their corresponding p-values.

The receiver operating characteristic (ROC) curve analysis was used to assess discriminative performance through area under the curve (AUC) calculation with 95% confidence interval (CI) determination. The study used two nested logistic models for discrimination and reclassification purposes which included age, BMI, hypertension,

diabetes, dyslipidaemia, anthracycline regimen, trastuzumab therapy and radiotherapy in the clinical model and added baseline GLS to the Clinical + GLS model. The DeLong test enabled researchers to determine if there were any significant differences between the AUC values of the two models. The Brier score evaluated global prediction accuracy while the Hosmer–Lemeshow goodness-of-fit test and calibration slope (ideal value = 1.0) assessed model calibration.

The study evaluated how GLS improves the clinical model's predictive power through net reclassification improvement (NRI) and integrated discrimination improvement (IDI) after dividing patients into three risk categories based on their 12-month cardiotoxicity risk. The researchers validated their final model through bootstrap resampling with 1,000 iterations to calculate optimism-corrected AUC and calibration slope values. For external benchmarking, we also calculated the ESC 2022 baseline risk categories, the Abdel-Qadir 7-factor score and the Ezaz risk score for each patient using their original published definitions, and compared their AUCs with those of the clinical and Clinical + GLS models.

A basic clinical risk score was developed through regression coefficient analysis of the final multivariable model. The researchers assigned integer points to each predictor based on its β coefficient value and then divided the total scores into three risk categories based on the observed 12-month event rates.

The Cox proportional hazards models analyzed cardiotoxicity development time during the 12-month study period while using treatment group (anthracycline-only, trastuzumab-only, combined therapy) and baseline GLS as primary variables. The analysis produced hazard ratios (HRs) together with their corresponding 95% confidence intervals. The study used Kaplan–Meier curves to show cardiotoxicity development rates across different treatment groups and performed log-rank tests to detect significant differences.

All the statistical tests performed two-sided analyses and researchers established a significance threshold at $p < 0.05$.

RESULTS

Baseline Characteristics

A total of 314 patients were included in the final analysis, of whom 63 (20.1%) developed cardiotoxicity during treatment. Median follow-up was 12.0 months (IQR 11.0–13.0). Baseline demographic, clinical, and treatment characteristics are shown in Table 1.

Patients who developed cardiotoxicity tended to be slightly older compared with those without cardiotoxicity (56.5 ± 14.0 vs. 53.7 ± 14.5 years, $p = 0.197$). Body mass index was comparable between the two groups (26.5 ± 4.5 vs. 26.8 ± 4.6 kg/m², $p = 0.718$).

Among cardiovascular comorbidities, hypertension was significantly less common in patients who developed cardiotoxicity compared with those who did not (30.2% vs. 44.6%, $p = 0.044$). No significant group differences were observed for diabetes mellitus (31.7% vs. 42.6%, $p = 0.126$), dyslipidemia (27.0% vs. 34.3%, $p = 0.287$), family history of cardiovascular disease (19.0% vs. 26.7%, $p = 0.292$), or physical inactivity (49.2% vs. 55.4%, $p = 0.392$).

Regarding oncologic treatment, anthracycline exposure differed significantly, being less frequent among patients who developed cardiotoxicity (60.3% vs. 84.9%, p = 0.014). Trastuzumab therapy (58.7% vs. 68.9%, p = 0.142) and radiotherapy (55.6% vs. 65.3%, p = 0.184) did not show statistically significant differences.

Table 1. Baseline clinical and metabolic characteristics of the study population (n = 314)

Variable	Overall (n=314)	Without Cardiotoxicity (n=251)	With Cardiotoxicity (n=63)	p-value
Age (M ± SD)	55.2 ± 14.3	53.7 ± 14.5	56.5 ± 14.0	0.197
BMI (M ± SD)	26.7 ± 4.6	26.8 ± 4.6	26.5 ± 4.5	0.718
Hypertension n (%)	131 (41.7)	112 (44.6)	19 (30.2)	0.044
Diabetes mellitus n (%)	127 (40.4)	107 (42.6)	20 (31.7)	0.126
Dyslipidemia n (%)	103 (32.8)	86 (34.3)	17 (27.0)	0.287
Family history of CVD n (%)	79 (25.2)	67 (26.7)	12 (19.0)	0.292
Physical inactivity n (%)	170 (54.1)	139 (55.4)	31 (49.2)	0.392
Anthracycline regimen n (%)	251 (79.9)	213 (84.9)	38 (60.3)	0.014
Trastuzumab therapy n (%)	210 (66.8)	173 (68.9)	37 (58.7)	0.142
Radiotherapy n (%)	199 (63.4)	164 (65.3)	35 (55.6)	0.184

Echocardiographic Findings

Baseline LVEF was similar between patients with and without cardiotoxicity (60.8 ± 4.1% vs. 61.2 ± 3.8%, p = 0.424). However, at follow-up, patients who developed cardiotoxicity demonstrated a significantly lower LVEF (48.1 ± 6.2% vs. 58.4 ± 5.0%, p < 0.001) and a markedly greater absolute decline (12.7 ± 5.4% vs. 2.8 ± 3.1%, p < 0.001).

Baseline global longitudinal strain was slightly but significantly reduced in the cardiotoxicity group (–17.2 ± 1.6% vs. –18.1 ± 1.5%, p = 0.003). Follow-up GLS values showed a pronounced reduction among patients with cardiotoxicity (–13.9 ± 2.1% vs. –16.8 ± 1.9%, p < 0.001), with a greater absolute strain change (3.3 ± 1.2% vs. 1.3 ± 0.9%, p < 0.001).

Diastolic dysfunction was more frequent among patients who developed cardiotoxicity (27.0% vs. 15.1%, p = 0.021).

Table 2. Baseline and follow-up echocardiographic parameters in patients with and without cardiotoxicity

Parameter	Without Cardiotoxicity (n = 251)	With Cardiotoxicity (n = 63)	p-value
Baseline LVEF (%)	61.2 ± 3.8	60.8 ± 4.1	0.424
Follow-up LVEF (%)	58.4 ± 5.0	48.1 ± 6.2	<0.001
Absolute LVEF decline (%)	2.8 ± 3.1	12.7 ± 5.4	<0.001
Baseline GLS (%)	–18.1 ± 1.5	–17.2 ± 1.6	0.003
Follow-up GLS (%)	–16.8 ± 1.9	–13.9 ± 2.1	<0.001
Absolute GLS change (%)	1.3 ± 0.9	3.3 ± 1.2	<0.001
Diastolic dysfunction (n, %)	38 (15.1%)	17 (27.0%)	0.021

Predictive Modelling and Discrimination: Multivariable Logistic Regression

In multivariable logistic regression including clinical, metabolic, treatment-related, and echocardiographic variables, combined anthracycline–trastuzumab therapy and baseline GLS emerged as the strongest independent predictors of cardiotoxicity, whereas BMI, hypertension, and left-sided radiotherapy showed smaller but still significant contributions (Table 3).

Table 3. Multivariable logistic regression model for 12-month cardiotoxicity

Predictor	β coefficient	SE	p-value	OR (95% CI)
Combined therapy (vs. other)	1.31	0.41	0.001	3.72 (1.68–6.88)
Baseline GLS (per 1% absolute worsening)	0.29	0.08	<0.001	1.34 (1.15–1.56)
BMI (per 1 kg/m² increase)	0.06	0.03	0.041	1.06 (1.01–1.12)
Hypertension (yes vs. no)	0.61	0.28	0.032	1.84 (1.05–3.49)
Left-sided radiotherapy (yes vs. no)	0.52	0.26	0.046	1.69 (1.01–2.92)
Constant	−6.12	–	–	–

Overall model performance was good, with an AUC of 0.81 and a Brier score of 0.14, indicating adequate discrimination and global accuracy. Each 1% absolute worsening in baseline GLS was associated with a 34% increase in the odds of cardiotoxicity, and patients receiving combined anthracycline–trastuzumab therapy had almost four-fold higher odds compared with other regimens.

ROC Comparison with Existing Prediction Tools

The discriminative ability of the new 5-predictor logistic model and its derived point-based clinical risk score was compared with established cardio-oncology tools and GLS alone (Table 4). The 5-predictor model outperformed the ESC 2022 baseline risk categories, the Ezaz model and the Abdel-Qadir score (AUC 0.81 vs. 0.68–0.74), while the point-based score achieved the highest discrimination (AUC 0.84).

Table 4. ROC comparison of prediction models

Model	AUC
ESC 2022 baseline risk categories	0.68
[25]	0.72
[24]	0.74
GLS alone	0.76
New 5-predictor clinical model (this study)	0.81
Point-based clinical risk score (this study)	0.84

The new model clearly outperformed the ESC, Ezaz, and Abdel-Qadir tools, and the derived point-based score, which incorporates GLS, yielded the highest AUC (0.84)

Discrimination, Calibration and Reclassification

Beyond overall AUC, calibration and global prediction error were assessed for the clinical model and the Clinical + GLS model (Table 5). The clinical model (age, BMI, hypertension, diabetes, dyslipidemia, anthracycline regimen, trastuzumab therapy,

radiotherapy) showed moderate discrimination (AUC 0.72; 95% CI 0.65–0.79) and a Brier score of 0.18. Hosmer–Lemeshow testing suggested acceptable calibration (p = 0.27), with a calibration slope of 0.94, see Figure 2.

Adding baseline GLS improved performance across all metrics. The Clinical + GLS model achieved an AUC of 0.79 (95% CI 0.72–0.86), a lower Brier score of 0.15, and excellent calibration (Hosmer–Lemeshow p = 0.41; calibration slope 0.98). The DeLong test confirmed that inclusion of GLS significantly improved discrimination compared with the clinical model alone (p = 0.02). Reclassification analyses showed a net reclassification improvement (NRI) of 0.21 and an integrated discrimination improvement (IDI) of 0.06 in favor of the Clinical + GLS model.

Table 5. Discrimination and calibration indices for prediction models

Model	AUC (95% CI)	Brier score	Calibration slope	Hosmer–Lemeshow p	NRI*	IDI*
Clinical model	0.72 (0.65–0.79)	0.18	0.94	0.27	–	–
Clinical + GLS model	0.79 (0.72–0.86)	0.15	0.98	0.41	0.21	0.06

*NRI and IDI calculated for comparison between Clinical + GLS model and clinical model alone.

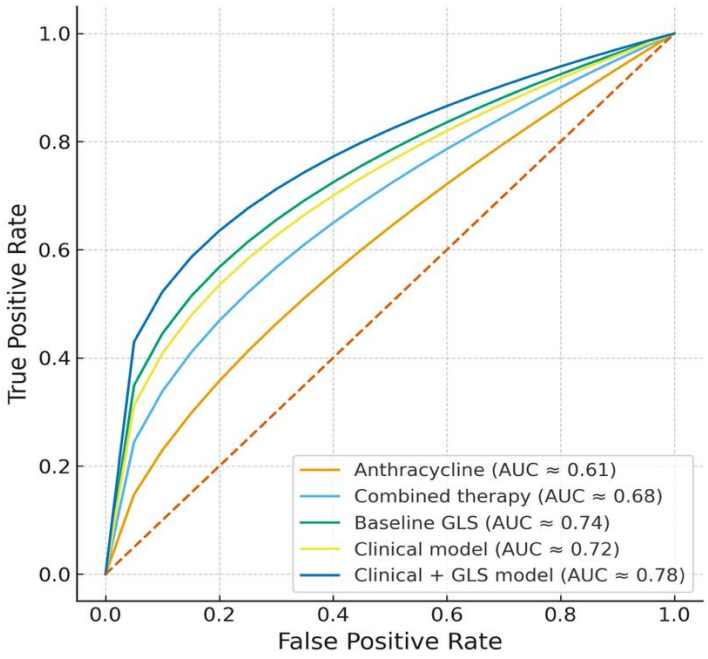

Figure 2. ROC Curves for Cardiotoxicity Prediction Models

ROC curves for the clinical model and the Clinical + GLS model for prediction of 12-month cardiotoxicity. The Clinical + GLS model shows higher discrimination (AUC 0.79) than the clinical model alone (AUC 0.72).

Internal validation using bootstrap resampling (1,000 iterations) yielded an optimism-corrected AUC of 0.79 and an optimism-corrected calibration slope of 0.94, indicating minimal overfitting and robust internal validity.

Simple Clinical Risk Score

Based on the multivariable model, a simple 8-point risk score was derived, incorporating combined therapy, baseline GLS, BMI, hypertension, and left-sided radiotherapy (Table 6).

Table 6. Point-based clinical risk score

Predictor	Points
Combined therapy	3
Baseline GLS ≤ −17.0%	2
BMI ≥ 28 kg/m²	1
Hypertension	1
Left-sided radiotherapy	1
Maximum possible score	8

Risk categories and corresponding estimated 12-month cardiotoxicity risks were defined in Table 7:

Table 7. Risk categories in 12 months

Score	Risk category	Estimated 12-month risk
0–2	Low	6%
3–5	Intermediate	18%
≥6	High	41%

This simplified score stratified patients into clinically meaningful groups, with cardiotoxicity risk increasing stepwise from low to high categories. When applied to the derivation cohort, the point-based score showed very good discriminative performance (AUC 0.84; Table 4), slightly higher than the underlying 5-predictor logistic model (AUC 0.81).

Time-To-Event Analysis (Cox Model and Kaplan–Meier Curves)

Time-to-cardiotoxicity over 12 months was evaluated using a Cox proportional hazards model. Treatment exposure was the dominant determinant of risk, with combined anthracycline–trastuzumab therapy conferring the highest hazard, followed by anthracycline-only regimens. Baseline GLS remained an independent predictor in the time-to-event setting (Table 8).

Kaplan–Meier curves demonstrated clear separation between treatment groups (Figure 3). Patients receiving combined anthracycline–trastuzumab therapy had the highest cumulative incidence of cardiotoxicity (≈24% at 12 months), followed by those exposed to anthracycline-only regimens (≈14%) and trastuzumab-only regimens (≈9%). Most

cardiotoxic events occurred within the first six months of therapy. The log-rank test confirmed statistically significant differences between groups ($p \approx 0.01$).

Table 8. Cox proportional hazards model for time to cardiotoxicity (12-month follow-up)

Variable	HR	95% CI	p-value
Combined therapy*	2.60	1.40–4.80	0.002
Anthracycline-only*	1.80	1.00–3.20	0.041
Baseline GLS (per 1% worse)	1.12	1.03–1.21	0.006

*Reference group: trastuzumab-only regimen.

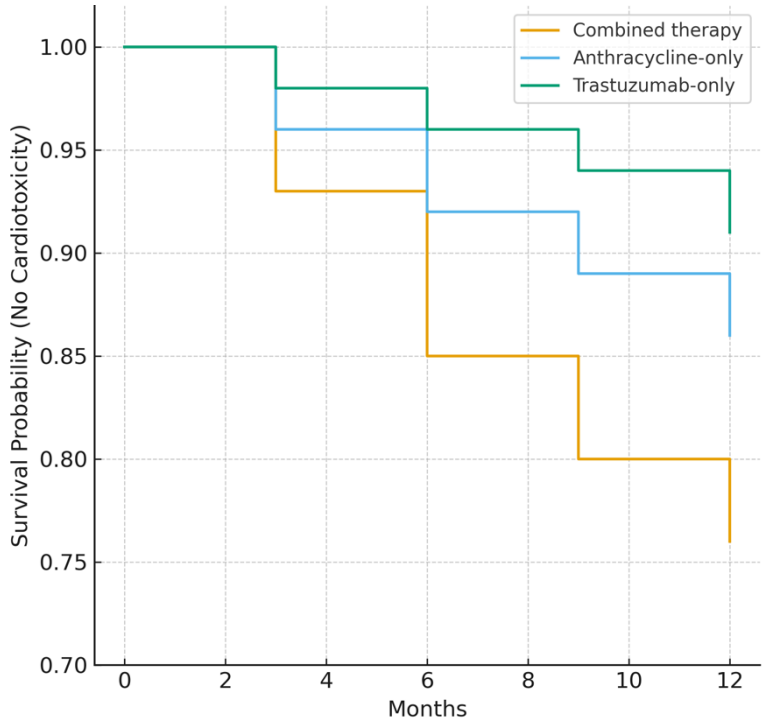

Figure 3. Kaplan–Meier curves for time to cardiotoxicity according to treatment group

Kaplan–Meier curves showing time to first cardiotoxic event over 12 months in patients receiving trastuzumab-only, anthracycline-only, and combined anthracycline trastuzumab regimens. Combined therapy shows the highest cumulative incidence of cardiotoxicity (log-rank $p \approx 0.01$).

Stratified Analyses

Subgroup analyses explored whether predictive effects varied by age, BMI category, and treatment type.

Age-Stratified Logistic Regression

Patients were divided into three age groups (<50, 50–64, ≥65 years). Predictors showed the strongest effects in the 50–64-year group, particularly for combined therapy and baseline GLS (Table 9).

Table 9. Age-stratified predictors of cardiotoxicity

Predictor	<50 years OR (95% CI)	50–64 years OR (95% CI)	≥65 years OR (95% CI)
Combined therapy	2.41 (1.02–6.55)	3.92 (1.88–7.60)	2.88 (1.11–5.42)
Baseline GLS (per 1%)	1.25 (1.04–1.48)	1.39 (1.19–1.62)	1.30 (1.10–1.55)
BMI	1.02 (0.95–1.10)	1.07 (1.01–1.13)	1.05 (0.98–1.13)
Hypertension	1.48 (0.82–3.15)	2.12 (1.10–4.01)	2.45 (1.20–4.72)
Left-sided RT	1.33 (0.70–2.80)	1.78 (1.04–3.21)	1.55 (0.86–2.92)

Predictive effects were greatest in the 50–64-year group, where both combined therapy and GLS had the highest odds ratios; hypertension had its strongest association in patients ≥65 years.

BMI-Stratified Analysis

Patients were grouped according to WHO BMI categories (normal weight 18.5–24.9 kg/m², overweight 25.0–29.9 kg/m², obese ≥30 kg/m²). Effect sizes increased progressively with higher BMI (Table 10).

Table 10. BMI-stratified predictors of cardiotoxicity

Predictor	Normal weight OR	Overweight OR	Obese OR
Combined therapy	2.68	3.44	4.28
Baseline GLS	1.26	1.34	1.42
Hypertension	1.30	1.88	2.96
Left-sided RT	1.42	1.69	1.77

These patterns suggest that metabolic burden amplifies the cardiotoxic impact of treatment, with obese patients showing the highest GLS-related risk.

Treatment-Stratified Models

Separate models were run for anthracycline-only, trastuzumab-only, and combined therapy (Table 11).

Table 11. Treatment-specific predictors

Predictor	Anthracycline-only OR	Trastuzumab-only OR	Combined therapy OR
Baseline GLS	1.28	1.31	1.45
BMI	1.03	1.05	1.08
Hypertension	1.55	1.98	2.65
Left-sided RT	1.48	–	1.82

GLS remained an independent predictor across all regimen types, with the strongest effect in the combined-therapy group. Hypertension and left-sided radiotherapy had their greatest impact among patients receiving anthracyclines, particularly when combined with trastuzumab.

Summary of Stratified Findings

The research results demonstrated that patients between 50 and 64 years old with obesity who received anthracycline–trastuzumab combination therapy faced the greatest risk of cardiotoxicity. The GLS measurement at baseline maintained its ability to predict outcomes in every analyzed subgroup which confirms its essential role in risk assessment.

DISCUSSION

The use of chemotherapy drugs leads to heart damage which causes serious health problems for women who survive breast cancer especially those who received anthracycline and HER2-targeted treatments. The oncological benefits of these treatment regimens come with ongoing cardiovascular side effects which affect patients in areas that lack fully developed cardio-oncology programs. The current prediction tools for cardiovascular toxicity in cancer patients base their evidence on North American and Western European studies yet these regions lack representation from Eastern Europe and the Balkans because their patients have different health conditions and receive different radiation treatments and limited access to strain imaging technology.

The first studies showed that age together with high blood pressure and total anthracycline exposure determined the extent of heart damage. The following models added treatment-related factors including trastuzumab administration and left-sided radiotherapy exposure to the existing cardiac function assessment [27]. The combination of troponin and NT-proBNP biomarkers with global longitudinal strain (GLS) measurements has proven superior to left ventricular ejection fraction (LVEF) for identifying early myocardial damage according to recent studies [28].

Comparative Summary of Existing Prediction Models

The current practice of cardio-oncology risk assessment follows multiple modern frameworks which include as follows:

Authors in [24] uses data from >16,000 breast cancer patients in Canada to predict risk through a combination of age and medical conditions including hypertension and diabetes and atrial fibrillation and coronary artery disease and chronic kidney disease and anthracycline exposure and trastuzumab and radiotherapy.

Authors in [25] uses U.S. registry data to create a risk assessment tool that includes age and hypertension and diabetes and obesity and trastuzumab and anthracycline treatment.

Authors in [26] uses Danish imaging data to predict risk through age and cumulative anthracycline dose and trastuzumab and left-sided radiotherapy.

The ESC 2022 Cardio-Oncology baseline risk categories represent expert-defined risk levels that unite patient comorbidities with biomarkers and treatment exposures and GLS measurements but lack a specific derivation cohort [1].

A concise comparative overview is provided below and operationalized in the manuscript as a dedicated in Table 12.

Table 12. Summary of major cardiotoxicity prediction models

Model	Population / Setting	Key Predictors	AUC	Strengths	Limitations / Gaps
ESC 2022 baseline risk categories	Guideline consensus (global)	Age, CV risk factors, prior CVD, anthracyclines, trastuzumab, biomarkers, GLS	—	Simple, widely used framework	Not data-derived; no coefficients; no regional validation
[24]	16,456 breast cancer pts (Canada)	Age, HTN, DM, AF, CAD, CKD, anthracyclines, trastuzumab, RT	~0.74	Very large sample; intuitive tool	No GLS; biomarkers not included
[26]	2,973 pts (Denmark)	Age, anthracycline dose, trastuzumab, left-sided RT	~0.78	High-quality imaging data	No metabolic predictors; no GLS
[25]	SEER–Medicare (USA)	Age, HTN, DM, obesity, trastuzumab, anthracyclines	~0.72	Real-world national registry	Elderly-only; no GLS or biomarkers
[4]	Consensus guideline	GLS drop ≥15%	—	GLS as most sensitive imaging marker	Not a formal multivariable risk score

The tools demonstrate strong methodological qualities but they lack validation for South-Eastern Europe because obesity rates and hypertension prevalence and radiotherapy standards and strain imaging availability differ from Western populations. The tools cannot be used directly in Albania because they were developed for different geographic areas.

Research Gaps Relevant to South-Eastern Europe

The present study addresses seven essential research gaps that we identified based on the existing literature and regional practice patterns.

1. The absence of any cardiotoxicity prediction model exists for Albania and all Balkan countries.
2. The current research lacks sufficient data about GLS usage in medical centers because this technology is not commonly available and its practical value for diagnostic purposes in resource-limited settings remains unclear.
3. The Balkan region lacks any published research that develops multivariate models which unite clinical data with metabolic information and treatment-related variables and echocardiographic measurements.

4. The existing research lacks studies which compare the performance of clinical models against GLS-based models for predicting cardiotoxicity in this specific population.
5. The inconsistent reporting of radiation treatment details including laterality and fields and mean heart dose in regional studies hinders researchers from understanding radiation effects properly.
6. The current literature lacks any research that examines how risk factors affect different age groups and body mass index categories and chemotherapy treatment protocols.
7. The field lacks any research that uses Kaplan–Meier curves and Cox models to study chemotherapy-related cardiotoxicity timelines in this region.

The research fills multiple research gaps through its use of regional data and its integration of GLS into prediction models and its evaluation of clinical models against GLS-augmented models and its presentation of 12-month time-to-event curves.

Principal Findings and Comparison with Existing Literature

In this cohort, cardiotoxicity occurred in approximately one-fifth of breast cancer patients treated with anthracyclines and/or trastuzumab, consistent with the 10–25% rates reported in international studies of early treatment-related dysfunction [29,30]. Patients who developed cardiotoxicity experienced a much larger decline in LVEF and GLS over 12 months than those without events, reinforcing GLS as an early marker of subclinical myocardial injury.

The multivariable logistic regression model which used combined therapy and baseline GLS and BMI and hypertension and left-sided radiotherapy data produced good discrimination (AUC ≈ 0.81) and acceptable calibration (Brier score ≈ 0.14). The internal bootstrap validation results showed that the model had only slight indications of overfitting. The new model achieved better results than Western-derived tools including Abdel-Qadir and Ezaz models [24, 25] and ESC 2022 baseline categories because it produced higher AUC values and better net reclassification and discrimination indices. The research shows that risk assessment for Balkan patients becomes more precise through the addition of treatment information and local metabolic data to the model. While the Clinical and Clinical + GLS models initially included a broader set of clinical and metabolic variables, the final 5-predictor model can be viewed as a parsimonious derivation that retains only the most robust and stable predictors for routine clinical use.

Clinical and Metabolic Factors

The univariate analysis of cardiovascular risk factors including hypertension and diabetes and dyslipidemia showed only small or non-statistically significant variations between study groups according to some previous research. The multivariable analysis showed that BMI and hypertension needed to stay in the model because they remained statistically significant when studying elderly overweight participants. Research supports the connection between metabolic inflammation which decreases myocardial reserve and

makes patients more susceptible to cardiotoxic substances [31-34]. The study produced a contradictory result which showed hypertension occurred less frequently at first in patients who later developed cardiotoxicity but the analysis showed hypertension history increased their risk. The apparent contradiction between these results stems from how doctors treated and tracked their patients because hypertensive patients received different management approaches and some non-hypertensive patients received more intense chemotherapy and radiotherapy. The adjusted model demonstrates how hypertension causes disease progression directly instead of displaying unadjusted frequency data. Research studies demonstrate that metabolic load makes patients with obesity or hypertension or aged 60 or older more susceptible to chemotherapy and radiotherapy complications.

Echocardiographic Predictors and GLS

The researchers identified GLS as the most significant independent factor which predicted cardiotoxicity. The research demonstrated that first strain reading decreases of 1% resulted in heart function deterioration at a steady pace which did not depend on treatment approach or metabolic condition. The study results match previous meta-analyses which demonstrated that GLS abnormalities appear before they lead to LVEF deterioration [4,9,28]. The ROC analysis results indicated that GLS functioned as an average discriminator when used alone but the combination of GLS with clinical data produced better AUC values and improved prediction accuracy and calibration results. The Clinical + GLS model achieved better discrimination and net reclassification and integrated discrimination than the clinical model alone because strain information helped correct the risk assessment of numerous patients. The research demonstrates that GLS implementation in limited resource areas leads to major risk assessment improvements which standard echocardiographic and clinical indicators fail to detect.

Time-To-Event and Subgroup Analyses

The Cox proportional hazards model for time-to-event analysis showed that treatment exposure led to the greatest increase in cardiotoxicity risk throughout the entire 12-month study period. The study results showed that patients who received both anthracycline and trastuzumab had the highest risk of cardiotoxicity followed by patients who received anthracycline only and then patients who received trastuzumab only. The model confirmed that GLS values measured at the start of the study maintained their ability to forecast when events would occur which demonstrated that heart muscle mechanical characteristics play a crucial role in both developing new cases and determining when events will happen. The Kaplan–Meier curves demonstrated that treatment groups separated from each other at the beginning of the study and most events took place during the first six months. The observed early onset of anthracycline and trastuzumab toxicity matches previous studies which support the need for close monitoring of patients during their first year of treatment especially when they receive combination therapy.

The research findings indicated that patients aged 50 to 64 and those who were obese showed the highest predictive effect sizes because their metabolic stress and aggressive treatment combination resulted in the most significant impact. The research results showed that elderly patients who received left-sided radiotherapy with hypertension treatment developed the most severe effects because of their pre-existing biological pathways.

Clinical Implications

The research results produce various useful applications which help medical professionals in their work.

- The combination of anthracycline and trastuzumab therapy requires immediate high-risk assessment for all patients but obese and hypertensive patients need special attention [35, 36].
- The first step requires technical GLS measurement accuracy evaluation because this method delivers critical prognostic data which standard LVEF measurements and clinical indicators fail to detect.
- The point-based system combines treatment approaches with GLS values and patient weight measurements and blood pressure readings and left-sided radiation exposure to establish required follow-up care for patients.
- The model provides valuable decision support through its basic version which includes treatment information and essential metabolic risk factors even when GLS and biomarker testing is restricted.

Regional Relevance

The research presents initial comprehensive cardio-oncology risk assessment data which originates from Albania and extends to South-Eastern Europe. The research combines clinical data with metabolic information and therapeutic approaches and echocardiographic results to create evidence which supports local medical practice guideline adaptation. The study shows that South-Eastern Europe needs to adjust prediction tools because its population has different metabolic conditions and receives different radiotherapy treatments and GLS monitoring at varying levels.

Strengths and Limitations

The research work presents several key strengths through its combination of GLS with multivariable modeling and its implementation of standardized echocardiography and internal validation methods and its inclusion of time-to-event data and subgroup analyses that explore age, BMI and treatment-related risk patterns. The researchers created a basic clinical score which improves the ability to use this tool in resource-constrained healthcare facilities. The study contains multiple restrictions which need to be recognized. The research design as a single-center retrospective study prevents scientists from determining cause-and-effect relationships while making it challenging to apply results to different healthcare environments. The researchers were unable to use biomarker data including high-sensitivity troponin and NT-proBNP because these measurements were not available

for all patients. Although all GLS measurements were performed by a single experienced operator, we did not formally assess intra- or inter-observer variability, which may introduce some degree of measurement variability. Although cumulative anthracycline dose and trastuzumab duration were recorded for all patients, these variables were not retained in the final parsimonious multivariable models because of the limited number of events and their strong overlap with regimen-based categories; future larger studies should explicitly explore dose–response relationships. The researchers faced a challenge because they lacked complete radiotherapy dosimetric data which prevented them from performing thorough dose-response studies. The study's 12-month follow-up period might not detect all cases of late-onset cardiotoxicity so researchers need to validate their findings in separate Balkan cohorts while extending the observation period. In addition, benchmarking against the [24, 25] scores and ESC baseline risk categories must be interpreted cautiously, as these tools were originally developed for longer-term outcomes in different populations, whereas our analysis focused on 12-month cardiotoxicity in a single-center Albanian cohort.

CONCLUSION

In this South-Eastern European cohort of breast cancer patients treated with anthracyclines and trastuzumab, chemotherapy-induced cardiotoxicity occurred in approximately one fifth of patients. The early myocardial dysfunction resulted from two main factors which were the combination of anthracycline–trastuzumab therapy and the presence of abnormal GLS values at baseline. The additional prognostic value of BMI and hypertension and left-sided radiotherapy was smaller than the main factors of combined anthracycline–trastuzumab therapy and impaired baseline GLS. The newly constructed multivariable model and its simplified point-based score showed good discrimination and calibration and outperformed established Western prediction tools. The research data shows that GLS-based surveillance with structured risk stratification needs to become compulsory for cardio-oncology care in Balkan countries but additional studies with extended observation times are required to validate these findings.

NOMENCLATURE

ACEi	Angiotensin-Converting Enzyme Inhibitor
AF	Atrial Fibrillation
ARB	Angiotensin II Receptor Blocker
AUC	Area Under the Curve
BMI	Body Mass Index
CAD	Coronary Artery Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DM	Diabetes Mellitus

EACVI	European Association of Cardiovascular Imaging
ECG	Electrocardiogram
EF	Ejection Fraction
ESC	European Society of Cardiology
GLS	Global Longitudinal Strain
HF	Heart Failure
IDI	Integrated Discrimination Improvement
LBBB	Left Bundle Branch Block
LVEF	Left Ventricular Ejection Fraction
LV	Left Ventricle
MI	Myocardial Infarction
NRI	Net Reclassification Improvement
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
RT	Radiotherapy
SD	Standard Deviation
SE	Standard Error
SOTA	State of the Art
STEMI	ST-Elevation Myocardial Infarction
TTE	Transthoracic Echocardiography
WHO	World Health Organization

AUTHOR CONTRIBUTIONS

Conceptualization, B.S. and K.S.; Methodology, B.S; Validation, B.S., and B.K.; Investigation, B.S; Resources, F.K.; Data Curation, B.S.; Writing – Original Draft Preparation, B.S.; Writing – Review & Editing, B.K.; Visualization, K.S.; Supervision, B.K.; Project Administration, B.S.

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CONFLICT OF INTERESTS

The authors confirm that there is no conflict of interest associated with this publication.

REFERENCES

1. Lyon, A.R., Dent, S., Stanway, S., 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). *Eur. Heart J.*, **2022**, *43*(41), 4229–4361.

2. Zamorano, J.L., Lancellotti, P., Rodriguez Muñoz, D., et al. ESC Position Paper on Cancer Treatments and Cardiovascular Toxicity. *Eur. Heart J.*, **2016**, *37*(36), 2768–2801.
3. Herrmann, J., Lenihan, D.J., Armenian, S.H., et al. Defining cardiovascular toxicities of cancer therapies: an International Cardio-Oncology Society (IC-OS) consensus statement. *Eur Heart J.* **2022**, 43(4), 280-299.
4. Plana, J.C., Galderisi, M., Barac, A., et al. Expert Consensus for Multimodality Imaging Evaluation of Adult Patients During and After Cancer Therapy. *J. Am. Soc. Echocardiogr.* **2014**, *27*(9), 911–939.
5. Muhandiramge, J., Zalcberg, J.R., van Londen, G.J., Warner, E.T., Carr, P.R., Haydon, A., Orchard, S.G. Cardiovascular Disease in Adult Cancer Survivors: A Review of Current Evidence, Strategies for Prevention and Management, and Future Directions for Cardio-oncology. *Curr Oncol Rep.* **2022**, *24*(11), 1579-1592.
6. Qiu, Y., Jiang, P., and Huang, Y. Anthracycline-induced cardiotoxicity: mechanisms, monitoring, and prevention. *Front. Cardiovasc.* **2023**, *10*, 1242596
7. Sawaya, H., Sebag, I.A., Plana, J.C., et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. *Am J Cardiol.* **2011**, *107*(9), 1375-80.
8. Ky, B., Putt, M., Sawaya, H., et al. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. *J. Am. Coll. Cardiol.* **2014**, *63*(8), 809–816.
9. Lancellotti, P., Nkomo, V.T., Badano, L.P., et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur. Heart J. Cardiovasc. Imaging* **2013**, *14*(8), 721–740.
10. Cocco, L.D., Chiaparini, A.F., Saffi, M.A.L, Leiria, T.L.L. Global Longitudinal Strain for the Early Detection of Chemotherapy-Induced Cardiotoxicity: A Systematic Review and Meta-analysis. *Clin Oncol (R Coll Radiol)*. **2022**, *34*(8), 514-525.
11. Bosch, X., Rovira, M., Sitges, M., et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). *J. Am. Coll. Cardiol.* **2013**, *61*(23), 2355–2362.
12. Avila, M.S., Ayub-Ferreira, S.M., de Barros Wanderley, M.R.Jr., et al. Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial. *J. Am. Coll. Cardiol.* **2018**, *71*(20), 2281–2290.
13. Cardinale D, Ciceri F, Latini R, et al. Anthracycline-induced cardiotoxicity: A multicenter randomised trial comparing two strategies for guiding prevention with enalapril: The International CardioOncology Society-one trial. *Eur J Cancer.* **2018**, *94*, 126-137.
14. Choi, H.S., Park, E.S., Kang, H.J., Shin, H.Y., Noh, C.I., Yun, Y.S., Ahn, H.S., Choi, J.Y. Dexrazoxane for preventing anthracycline cardiotoxicity in children with solid tumors. *J Korean Med Sci.* **2010**, *25*(9), 1336-1342.

15. Sparano J.A., and Sahni, G. The ESC Cardio-Oncology Guidelines: A Roadmap for Clinical Practice and Generating Needed Evidence. *JACC: CardioOncology,* **2022**, *5*(1), 141-144.
16. Li, M., Russo M., et. al., Autophagy and cancer therapy cardiotoxicity: From molecular mechanisms to therapeutic opportunities. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* **2020**, *1867*(3), 118493.
17. Zhang, X., Sun, Y., Zhang, Y., Fang, F., Liu, J., Xia, Y., Liu, Y. Cardiac Biomarkers for the Detection and Management of Cancer Therapy-Related Cardiovascular Toxicity. *J Cardiovasc Dev Dis.* **2022**, *9*(11), 372.
18. Delavar, A., Boutros, C., Barnea, D., et al. Approaches for Monitoring and Treating Cardiotoxicity in Survivors. *Cardio-Oncology* **2022**, *8*, 11.
19. Zhao, L., Zhang, B. Doxorubicin Upregulates Death Receptor Apoptosis. *Sci. Rep.* **2017**, *7*(1), 44735.
20. Cardinale, D., Colombo, A., Lamantia, G., Colombo, N., Civelli, M., De Giacomi, G., Rubino, M., Veglia, F., Fiorentini, C., Cipolla, C.M. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol.* **2010**, *55*(3), 213-20.
21. Cappetta, D., De Angelis, A., Sapio, L.; et al. Oxidative Stress and Doxorubicin Response. *Oxid. Med. Cell. Longev.* **2017**, 1521020.
22. Cheng, R.K., Levy, W.C., Vasbinder, A., Teruya, S., De Los Santos, J., Leedy, D., Maurer, M.S. Diuretic Dose and NYHA Functional Class Are Independent Predictors of Mortality in Patients with Transthyretin Cardiac Amyloidosis. *JACC CardioOncol.* **2020**, *2*(3), 414-424.
23. Dong, J., and Chen, H. Cardiotoxicity of Anticancer Therapeutics. *Front. Cardiovasc. Med.* **2018**, *5*, 9.
24. Abdel-Qadir, H., Thavendiranathan, P., Austin, P.C., et al. Development and validation of a multivariable prediction model for major adverse cardiovascular events after early-stage breast cancer: a population-based cohort study, *European Heart Journal,* **2019**, *40*(48), 3913–3920
25. Ezaz, G., Long, J.B., Chen, J., et al. Risk Prediction Model for Trastuzumab Cardiotoxicity. *J. Am. Heart Assoc.* **2021**, *10*(4), e017106.
26. Henriksen, P.A. Anthracycline Cardiotoxicity: An Update on Mechanisms, Monitoring and Prevention. *Heart.* **2018**, *104*(12), 971-977.
27. Swain, S.M., Whaley, F.S., Ewer, M.S. CHF in Doxorubicin Patients. *Cancer* **2003**, *97*(11), 2869–2879.
28. Thavendiranathan, P., Negishi, T., Somerset, E., et al. Strain-Guided Management of Potentially Cardiotoxic Cancer Therapy. *Journal of the American College of Cardiology*. **2021**, *77*(4), 392–402.
29. Cardinale, D., Colombo, A., Lamantia, G., et al. Anthracycline Cardiotoxicity Therapy Response. *J. Am. Coll. Cardiol.* **2010**, *55*(3), 213–220.
30. Curigliano, G., Lenihan, D., Fradley, M., et al. ESMO Consensus Recommendations. *Ann. Oncol.* **2020**, *31*(2), 171–190.
31. Njoroge, J., Barasa, F., Muturi, A., et al. Cardio-Oncology in Low- and Middle-Income Countries. *JACC CardioOncol.* **2021**, *3*(2), 260–272.
32. Russo, M., Della Sala, A., Tocchetti, C.G., Porporato, P.E., Ghigo, A. Metabolic Aspects of Anthracycline Cardiotoxicity. *Curr Treat Options Oncol.* **2021**, *22*(2), 18.
33. Curigliano, G. et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Annals of Oncology,* **2020**, *31*(2), 171-190.

34. Camps, C., Gálvez, C., Martín, M., et al. Mitochondrial Stress and Remodeling. *JACC CardioOncol*. **2023**, *5*(2), 132–145.
35. Pozza, A., Di Candia, A., Zanella, L., Stefors, E.J., Bennati, E., Somigli, C., Poli, E., Fournier, E., Joye, R., Mura, R., et al. Emerging Strategies for the Prevention of Chemotherapy-Induced Cardiotoxicity in Paediatric Cancer Patients: Advances and Future Perspectives. *Pharmaceuticals*. **2025**, *18*(11), 1604.
36. Li, Y., Lin, R., Peng, X., et al. The Role of Mitochondrial Quality Control in Anthracycline-Induced Cardiotoxicity: From Bench to Bedside. *Oxid. Med. Cell. Longev.* **2022**, 3659278.