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Cancer treatment-related cardiac dysfunction in breast cancer survivors: A retrospective descriptive study using electronic health records from a Korean tertiary hospital

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ABSTRACT

Purpose: The population overlap of breast cancer and cardiovascular diseases (CVDs) has increased due to early breast cancer detection and treatment and aging population trends. Moreover, breast cancer patients are at an increased risk for CVDs consequent to cancer treatments. We aimed to understand the characteristics of breast cancer patients with pre-existing CVDs and of those diagnosed with CVDs after receiving chemotherapy, and cancer treatment-related cardiac dysfunction's occurrence among Korean breast cancer patients with CVDs.
Methods: This retrospective descriptive study, which collected clinical data from electronic health records from a Korean tertiary hospital, included 1200 female breast cancer patients with CVDs, aged 15–75 years.
Results: A total of 45.7% had pre-existing CVDs, and 91.6% were classified as very high-risk for cardiotoxicity in the pre-existing CVDs group. Among the 1200 breast cancer patients with CVDs, only 439 patients had left ventricular ejection fraction (LVEF) data during their cancer treatment, and 121 received baseline assessment for LVEF. Of the 439 patients with LVEF data, 134 patients have been classified into cancer treatment-related cardiac dysfunction (CTRCD), and the median period from cancer diagnosis to CTRCD occurrence was 26.5 months.
Conclusion: Despite the high cardiotoxicity risk of breast cancer patients with pre-existing CVDs, baseline studies of the risk assessment before chemotherapy were insufficient to support the prevention and early detection of cardiotoxicity. Therefore, it is paramount to consider how nurses focus on risk stratification before chemotherapy and support the regular monitoring of breast cancer survivors' cardiac functioning, to maintain optimal health status.

1. Introduction

Breast cancer is the most frequently occurring cancer among women worldwide (Sung et al., 2021). It develops at a relatively early age and has a low mortality rate relative to its incidence rate (Sung et al., 2021; Tao et al., 2015). The personal and national burden of breast cancer is constantly increasing due to advancements in the early detection and treatment of cancer (Tao et al., 2015), and the increasing number of long-term breast cancer survivors require continuous health management – from diagnosis to end of life.

Along with the aging population, cancer patients with pre-existing cardiovascular diseases (CVDs) are increasing (Herrmann et al., 2014). Patients without pre-existing CVDs could also develop cardiovascular complications, such as hypertension, arrhythmia, and ventricular dysfunction, as a result of chemotherapy or radiotherapy (Perez et al., 2019). These trends demonstrate that the population overlap for cancer and CVDs seems to be an inevitable concern for both oncology and cardiology (Cardinale et al., 2008; Herrmann et al., 2014).

During their treatment, breast cancer patients are frequently at risk for cancer treatment-related cardiac dysfunction (CTRCD), which occurs in approximately 10% of breast cancer patients (Cardinale et al., 2015). Although official consensus has not yet been reached, the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) define CTRCD as more than 10% decline in left ventricular ejection fraction (LVEF), to a final value less than 53% confirmed on subsequent imaging performed two to three weeks after

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the initial measurement (Perez et al., 2019; Plana et al., 2014). This adverse treatment effect is caused by cardiotoxic agents, such as trastuzumab and anthracycline, frequently used in breast cancer treatment (Bloom et al., 2016; Kim et al., 2018). In addition, chest radiation therapy is also known as a risk factor for cardiotoxicity (Perez et al., 2019).

However, concerns regarding treatment-related cardiotoxicity may serve as obstacles to receiving proper cancer treatment. For example, a recent study noted that pre-existing CVDs, which is known to be a risk factor for cardiotoxicity, were related to lower odds of receiving chemotherapy, radiotherapy, and surgery for lung cancer (Batra et al., 2020). This may be because these patients were considered too frail to receive standard treatments or at an intensified risk for cardiotoxicity due to cancer treatments.

Cardio-oncology was developed due to the need to comprehensively manage patients with co-morbid cancer and CVD (Cardinale et al., 2008). Guidelines for the prevention and treatment of CTRCD recommend cardiovascular risk assessment before chemotherapy. Serial echocardiogram follow-up and the use of biomarkers, such as Troponin I level, are also recommended for early screening of cardiovascular complications (Herrmann et al., 2014; Kim et al., 2018).

Despite these recommendations, however, standardized clinical guidelines are still lacking, and previous findings suggest that compliance with existing guidelines is insufficient to prevent and manage cancer treatment-related CVDs (Koop et al., 2020). Moreover, there are currently a limited number of studies that compare breast cancer patients with pre-existing CVDs with those who have developed CVDs after chemotherapy, and only a few baseline studies on CTRCD have been conducted in Korea (Yoon et al., 2016). In this study, we explored the following research questions to examine the current disease status of breast cancer patients using electronic health records from a Korean tertiary hospital.

Research Question1. What are the characteristics of breast cancer patients with pre-existing CVDs and patients who develop CVDs after chemotherapy?

Research Question 2. Are breast cancer patients identified as a high-risk group for cardiac toxicity based on their chemotherapy prescriptions and cardiotoxicity risk scores?

Research Question 3. What are characteristics of breast cancer patients who suffer from CTRCD?

2. Methods

2.1. Study design and patients

This retrospective descriptive study collected clinical data from electronic health records of patients with breast cancer at a tertiary hospital in Korea. We included women, aged 15–75 years, who were diagnosed with breast cancer between July 1, 2008, and June 30, 2018, with at least two years of inpatient or outpatient follow-up, and had a diagnosis of CVDs at the time of data extraction. Of the 2202 patient records reviewed, we analysed data of 1200 patients who received chemotherapy (Fig. 1). We categorized the patients into two groups according to the date of their CVD diagnosis and the date when they began chemotherapy: 1) Patients with pre-existing CVDs—those whose CVD diagnosis preceded their first dose of chemotherapy and 2) patients diagnosed CVDs after their first dose of chemotherapy. After excluding patients missing LVEF data, a total of 439 patients were included in the final analysis. This study was conducted after receiving approval from the institutional review board at Yonsei University Health System (reference no. Y-2020-0089). The need for informed consent was waived as anonymized data were used in this retrospective analysis. The investigation conformed with the principles outlined in the Declaration of Helsinki (Rickham, 1964).

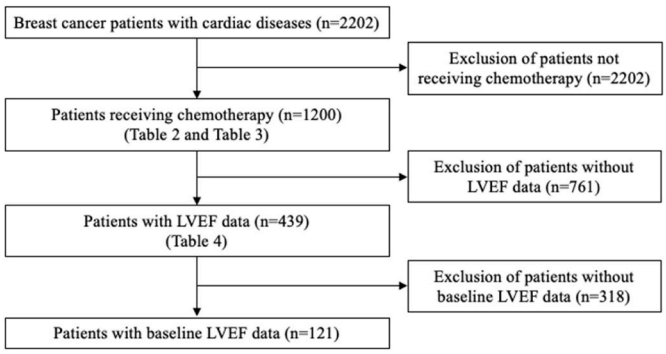

Fig. 1. Flow diagram of the study's patients.

2.2. Variables

2.2.1. Demographic and clinical characteristics

We used age at the time of breast cancer diagnosis, gender (all female), and body mass index (BMI) as demographic characteristics. Based on the Asian-Pacific classification, BMI was categorized into four groups. Origin and type of breast cancer, pathological stage of cancer, type of CVD, and time between the first dose of chemotherapy and CVD diagnosis were used to understand patients' clinical characteristics. Patients' characteristics were described using frequency analysis, means, and standard deviations.

2.2.2. Prescriptions for anti-cancer agents

We analysed the number and frequency of prescriptions according to the type of chemotherapy. Prescriptions for the same patient with different execution dates were considered independent cases. Following this, the cumulative dose for doxorubicin, well-known as a type of dose-dependent cardiotoxic agent anthracycline, was calculated by adding each dose in entire prescription lists and dividing it by patients' body surface area. Other anthracyclines' cumulative doses, including idarubicin, epirubicin, and liposomal doxorubicin, were not calculated, because they were barely used for the patients.

2.2.3. Cardiotoxicity risk score

The cardiotoxicity risk score was proposed by Mayo clinic (Herrmann et al., 2014). This method assesses medication-related factors by evaluating the use of cardiotoxic agents. High-risk agents, such as anthracyclines and Herceptin, yield a risk score of 4; intermediate, low, and rare risk agents yield risk scores of 2, 1, 0, respectively. For patient-related factors, patients with cardiomyopathy or heart failure, coronary artery diseases or peripheral artery diseases, hypertension, diabetes mellitus obtained one point for each disease. Moreover, patients who received prior or concurrent anthracycline and chest radiation obtained one point. Lastly, patients aged <15 or >65 years and female patients also yield one point. Adding each score, patients with scores >6 points are at very high risk, and those with scores 5–6, 3–4, 1–2, 0, are at high, intermediate, low, and very low risks, respectively. The total scores range 0–12. The cardiotoxicity risk score was calculated when the patients received their first dose of chemotherapy for breast cancer.

2.2.4. Cancer treatment-related cardiac dysfunction

Patients with repeatedly measured echocardiogram data were classified based on the ASE and EACVI's criteria for CTRCD. Patients with a decline of more than 10% in baseline LVEF, with a final value below 53% confirmed on subsequent imaging performed two to three weeks after the initial measurement, were considered CTRCD cases. However, as many cases did not have baseline echocardiogram data, we also considered patients diagnosed with heart failure (HF) after receiving the first dose of chemotherapy as CTRCD; their information is presented in

the separate columns in Table 4. Then, we reported the cumulative doxorubicin dose, since anthracycline is known to cause dose-dependent and irreversible cardiac dysfunction (Plana et al., 2014), and because doxorubicin was the most frequently used agent among anthracycline in this dataset. Trastuzumab is generally not considered an agent causing a dose-dependent cardiac dysfunction (Plana et al., 2014), and we did not calculate its cumulative dose.

2.3. Analysis

Data curation and analysis were conducted using R software (R Core Team, 2020). After acquiring electronic health records data from Severance hospital of Yonsei University Health System, data were imported into R. Next, variables were selected and merged for analysis, using research identification numbers. Patients with pre-existing CVDs and those with CVDs after chemotherapy were compared by using *t*-test and chi-square test to address their differences in characteristics (Table 1). Patients with missing data in echocardiogram results were excluded from the final analysis (Table 4). After classifying the CTRCD and no-CTRCD groups, we compared them using *t*-test for continuous variables and chi-square for nominal variables. We considered a two-sided p-value of less than 0.05 statistically significant.

3. Results

Among the breast cancer patients with CVDs who were receiving chemotherapy, only 36.5% had LVEF data. Moreover, the initial echocardiogram prior to receiving chemotherapy had been conducted only for 10% of the patients who were receiving chemotherapy. This means that 90% of patients' CTRCD occurrence may not have been identified because they did not have baseline LVEF data to detect the decline of their ejection fraction (Fig. 1).

We divided the breast cancer patients into two groups based on the onset of CVDs. Of the included patients, 45.7% (n = 548) were diagnosed with CVDs before receiving chemotherapy, and the rest of them developed CVDs after receiving chemotherapy. In terms of demographic and clinical characteristics (Table 1), patients' mean age at breast cancer diagnosis was 59.4 ± 9.4 years in the pre-existing CVDs group and 54.1 ± 9.4 years in the CVDs after receiving chemotherapy group. Infiltration ductal carcinoma was the most common type of breast cancer, and approximately 70% of the patients were categorized as being in stage I or II in both groups. Hypertension was the most common pre-existing CVD (94.5%), followed by arrhythmia, such as atrial fibrillation or atrial flutter. In the CVDs after chemotherapy group, hypertension was the most frequently occurring disease, followed by HF or cardiomyopathy. Among them, 42% were diagnosed with CVDs within one year after chemotherapy. The median time between breast cancer and CVD diagnoses was 17 months. Patients with pre-existing CVDs were more likely to receive baseline LVEF assessment, while those who developed CVDs after chemotherapy had more overall LVEF follow-up data.

The prescription record contained 60,053 chemotherapy drug orders for 1200 breast cancer patients (Table 2). Hormonal agents, such as tamoxifen and letrozole (11,497, 29.1%), were the most frequently ordered drug category. HER-2 inhibitors and anthracycline, known cardiotoxic agents, ranked third and fifth in frequency (6,145, 15.6% and 4,682, 11.9%, respectively). This finding indicates that breast cancer patients were often exposed to cardiotoxic agents during their treatments.

Table 3 presents the patients' cardiotoxicity risk scores when they received their first dose of chemotherapy. In the medication-related factor category, approximately 90% of the patients received high-risk agents, such as anthracyclines and trastuzumab, in both of the groups. In terms of patient-related factors, approximately 2% of the patients had received chest radiation before chemotherapy in both of the groups. In the pre-existing CVDs group, 94.5% had hypertension and 41.6% had diabetes mellitus. Thus, most patients (91.6%) were at a very high risk

Table 1
Demographic and clinical characteristics of breast cancer patients with cardiac diseases (N = 1200).

Variables	Pre-existing CVDs (n = 548)	CVDs after CTx (n = 652)	P
Age at breast cancer diagnosis (years)	59.4 ± 9.4	54.1 ± 9.4	<.001
<30	1 (0.2)	4 (0.6)	<.001
30–39	8 (1.5)	37 (5.7)	
40–49	73 (13.3)	173 (26.5)	
50–59	191 (34.9)	248 (38.0)	
60–69	195 (35.6)	154 (23.6)	
≥70	80 (14.6)	36 (5.5)	
Gender			–
Female	548 (100)	652 (100)	
Body Mass Index (kg/m^2)	26.6 ± 19.7	24.6 ± 3.6	.021
Underweight (<17.9)	8 (1.5)	17 (2.6)	.018
Normal (18–22.9)	137 (25.2)	208 (32.1)	
Overweight (23–24.9)	122 (22.4)	138 (21.3)	
Obesity (≥25)	277 (50.9)	284 (43.9)	
Origin of breast cancer			.087
Upper-outer quadrant of breast	156 (28.5)	177 (27.1)	
Overlapping lesion of breast	155 (28.3)	145 (22.2)	
Breast, not otherwise specified	97 (17.7)	160 (24.5)	
Upper-inner quadrant of breast	59 (10.8)	70 (10.7)	
Lower-outer quadrant of breast	30 (5.5)	44 (6.7)	
Central portion of breast	35 (6.4)	39 (6.0)	
Lower-inner quadrant of breast	14 (2.6)	16 (2.5)	
Nipple and areola	2 (0.4)	1 (0.2)	
Types of breast cancer			.517
Infiltrating duct carcinoma	474 (86.5)	553 (84.8)	
Lobular carcinoma	21 (3.8)	31 (4.8)	
Infiltrating duct and other types of carcinomas	15 (2.7)	20 (3.1)	
Tubular, mucinous, or papillary adenocarcinoma	4 (0.7)	8 (1.2)	
Malignant lymphoma	3 (0.5)	4 (0.6)	
Intraductal carcinoma	5 (0.9)	1 (0.2)	
Others	26 (4.7)	35 (5.4)	
Pathological stage			.095
CIS	12 (2.2)	18 (2.8)	
I	181 (34.2)	194 (31.3)	
II	218 (41.1)	234 (37.8)	
III	57 (10.8)	72 (11.6)	
IV	6 (1.1)	15 (2.3)	
No information	74 (14.0)	119 (19.2)	
Types of cardiac diseases			
Hypertension	518 (94.5)	520 (79.8)	
Heart failure or cardiomyopathy	5 (0.01)	118 (18.1)	
Coronary or peripheral artery disease	16 (2.9)	67 (10.3)	
Arrhythmia	19 (3.5)	28 (4.3)	
Others (Thromboembolism, pericarditis)	1 (0.002)	3 (0.01)	
Duration until cardiac diseases diagnosis[a] (months) (n = 652)		17.0 [5–42]	
<6		187 (28.5)	
6–11		89 (13.5)	
12–23		122 (18.6)	
24–35		65 (9.9)	
36–47		43 (6.5)	
48–59		39 (5.9)	
≥60		112 (17.0)	
LVEF data			<.001
Yes	171 (31.2)	268 (41.1)	
No	377 (68.8)	384 (58.9)	
Baseline LVEF data			<.001
Yes	84 (15.3)	37 (5.8)	
No	464 (84.7)	615 (94.2)	

CIS: carcinoma in situ, CTx: chemotherapy, CVD: cardiovascular disease, LVEF: left ventricular ejection fraction.
[a] Median [Q1–Q3].

Table 2
Number of chemotherapy orders for 1200 breast cancer patients with cardiac diseases (N = 60,053).

Category	Example	n (%)
Hormonal agents	Tamoxifen, Letrozole, Anastrozole, Megestrol, Goserelin	11,497 (29.1)
Taxanes	Paclitaxel, Docetaxel	6217 (15.8)
Her 2 inhibitors	Trastuzumab, Pertuzumab	6145 (15.6)
Alkylating agents	Cyclophosphamide, Carboplatin, Cisplatin, Oxaliplatin, Ifosfamide	4700 (11.9)
Anthracycline	Doxorubicin, Epirubicin, Idarubicin	4682 (11.9)
Fluoropyrimidines	Fluorouracil, Capecitabine	2483 (6.3)
Antimetabolites	Methotrexate, Gemcitabine, Hydroxyurea, Cytarabine, Decitabine	2046 (5.2)
Others	Vinca alkaloids, Tyrosin kinase inhibitors etc.	1702 (4.3)

Table 3
Cardiotoxicity risk score of breast cancer patients with cardiac diseases (N = 1200).

Category	Variables	Pre-existing CVDs (n = 548)	CVDs after CTx (n = 652)
Medication-related factors n (%)	High (risk score 4) Anthracyclines, trastuzumab, Cyclophosphamide, ifosfamide, and clofarabine	505 (92.2)	569 (87.3)
	Intermediate (risk score 2) Docetaxel, pertuzumab, sunitinib, and sorafinib	5 (0.9)	11 (1.7)
	Low (risk score 1) Bevacizumb, dasatinib, imatinib, and lapatinib	0 (0.0)	1 (0.2)
	Rare (risk score 0) e.g., Etoposide, rituximab, thalidomide	38 (6.9)	71 (10.9)
Patient-related factors n (%)	Age >65 years (at breast cancer diagnosis)		
	No	396 (72.3)	571 (87.6)
	Yes	152 (27.7)	81 (12.4)
	Woman		
	Yes	548 (100.0)	652 (100.0)
	Prior or concurrent chest radiation		
	No	533 (97.3)	642 (98.5)
	Yes	15 (2.7)	10 (1.5)
	Prior or concurrent anthracycline		
	No	150 (27.4)	150 (23.0)
	Yes	398 (72.6)	502 (77.0)
	Hypertension		
	No	30 (5.5)	652 (100)
	Yes	518 (94.5)	0 (0)
	Diabetes mellitus		
	No	320 (58.4)	469 (71.9)
	Yes	228 (41.6)	183 (28.1)
	Coronary or peripheral artery disease		
	No	532 (97.1)	652 (100)
	Yes	16 (2.9)	0 (0)
	Heart failure or cardiomyopathy		
	No	543 (99.1)	652 (100)
	Yes	5 (0.9)	0 (0)
Overall score (Mean ± SD) n (%)	Cardiotoxicity Risk Score	7.1 ± 1.4	5.7 ± 1.6
	Very high (>6)	477 (91.6)	171 (85.4)
	High (5–6)	31 (2.2)	399 (5.4)
	Intermediate (3–4)	22 (5.3)	20 (7.5)
	Low (1–2)	18 (0.9)	62 (1.7)

CTx: chemotherapy, CVD: cardiovascular disease.

for cardiotoxicity, with a mean cardiotoxicity risk score of 7.1 ± 1.4. However, in the CVDs after chemotherapy group, only a history of diabetes mellitus was a risk factor for cardiotoxicity because they were not diagnosed with CVDs prior to starting chemotherapy. In this group, 85.4% were at a very high risk and 5.4% were high risk for cardiotoxicity with a mean cardiotoxicity risk score of 5.7 ± 1.6.

Patients with LVEF data were classified into three groups (Table 4.) The HF diagnosis group (n = 95, 21.6%) comprised patients diagnosed with HF after chemotherapy, as described in the electronic health records, while patients in the ASE and EACVI definition group met the ASE and EACVI criteria for CTRCD (n = 39, 8.9%). Together, these groups formed the CTRCD group (n = 134, 30.5%). The no-CTRCD group comprised patients who were neither diagnosed with HF nor had a decline in LVEF (n = 305, 69.5%). There was a statistically significant difference in the mean age between the CTRCD group (53.4 ± 10.2 years) and the no-CTRCD group (58.8 ± 9.9 years). In the CTRCD group, 44.0% of the patients received anthracycline agents, compared to 49.2% in the no-CTRCD group. However, the cumulative dose of doxorubicin was slightly higher in the CTRCD group (149.6 ± 40.2) than in the no-CTRCD group (143.3 ± 50.5). Moreover, the cumulative dose of the ASE and EACVI's definition group (160.0 ± 51.6) was higher than that of the HF diagnosis group (145.1 ± 33.6). Regardless, the cumulative dose of most of the patients in all the groups was below 300 mg/m^2. The median time from starting chemotherapy until CTRCD occurrence was 26.5 months, and the patients' mean age when CTRCD occurred was 56.9 years. There was a lower proportion of patients with pre-existing CVDs in the CTRCD group (26.9% in the CTRCD group and 43.6% in the no CTRCD group).

4. Discussion

Cancer treatment-related cardiotoxicity is a significant concern among a growing number of breast cancer patients (Chung et al., 2013; Conway et al., 2015). Findings from this study show that cardiotoxic anti-cancer agents are frequently used in the treatment of breast cancer patients, and that most breast cancer patients had high cardiotoxicity risk scores. Based on the literature, the comorbidity of cancer and CVDs is increasing, given the aging population with CVDs and the increasing number of cancer survivors (Cardinale et al., 2008; Gulati and Mulvagh, 2018). In this regard, the current findings show that specialized care for cancer patients with CVDs is necessary to avoid worsening pre-existing CVDs and prevent the development of new CVDs. However, the low proportion of baseline echocardiograms that were performed on patients indicate the gap between the existing guidelines and actual practice.

Recent guidelines recommend a careful assessment of cardiovascular risk factors and the occurrences of CVDs at each point during the treatment using clinical imaging, symptom monitoring, or biomarker measurements (Minasian et al., 2019). However, patients receiving chemotherapy lacked baseline assessment and regular cardiac function monitoring during their treatment, although those with pre-existing CVDs were more likely to have baseline LVEF data, in this study. Therefore, risk stratification for cancer treatment-related cardiotoxicity before starting chemotherapy is necessary to identify groups at a high-risk for CVDs. Similarly, Clark and colleagues' study found that only 15% of patients with cardiotoxicity were referred to cardiologists at the pre-treatment stage in Australia (Clark et al., 2019). This demonstrated that this is not only an issue in Korea. However, the positive aspect is that all the cardiology referrals in Clark and colleagues' study occurred after 2012, when the first clinical guidelines for monitoring cardiotoxicity were released, implying that having published guidelines may improve patient care (Clark et al., 2019). Since the present study included patients who were diagnosed with breast cancer between 2008 and 2018, we can expect the more recent data to reflect the improved compliance with the guidelines for assessment of cardiovascular risk factors and CVDs, although this was not available to demonstrate with our data.

Table 4
Descriptive analysis for clinical characteristics according to cancer treatment-related cardiac dysfunction (CTRCD) occurrence (N = 439).

Variables	Total (n = 439)	No CTRCD (n = 305)	CTRCD (n = 134)		
			HF diagnosis or ASE&EACVI definition	HF diagnosis[a] (n = 95)	ASE &EACVI definition[b] (n = 39)
Age at breast cancer diagnosis (years)	56.6 ± 10.2	58.0 ± 9.9	53.4 ± 10.2**	52.8 ± 10.2	54.8 ± 10.0
20–39	28 (6.4)	14 (4.6)	14 (10.4)	11 (11.6)	3 (7.7)
40–59	237 (54.0)	154 (50.5)	83 (61.9)	56 (58.9)	27 (69.2)
≥60	174 (39.6)	137 (44.9)	37 (27.6)	28 (29.5)	9 (23.1)
Female gender	439 (100)	305 (100)	134 (100)	95 (100)	39 (100)
Body mass index (kg/m^2)	24.6 ± 4.0	24.8 ± 4.0	24.2 ± 4.1	24.2 ± 3.7	24.1 ± 4.9
Pre-existing CVDs	169 (38.5)	133 (43.6)	36 (26.9)*	20 (21.1)	16 (41.0)
Hypertension	154 (35.1)	123 (40.3)	31 (23.1)*	20 (21.1)	11 (28.2)
CAD or PAD	13 (3.0)	9 (3.0)	4 (3.0)	1 (1.1)	3 (7.7)
Arrhythmia	12 (2.7)	8 (2.6)	4 (3.0)	1 (1.1)	3 (7.7)
Chest radiation					
Yes	337 (76.8)	240 (78.7)	97 (72.4)	67 (70.5)	30 (76.9)
No	102 (23.2)	65 (21.3)	37 (27.6)	28 (29.5)	9 (23.1)
Chemotherapy					
Anthracycline	209 (47.6)	150 (49.2)	59 (44.0)	42 (44.2)	17 (43.6)
Trastuzumab	34 (7.7)	23 (7.5)	11 (8.2)	7 (7.4)	4 (10.3)
Both	120 (27.3)	73 (23.9)	47 (35.1)	32 (33.7)	15 (38.5)
Other	76 (17.3)	59 (19.3)	17 (12.7)	14 (14.7)	3 (7.7)
Cumulative dose of doxorubicin (n = 326)	146.8 ± 51.1	143.3 ± 50.5	149.6 ± 40.2	145.1 ± 33.6	160.0 ± 51.6
<150 mg/m^2	229 (70.2)	159 (72.3)	70 (66.0)	54 (73.0)	16 (50.0)
150–300 mg/m^2	90 (27.6)	56 (25.5)	34 (32.1)	19 (25.7)	15 (46.9)
≥300 mg/m^2	7 (2.1)	5 (2.3)	2 (1.9)	1 (1.4)	1 (3.1)
Period until CTRCD[c] (months) (n = 134)	–	–	26.50 [10–67]	28.00 [10–67.5]	20.00 [10–62]

*p-value = 0.001; ** p-value < 0.001.
t-test was used for continuous variables, and chi-square test for nominal variables.
BC: Breast cancer, CAD: Coronary artery disease, CVD: Cardiovascular disease, CTRCD: Cancer treatment-related cardiac dysfunction, PAD: Peripheral artery disease.
[a] Patients with no baseline LVEF data, diagnosed heart failure after chemotherapy.
[b] Patients who meet American Society of Echocardiography and European Association of Cardiovascular Imaging's definition of CTRCD.
[c] Median [Q1–Q3].

Contrary to our expectations, the proportion of patients with pre-existing hypertension in the CTRCD group was lower than in the no-CTRCD group. Generally, hypertension is considered a risk factor for CTRCD (Albini et al., 2010; Bloom et al., 2016). Although the available data did not allow us to determine the exact number of patients, in our dataset, who were referred to the cardiology department before receiving chemotherapy, it is possible that more patients with pre-existing CVDs were referred to the cardiology department and received the appropriate treatment, compared to those without pre-existing CVDs. The higher proportion of baseline LVEF assessment in the pre-existing CVDs group, compared to the other group supports this explanation. Moreover, beta-blockers and angiotensin-converting enzyme inhibitors, frequently used for hypertension, are recommended to prevent chemotherapy-related cardiac complaints (Cardinale et al., 2010; Hamo et al., 2016). Cardioprotective agents, such as dexrazoxane, that are used for metastatic breast cancer patients receiving high-dose anthracycline therapy, also yield significant cardioprotective effects by preventing the thickening of the heart muscles (Mao et al., 2019). Therefore, the use of these medications and preventive monitoring may also be conducive to avoiding CTRCD. However, despite these possibilities, our finding did not adjust other factors related to the occurrence or prevention of CTRCD using adequate statistical methods. Further research is needed to verify the prevention effect of medication on CTRCD occurrence in patients with pre-existing CVDs.

Self-assessment for cardiac symptoms combined with cardiac monitoring are critical for the early detection of CTRCD. According to the definition of CTRCD from the cardiac review and evaluation committee in trastuzumab trials, the presence of heart failure symptoms is one of the criteria of the LVEF reduction range (Seidman et al., 2002). Although early cardiac monitoring effectively detects asymptomatic CTRCD (Chung et al., 2013), cases of heart failure with preserved ejection fraction (HFpEF), may not be detected by echocardiogram only. Traditionally, most studies have focused on left ventricular systolic dysfunction (Haykowsky et al., 2016); however, older breast cancer patients also have risk factors associated with heart failure with preserved ejection fraction. For example, mediastinal radiation may deteriorate HFpEF by affecting cardiac structures (Haykowsky et al., 2016; Suter and Ewer, 2018). Therefore, we should consider patients' self-monitoring for cardiac symptoms, as well as other cardiac function measurements.

Although our study does not include any variables indicating patients' self-monitoring or lifestyle, encouraging patients to engage in prevention and early detection of CVDs may be an important factor in establishing and following systematic guidelines for breast cancer survivors. In the past two decades, many guidelines, for healthcare professionals, have been released regarding the prevention of CTRCD (Hamo et al., 2016). However, formal guidelines for patients and families are still limited. Moreover, oncologists find it difficult to explain the potential risks of cancer treatment and tend to assume that cancer patients are not concerned about the occurrence of CVDs (Koop et al., 2021). These can be obstacles in encouraging patients' engagement in CTRCD prevention, therefore, it is essential for oncology professionals to recognize the benefits of early cardiac monitoring in women who survive breast cancer (Koop et al., 2021), and the importance of collaboration between healthcare professionals and patients.

Our study has significance given that electronic health records were investigated to analyse the status of cardiac surveillance, and the characteristics and occurrence of CTRCD, focusing on Korean, female breast cancer patients with CVDs. However, there are several limitations. First, due to the retrospective design, we cannot verify the causal relationship between the certain chemotherapy and the occurrence of cardiovascular complications. Moreover, as we only collected the data among breast cancer patients with CVD diagnosis at the time of data extraction and since many patients received chemotherapy without a baseline

echocardiogram, we cannot establish an accurate occurrence rate for CTRCD. Although few patients in our dataset met the criterion regarding using dexrazoxane, which is only suggested for patients with over 300 mg/m^2 cumulative dose of doxorubicin, it may be a limitation, since we cannot identify and adjust cardio-protect effect of relevant medications in our sample. Finally, the various aims of patients' cancer treatment (e.g., adjuvant, neo-adjuvant, palliative) cannot be investigated. As this can affect dosage, treatment aims should be considered in future studies, along with long-term observation for the occurrence of CTRCD and other CVDs, to verify the current findings. Moreover, the most recent treatment trends for cancer patients with CVDs should be analysed, using recent data.

5. Conclusion

Despite breast cancer patients with pre-existing CVDs being at a high risk for cardiotoxicity, baseline studies regarding the risk assessment before chemotherapy were insufficient to support the prevention and early detection of cardiotoxicity. Therefore, it is paramount to implement cardiac function monitoring at pre-treatment and each treatment stage for high-risk patients, if risk stratification using a cardiotoxicity risk score is possible. Moreover, both oncology and cardiology nurses should consider how they monitor and manage cancer survivors' cardiac function to maintain their optimal health status.

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CRediT authorship contribution statement

Arum Lim: Data curation, Formal analysis, Writing – original draft, review and editing draft, final approval. **Hyoeun Jang:** Formal analysis, Writing – review & editing, final approval. **Misun Jeon:** Formal analysis, Writing – review & editing, final approval. **Anecita P. Fadol:** Conceptualization, Formal analysis, Writing – review & editing, final approval. **Sanghee Kim:** Conceptualization, Methodology, Formal analysis, Resources, Writing – review & editing, final approval, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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