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Association between Right Ventricle Function with Left Ventricle Cardiotoxicity in Breast Cancer Patients Underwent Anthracycline Chemotherapy at Dr Sardjito Hospital

Anggit Prawasti[1]*, Susanna Hilda Hutajulu[2]*, Nahar Taufiq[1], Hasanah Mumpuni[1]

[1]Departemen Kardiologi dan Kedokteran Vaskular, Fakultas Kedokteran, Kesehatan Masyarakat, dan Keperawatan, Universitas Gadjah Mada

[2]Divisi Hematologi dan Onkologi Medik, Departemen Ilmu Penyakit Dalam. Fakultas Kedokteran, Kesehatan Masyarakat, dan Keperawatan, Universitas Gadjah Mada

ARTICLE INFO

*Corresponding author

Email:
anggit.prawasti@mail.ugm.ac.id

Address:
Jl. Pandega Tamtama G.18, RT 16, RW 06, Caturtunggal, Depok, Yogyakarta, 55281

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ABSTRACT

Background: In Indonesia, breast cancer remains the leading cause of newly diagnosed cancers. Anthracyclines are the first-line treatment for solid tumors, but the presence of cardiotoxic side effects has diminished the efficacy of anticancer therapy. Left ventricular systolic dysfunction and right ventricle dysfunction can both be caused by anthracyclines because these drugs can damage and kill the heart muscle cells. Currently, the assessment of anthracycline-induced cardiotoxicity has only focused on the left ventricle, despite the fact that right ventricular structures are also susceptible to anthracycline-induced damage. Global longitudinal strain is a novel echocardiographic parameter that can detect early alterations in contractility function.

Aim: To determine the association between right ventricular function and left ventricular cardiotoxicity in breast cancer patients undergoing anthracycline chemotherapy.

Research Methods: This research is an observational cross-sectional study with retrospective data collection. Includes data from 36 over 18-year-old patients with breast cancer who received anthracycline chemotherapy for the first time as a basic regimen at RSUP Dr. Sardjito between July 2018 and November 2021 and underwent a baseline echocardiography exam and an evaluation echocardiography after administration of anthracycline chemotherapy. Right ventricular function was measured using RV-GLS parameters, and left ventricular cardiotoxicity was assessed as a 15% or greater decrease in LV-GLS from baseline.

Results: This study included 36 female breast cancer patients with a mean age of 53,19 ± 8,50 years. Nine patients were diagnosed with left ventricular cardiotoxicity. Patients with right ventricular systolic dysfunction (RV-GLS -20%) comprised 7 (78%) of those who developed left ventricular cardiotoxicity, while patients with normal right ventricular function (RV-GLS -20%) comprised only 2 (22%). Patients with left ventricular cardiotoxicity had a prevalence of right ventricular systolic dysfunction (RV-GLS -20%) of 78%, while patients without left ventricular cardiotoxicity had a prevalence of right ventricular systolic dysfunction (RV-GLS -20%) of 44%, resulting in a prevalence ratio (PR) of 1.78, but this difference was not statistically significant (PR 1,78 p = 0.128, 95% CI 0.75-13.07).

Conclusions: Patients with left ventricular cardiotoxicity had a higher incidence of right ventricular systolic dysfunction than patients without left ventricular cardiotoxicity, although the association was not statistically significant.

INTISARI

Latar Belakang: Insiden kanker payudara masih menduduki peringkat pertama kasus kanker baru di Indonesia. Antrasiklin merupakan terapi lini pertama pada tumor solid, namun kesuksesan terapi antikanker termarginalkan dengan adanya efek samping kardiotoksik. Antrasiklin dapat menyebabkan kerusakan dan kematian sel otot jantung sehingga menyebabkan disfungsi sistolik ventrikel kiri dan ventrikel kanan. Saat ini penilaian kardiotoksik terinduksi antrasiklin hanya berfokus pada ventrikel kiri, dimana struktur ventrikel kanan juga rentan terhadap kerusakan oleh terapi antrasiklin. Global longitudinal strain merupakan merupakan parameter ekokardiografi baru yang dapat mendeteksi perubahan fungsi kontraktilitas pada stadium awal.

Tujuan: Untuk mengetahui hubungan fungsi ventrikel kanan dengan kardiotoksik ventrikel kiri pada pasien kanker payudara yang mendapat kemoterapi antrasiklin.

Metode Penelitian: Penelitian ini merupakan penelitian observasional dengan metode potong lintang dan mengambil data secara restrospektif. Mencakup data dari 36 pasien berusia ≥ 18 tahun dengan diagnosis kanker payudara yang mendapatkan kemoterapi antrasiklin pertama kali sebagai regimen dasar di RSUP Dr. Sardjito dari Juli 2018 hingga November 2021 dan telah menjalani pemeriksaan ekokardiografi basis dan ekokardiografi evaluasi pasca pemberian kemoterapi antrasiklin. Fungsi ventrikel kanan diukur menggunakan parameter RV-GLS dan kardiotoksik ventrikel kiri (dinilai dengan penurunan LV-GLS ≥ 15% dibandingkan LV-GLS basis).

Hasil: Dalam penelitian ini terdapat 36 pasien wanita dengan kanker payudara yang dengan rerata usia 53,19 ± 8,50 tahun. Terdapat sembilan pasien yang mengalami kardiotoksik ventrikel kiri. Kelompok pasien yang mengalami kardiotoksik ventrikel kiri, pasien dengan disfungsi sistolik ventrikel kanan (RV-GLS < -20%) sebanyak 7 (78%) sedangkan pasien dengan normal fungsi ventrikel kanan (RV-GLS ≥ -20%) sebanyak 2 (22%). Prevalensi disfungsi sistolik ventrikel kanan (RV-GLS < -20%) pada pasien yang mengalami kardiotoksik ventrikel kiri sebesar 78% dan prevalensi disfungsi sistolik ventrikel kanan (RV-GLS <-20%) pada pasien yang tidak mengalami kardiotoksik ventrikel kiri sebesar 44%, sehingga rasio prevalensi (prevalence ratio/PR) sebesar 1,78. Kejadian disfungsi sistolik ventrikel kanan pada pasien yang mengalami kardiotoksik ventrikel kiri mempunyai 1,78 kali dibandingkan dengan pasien yang tidak mengalami kardiotoksik ventrikel kiri, namun secara statistik tidak menunjukkan perbedaan yang signifikan, nilai p = 0,128, (PR 1,78, p = 0,128, IK95% 0,75-13,07).

Simpulan: Kejadian disfungsi sistolik ventrikel kanan pada pasien yang mengalami kardiotoksik ventrikel kiri lebih besar dibandingkan dengan pasien yang tidak mengalami kardiotoksik ventrikel kiri, namun hubungan tersebut tidak signifikan secara statistik.

Introduction

According to data from Global Cancer Statistics (GLOBOCAN) 2020, an estimated 19.3 million new cases of cancer and over 10 million deaths from cancer occurred worldwide in 2020. Breast cancer is the most prevalent cancer in women, surpassing lung cancer with an expected 2.3 million new cases (11.7%), and is the fifth leading cause of cancer-related mortality (6.9%)[1]. Breast cancer is a malignant disease that begins in the ductal epithelium or lobules of the breast, and it can be invasive (stages I-IV) or non-invasive (carcinoma in situ). Breast cancer is the most prevalent cancer worldwide, particularly in emerging nations like Indonesia. In 2005-2007, the incidence of breast cancer in the province of the Special Capital Region of Jakarta was 31,2/100,000 women per year, according to statistics from the Jakarta population-based cancer registry (PBCR). The distribution of cancer cases in the Government General Hospital (RSUP) Dr. Sardjito, for the data collection period from September 2016 to March 2021, there were 26,574 cases of cancer diagnosed between 2008 and 2018, the distribution of 10 cancer cases with the highest incidence rate was still dominated by breast cancer in the first place with 4,999 cases, followed by cervical, colorectal, and ovarian cancers in that order[2].

Adjuvant chemotherapy is provided with the purpose of eliminating cancer cells in the body with the intention of preventing a return of the disease and the spread of the cancer to other parts of the body. According to the findings of the ABC trials, which were published in 2017, chemotherapy with a basic anthracycline regimen demonstrated a superior clinical outcome than taxane in patients with early-stage breast cancer[3]. However, the prevalence of cardiotoxic side effects has minimized the success of numerous anticancer medicines in extending cancer patients' survival rates in recent years[4].

Anthracycline is a chemotherapeutic agent produced by a variety of streptomyces species and plays a crucial role in the treatment of cancer. Anthracyclines (doxorubicin, daunorubicin, epirubicin, and idarubicin) are extensively utilized in the treatment of cancer, particularly breast cancer and lymphoma. Anthracyclines are commonly used first-line treatments for solid tumors and hematological malignancies, including breast cancer, lung cancer, lymphoma, leukemia, and sarcoma[5,6]. However, the administration of anthracyclines is related with the damage and death of cardiac muscle cells, leading to dysfunction of the left and right ventricles and heart failure[7]. The spectrum of anthracycline-induced cardiotoxicity manifesting as cardiomyopathy ranges from asymptomatic reduced left ventricular function to heart failure with usual signs and symptoms[8].

In a retrospective analysis study involving more than 4000 patients receiving doxorubicin, it was found that 2.2% of patients developed clinical signs and symptoms of congestive heart failure[9]. Between 1988 and 1992, doxorubicin therapy was administered to patients in three prospective clinical trials to examine cardiotoxic effects. The rate of congestive heart failure associated with doxorubicin administration was 5% at a cumulative dose of 400 mg/m2, 16% at a dose of 500 mg/m2, and 26% at a dose of 550 mg/m2[10]. Anthracycline treatment was associated with cardiotoxic events in 9% of all patients, with 98% of instances occurring in the first year and being asymptomatic, according to a study that was conducted by Cardinale et al., (2015) and that involved 2625 patients who were followed for 5.2 years. Subclinical cardiotoxic side effects also occurred in 30% of patients receiving doxorubicin at a dose of 180-240 mg/m2 under surveillance for 13 years after therapy was received[11]. Asymptomatic reduced left ventricular function is linked to a higher risk of heart failure and death later in life8. Early diagnosis of subclinical cardiotoxicity in breast cancer patients receiving anthracycline chemotherapy is critical because it can serve as a guideline for initiating cardioprotective medication and averting more severe cardiac failure[12].

Currently, guidelines for the prevention and treatment of anthracycline-induced cardiotoxicity refer to the left ventricle, although the involvement of the right ventricle is also the subject of intensive investigation. Since the prognostic role of right ventricular structure and function has been demonstrated in numerous cardiovascular disease entities, including heart failure, coronary artery disease, valvular heart disease, pulmonary hypertension, and hypertrophic cardiomyopathy, the assessment of the right ventricle in oncology patients has increased[13].

Transthoracic echocardiography (TTE) is recommended as the preferred technique for diagnosing anthracycline-induced cardiotoxicity. Global longitudinal strain (GLS) is an echocardiographic metric for detecting subclinical ventricular dysfunction that is more significantly associated with prognosis in the non-oncological heart disease population than left ventricular ejection fraction parameters[14]. Several observational studies have shown a significant reduction in GLS results for predicting a decrease in left ventricular ejection fraction or cardiotoxic events in populations of breast cancer patients who were receiving anthracycline chemotherapy regimens[15–18]. At currently, the assessment of GLS parameters for subclinical cardiotoxicity is concentrating more on the left ventricle than it has in the past. In the meantime, patients diagnosed with cancer have an increased risk of developing right ventricular abnormalities for a number of reasons. These include a preexisting dysfunction in the right ventricle, involvement of cancer itself (either primary or metastatic), or the cardiotoxic effects of chemotherapy[7]. An early anthracycline-induced cardiotoxicity study (Adriamycin) including a right ventricular endomyocardial biopsy was the first investigation into chemotherapy-induced involvement of the right ventricle. Although there are still discrepancies in the outcomes of follow-up studies of right ventricular cardiotoxicity, a number of research suggest the prevalence of subclinical right ventricular dysfunction due to anthracycline medication[12,19,20]. Another study indicated that there was no substantial change in the function of the right ventricle[21,22].

Even now, there are a limited number of studies that investigate the cardiotoxic effects of anthracycline treatment on the right ventricular[7]. Anthracycline treatment can also cause damage to the right ventricle because of its more fragile structure, which contains less myofibrils. This makes the right ventricle more susceptible to this type of injury[23]. Several investigations have revealed that anthracycline medication results in abnormalities of right ventricular wall motion or functional abnormalities of the right ventricle, but these findings have not been frequently documented. Complex anatomical geometry, the position of the right ventricle in the chest cavity, and the pattern of right ventricular contractions make it difficult to detect subclinical involvement of right ventricular function using conventional echocardiography technologies. Existing research have yielded inconclusive findings on an increase in the dimensions of the right ventricle and/or right atrium, structural changes following chemotherapy and/or radiotherapy, and changes in right ventricular diastolic function and right ventricular systolic function. Data on right ventricular systolic function that have been routinely examined, such as fractional area change (FAC), right ventricular ejection fraction (RVEF), tricuspid annular plan systolic excursion (TAPSE), RV tissue

doppler S', or RV myocardial perfusion index (MPI), continue to produce varying results[13]. Cardiac magnetic resonance (CMR) is the gold standard for determining the size and function of the right ventricle, although it has limitations for examining the characteristics of the right ventricle's thin tissue. There are only a few studies involving a small number of patients that examine right ventricular systolic function following chemotherapy[13].

The GLS test has been recommended by the European Society of Cardiology (ESC) for identifying subclinical left ventricular cardiotoxicity because it has been proven to be more sensitive than other traditional echocardiographic measures[24]. Currently, a new echocardiographic method known as right ventricular speckle tracking echocardiography (STE) is providing new insights into the process of determining how well the right ventricle is working[12]. Speckle tracking echocardiography 2D (2D-STE) is an echocardiographic parameter that permits tracking the actual time of frame-to-frame myocardial movement, hence overcoming the majority of the restrictions of conventional echocardiography. Specifically, 2D-STE is less angle- and load-dependent, as well as less impacted by passive tethering, allowing for accurate assessment of regional and global myocardial function, which reflects more accurate myocardial contractility[25]. Right ventricular peak systolic longitudinal strain and strain rate are assessed on a four-chamber view, where the right ventricle-free wall strain and septum are each divided into three segments, namely basal, mid, and apex, resulting in regional strain values that become right ventricle global longitudinal strain (RV-GLS) and right ventricle-free wall longitudinal strain, respectively (RV-FWLS)[25]. RV-GLS correlates with CMR-determined right ventricular ejection fraction and is a reliable predictor of right ventricular dysfunction[26]. Several studies in breast cancer populations evaluated the systolic function of the right ventricle utilizing RV-GLS and RV-FWLS[27–30]. In cancer patients, right ventricular longitudinal strain is the only metric that assesses right ventricular systolic function with reliable and uniform data. During or after chemotherapy, right ventricle global longitudinal strain (RV-GLS) and right ventricle-free wall longitudinal strain (RV-FWLS) reduced. The difference between RV-GLS and RV-FWLS is that the involvement of the interventricular septum during measurement partially reflects changes in the left ventricle because the septum is between the two ventricles, whereas RV-FWLS only focuses on the free wall of the right ventricle and excludes the septum's contribution, but with a deficiency. Undiagnosed right ventricular septal alterations are possible[28]. In cardio-oncology clinics, RV-GLS is a reliable, robust, and easy-to-use right ventricular systolic function measurement[13].

Methods

This research is an observational cross-sectional study with retrospective data collection. Includes data from 36 over 18-year-old patients with breast cancer who received anthracycline chemotherapy for the first time as a basic regimen at RSUP Dr. Sardjito between July 2018 and November 2021 and underwent a baseline echocardiography exam and an evaluation echocardiography after administration of anthracycline chemotherapy. Right ventricular function was measured using RV-GLS parameters, and left ventricular cardiotoxicity was assessed as a 15% or greater decrease in LV-GLS from baseline.

The following were among the inclusion criteria for the study's participants: 1) Patients with or without metastases who underwent their initial treatment with the standard anthracycline regimen (doxorubicin or epirubicin) for adjuvant and palliative purposes, 2) Patients with breast cancer, whether they had previously had radiation or not, 3) Patients with TAPSE 17 on initial echocardiography prior to chemotherapy, 4)patients with an ejection fraction of 54%, and 5) patients who are willing to participate in research are all required. Exclusion criteria in this study were: 1) patients with chronic renal failure, 2) significant valvular heart disease (more than a mild degree of either regurgitation or stenosis of the mitral or aortic valves), 3) pulmonary hypertension patients, 4) patients with shunt abnormalities : atrial septal defect, Partial Anomalous Pulmonary Venous Drainage (PAPVD), ventricular septal defect, Patent Ductus Arteriosus (PDA), pulmonary stenosis, 5) patients with comorbid chronic obstructive pulmonary disease (COPD), 6) patients who have not completed the entire chemotherapy cycle breast cancer, 7) patients with inadequate echocardiographic images, 8) breast cancer patients receiving anti-HER2 (trastuzumab) therapy, 9) Incomplete medical record data

Research Protocol

Periodic TTE examination in breast cancer patients who had anthracycline chemotherapy as the basic regimen before treatment was referred to as a baseline echocardiogram, followed by an evaluation echocardiography at the completion of chemotherapy and every 6 months after chemotherapy. The TTE was performed at the echocardiography room of the Integrated Heart Center on the first floor of RSUP Dr. Sardjito. The VividTM E95 GE Healthcare Ultrasound echocardiography equipment was used to perform transthoracic echocardiogram on the patient who was laying supine slightly to the left. The data collected included a routine TTE examination and a four-chamber apical view video focusing on the right ventricle. According to the ASE/EACVI 2020 methodology, this TTE examination is used to determine the existence or absence of structural heart defects, coronary heart disease, and to establish a left ventricular cardiotoxic diagnosis.

The right ventricular strain parameter (RV-GLS) was measured from the previously taken TTE video recording data. RV-GLS measurements used 6 right ventricular myocardium segments from a 4-chamber apical view (3 free wall segments and 3 interventricular septal segments) and were analyzed using Viewpoint 6 with EchopacTM Suite software by a cardiologist who was

blind to this study. Once collected, the data is entered in Microsoft Excel software and statistical analysis is performed.

Statistical Analysis

Data were analyzed with Statistical Package for the Social Science (SPSS) International Business Machine (IBM) software version 25. Univariate analysis numeric variable using Kolmogorov-Smirnov test where p >0.05 showed normally distributed data. Numeric variables will be shown as mean/median + standard deviation (SD).

Numeric variable with normal distribution will be bivariate analysis with independent T-test. Meanwhile data with abnormal distribution will be tested with non-parametric Mann-Whitney-U test. The categorical variable will be analyzed with the Chi-Square test; if there were less than five expected counts, the Fisher-exact test will be used. All variables with p>0.25 will be analyzed in multivariate analysis with logistic regression to determine confounding variables.

Result

Baseline Characteristics of Study Subjects

This study included 36 female breast cancer patients who met the inclusion and exclusion criteria with a mean age of 53,19 ± 8,50 years. Baseline characteristic data are shown in Table 1.

Seven participants (19.4%) had concomitant hypertension, one subject (2.8%) had dyslipidemia, and one subject (2.8%) had experienced a stroke or had a history of stroke. The individuals of this study had no additional concomitant illnesses, such as DM or CHD. A total of 2 subjects (5.6%) received ACE-inhibitors/ARBs, while 34 subjects (94.4%) did not. None of the participants received treatment with beta blockers.

According to oncology statistics, the majority of breast cancer locations in 24 patients (66.7%) were on the left side, 10 subjects (27.8%) were on the right side, and 2 subjects (5.6%) were bilateral. Six participants (16.7%) had lung metastases and ten subjects (27.8%) had other organ metastases. On the basis of histological findings, 34 cases (94.4%) had infiltrative ductal carcinoma, 1 subject (2.8%) had metaplastic carcinoma, and 1 subject (2.8%) had lobular carcinoma. Twenty-nine patients (80.6%) received doxorubicin regimen, seven patients (19.4%) received epirubicin regimen, and the vast majority of patients (34 patients, or 94.4%) received locoregional radiation. Dosing regimens for doxorubicin with a median of 240 mg/m2 (range: 120-400 mg/m2) and epirubicin with a median of 300 mg/m2 (range: 150-400 mg/m2).

In this investigation, the echocardiographic parameters measured were LV-EF, LV-GLS, TAPSE, RV-FAC, and RV-GLS. In accordance with the criteria of the ESC 2022 cardio-oncology guidelines for determining the anthracycline-induced left ventricular cardiotoxic group, 9 subjects were determined to have left ventricular cardiotoxicity and were divided into 3 patients diagnosed at the end of chemotherapy, 4 patients diagnosed at 6 months after chemotherapy, 1 patient diagnosed at 12 months after chemotherapy, and 1 patient diagnosed at 18 months after chemotherapy. In this study, all participants underwent anthracycline-based chemotherapy regimens, and 94.4% got locoregional radiation. During the observation period, 9 patients (25%) suffered cardiotoxicity of the left ventricle.

Table 1. Baseline characteristics

Variable	Subject (n= 36)
Age (year), mean+SD	53,19 ± 8,50
Weight (kg), mean+SD	55,67 ± 9,75
Height (cm), median (min-max)	153 (136-165)
BMI (kg/m2), median (min-max)	23,4 (14,6-34,1)
Sex	36 (100%)
Comorbid	
Hypertension	7 (19,4%)
Dyslipidemia	1 (2,8%)
DM	0 (0%)
Stroke/ history of Stroke	1 (2,8%)
CHD/ history of CHD	0 (0%)
Oncology data	
Lung Metastases	6 (16,7%)
Other organs Metastases	10 (27,8%)
Anthracycline Regimen	
Doxorubicin	29 (80,6%)
Epirubicin	7 (19,4%)
Anthracycline Dose	
Doxorubicin Dose (mg/m2), media (min-max)	240 (120-400)
Epirubicin Dose (mg/m2), media (min-max)	300 (150-400)
Radiotherapy	34 (94,4%)
Drugs	
ACE-inhibitor/ARB	2 (5,6%)
Beta-blocker	0 (0%)
Baseline Echocardiography	
Left ventricular systolic function	
LV-EF (%), mean + SD	69,64 ± 6,22
LV-GLS (%), mean + SD	-20,21±2,81
Right ventricular systolic function	
TAPSE (mm), median (min-max)	22 (19-32)
RV-FAC (%)	-*
RV-GLS (%)	-*
Evaluation Echocardiography	
Left ventricular systolic function	
LVEF (%), median (min-max)	69,5 (57-76)
LV-GLS (%), median (min-max)	-19 (16,6-24,3)
Right ventricular systolic function	
TAPSE (mm), mean + SD	21,97 ± 2,77
RV-FAC (%), mean + SD	49,78 ± 10,19
RV-GLS (%), mead + SD	-19,61± 3,60

Note: * data retrieval is not possible owing to technological constraints; BMI, body mass index; DM, diabetic mellitus; CHD, coronary heart disease; ACE-inhibitors, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

On the baseline of echocardiography, the left ventricular systolic function of patients prior to receiving anthracycline chemotherapy regimens was still within normal limits, with an average LVEF of 69.64% ±6.22% and a normal LV-GLS value of -20.21%±2.88%, as well as a TAPSE of 22 mmHg for the right ventricular systolic function (19-32 mm). On echocardiography evaluation, the results of LV-GLS deteriorated by -19% (-16.6% to -24.3%), despite the average left ventricular ejection fraction (LVEF) remaining within acceptable limits at 69.5% (57% to 76%). Similarly, for right ventricular systolic function, the mean RV-GLS result was below the normal value, at -19.61%±3.60 %, although the mean TAPSE was within the normal range at 21.97±2.70 mm.

Analysis of the Relationship between Right Ventricular Function and Left Ventricular Cardiotoxicity

In this study, right ventricular function was divided into right ventricular systolic dysfunction and normal right ventricular systolic function based on the cut-off value for normal right ventricular systolic function, which was TAPSE 17 mm or RV-FAC 35% or RV-GLS - 20%. In this study, patients with right ventricular systolic dysfunction (RV-GLS -20%) comprised 7 (78%) of those who developed left ventricular cardiotoxicity, while patients with normal right ventricular function (RV-GLS -20%) comprised only 2 (22%). Patients with left ventricular cardiotoxicity had a prevalence of right ventricular systolic dysfunction (RV-GLS -20%) of 78%, while patients without left ventricular cardiotoxicity had a prevalence of right ventricular systolic dysfunction (RV-GLS -20%) of 44%, resulting in a prevalence ratio (PR) of 1.78. Table 2 displays that the incidence of right ventricular systolic dysfunction in patients with left ventricular cardiotoxicity was 1.78 times that of patients without left ventricular cardiotoxicity, although the difference was not statistically significant (p = 0.128).

Table 2. Relationship between Right Ventricular Function and Left Ventricular Cardiotoxicity

Variable	Left ventricular cardiotoxicity		p-value	PR	CI 95%
	Yes	No			
Right ventricular systolic dysfunction	7 (78%)	12 (44%)	0,128	1,78	0,75-13,07
Normal right ventricular systolic function	2 (22%)	15 (56%)			

Note : PR, prevalence ratio; CI, confidence interval

Sub-analysis comparing echocardiographic characteristics between patients with and without left ventricular cardiotoxicity

On basic echocardiography, the mean value of LV-GLS in the group with left ventricular cardiotoxicity was -22.24% ±1.95% higher than in the non-cardiotoxic group, which was -20.2% ± 2.74%; this difference was statistically significant with p = 0.001, despite the fact that both mean values are still within the normal range. Echocardiographic evaluation revealed that the LV-GLS in the group with left ventricular cardiotoxicity was -18% (-16.6-21.3%) lower than the non-cardiotoxic group -20.1% (-16.6-24, 3%), however this difference was not statistically significant (p=0.07). Table 3 displays that the average RV-GLS was -17.99% ± 3.63 % lower in the group with left ventricular cardiotoxicity than in the non-cardiotoxic group -20.14% ± 3.49%, although this difference was not statistically significant (p= 0.121).

Table 3. Comparison echocardiographic characteristics between patients with and without left ventricular cardiotoxicity

Variable	Left ventricular cardiotoxicity		p
	Yes n=9	No n=27	
Baseline Echocardiography			
LVEF (%), rmean + SD	68,78 ± 8,12	69,93 ± 5.61	0,638
LV-GLS (%), mean + SD	-22,24 ± 1,95	-20,2 ± 2,74	0,011¥
TAPSE (mm), median (min-max)	23 (20-30)	22 (19-32)	0,686
RV-FAC (%)	-*	-*	
RV-GLS (%)	-*	-*	
Evaluation Echocardiography			
LVEF (%), median (min-max)	72 (57-74)	69 (62-76)	0,741
LV-GLS (%), median (min-max)	-18 (16,6-21,3)	-20.1 (16,5-24,3)	0,070
TAPSE (mm), mean + SD	21,00 ± 3,04	22,29 ± 2,66	0,230
RV-FAC (%), mean + SD	44,33 ± 11,23	51,59 ± 9,34	0,063
RV-GLS (%), mean + SD	-17,99 ± 3,63	-20,14 ± 3,49	0,121

Note: mean ± standard deviation: independent T test; median (min-max): Mann Whitney test; p-value 0.05; * data unavailable due to technical limitations.

Discussion

Baseline Characteristics of Study Subjects

This study included 36 female participants with an average age of 53.19 8.50 years. This study's average age was nearly identical to the data from the Jogja Cancer Registry, which indicated that, when instances of breast cancer were grouped by age, the majority of patients were adults (36.9% in the 41-50 year age group and 30.0% in the 51-60 years, followed by 14.8% in the 31-40 age group)[2]. Similarly, in a number of research on the breast cancer population, the average age was shown to be highest in the fourth and fifth decades[19,27,28].

All patients received six to eight cycles of anthracycline-based chemotherapy. 80.6% of patients received doxorubicin at a dose of 240 mg/m2 (120-240 mg/m2), followed by 19.4% of patients who received epirubicin at

a dose of 300 mg/m2 (150-400 mg/m2). The probability of anthracycline-induced cardiotoxicity increases with cumulative dose: 3-5% at a cumulative dose of 400 mg/m2, 7-26% at a cumulative dose of 550 mg/m2, and 18-48% at a cumulative dose of 700 mg/m2[31]. In this particular investigation, the anthracycline dose regimen that was utilized placed the study individuals at a risk level that ranged from low to moderate for anthracycline-induced cardiotoxicity.

On the basis of echocardiography, the left ventricular systolic function of patients prior to starting anthracycline chemotherapy regimens was within normal limits, with an average LVEF of 69.64±6.2% and an average LV-GLS value of -20.21 2.8%. With a TAPSE of 22 mm, the right ventricular systolic function is also within acceptable ranges (19-32 mm). These basic echocardiographic parameters have the same normal values as in the female population, where LVEF is normal at 64 5%, LV-GLS is normal at -20%, and TAPSE is normal at 24±3.5 mm[32].

On echocardiography evaluation, the results of LV-GLS decreased with a value of -19% (-16.6% - -24.3%), even though the average left ventricular ejection fraction was still within normal limits LVEF 69.5% (57% -76%). This is consistent with a study by Xu et al., in which the breast cancer population that received anthracycline-based chemotherapy demonstrated a statistically significant decrease in LV-GLS. Likewise in right ventricular systolic function, the average RV-GLS result was below the normal value, namely -19.61 ± 3.60%, even though the TAPSE mean of 21.97 ± 2.77 mm was within the normal range. These results are close to the results of a study by Xu et al., found that the RV-GLS evaluation at 12 months after chemotherapy was -18.6 ± 2.6%[12].

Analysis of the Relationship between Right Ventricular Function and Left Ventricular Cardiotoxicity

The incidence of right ventricular systolic dysfunction was 1.78 times higher in patients with left ventricular cardiotoxicity than in patients without left ventricular cardiotoxicity, although the difference was not statistically significant (p = 0.128). Multiple investigations have concluded that anthracycline treatment has no deleterious effects on the right ventricle. Research including 23 individuals who received low-dose anthracyclines (doxorubicin) revealed that the Tei RV index did not alter significantly after chemotherapy[21]. Another study assessing the lowering of RV EF in women with breast cancer also showed no meaningful results[33]. Xu et al., observed that there was no significant difference between patients with and without left ventricular cardiotoxicity in terms of 3D RVEF (-10.8% to -5.4%, p=0.383) and RV-GLS (-18.2% to -11.3%, p=0.159)[12].

In another study that assessed changes in RV-GLS and RV-FWLS after anthracycline chemotherapy, the results showed significant changes where the RV-GLS was based, compared to the end of chemotherapy and 12 months after chemotherapy (-21.5% ± 3.2%; -20.8%±3.0%; -18.6%±2.6%, p<0.05) and RV-FWLS basis compared with end of chemotherapy and 12 months post chemotherapy (-25.8%±2 .9%; -23.9%±2.8%;-21.6±2.5%, p < 0.05). However, in this study, the RV-GLS data on basic echocardiography could not be retrieved, so it was not possible to compare the RV-GLS changes that occurred before and after chemotherapy. The results in this study were also different from the results of the RV-FWLS parameter variation where there was a significant difference between patients with left ventricular cardiotoxicity and those without (-20.6% versus -13.1%, p=0.020). RV-FWLS is significantly associated with a decrease in LVEF > 10% to a value of < 50% (r=0.42, p <0.001)[12]. This disparity may be the result of discrepancies between the RV-FWLS and RV-GLS, with the RV-FWLS measuring just three segments of the right ventricular free wall and the RV-GLS measuring six segments, including the interventricular section. Due to software restrictions, RV-FWLS data were not obtained for this investigation.

Sub-analysis comparing echocardiographic characteristics between patients with and without left ventricular cardiotoxicity

On evaluation of echocardiography, the LV-GLS in the group with left ventricular cardiotoxicity was -18% (-16.6-21.3%) lower than in the non-cardiotoxic group -20.1% (-16.6-24.3%), however this difference was not statistically significant (p=0.07). In another study, the results of decreasing LV-GLS at the end of chemotherapy and evaluation 12 months after chemotherapy, even though the EF value was still within the normal range, demonstrate that GLS is more sensitive than conventional echocardiography parameters in identifying subclinical left ventricular cardiotoxicity[12].

The mean value of RV-GLS in the group with left ventricular cardiotoxicity was -17.99% ± 3.63% lower than the non-cardiotoxic group -20.14 ± 3.49%, although this difference was not statistically significant p=0.121 but the average value is almost the same as other studies with an average RV-GLS after anthracycline chemotherapy -18.6 ± 2.6%[12].

Conclusions

Patients with left ventricular cardiotoxicity had a higher incidence of right ventricular systolic dysfunction than patients without left ventricular cardiotoxicity, although the association was not statistically significant.

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Disclosures and Ethics

The authors have no conflicts of interest to declare. This study has been approved by medical ethics committee of Faculty of Medicine, Nursing, and Public Health, Gadjah Mada University number KE/FK/1050/EC/2022

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