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Prediction of Cardiac Toxicity by Measurement of Coronary Artery Calcium Scoring Method Using Chest Computed Tomography in Early Breast Cancer Patients Treated with Trastuzumab

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Keywords
Breast cancer · Trastuzumab · Human epidermal growth factor receptor 2 · Cardiac toxicity · Coronary calcium artery

Abstract

Background: In human epidermal growth factor receptor 2 (HER2)-positive early stage breast cancer, prediction of trastuzumab-related cardiac toxicity remains a challenge. The coronary calcium artery (CAC) reflects the total coronary plaque burden, which predicts the risk of atherosclerosis. We investigated the prediction of left ventricular ejection fraction (LVEF) decline in breast cancer according to CAC scores. ***Methods:*** A total of 347 patients were enrolled from Seoul St Mary's Hospital between January 2010 and December 2019. Chest computed tomography (CT) was performed at a single tertiary center. Patients who received trastuzumab for HER2-positive early breast cancer were included in this study. ***Results:*** Of the 347 patients, 312 and 35 had CAC scores of 0 and ≥1, respectively. The CAC ≥1 group was associated with older age, body mass index, and receipt of left breast irradiation. The CAC ≥1 group was significantly associated with LVEF decline (absolute value, ≤50%) (hazard ratio [HR] 12.038, 95% confidence interval [CI] 2.845–50.937, $p = 0.001$), LVEF decline (absolute value, ≤55%) (HR 4.439, 95% CI: 1.787–11.028, $p = 0.001$), and decline in LVEF of ≥10% points compared with baseline echography (HR 5.083, 95% CI: 1.658–15.582, $p = 0.004$). Even after adjusting for other clinical factors, CAC ≥1 remained a significant predictor of decreased LVEF. ***Conclusion:*** Our findings suggest that the CAC score is a significant predictor of cardiac toxicity following trastuzumab treatment in HER2-positive breast cancer. Therefore, CAC measurement could reduce cardiac toxicity by distinguishing patients at high risk for trastuzumab.

Introduction

Breast cancer is the most common cancer among women worldwide, with approximately 2.26 million women diagnosed with it each year [1]. Approximately, 20% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2) [2]. HER2-overexpression in breast cancer is associated with an aggressive form of the disease, and trastuzumab, a humanized monoclonal antibody, is used as the standard treatment for these breast cancers. The clinical efficacy of trastuzumab has been proven in many clinical trials [3–5]. HER2 signaling is involved in myocardial cell homeostasis. Trastuzumab treatment is associated with cardiac toxicity, especially in patients who use anthracyclines as a chemotherapy regimen [6, 7]. Long-term follow-up data on cardiac safety in clinical trials using trastuzumab showed a higher incidence of adverse cardiac events in combination groups than in controls [8].

Recent improvements in breast cancer treatment can reduce cancer-specific mortality in patients with breast

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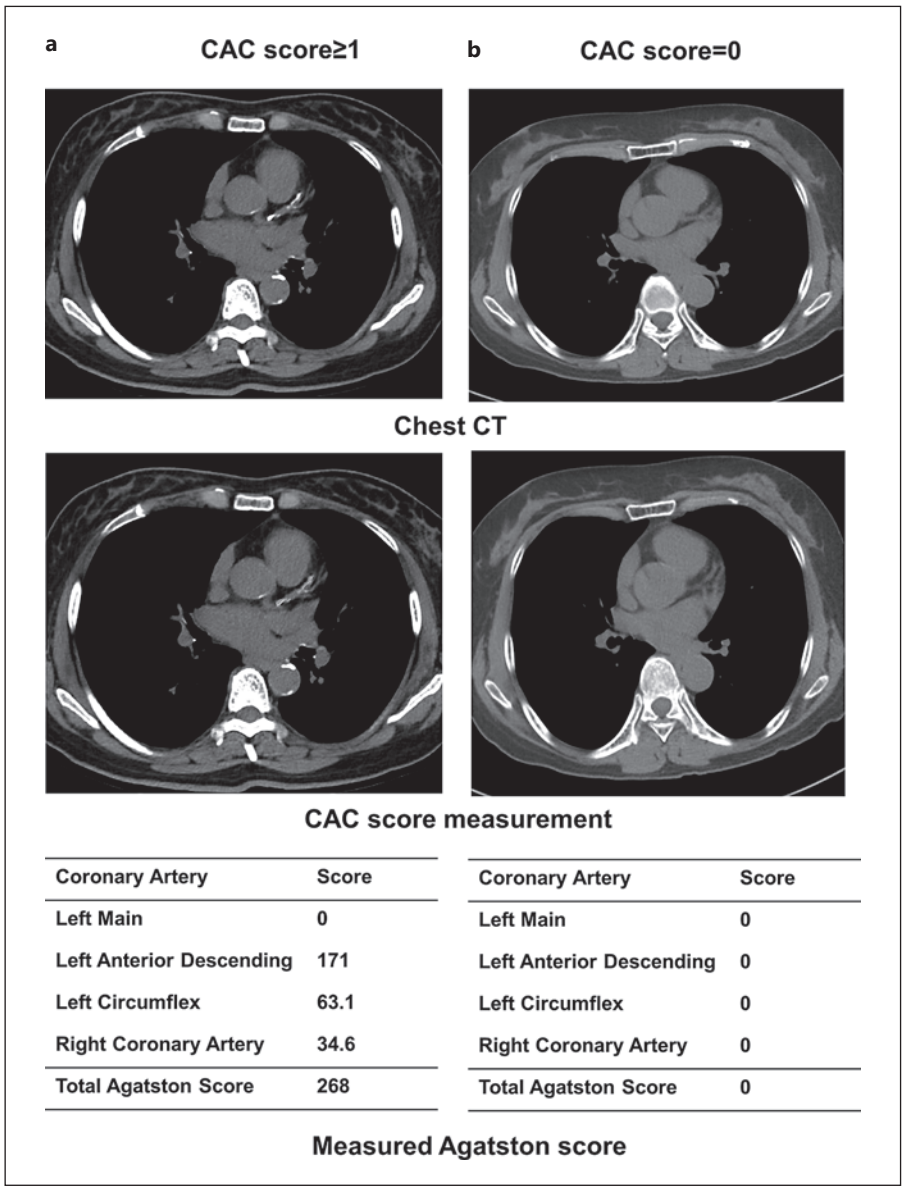

Fig. 1. Representative images of chest CT, CAC score measurement, and the measured Agatston score in the CAC score ≥1 group (**a**), and chest CT, CAC score measurement, and the measured Agatston score in the CAC score = 0 group (**b**). CT, computed tomography; CAC, coronary artery calcium.

cancer [9]. As the survival rate of patients with breast cancer improves, patients become more interested in the adverse events of treatment and quality of life. Cardiovascular events are the major cause of mortality in breast cancer survivors; therefore, more attention is needed to identify cardiac risk in treating patients with breast cancer [10]. Therefore, predicting the risk of cardiac toxicity in patients with breast cancer is important.

Coronary artery calcium (CAC) is a marker of subclinical atherosclerosis that correlates with total coronary plaque burden and is associated with atherosclerotic cardiovascular disease (ASCVD) [11]. In the multi-ethnic study of atherosclerosis, the patients with CAC scores of 1–100, 101–300, and above 300 had a 3.61, 7.73, and 9.67-fold increased risk of adjustment for coronary events compared to participants with no coronary calcium, respectively [11]. A CAC score of ≤100 has been reported to equal 10-year ASCVD incidence rates of 7.5 or more events per 1,000 person-years. In contrast, a CAC score of 0 was associated with a low risk of ASCVD over the next 10 years, even with multiple traditional risk factors. There have been many articles on ASCVD prediction according to CAC scores; however, there are no data to predict cardiac toxicity according to CAC scores in patients with breast cancer. This study evaluated cardiac toxicity according to the CAC score in patients with operable early breast cancer who received trastuzumab.

Materials and Methods

Study Population and Inclusion/Exclusion Criteria

We retrospectively reviewed the data of patients who underwent primary curative surgery for breast cancer at Seoul St. Mary's Hospital in Seoul, Korea, from January 2010 to December 2019.

Patients >19 years and <80 years, diagnosed with histologically confirmed invasive HER2-positive breast carcinoma with stages I–III, who were treated with (neo)adjuvant chemotherapy and trastuzumab, were enrolled. Positive HER2 status by immunohistochemistry 3+ or silver in situ hybridization was confirmed (in situ hybridization positivity was mandatory for immunohistochemistry 2+ tumors). Patients with bilateral breast cancer, recurrent breast cancer, organ failure (liver, lung, heart, etc.), any other malignancy except thyroid cancer, history of myocardial infarction, decline in left ventricular ejection fraction (LVEF) of <50% points before treatment, or those who could not undergo echocardiography/chest computed tomography (CT) before systemic treatment were excluded.

Clinical data were collected as follows: age at surgery, height, weight, body mass index (BMI), history (hypertension, diabetes, and dyslipidemia), surgery for breast cancer, neoadjuvant and/or adjuvant chemotherapy regimen, tumor location (left or right), receipt of a target agent and/or endocrine therapy, echocardiography, and chest CT. Echocardiography was carried out at baseline (before [neo]adjuvant trastuzumab treatment) and 3, 6, 9, and 12 months after treatment. The study was approved by the Institutional Review Board (IRB) of Seoul St. Mary's Hospital (IRB No. KC21RISI0704). The requirement for informed consent was waived due to the retrospective design of the study.

The primary endpoint was to predict a decrease in LVEF (absolute value, ≤50%) following trastuzumab administration according to CAC scoring in breast cancer. This endpoint was the same as that used in the TRYPHAENA trial [12]. The secondary endpoint was to predict a decrease in LVEF (absolute value, ≤55%) following trastuzumab treatment according to CAC scoring. Another endpoint was to predict a decline in LVEF of >10% points compared with baseline LVEF following trastuzumab treatment according to CAC scoring.

Treatment and Chest CT Scan

Trastuzumab was administered intravenously or subcutaneously on a 3-weekly schedule and consecutively on the same day in the following sequence: an initial dose of 8 mg/kg, followed by 6 mg/kg. The chemotherapy regimen was approved by the Korean National Health Insurance as a standard protocol, and the analysis was conducted with and without anthracycline.

A baseline chest CT scan was performed before surgery or neoadjuvant chemotherapy. Echocardiography was performed before chemotherapy, trastuzumab administration, and treatment. The LVEF was measured using echocardiography, and the same method was used for individual patients throughout the study.

Noncontrast and nonelectrocardiogram (ECG)-gated chest CT scans were acquired with multi-detector CT scanners (Somatom Definition AS+ or Somatom Sensation Open, Siemens), 120 kVp, and automatic tube current modulation (50–500 mA). Each scan was completed within a single breath hold. A standard kernel and 3–5-mm slice thickness were used for reconstruction.

CAC Scoring by the Agatston Method

CAC scoring on chest CT was performed using commercially available calcium scoring software (Aquarius iNtuition V4.4.13; TeraRecon), which was used to identify and score any calcium in the four main coronary arteries, the left main, left anterior descending, left circumflex, and right coronary arteries, based on established minimum attenuation values. The Agatston score was generated by summing the scores of all lesions, which were derived by multiplying the lesion area by the density in Hounsfield units [13]. All identified plaques were manually evaluated by an investigator to exclude non-CAC levels. The differences in the CAC scores on chest CT are shown in Figure 1. The analysis was divided into two groups according to the CAC score of the patient, and the cut-off was set to a CAC score of 1≤ and 0.

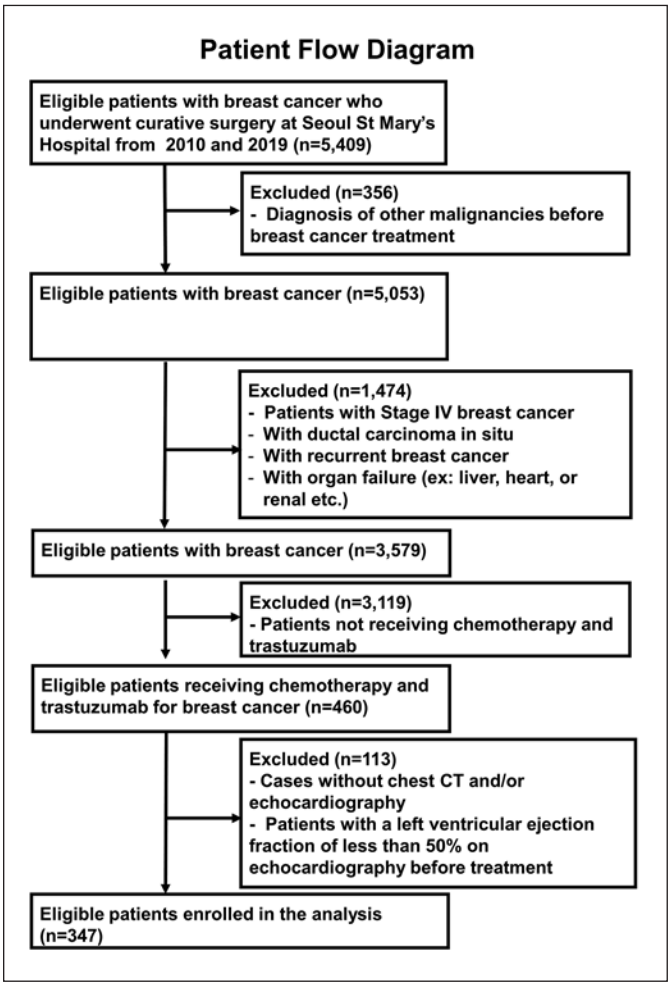

Fig. 2. Patient flow diagram for the selection and enrollment of eligible participants in this study.

Statistical Analysis

Continuous variables between the two groups (CAC score 0 vs. CAC score ≥1) were compared using Student's *t* test or the Mann-Whitney test. Categorical variables were compared using the χ^2 test or Fisher's exact test. Variables associated with LVEF decline were analyzed using logistic regression analysis. Variables showing statistically significant differences in the univariate analysis were used in multivariate logistic regression analysis.

Statistical analyses were performed using SPSS version 24 (SPSS, Chicago, IL, USA). The threshold for statistical significance was set at $p < 0.05$, with a 95% confidence interval not including 1.

Results

Patient Characteristics

In total, 5,409 patients with breast cancer were included in this study (Fig. 2). We excluded 356 patients with malignancies other than thyroid cancer before breast cancer diagnosis. After excluding patients diagnosed with

Table 1. Baseline characteristic according to CAC scoring in breast cancer patients using trastuzumab

	CAC score = 0, *n* = 312 (%)	CAC score ≥1, *n* = 35 (%)	*p* value
Age (continuous, year)	51.09±9.00	60.34±9.26	<0.001
Height (m, continuous)	1.576±0.545	1.540±0.0672	<0.001
Weight (kg, continuous)	59.17±9.09	59.14±8.49	0.985
BMI (continuous)	23.79±3.24	24.97±3.52	0.046
Radiotherapy			
Done	263 (84.3)	30 (85.7)	0.826
Not done	49 (15.7)	5 (14.3)	
Left breast irradiation			
Done	125 (40.1)	23 (65.7)	0.004
Not done	187 (59.9)	12 (34.3)	
Hypertension			
No	260 (83.3)	29 (82.9)	0.943
Yes	52 (16.7)	6 (17.1)	
Diabetes			
No	291 (93.3)	33 (94.3)	0.819
Yes	21 (6.7)	2 (5.7)	
Dyslipidemia			
No	306 (98.1)	35 (100)	0.408
Yes	6 (1.9)	0	
Baseline LVEF before chemotherapy (%, continuous)	64.28±3.18	63.75±2.94	0.344
Baseline LVEF before trastuzumab (%, continuous)	63.34±2.95	62.19±2.81	0.028
Breast operation			
Wide excision	191 (61.2)	24 (68.6)	0.620
Total mastectomy	118 (37.8)	11 (31.4)	
None (occult breast cancer)	3 (1.0)	0	
Axilla operation			
SLNB	165 (52.9)	18 (51.4)	0.870
ALND	147 (47.1)	17 (48.6)	
Anthracycline			
Done	67 (21.5)	9 (25.7)	0.565
Not done	245 (78.5)	26 (74.3)	
Pertuzumab			
Done	2 (0.6)	0	0.635
Not done	310 (99.4)	35 (100)	
Endocrine treatment			
Done	194 (62.2)	24 (68.6)	0.515
Not done	114 (36.5)	11 (31.4)	
Missing	4 (1.3)	0	

CAC, coronary artery scoring; BMI, body mass index; LVEF, left ventricular ejection fraction; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection.

metastatic breast cancer, ductal carcinoma in situ, recurrent breast cancer, bilateral breast cancer, organ failure, and a history of myocardial infarction, there were 3,579 patients in the study. After excluding patients not receiving chemotherapy and trastuzumab, 460 eligible patients were included. A total of 347 patients were analyzed in this study, except for patients who could not undergo chest CT and echocardiography and patients with baseline LVEF ≤50%. Of these, a total of 101 patients (29.1%) received neoadjuvant chemotherapy.

The median age of the patients was 52 (31–76) years. The CAC score 0 and CAC score ≥1 groups included 312 (89.9%) and 35 (10.1%) patients, respectively. Clinical characteristics were compared according to the CAC score (Table 1). The CAC score ≥1 group was associated with older age, higher BMI, higher receipt of left breast irradiation, and lower baseline LVEF before trastuzumab treatment. However, there were no statistical differences in surgery, radiotherapy, anthracycline regimen, history (hypertension, diabetes, and dyslipidemia), and baseline LVEF before chemotherapy between the two groups.

Cardiac Risk Assessment according to the CAC Score

Among the 347 patients, 8 (2.3%) developed an LVEF decline (absolute value, ≤50%) following trastuzumab treatment. A decrease in LVEF (absolute value, ≤55%) oc-

Table 2. HRs and 95% CIs using logistic regression analysis for LVEF decline (absolute value, ≤50%)

	Univariate analysis		Multivariate analysis	
	HRs (95% CIs)	*p* value	HRs (95% CIs)	*p* value
Age (continuous, year)	1.036 (0.956–1.124)	0.385		0.001
BMI (kg/m^2, continuous)	1.341 (1.149–1.566)	<0.001	1.321 (1.128–1.548)	
Radiotherapy				
Not done	Reference	0.597		
Done	0.645 (0.127–3.275)			
Left breast irradiation				
Not done	Reference	0.868		
Done	0.885 (0.208–3.763)			
Hypertension				
No	Reference	0.997		
Yes	NA			
Diabetes				
No	Reference	0.405		
Yes	2.508 (0.288–21.803)			
Dyslipidemia				
No	Reference	0.999		
Yes	NA			
Baseline LVEF before chemotherapy (%, continuous)	1.019 (0.820–1.266)	0.867		
Baseline LVEF before trastuzumab (%, continuous)	1.038 (0.818–1.319)	0.758		
Breast operation				
Wide excision	Reference	0.276		
Total mastectomy	2.319 (0.510–10.539)			
Axilla operation				
SLNB	Reference	0.216		
ALND	2.841 (0.543–14.853)			
Anthracycline				
Not done	Reference	0.503		
Done	0.486 (0.059–4.012)			
Endocrine treatment				
Not done	Reference			
Done	0.955 (0.224–4.064)			
CAC score				
0	Reference	0.001	Reference	0.003
≥1	12.038 (2.845–50.937)		10.558 (2.186–50.999)	

HR, hazard ratio; 95% CI, 95% confidence interval; LVEF, left ventricular ejection fraction; BMI, body mass index; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; CAC, coronary artery scoring; NA, not assessed.

curred in 32 of 347 (9.2%) patients. Decline in LVEF of ≥10% points compared with baseline echocardiography occurred in 17 of 347 (4.9%) patients.

The CAC score ≥1 group was significantly associated with decreased LVEF (absolute value, ≤50%) than the CAC score 0 group (Table 2, hazard ratio [HR], 12.038, 95% confidence interval [CI] 2.845–50.937, $p = 0.001$). A higher BMI was also significantly associated with decreased LVEF (absolute value, ≤50%), as assessed by univariate analysis (Table 2). The CAC score ≥1 group was still a significant determinant of decreased LVEF (absolute value, ≤50%) after adjustment for BMI by Cox logistic regression analysis (HR 10.558, 95% CI: 2.186–50.999, $p = 0.003$).

Even in other secondary endpoints, such as decreased LVEF (absolute value, ≤55%), the CAC score ≥1 group had a significantly higher incidence of LVEF decline than the CAC score 0 group (Table 3, HR 4.439, 95% CI: 1.787–11.028, $p = 0.001$). A higher BMI and nonadministration of anthracycline were significant factors for decreased LVEF (absolute value, ≤55%) in the univariate analysis (Table 3). In the multivariate analysis adjusted for other factors, a CAC score ≥1 was a significant predictor of LVEF decline (absolute value, ≤55%) (Table 3, HR 3.742, 95% CI: 1.380–10.143, $p = 0.009$).

In the univariate analysis, the CAC score ≥1 group was significantly associated with a decrease of ≥10% points from the baseline LVEF than the CAC score 0 group (Table 4, HR 5.083, 95% CI: 1.658–15.582, p =

Table 3. HRs and 95% CIs using logistic regression analysis for LVEF decline (absolute value, ≤55%)

	Univariate analysis		Multivariate analysis	
	HRs (95% CIs)	*p* value	HRs (95% CIs)	*p* value
Age (continuous, year)	0.986 (0.946–1.027)	0.492		
BMI (kg/m^2, continuous)	1.131 (1.025–1.248)	0.014	1.109 (1.002–1.226)	0.045
Radiotherapy				
Not done	Reference	0.891		
Done	0.937 (0.368–2.383)			
Left breast irradiation				
Not done	Reference	0.126		
Done	1.769 (0.852–3.672)			
Hypertension				
No	Reference	0.909		
Yes	0.943 (0.346–2.569)			
Diabetes				
No	Reference	0.989		
Yes	1.010 (0.225–4.541)			
Dyslipidemia				
No	Reference	0.518		
Yes	2.053 (0.232–18.156)			
Baseline LVEF before chemotherapy (%, continuous)	1.080 (0.968–1.206)	0.168		
Baseline LVEF before trastuzumab (%, continuous)	0.949 (0.837–1.075)	0.407		
Breast operation				
Wide excision	Reference	0.321		
Total mastectomy	1.458 (0.692–3.073)			
Axilla operation				
SLNB	Reference	0.106		
ALND	1.866 (0.875–3.978)			
Anthracycline				
Not done	Reference	0.035	Reference	0.037
Done	0.210 (0.049–0.898)		0.208 (0.048–0.907)	
Endocrine treatment				
Not done	Reference	0.522		
Done	1.291 (0.590–2.822)			
CAC score				
0	Reference	0.001	Reference	0.009
≥1	4.439 (1.787–11.028)		3.742 (1.380–10.143)	

HR, hazard ratio; 95% CI, 95% confidence interval; LVEF, left ventricular ejection fraction; BMI, body mass index; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; CAC, coronary artery scoring.

0.004). No significant factors were related to ≥10% points decrease from the baseline LVEF, except for the CAC score.

Discussion

The objective of our study was to evaluate the risk of cardiac toxicity according to the CAC scoring system for cardiac dysfunction during trastuzumab treatment of primary HER2-positive breast cancer. After adjusting for other clinical factors, the positive CAC score was a significant factor for LVEF decline. In our results, the administration of anthracycline was related to less cardiotoxicity. This finding was analyzed in the enrolled patients, except for those with reduced LVEF after anthracycline administration, resulting in the opposite result from previous studies. This finding may be a selection bias due to the outcome of excluding patients receiving anthracyclines and developing cardiotoxicity. To our knowledge, this is the first study to assess the cardiac risk of trastuzumab using the CAC scoring system.

Meta-analysis for cardiac safety in patients with breast cancer receiving trastuzumab showed that the overall incidence of congestive heart failure (CHF) among 6,801 patients from 10 trials was 1.9% (95% CI, 1.0–3.8%), and the overall incidence of asymptomatic LVEF decreased among 5,946 patients in eight trials was 7.5% (95% CI, 4.2–13.1%) [14]. The overall relative risk of asymptomatic LVEF decrease for trastuzumab compared with the controls was 2.13 (95% CI, 1.31–3.49, $p = 0.003$).

Table 4. HRs and 95% CIs using logistic regression analysis for decline in LVEF of ≥10% points compared with baseline echography

	Univariate analysis	
	HRs (95% CIs)	*p* value
Age (continuous, year)	0.990 (0.937–1.045)	0.715
BMI (kg/m^2, continuous)	1.042 (0.907–1.198)	0.562
Radiotherapy		
Not done	Reference	0.981
Done	1.016 (0.283–3.648)	
Left breast irradiation		
Not done	Reference	0.564
Done	1.333 (0.502–3.544)	
Hypertension		
No	Reference	0.568
Yes	0.645 (0.144–2.901)	
Diabetes		
No	Reference	0.929
Yes	0.911 (0.115–7.204)	
Dyslipidemia		
No	Reference	0.999
Yes	NA	
Baseline LVEF before chemotherapy (%, continuous)	1.084 (0.946–1.265)	0.227
Baseline LVEF before trastuzumab (%, continuous)	1.037 (0.874–1.231)	0.678
Breast operation		
Wide excision	Reference	0.378
Total mastectomy	1.554 (0.583–4.138)	
Axilla operation		
SLNB	Reference	0.982
ALND	0.989 (0.372–2.628)	
Anthracycline		
Not done	Reference	0.290
Done	0.446 (0.100–1.992)	
Endocrine treatment		
Not done	Reference	0.678
Done	0.810 (0.301–2.185)	
CAC score		
0	Reference	0.004
≥1	5.083 (1.658–15.582)	

HR, hazard ratio; 95% CI, 95% confidence interval; LVEF, left ventricular ejection fraction; BMI, body mass index; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; CAC, coronary artery scoring; NA, not assessed.

Trastuzumab causes cardiac dysfunction in cardiomyocytes by disrupting the HER2 signaling pathway, including growth, repair, and cell survival [15]. The exact mechanism of trastuzumab-induced cardiac toxicity is still unknown; however, a mouse model with HER2-defect showed abnormal cardiogenesis and cellular response to stress [16].

The presence of calcium in the coronary arteries is an indicator of atherosclerosis, and the extent of coronary calcification correlates with the severity of coronary stenosis and frequency of myocardial infarction [13]. Coronary artery calcification occurs in the intimal layer, resulting from a complex interplay between inflammation, hyperlipidemia, and hyperglycemia, and is pathognomonic of atherosclerosis [17]. Rumberger et al. [18] showed no detectable calcified atherosclerosis in a histopathologic correlative study when the total calcium scores were 0. Currently, CAC scoring has emerged as a mainstay of personalized risk assessment and is endorsed as a standard tool in the USA and European guidelines [19].

Traditional cardiovascular risk factors in patients with breast cancer are age (≥60 years), pre-existing cardiovascular disease (hypertension, dyslipidemia, and diabetes mellitus), smoking, obesity, organ failure, anthracycline use, and left-sided radiation therapy. The American Society of Clinical Oncology clinical practice guidelines for prevention and monitoring of cardiac dysfunction in survivors of adult cancers have proposed the criteria for patients at the risk of cardiac dysfunction following treatment that is based on both conventional risk and breast cancer treatment [20]. In previous studies, HER2-positive breast cancer patients with metabolic syndrome and/

or ASCVD treated with trastuzumab have an increased incidence of cardiotoxicity [21]. In SER-Medicare and in the Texas Cancer Registry database, the incidence of CHF after administering trastuzumab treatment was significant higher than nonuser (29.4% vs. 18.9%, $p < 0.001$). Among trastuzumab-treated patients, coronary artery disease (HR 1.82, 95% CIs: 1.34–2.48) increased the risk of CHF [22]. In Ontario Cancer Registry, adjuvant trastuzumab is independently associated with the increased incidence of heart failure, and comorbidity such as diabetes also increases the risk of heart failure (HR 1.47, 95% CI: 1.11–1.95) [23]. However, the diagnostic value of these criteria has not been studied. Several studies have developed and validated cardiovascular risk score systems for breast cancer using large population-based cohorts [20, 21]. To date, no model has included the CAC score in the risk prediction model for cardiotoxicity.

This study had several limitations. First, it included a limited number of patients. Moreover, our study had a relatively short follow-up period; therefore, the risk of major cardiovascular events such as myocardial infarction could not be evaluated. Second, our study was only conducted in Koreans, and the findings may not be generalizable to patients in other countries or different ethnicities. Third, standard CAC quantification via multidetector CT was performed using prospective ECG gating with a tube voltage of 120 kVp, tube current of 50–100 mA, and slice thickness of 2–3 mm. However, a fundamental limitation was that chest CT was not performed with the standard CAC scoring setting (ECG-gated CT). Due to the design of the retrospective study, data on radiation dose and mean cardiac dose that could affect the ejection fraction could not be collected in all patients. The echography used as an endpoint in the study has an intrinsic limitation that there may be some discrepancies between observers and even within observers.

Despite these limitations, our study demonstrated that a positive CAC score using chest CT prior to trastuzumab treatment in HER2-positive breast cancer increased the risk of cardiac toxicity. This finding provides the basis for warning physicians about the risk of developing cardiac toxicity as a result of receiving trastuzumab through preoperative chest CT in HER2-positive breast cancer. Further investigation is needed to evaluate the risk of developing ASCVD according to the CAC score in patients with breast cancer receiving trastuzumab.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1,964 Helsinki Declaration and its later amendments or comparable ethical standards. This study protocol was reviewed and approved by Institutional Review Board of Seoul St Mary's Hospital (IRB No. KC21RISI0704). The need for informed consent was waived by the IRB due to the retrospective study design. The need for informed consent was waived by the IRB due to the retrospective study design. For this type of study, formal consent is not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Chang Ik Yoon and Woo-Chan Park had full access to all of data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Chang Ik Yoon, Suyon Chang, and Woo-Chan Park: conceptualization, resources; Chang Ik Yoon, Jeaneum Park, and Suyon Chang: data curation; none: funding acquisition; Chang Ik Yoon and Suyon Chang: investigation; Chang Ik Yoon and Woo-Chan Park: methology; Chang Ik Yoon: formal analysis and writing – original draft; Dooreh Kim, Young Joo Lee, Soo Youn Bae, and Woo-Chan Park: supervision.

Data Availability Statement

All data generated or analyzed during this study are included in this research article and its additional files.

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