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# Strategy of implementing aerobic exercise as a pleiotropic effect in cancer patients with a history of administration cardiotoxic agents: a systematic review



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## ABSTRACT

The development of health science, with the discovery of a type of treatment to reduce mortality due to cancer, namely using chemotherapy agents such as anthracycline and trastuzumab. From the number of studies that have been done, the types of drugs such as anthracycline and trastuzumab have a cardiotoxic effect which is often associated with decreased heart-lung function and the incidence of cardiomyopathy. Exercise is reported to have a pleiotropic effect. Therefore, this study aims to synthesize evidence from the application of pleiotropic exercise in cancer patients undergoing chemotherapy with cardiotoxic agents. The search was performed according to the recommended reporting items for systematic review and meta-analyses (PRISMA). Obtained an accumulation of 2397 articles from PubMed and Google Scholar (2016-2020), which were assisted by the PICO search engine. The article was reviewed by the author within sorting using inclusion and exclusion criteria and obtained 28 articles accordingly. Aerobic exercise has pleiotropic effects by stimulating antioxidants and reducing reactive oxygen species (ROS) levels, reducing pro-apoptosis molecular signaling, stimulating myofilament, facilitating concentric cardiac hypertrophy remodeling, and changing cardiac metabolism via adenosine monophosphate (amp) with kinase-mediated. Pretreatment aerobic exercise with minimal supervised 30-min exercise sessions 3 times/week for  $\geq 12$  weeks effectively reduce the risk of chemotherapy-induced cardiomyopathy (CRC). Aerobic exercise has a significant pleiotropic effect in patients undergoing chemotherapy with cardiotoxic agents.

**Keywords:** Cardiomyopathy, Aerobic Exercise, Cardio-protection, Cardiotoxic.

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## INTRODUCTION

According to WHO data in 2018, cancer contributes to 9.6 million deaths worldwide. Cancer is also the second leading cause of death in the world, which is 13%.<sup>1</sup> Cancer also affects the psychology and quality of life of patients and their families. Patients with cancer tend to be dependent on others.<sup>2</sup> The development of health science, with the discovery of a type of treatment to reduce mortality due to cancer, namely using chemotherapy agents such as anthracycline and trastuzumab.<sup>2</sup>

From the number of studies that have been done, the types of drugs such as anthracycline and trastuzumab have a cardiotoxic effect which is often associated with decreased heart-lung function and the incidence of cardiomyopathy. A study by El Vandescruyet et al. in Belgium in 2011

found a 30% incidence of cardiomyopathy in children with anthracycline-related cancer.<sup>3</sup> In Indonesia, according to research conducted by Riko in 2014 at RSUP DR M Djamil Padang in 25 adult nasopharyngeal cancer patients, 100% of patients experienced a decrease in left ventricle ejection fraction (LVEF) after three months of chemotherapy.<sup>2</sup>

The American College of Sports Medicine (ACSM) suggests exercise training has a pleiotropic effect and helps improve quality of life and cancer-related fatigue in cancer survivors.<sup>4</sup> Prevention of chemotherapy-induced heart failure in high-risk patients is critical for their long-term health. This prevention requires multidisciplinary collaboration between oncologists, cardiologists, and primary care providers. This study aims to analyze evidence from the application of pleiotropic

exercise in cancer patients undergoing chemotherapy with cardiotoxic agents.

## METHODS

### Searching Literature

We conducted searches in Google Scholar (from 2016-2020) and PubMed using the PICO engine on the study of chemotherapy-related cardiomyopathy and exercise intervention. Two authors read every title and abstract, obtained full texts of potentially relevant papers, and scrutinized reference lists of included papers. Review inclusion criteria were applied, and uncertainties were discussed with a third author.

### Inclusion and Exclusion Criteria

We included studies if they: (i) were written in English. (ii) were published

in peer-reviewed journals, (iii) recruited patients at any stage of cancer with a history of administration chemotherapy drug, (iv) patient ages >18 years, (v) discuss anthracycline/trastuzumab which induces cardiotoxicity, (vi) relevant aerobic exercise-related cardiotoxic. We excluded case reports, abstracts pediatric studies, dissertations, and articles with less focus on discussing anthracycline-trastuzumab and aerobic exercise also less focus on discussing anthracyclines-trastuzumab in causing cardiotoxic effects.

### Data synthesis

We tabulated results and performed a narrative review of the effect and table based on measuring criteria. We divided the discussion into four categories, based on the assessment indicators namely VO2 max, Left Ventricular Ejection Fraction (LVEF), N-terminal pro-brain natriuretic peptide (NT-proBNP), Framingham score, and LVEF-VO2 max in assessing the effectiveness of exercise training.

## LITERATURE REVIEW

### Searching Result

The electronic search identified 2390 citations, and 33 full texts were retrieved for detailed evaluation (Figure 1) five studies were excluded. The main reason for exclusion was that the studies are less focused on discussing the combination of anthracycline-trastuzumab and aerobic exercise. Ten studies (total number 515 patients, range 18-55 years old) fulfilled our inclusion criteria. Three of these studies examined the impact of exercise training on the observed cardiotoxic effects of VO2 max. One of them used NT Pro BNP as a reference, Three other studies used Left Ventricle Ejection Fraction (LVEF) as a reference. One study explained Framingham's risk score as an indicator to assess the exercise effect. and eighteen studies presented data as a reference in discussing exercise training related to cardiotoxicity effect from the use of chemotherapy drugs.

### Cancer-Related Cardiomyopathy (CRC)

CRC is a heart disorder related to the use of drugs, especially chemotherapy drugs, with various causes of pathomechanism.

Furthermore, CRC classified into two types, type 1 is associated with permanent or irreversible effects while type 2 is reversible while influenced by dose, administration, age, sex, and the presence of comorbidities.<sup>5</sup>

### Anthracycline Mechanism Exerts Cardiotoxic Effects

The effectiveness of anthracycline (ACs) in chemotherapy treatment makes it the

mainstay of therapy used. The use of ACs cause Left Ventricle (LV) dysfunction and heart failure in a dose-dependent manner. However, there is no threshold dose below which cardiotoxicity does not occur. Although the mechanism of ACs causing cardiotoxic effects has not been clearly defined, there are several hypotheses to explain this situation.<sup>7</sup>

The first hypothesis related to ROS suggests that increased concentration

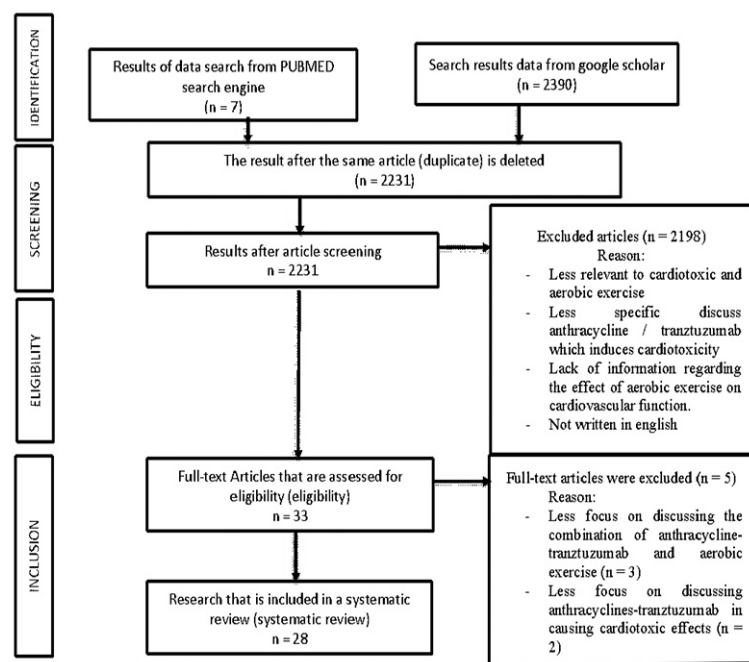


Figure 1. Flow diagram of included and excluded studies.

Table 1. Type 1 and 2 Cancer-Related Cardiomyopathy (CRC).<sup>6</sup>

Differences	Type 1	Type 2
Types of Chemotherapy Agents	Doxorubicin, mitoxantone dan siklofosamid	Trastuzumab, imatinib, sunitinib
Clinical manifestations	Clinically stable but permanent and irreversible damage to heart tissue	Can return to the original heart condition (reversible) in 2-4 months
The dose effect	Cumulative, depending on the dose	Dose Independent
Mechanism	The formation of free radicals or oxidative stress	Blocks the EerB2 signal
Pathological findings	The vacuole, myocyte tissue damage	There were no abnormalities in the large structures
Effect if given back	There is a high chance of relapse and progressive heart dysfunction which can lead to heart failure and cardiomyopathy	Most of the literature says it is safe to be given a second time, but further research is still needed

of ROS leads to increased expression of proteins that are involved in cardiac autophagy, pathological myocardial hypertrophy via calcium overload, and inhibition of myoprotein synthesis.<sup>8,9</sup> The topoisomerase (Top) 2B hypothesis suggests that ACs bind to Top 2B, distorting its structure and preventing Top 2B from unwinding DNA.<sup>7</sup> This action causes double-stranded DNA breaks, activates apoptotic pathways, and causes cardiomyocyte death. The Top 2B hypothesis could potentially initiate the pathway of the ROS hypothesis where inactivated Top 2B reduces antioxidant gene transcription and leads to increased ROS production.<sup>7</sup>

### The Trastuzumab Mechanism Exerts Cardiotoxic Effects

Trastuzumab disrupts (Human epidermal growth factor receptor) HER signaling by inducing phosphorylation of HER1 and HER2 at 845 and 1248 sites, respectively, and activates autophagy-inhibitory Erk/mTOR/Ulk 1 signaling cascade, thereby compromising cardiomyocyte's

ability to recycle toxic cellular and increase reactive oxygen species (ROS) accumulate substrates causing cardiotoxicity. Trastuzumab-induced cardiac dysfunctions were regarded as less severe and largely reversible because primary cardiomyocyte did not show ultrastructure changes that were associated with anthracycline-induced cardiotoxicity, and primary myocyte injury did not occur in patients that were treated with trastuzumab.<sup>10</sup>

### VO2 max

Physical fitness determines a person's capacity to carry out an activity and affects health. VO2 max is a measurement for the amount of oxygen distributed to all muscles which is the result of the maximum cardiac output and maximal O2 extraction from the tissue during exercise which is used for the purposes of cell metabolism and energy production for the body. VO2 max is often used as a reflection of cardiorespiratory function.<sup>11</sup>

Exercise is scientifically proven to increase VO2 max capacity as shown in a

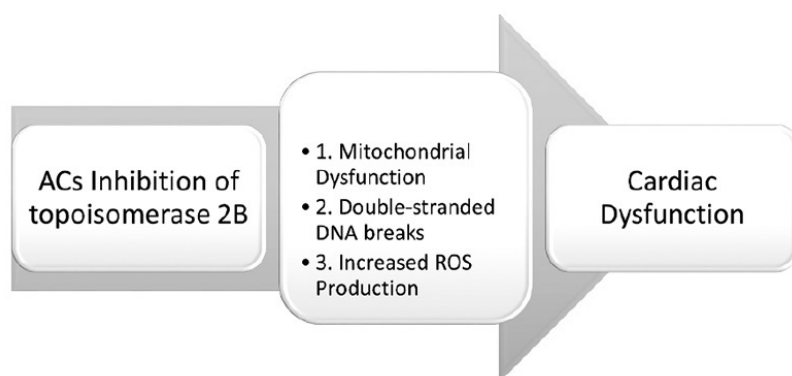
randomized control trial (RCT) conducted by Kyuwan Lee et al. in 2019, 30 patients with stage 1 and 2 breast cancer who had the habit of sitting and were receiving anthracycline chemotherapy with doxorubicin every 2 weeks 4 cycles showed that high-intensity exercise 3 times a week for 30 minutes in 8 weeks could increase VO2 max capacity.<sup>12</sup> Similar results were also obtained by the RCT study Zakaria Mowafy et al. in 2016, 40 breast cancer patients aged 35-55 years who were receiving anthracycline chemotherapy were divided into two groups, namely group a (recipients of aerobic-cycling for 25 minutes per day for 4 months and anthracycline intervention) and group b (anthracycline only) and it turned out that group A gave a significant increase in VO2 max.<sup>13</sup> Similar to the research of Zakaria Mowafy et al, Scott C. Adams et al. in his 2017 RCT study conducted on 63 stages 1-3 testicular cancer patients receiving anthracycline chemotherapy who were given intervention in the form of thrice-weekly supervised exercise sessions total of 35 minutes in one session during 6 weeks program showed a significant increase in the patient's VO2 max.<sup>14</sup>

Based on the results of these studies, aerobic exercise which is done 3 times a week with a duration of 25-35 minutes per day for 6-16 weeks has been shown to increase VO2 max capacity so that it can prevent cardiotoxic effects on cancer patients who received chemotherapy agents.

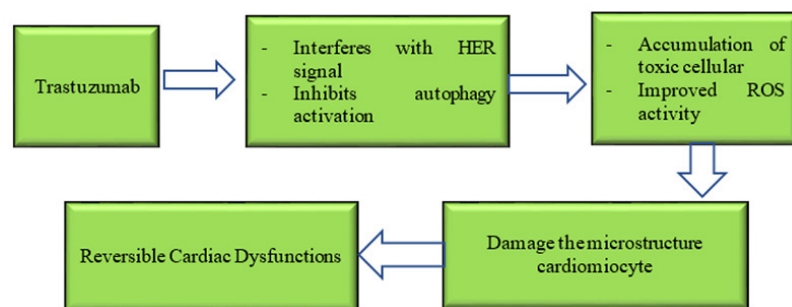
### LVEF

Left Ventricle Ejection Fraction (LVEF) is an indicator used to assess heart function, especially the left ventricle. LVEF is a measurement of the volume of blood pumped out of the left ventricle. According to the Indonesian cardiologist association, LVEF has a normal range value of > 45%.<sup>15</sup> A decrease in the value of the LVEF represents a decrease in cardiovascular function. Exercise will increase cardiac output. Increased cardiac output will increase LVEF. Increased cardiac output can be achieved by doing exercise.<sup>16</sup>

RCT study of Quentin Jacquinot et al. in 2017, 112 breast cancer patients with stage 1-3 who received trastuzumab therapy with HER 2 were positive, after



**Figure 2.** Potential mechanisms of anthracycline (ACs)-induced cardiotoxicity (1–3) cause cardiac dysfunction.<sup>7</sup>



**Figure 3.** Potential mechanisms of Trastuzumab-induced cardiotoxicity.<sup>10</sup>

being given an intervention supervised exercise program (intermittent exercise, combining moderate and high intensities; 55 minutes duration, 3 times per week) in 3 months. Result obtained an increase in LVEF by 50% from the previous LVEF value of 35%.<sup>17</sup>

Similar results were obtained in the RCT study conducted by Costello Benedict T. et al. in 2019, 27 breast cancer patients with stage 1-2 receiving anthracycline chemotherapy were treated in the form of a moderate- to vigorous-intensity aerobic and resistance training regimen (3x/week,

60min/session, 2supervised, 1home-based) for 6 weeks significantly increased the left ventricular ejection fraction.<sup>18</sup> Inversely to the RCT study conducted by Amy A. Kirkham et al. in 2020, 26 breast cancer patients receiving anthracycline chemotherapy (doxorubicin) were given treatment in the form of treadmill exercise with a duration of 20 to 30 minutes 2 times per week for 2 weeks of giving doxorubicin was proven not to significantly improve LVEF function.<sup>19</sup>

Based on the results of this study, it can be concluded that the exercise that

is carried out within 2 weeks has not had an impact, while 3 times a week of exercise training with a duration of 55-60 minutes for 6-12 weeks has been shown to increase and improve LVEF function so that it can prevent cardiotoxic effects from Chemotherapy.

### NT Pro BNP

N-Terminal Pro Brain Natriuretic Peptide (NT Pro BNP) is a type of hormone produced by ventricular myocyte cells in response to increased pressure on the ventricular wall. Increased pressure

**Table 2. Research summary of the application of exercise training**

Author (year)	Malignancy	Number of samples	Indicator	Intervention	Outcome
Kyuwan lee et al. (2019)	Breast cancer stages 1 and 2	30	VO2 max capacity	High-intensity exercise training that is done 3 times a week for 30 minutes for 8 weeks	Increase VO2 max capacity
Zakaria Mowafy et al. (2016)	Breast cancer patients aged 35-55 years	40	VO2 max capacity	Aerobic cycling for 25 minutes per day for 4 months	Increase VO2 max capacity
Scott C. Adams et al. (2017)	Testicular cancer patients stage 1-3	63	VO2 max capacity	Thrice-weekly supervised exercise sessions total of 35 minutes in one session during 6 weeks	Increase VO2 max capacity
Quentin Jacquinet et al.(2017)	Breast cancer stage 1-3	112	LVEF	3 months supervised exercise program (intermittent exercise, combining moderate and high intensities; 55 minutes duration, 3 times per week)	Increase in LVEF
Costello Benedict T. et al. (2019)	Breast cancer stage 1-2	27	LVEF	Moderate- to vigorous-intensity aerobic and resistance training regimen (3x/week, 60 min/session, 2 supervised, 1 home-based) for 6 weeks	Increase in LVEF
Amy A. Kirkham et al.(2020)	Breast cancer	26	LVEF	Treadmill exercise with a duration of 20 to 30 minutes 2 times per week for 2 weeks of giving doxorubicin	Did not significantly improve the LVEF function
Kirkham, A et al.(2020)	Breast cancer stage 1-3	27	NT-Pro BNP	Treadmill exercise for 24 hours before starting doxorubicin therapy for 45 minutes	Significantly inhibits NT-Pro BNP secretion and improves cardiac systolic function
Kyuwan Lee et al.(2019)	Breast cancer stage 1-3	100	Framingham risk score	Aerobic and resistance exercise 3 times a week for 150 minutes for 16 weeks	Significantly lowered the Framingham risk score
Edward Tsai et al.(2019)	Patient with HF NYHA class I, II and III with history of anthracycline chemotherapy	20	VO2 max and LVEF	The exercise program was based on HF-ACTION and consisted of supervised 30 minutes exercise sessions 3 times/week for 16 week "6-20" rating of perceived exertion (RPE)	Significant improvements in VO2 max and LVEF
Zhijun Ma (2018)	Women with breast cancer after Operation with history of administration chemotherapy	70	VO2 max and LVEF	Aerobic exercise during 50 minutes in 16 weeks	significant improvements in VO2 max and LVEF



(stress) on the ventricular walls is often associated with myocardial damage that can be caused by chemotherapy. Exercise can prevent the formation of ROS which has inflammatory effect so as to prevent the increase in NT Pro BNP.<sup>20</sup>

This statement is evidenced by the RCT study conducted by Kirkham, A et al. in 2020, 27 patients with stage 1-3 breast cancer received anthracycline chemotherapy who were given intervention treadmill exercise for 24 hours before starting doxorubicin therapy for 45 minutes significantly inhibits NT-Pro BNP secretion and improves cardiac systolic function.<sup>21</sup> Based on the results of this study, it can be concluded that the exercise carried out 24 hours before chemotherapy for 45 minutes was proven to inhibit the formation of NT-Pro BNP, thereby preventing the occurrence of cardiotoxic effects due to chemotherapy use.

### Framingham Risk Score

The Framingham risk score is a scoring system developed by the Canadian Cardiovascular Society which is used to predict the incidence of cardiovascular disease for the next 10 years.<sup>22,23</sup> One way to reduce the risk of cardiovascular disease is exercise. This can be proven from the RCT study conducted by Kyuwan Lee et al. in 2019, 100 stage 1-3 breast cancer patients receiving anthracycline chemotherapy who were given treatment in the form of aerobic and resistance exercise 3 times a week for 150 minutes for 16 weeks significantly reduced the Framingham risk score.<sup>24</sup>

### LVEF dan VO2 Max

Increased LVEF and VO2 max represent a good cardiovascular function. Increased LVEF and VO2 max can occur due to increased cardiac output caused by exercise. This is consistent with the RCT study conducted by Edward Tsai et al. in 2019, 20 HF NYHA class I, II, and III patients with a history of anthracycline chemotherapy were given an intervention HF-ACTION-based exercise program and consisted of a 30-minute guided exercise session 3 times/week for 16 weeks. The "6-20" rating of perceived exertion (RPE) significant improvement in VO2max and

LVEF was observed in the intervention group.<sup>25</sup>

Similar results were also obtained from RCT research conducted by Zhijun Ma in 2018 on 70 women with breast cancer after surgery for anthracycline chemotherapy recipients who were given the intervention of aerobic exercise for 50 minutes within 16 weeks to increase VO2 max and LVEF and to some extent, it could reverse the damage of chemotherapy drugs to the heart.<sup>26</sup> Based on the results of these studies, exercise was carried out 3 times per week for 30-50 minutes in 16 weeks has been shown to increase VO2 max and LVEF, so that it can maintain cardiovascular function and prevent cardiotoxic effects from Chemotherapy.

### CONCLUSION

Based on the results of a systematic review, it was found that aerobic exercise has a significant pleiotropic effect in patients undergoing chemotherapy with cardiotoxic agents by stimulating antioxidants and reducing elevated ROS levels, reducing proapoptotic molecular species and signaling, stimulation of myofilament synthesis, facilitating physiological concentric hypertrophy in myocardial remodeling and altering cardiac metabolism through AMP-mediated kinases. Pretreatment aerobic exercise 24 hours before chemotherapy anthracycline-trastuzumab with minimal supervised 30-min exercise sessions 3 times/week for  $\geq 12$  weeks effective reduce risk of CRC. Hopefully, these findings can be useful for health workers as a strategy to prevent and reduce comorbidity due to the use of chemotherapy drugs.

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### AUTHOR CONTRIBUTION

In this article, all authors are involved and take part in making the article. the first author contributed to drafting and designing this manuscript. the second author provides concepting, designing, and supervising the manuscript.

### ETHICAL STATEMENT

Not applicable

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