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Association between chemotherapy-related cardiac dysfunction (CTRCD) and 6-minute walking distance (6MWD) in breast cancer patient receiving anthracycline-based chemotherapy

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ABSTRACT

Anthracycline chemotherapy is one of the most commonly given therapies to breast cancer patients. Anthracycline has a cardiotoxicity effect causing cardiac myocyte death. This chemotherapy-related cardiac dysfunction (CTRCD) will decrease oxygen delivery to tissues characterized by reduced cardiorespiratory fitness. The 6-min walking distance (6MWD) could be a predictor of cardiorespiratory fitness. This study aimed to investigate the association between CTRCD and the reduction in 6MWD after receiving anthracycline-based chemotherapy. It was an analytical observational study with a retrospective cohort design that conducted on breast cancer patients underwent anthracycline-based chemotherapy. Subjects were patients from the Cardio-oncocare registry who met the inclusion and exclusion criteria. The CTRCD was assessed using left ventricle ejection fraction (LVEF) and global longitudinal strain (LVGLS) by transthoracic echocardiography examination based on criteria from the European Society of Cardiology guidelines. The 6MWD was assessed by performing 6-min walking tests. The LVEF, LVGLS and 6MWD data were retrieved from the Cardio-oncocare registry database, which were performed before and after chemotherapy. The changes and association of LVEF, LVGLS and 6MWD from before to end of chemotherapy were analyzed. Of 250 Cardio-oncocare registered patients, 58 patients met the criteria. Among them, 17 patients (29%) had CTRCD, and 41 patients (71%) had no CTRCD after chemotherapy. A significant decrease in LVEF and LVGLS in patients with CTRCD was observed. The 6MWD before chemotherapy did not statistically differ between CTRCD and no CTRCD patients. After chemotherapy, the proportion of patients experienced reduction of 6MWD was not significantly different between CTRCD patients and no CTRCD patients [7 patients (41%) vs. 21 patients (51%); p=0.342]. In conclusion, there is no significant association between CTRCD and reduction of 6MWD in breast cancer patients receiving antracycline-based chemotherapy.

ABSTRAK

Antrasiklin adalah agen kemoterapi yang paling sering diberikan kepada pasien kanker payudara. Agen ini menyebabkan toksisitas jantung melalui kematian miosit jantung. Toksisitas jantung akibat terapi kanker (*chemotherapy-related cardiac dysfunction*/CTRCD) akan menurunkan penghantaran oksigen ke jaringan yang ditandai dengan penurunan daya tahan kardiorespirasi. Jarak tempuh uji jalan 6 menit (*6-min walking distance*/6MWD) dapat menjadi prediktor penurunan daya tahan kardiorespirasi. Tujuan penelitian ini yaitu untuk mengetahui hubungan CTRCD terhadap penurunan 6MWD pada pasien yang mendapatkan kemoterapi antrasiklin. Penelitian observasional analitik menggunakan desain kohort retrospektif ini dilakukan pada pasien kanker payudara yang memenuhi kriteria inklusi dan eksklusi. Toksisitas jantung akibat terapi kanker dinilai dengan ejeksi fraksi dan *global longitudinal strain* (GLS) ventrikel kiri berdasarkan kriteria dari pedoman *European Society of Cardiology* (ESC). Data ekokardiografi dan 6MWD diambil dari unit registri Cardio-oncocare yang dilakukan saat awal dan akhir kemoterapi. Dar 250 pasien yang teregistrasi, terdapat 58 pasien yang memenuhi kriteria yakni 17 subjek (29%) mengalami toksisitas jantung dan 41 subjek (71%) tidak mengalami toksisitas jantung. Penurunan ejeksi fraksi dan GLS ventrikel kiri berhubungan signifikan terhadap kejadian CTRCD. Pada akhir

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kemoterapi, proporsi pasien yang mengalami penurunan 6MWD tidak berbeda signifikan antara pasien yang mengalami CTRCD dan yang tidak mengalami CTRCD [7 pasien (41%) vs. 21 pasien (51%); p=0,342]. Simpulan, CTRCD tidak berhubungan penuruna penurunan jarak pada uji 6MWD pada pasien yang mendapatkan kemoterapi antrasiklin.

INTRODUCTION

Cancer constitutes a global public health challenge, with an annual mortality rate of 6 million.[1] In Indonesia, breast cancer stands out as the most prevalent form of cancer, accounting for 19.2% of all cancers.[2] A significant 14.3% of women in developing countries succumb to breast cancer.[1] According to the 2020 GLOBOCAN data from the Global Cancer Observatory, breast cancer is the predominant cancer in Indonesia.[3] Dr. Sardjito General Hospital, Yogyakarta recorded 33,550 cancer cases from 2008 to 2019, as outlined in the March 2022 Hospital-Based Cancer Registration (RKBRS) report. Specifically, breast cancer led the diagnoses with 6,249 cases (18.6%) during the period from 2008 to 2019.[4]

The therapeutic approach for breast cancer commonly involves chemotherapy, aiming to eradicate cancer cells and mitigate the risk of recurrence and distant metastasis. Anthracyclines, including doxorubicin, daunorubicin, epirubicin, and idarubicin, stand out as highly effective chemotherapy agents for various breast cancers. However, it is essential to acknowledge that anthracyclines carry the risk of cardiotoxicity or chemotherapy-related cardiac dysfunction (CTRCD).[5] A CTRCD resulting from anthracyclines is defined as a reduction of over 20% in the left ventricular ejection fraction compared to the initial normal ejection fraction or a decrease exceeding 10% in an already reduced initial ejection fraction.[5] Following the 2022 guidelines of the European Society of Cardiology (ESC), CTRCD is categorized into symptomatic and asymptomatic forms.[6] The initial assessment of left ventricular systolic function, including ejection fraction and global longitudinal strain, is recommended for monitoring the impacts of cardiotoxicity.[6]

The mechanism of action of anthracyclines involves damaging protein synthesis, increasing the production of reactive oxygen species, and inhibiting topoisomerase II to impede DNA repair. Consequently, this leads to the demise of cardiac myocytes. The resultant damage manifests as left ventricular dysfunction, heart failure, hypertension, and atherosclerosis.[5] Cardiovascular disorders, in turn, contribute to a decrease in tissue perfusion, consequently reducing peak VO_2, which derived from maximal cardiac output and maximal venous-arterial oxygen difference, is an objective measure to evaluate cardiorespiratory fitness and functional capacity.[7] It proves valuable in predicting cardiovascular morbidity and mortality in medically compromised populations.[7]

Cardiorespiratory fitness (CRF) reflects the cardiovascular system's ability to supply oxygen and energy substrates to skeletal muscles during activity.[6] Perturbations in CRF emerge as robust prognostic indicators for the onset of cardiovascular disease in cancer patients.[6] The decline in CRF significantly predicts therapeutic outcomes and intervention targets in this population.[6] Such reductions are associated with diminished quality of life, heightened morbidity, compromised cardiac function, and an exacerbated risk profile for cardiovascular disease.[6] Cardiopulmonary exercise testing (CPET) is the standard examination for assessing CRF, although its routine implementation

is hindered by the unavailability of sophisticated and expensive equipment.[8]

The 6-minute walking test (6MWT) measures the distance covered within a 6-minute timeframe or 6-minute walking distance (6MWD) and can effectively characterize an individual's capacity in daily activities.[9] Significantly, the 6MWT can be a viable alternative to CPET for assessing functional capacity.[10] Previous research has identified an association between 6MWD and maximal aerobic power, such as peak VO_2, in cancer patients.[10] The aim of this study was to investigate, in our patients, the association between CTRCD and the reduction in 6MWD after receiving anthracycline-based chemotherapy.

MATERIAL AND METHODS

Design and subjects

This research is an analytical observational study with a retrospective cohort design. This study was conducted on breast cancer patients, registered in Cardio-oncocare registry, at Dr. Sardjito Hospital Yogyakarta from January 2018 to July 2022, based on several criteria: (1) breast cancer patients who received chemotherapy for the first time with a basic anthracycline regimen, either adjuvant or palliative chemotherapy, who were included in the Cardio-oncocare registry; (2) the subject had completed complete anthracycline-based chemotherapy; and (3) echocardiography result and 6MWD data before and at the end of chemotherapy were completely listed in the database. The patient excluded from the study if: (1) patients with lung disease, (2) patients who experienced tumor metastases, and (3) patients with a METs score below 3.

Data collection

This research relies on secondary data extracted from the database of the Cardio-oncocare registry that were admitted from January 2018 to July 2022. The data, derived from Transthoracic Echocardiography (TTE) examinations and the 6MWT, which were conducted before and at the end of anthracycline-based chemotherapy. The TTE data aimed to identify the left ventricle global longitudinal strain (LVGLS) and ejection fraction (LVEF) for establishing anthracycline-induced cardiotoxicity. In this study, cardiotoxicity was categorized into two groups based on the criteria from the European Society of Cardiology (ESC). The criteria included an absolute decrease in LVEF of more than 10% points, resulting in an LVEF of 40-49%, or an LVEF ≥ 50%, accompanied by a decrease in LVGLS >15% compared to the initial LVEF and/or LVGLS at the end of chemotherapy.[6] Interobserver variation in echocardiography examination in our hospital echolab aligns with previous research when the value is> 80%.[11] During this period, 250 breast cancer patients were admitted to the Cardio-oncocare registry.

A total of 250 patients were enrolled in the Cardio-oncocare registry. As many as 192 patients did not fit the research criteria, namely 68 patients who experienced metastasis, 15 patients who did not undergo chemotherapy, 5 patients who died before chemotherapy, 26 patients who opted for chemotherapy regimens other than anthracycline-based, 14 patients who did not complete the entire course of chemotherapy and 64 patients who had insufficient echocardiography and 6-MWD data. Consequently, 58 patients were eligible for this study.

The protocol of the study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada-Dr. Sardjito General Hospital, Yogyakarta (KE-FK-1930-EC-2023).

Statistical analysis

Statistical analysis was performed using SPSS version 23 (IBM, USA). Data distribution was determined using the Kolmogorov-Smirnov normality test. Numerical variables and categorical data on the basic characteristics of research subjects are reported in terms of frequency or percentage for categorical data and mean/median data for numerical data. Categorical data was analyzed using the Chi-square or Fisher test. Meanwhile, an independent t-test or Mann-Whitney was used for numerical data. The significance level of $p < 0.05$ was employed as the criterion for determining statistical significance in this hypothesis test.

RESULTS

This study encompassed 58 subjects eligible in this study. Of these, 17 patients (29%) experienced CTRCD, while 41 patients (71%) did not experience CTRCD (no CTRCD). The CTRCD in these 17 patients was based on criteria involving a reduction in LVGLS, but without a concurrent decrease in LVEF. The characteristic data are presented in TABLE 1. The mean age of the patients was 51.9±7.87 yr. The mean height, body mass index (BMI), and hemoglobin levels exhibited nearly identical values between the two subject groups. Furthermore, no statistically significant differences were observed in the mean demographic parameters between the populations with and without CTRCD.

TABLE 1. The characteristic of all patients and groups of patients based on CTRCD occurrence

Variables	All patients (n=58)	CTRCD		p
		Yes (n=17)	No (n=41)	
Age (mean ± SD yr)	51.9 ± 7.87	52.4 ± 6.0	51.8 ± 8.6	0.804
Weight (mean ± SD kg)	76.5 ± 102	88.2 ± 118	71.6 ± 95.6	0.577
Height (mean ± SD cm)	154.2 ± 5.3	154.0 ± 5.7	154.0 ± 5.2	0.739
BMI (mean ± SD kg/m^2)	24.2 ± 4.5	24.7 ± 4.6	24.0 ± 4.5	0.597
Initial Hb (mean ± SD mg/dL)	12.9 ± 1.3	12.8 ± 1.4	12.9 ± 1.3	0.881
End chemotherapy Hb (mean ± SD mg/dL)	11.3 ± 0.9	11.6 ± 1.0	11.2 ± 0.9	0.074
Duration of monitoring after the last anthracycline (mean ± SD mo)	2.6 ± 1.1	3.0 ± 0.4	2.4 ± 1.3	0.049
Comorbidities [n (%)]				
• Hypertension	9 (15.5)	2 (12.0)	7 (17.0)	0.473
• Ischemic heart disease	0	0	0	-
• Diabetes mellitus	3 (5.8)	1 (6.0)	2 (5.0)	0.655
• Obesity	17 (29.0)	6 (35.0)	11 (26.0)	0.366
Anthracycline regimens [n (%)]				
• Doxorubicin	46 (79.0)	13 (76.0)	33 (80.0)	0.340
• Epirubicin	13 (22.0)	4 (24.0)	9 (22.0)	0.583
Anthracycline dosage (mg/m^2)				
Doxorubicin [median (min-max)]	240 (120-240)	240 (200-240)	240 (120-240)	0.740
Epirubicin [median (min-max)]	240 (90-400)	300 (240-400)	240 (90-300)	0.795

CTRCD: chemotherapy related cardiac dysfunction; BMI: body mass index; SD: standard deviation

TABLE 2. The echocardiogram (TTE) data and 6MWD of all patients and groups of patients based on CTRCD occurrence before (initial) and at the end of chemotherapy (end-chemotherapy)

Variables	All patients (n=58)	CTRCD		p
		Yes (n=17)	No (n=41)	
Echocardiography (mean ± SD)				
• Initial LVEF (%)	70.0 ± 7.0	70.7 ± 6.3	69.8 ± 7.3	0.643
• End-chemotherapy LVEF (%)	69.3 ± 5.3	69.6 ± 5.7	69.2 ± 5.2	0.808
• Initial LVGLS (%)	-18.7 ± 3.2	-20.5 ± 2.7	-17.9 ± 3.2	0.005
• End chemotherapy LVGLS (%)	-18.4 ± 3.3	-15.3 ± 3.3	-19.7 ± 2.3	<0.001
• LVEF reduction (%)	6.0 ± 4.5	9.5 ± 3.8	5.0 ± 4.3	0.035
• Relative % decrease in LVGLS (%)	-2.0 ± 28.0	25.7± 10.7	-13.4 ± 24,8	<0.001
• Absolute decrease in LVGLS (%)	-0.2 ± 4.3	-5.2 ± 2.0	1.8 ± 3.2	<0.001
• Initial E/A*	1.09 ± 0.3	1.16 ± 0.35	1.06 ± 0.30	0.322
• End chemotherapy E/A*	1.04 ± 0.3	0.96 ± 0.26	1.07 ± 0.29	0.201
6MWD (mean ± SD)				
• Initial 6MWD (m)	356.1 ± 56.0	368.3 ± 51.3	351.1 ± 57.7	0.573
• End chemotherapy 6MWD (m)	349.0 ± 54.2	376.2 ± 57.7	339.0 ± 49.4	0.016

CTRCD: chemotherapy related cardiac dysfunction; LVEF: left ventricle ejection fraction; LVGLS: left ventricle global longitudinal strain; 6MWD: 6-minute walking distance; SD: standard deviation. *Total subjects, n=55 (3 patients could not be assessed for diastolic function).

Subjects with diabetes mellitus and obesity were more prevalent among patients experiencing CTRCD, whereas hypertension was more commonly observed in subjects without CTRCD. Nevertheless, these distinctions did not attain statistical significance between the two subject groups in the study. Regarding oncological parameters, 46 patients (79%) received the doxorubicin regimen, while 13 patients (22%) were administered epirubicin regimen. The utilization of doxorubicin and epirubicin did not exhibit significant disparities between the two subject groups. Anthracycline-based chemotherapy was administered across 3-4 cycles as an integral part of the complete chemotherapy regimen in this study. The duration of monitoring, deemed statistically significant, extended from the final administration of anthracycline chemotherapy to the onset of CTRCD.

The mean initial LVEF is 70.0 ± 7.0%, with no significant difference observed between those experienced CTRCD and those who did not. At the end of chemotherapy, the mean LVEF slightly decreased to 69.3 ± 5.3%, with no significant difference between subjects experienced CTRCD and those without. The initial LVGLS value in subjects with CTRCD was significantly higher than in those without CTRCD (-20.5 ± 2.7% vs. -17.9 ± 3.2%; p=0.005). The LVGLS at the end of chemotherapy in subjects with CTRCD was decreased, while those without CTRCD experienced an increase in GLS values (-15.3 ± 3.3% vs. -19.7 ± 2.3%; p<0.001). The relative percentage decrease in LVGLS was the difference between the initial and end-chemotherapy LVGLS divided by the initial LVGLS. The relative percentage decrease in LVGLS was significantly greater in patients with CTRCD. Both

groups experienced a statistically significant reduction in LVEF and LVGLS, although LVEF values remain within the normal range (TABLE 2).

The mean initial 6MWD was not statistically different between patients experienced CTRCD and those without CTRCD (368.3 ± 51.3 m vs. 351.1 ± 57.7 m; p=0.573). The mean end-chemotherapy 6MWD was significantly different between patients experienced CTRCD and those without CTRCD (376.2 ± 57.7 m vs. 339.0 ± 49.4 m; p=0.016), in which patients with CTRCD had higher 6MWD (TABLE 2).

Among patients with CTRCD (n=17), 7 patients (41%) experienced a reduction in the 6MWD, while 10 patients (59%) did not. In patients with no CTRCD (n=41), 21 patients (51%) experienced a reduction in the 6MWD, while 20 patients (49%) did not. The analysis for the association between CTRCD and proportion of reduced 6MWD was using Chi-square test. The result suggested no statistically significant difference between proportion of 6MWD reduction in patients with CTRCD (TABLE 3).

Subsequent analysis showed that the aggregate reduction in 6MWD occurred in patients with no CTRCD [12.0 ± 50 m (13.0 ± 11.0 %)], in contrast to those with CTRCD who experienced aggregate increased in 6MWD [(7.9 ± 54 m (9.0±7.8 percent)]. However, statistical analysis indicates no significant difference between the groups, as outlined in TABLE 4. FIGURE 1 illustrates the difference between before and at the end of chemotherapy 6MWD on both subjects.

TABLE 3. The association between occurrence of CTRCD and the proportion of reduced 6MWD

Variables		Reduced 6MWD [n (%)]		p	RR	CI 95%
		Yes	No			
CTRCD	Yes	7 (41)	10 (59)	0.342	0.80	0.564-5.963
	No	21 (51)	20 (49)			

6MWD: 6-minute walking distance; CTRCD: chemotherapy related cardiac dysfunction; RR: relative risk; CI: confidence interval

TABLE 4. The mean reduction in 6MWD between patients with CTRCD and no CTRCD

Variables	CTRCD		p
	Yes (n=17)	No (n=41)	
6MWD reduction (mean ± SD m)	7.9 ± 54.0	-12.0 ± 50.0	0.495
6MWD reduction (mean ± SD m)	9.0 ± 7.8	-13.0 ± 11.0	0.154

6MWD: 6-minute walking distance; CTRCD: chemotherapy related cardiac dysfunction;

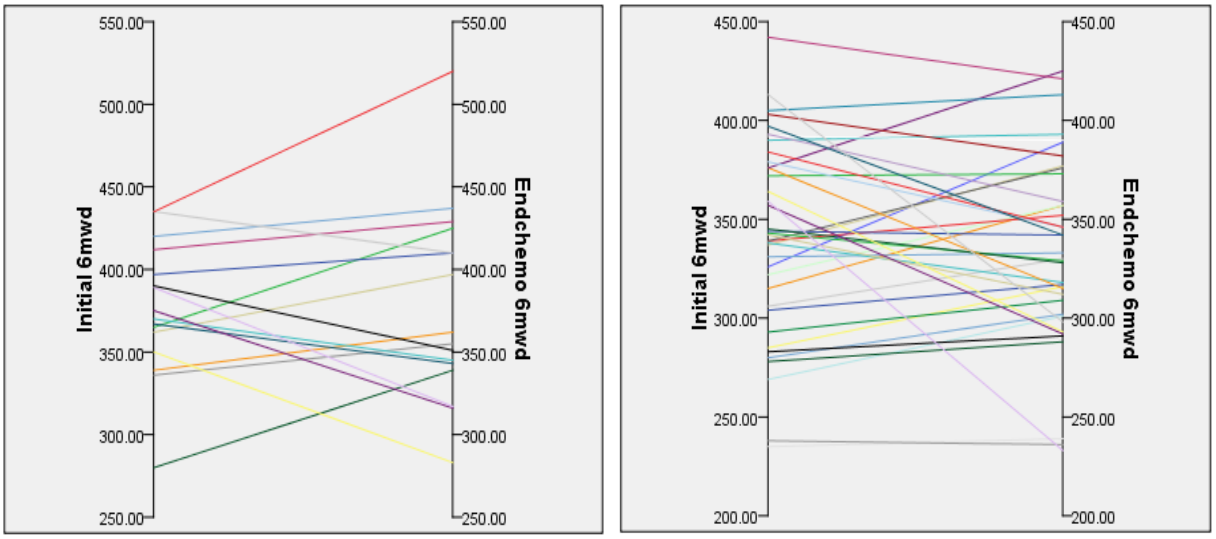

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FIGURE 1. Parallel coordinates plot illustrating the difference between initial (before) and at the end chemotherapy 6MWD on (A) subjects with CTRCD and (B) subjects with no CTRCD. 6MWD: 6-minute walking distance; CTRCD: chemotherapy related cardiac dysfunction

DISCUSSION

This study indicates that chemotherapy cardiotoxicity or CTRCD does not statistically significant associated with a decrease in the distance covered by the 6MWD. Only small proportion of patients with CTRCD exhibited reduction of 6MWD. Furthermore, comorbid factors do not influence the occurrence of CTRCD. The guidelines of the European Society of Cardiology stated that patients aged ≥ 60 yr have a moderate risk, while those aged ≥ 75 yr have a high risk of developing CTRCD.[6] Subjects experienced CTRCD received doxorubicin chemotherapy at the maximum dose of 240 mg/m^2, while epirubicin was administered at 400 mg/m^2. The American Society of Clinical Oncology (ASCO) states that doxorubicin > 250 mg/m^2 or epirubicin >600 mg/m^2, or doses below these thresholds but with a high cardiovascular risk, have a greater risk of CTRCD.[12] A study reported a 25.9% incidence of cardiotoxicity with an average cumulative dose of 233 mg/m^2 for doxorubicin.[13] This study reveals a higher toxicity rate than previous research with nearly the same dose and few comorbidities.

This study assessed the CTRCD after the completion of the entire chemotherapy regimen. This study's duration of chemotherapy monitoring refers to the period from the last anthracycline chemotherapy session to when we conducted echocardiography and the 6MWD evaluation at the last dose of the complete chemotherapy session. Based on the classification according to the onset of action, anthracycline-induced CTRCD can manifest as acute, early chronic, and late chronic.[14] This study indicates a significant relationship between the duration of monitoring and

the occurrence of CTRCD, suggesting that the longer the monitoring period, the more progressively CTRCD occurs.

This study reveals a significant association between the decrease in LVEF and LVGLS with CTRCD, even though LVEF values at the end of chemotherapy remain within the normal range. The mean LVGLS decreased with a final LVGLS value of -15.3 ± 3.3% at the end of chemotherapy. The study employed 2D measurements using the Teich method, potentially resulting in higher LVEF values than actual. According to the American Society of Echocardiography guidelines, the calculation of LVEF is better performed using Simpson's method.[15] Bayram *et al.*[16] demonstrated that LVEF assessment using Simpson's method was superior (sensitivity 88%) in evaluating left ventricular systolic function compared to Teich's method (sensitivity 58%). Evaluation using the Teich method remains valid, provided no kinetic disturbances in the left ventricular wall exist. In this study, no patients exhibited kinetic disturbances, thus justifying the use of the Teich method. A GLS decrease greater than 11% or a final GLS value less than -19% is a robust predictor of cardiotoxicity.[14] A study by Xu *et al.*[16] indicated a significant decrease in GLS at the end of chemotherapy.

The mean initial and final distances covered in this study's 6MWD were lower than in previous research, where the mean distance from a meta-analysis of breast cancer patients was 477 m.[10] This difference may be attributed to variations in height, stride length, exercise habits, and physical activity levels between the Indonesian and European populations. Sinclair *et al.*[17] it showed that patients with a 6MWD >563 m do not require routine CPET measurements. However, in patients with a distance <427 m, CPET is needed as an advanced examination to assess functional capacity during activity. This study has an average 6MWD of <427 m, suggesting that the functional capacity analysis in these study subjects would be better conducted using a CPET.

However, using 6MWD can still be contemplated as a predictor and a variable for risk stratification, as suggested by previous research. Reliability tests for the 6MWT and the 6MWD, both interobserver and intraobserver, should be implemented to prevent bias and enhance the examination's validity. Cardiopulmonary exercise testing (CPET) can serve as a modality to assess the functional capacity of breast cancer patients as recommended in the guidelines. Researchers still recommend 6MWD as a predictor and variable for risk stratification, as previous studies have shown its correlation with CTRCD. However, we believe that this study's limitations may have affected the results, necessitating further research

CONCLUSION

In conclusion, CTRCD does not exhibit a significant association with the reduction in the 6MWD, despite a relatively high incidence of CTRCD observed in patients undergoing anthracycline-based chemotherapy.

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