SYSTEMATIC REVIEW

Effects of exercise training on cardiotoxicity in cancer survivors. A systematic review [version 1; peer review: 1 approved with reservations]

Ravindra Reddy C¹, Stephen Samuel¹, Vijay Pratap Singh¹, Sourjya Banerjee²

¹Department of Physiotherapy, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, India
²Department of Radiotherapy and Oncology, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, India

Abstract

Background: Cardiotoxicity is a major long-term complication of anti-cancer drugs such as anthracycline and androgen deprivation therapy (ADT). These drugs also impact the quality of life, reduced functional capacity, and life expectancy. Exercise attenuates the cardiotoxic effects of anticancer treatments, as indicated by a growing body of evidence.

Methods: Studies for this review were retrieved from databases PubMed, SCOPUS, EMBASE, COCHRANE, and Web of Science and were restricted only to clinical trials. Study results were screened and synchronized to Mendeley. Studies that met the eligibility criteria were extracted into the spreadsheet, summarizing information regarding the site and cancer stages, adjuvant therapy, various exercise interventions, and outcome measures. Risk of bias quality analysis was done in accordance with the National Heart Lung Blood Institute.

Results: In this systematic review, 9021 articles were screened. After the exclusion criteria, seven articles were included for qualitative analysis. Outcome measures analyzed were measures of cardiotoxicity such as left ventricular ejection fraction (LVEF), cardiac biomarkers, and global longitudinal strain.

Conclusion: Although a structured exercise protocol including aerobic and resistance training has been found to improve, the functional capacity is an indirect measure of cardiotoxicity. There is a lack of data in terms of improvement seen in direct measurements of cardiotoxicity such as LVEF and cardiac biomarkers. A lack of evidence regarding the effects of exercise on the direct measurement of cardiotoxicity encourages the need for further research.
Keywords
Exercise, Cardiotoxicity, Cancer Survivors, Rehabilitation

This article is included in the Oncology gateway.

This article is included in the Manipal Academy of Higher Education gateway.

Corresponding author: Stephen Samuel (stephen.samuel@manipal.edu)

Author roles: Reddy C R: Conceptualization, Methodology, Resources, Writing – Original Draft Preparation, Writing – Review & Editing; Samuel S: Conceptualization, Methodology, Project Administration, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Singh VP: Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Banerjee S: Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2022 Reddy C R et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Reddy C R, Samuel S, Singh VP and Banerjee S. Effects of exercise training on cardiotoxicity in cancer survivors. A systematic review [version 1; peer review: 1 approved with reservations] F1000Research 2022, 11:497 https://doi.org/10.12688/f1000research.112667.1

First published: 05 May 2022, 11:497 https://doi.org/10.12688/f1000research.112667.1
Abbreviations
BNP: B-type natriuretic peptide
CG: Control Group
GLS: global longitudinal strain
HER: human epidermal growth factor receptor
IG: Interventional group
LVEF: left ventricle ejection fraction,
MET: Metabolic equivalent
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: Randomized control trial
ROS: Reactive oxygen species
RVEF: right ventricular ejection fraction

Introduction
Globally cancer and cardiovascular diseases cause morbidity and mortality. Despite various advances in cancer treatments, the detrimental effects of these treatment forms cause a significant burden to cancer survivors. The three most prevalent cancers are prostate, colorectal, and melanoma among males, and breast, uterine corpus, and colorectal cancer among females.1 The most common types of childhood cancer are leukemia, brain cancer, lymphoma, and solid tumors.2 Early screening for cancer helps slow down its progress and, if accompanied by appropriate treatment, can result in a significant decline in the mortality rate.3

One of the primary treatment strategies in cancer treatment involves chemotherapeutic drugs such as anthracycline, doxorubicin, Paclitaxel, Cyclophosphamide, and Trastuzumab used alone or in combination with radiation therapy.4–6 Despite the therapeutic effects of these drugs, cancer survivors have been found to have long-term adverse side effects such as cardiotoxicity, fatigue, cancer-related pain, sleep disorders, and psychological stress, which contribute to morbidity and mortality amongst them.7

Cardiotoxicity is considered a significant concern and severe issue in clinical practice patients receiving chemotherapy. Cardiotoxicity is damage to the heart manifested by either symptomatic or asymptomatic decline in left ventricular ejection fraction (LVEF).8 Although the mechanism of cardiotoxicity is poorly understood, the most agreed upon fact remains the increase of reactive oxygen species (ROS), activating cardiac autophagy and apoptotic pathways.9–12 Studies have defined cardiotoxicity as a decrease in LVEF of >10% points to a value of <53%(reference value).13 Echocardiography-LVEF, myocardial strain imaging, and cardio biomarkers are the standard marker or parameters for measuring the early and late cardiotoxic effects.11,13–18

The proposed strategies to reduce the cardiotoxic effects are: 1) anthracycline dose reduction, 2) altogether avoiding the radiotherapy/blockade of exposure to other areas, 3) usage of iron chelation, 4) treating the preexisting cardiovascular risk factors, 5) using other interventions such as exercise to alleviate its effects.

Exercise training, a most reliable and non-pharmacological option, brings positive outcomes and improves physical fitness by restoring physical function, enhancing the quality of life, and reducing cancer-related fatigue in cancer survivors. This training can be implemented before, during, and after cancer treatments,19–23 thus nullifying the cardiotoxic effects. Exercise interventions, including aerobic exercises such as treadmill walking, running, cycling, and resistance training such as weight training, strength training using Thera Band, and weight cuffs, are safe and feasible for all cancer populations. Over the past decade, steady growth in the body of evidence supports the importance of exercise in attenuating or mitigating the cardiotoxic effects induced by chemotherapeutic drugs.7,19,21,22,24–27 However, several outcome measures, such as VO2 max (maximum amount of oxygen utilized during exercise) and metabolic equivalent (MET), are used in measuring cardiotoxicity; the standard direct predictors are LVEF and cardiac biomarkers.

To the best of our knowledge, there is no systematic review on the effects of exercise training on cardiotoxicity in cancer survivors; this review aims to synthesize evidence regarding the role of exercise training on cardiotoxicity and identify potential knowledge gaps in terms of research in this area.

Methods
This systematic review of clinical trials on the Effects of exercise training on cardiotoxicity in cancer survivors is reported according to the PRISMA guidelines (See Reporting Guidelines).28
Search strategy and selection criteria
A detailed data search was performed on databases PUBMED, SCOPUS, EMBASE, COCHRANE, and WEB OF SCIENCE from August 2009 to March 2021. The search terms used were cancer, carcinoma, neoplasm (MeSH), cancer survivors (MeSH), adult cancer survivors, and pediatric cancer survivors. For intervention, search terms were exercise training, exercise therapy, prehabilitation, rehabilitation, aerobic training, resistant training, endurance training, treadmill, cycle ergometry, swimming, walking, running, free weights, manual, kettlebell exercises, dumbbell exercises, Pilates, yoga, flexibility training, stretching exercises, high-intensity interval training. For cardiotoxicity outcomes, the search terms are Cardiotoxicity, Cardiopulmonary fitness, functional capacity, left ventricle ejection fraction, heart failure, cardiovascular reserve capacity, coronary vascular disease, and physical fitness. The Boolean operator ‘AND’ or ‘OR’ combined the search terms. Potentially relevant studies were included from the reference list of the included articles. The search for clinical trials was limited to those involving human participants and those published in English. Two investigators, RR and SRS, independently searched the databases mentioned above. The studies were further screened by RR and SRS based on the preset inclusion criteria. A discussion with VPS sorted any further discrepancies.

Inclusion criteria
Type of participant: All kinds of cancer survivors who received chemotherapy.
Type of study design: Only clinical trials.

Exclusion criteria
Studies that use other interventions rather than exercise such as Music therapy and Cognitive behavioral therapy, Nordic Walking, speech therapy qualitative studies, Cross-sectional studies, and Systematic review.

Data extraction and management
RR and SRS performed full-text screening for the included articles independently, and any disagreements were sorted after discussion with VPS. Information on the objectives, site and cancer stages, adjuvant treatment, intervention details, comparator, outcome measures, study design, sample size, adverse events, and critical findings of the included studies were mentioned in the data extraction sheet.

Assessment of risk of bias
The included studies underwent the risk of bias assessment performed independently by RR and SRS using the National Heart Lung Blood Institute (NHLBI).29 The NIH checklist for each study type measures 14 unique questions and was scored to assess studies’ internal validity. The studies were scored under each query related to randomization, allocation concealment, blinding of participants and assessors, baseline characteristics, dropouts, intervention adherence, outcome data, and other biases. Studies were marked as ‘good,’ ‘fair,’ and ‘poor’ if they met 10-14, 5–9, and ≤4 scores accordingly (See Underlying data).28 Discussions with VPS sorted disagreements in the marking system of the studies between the two reviewers.

Results
Characteristics of the studies
In this review, 9021 articles were retrieved from a comprehensive search of the following databases; PubMed-611, web of science-1728, Scopus-4058, Embase-1069, Cochrane-1555. A total of 6089 articles were found after merging duplicates. Based on the title and abstract screening, 13 articles were eligible for full-text screening. Out of the 13 articles, seven met the inclusion criteria and were included in this review (See Underlying data).28

A quality analysis using NHLBI Questionnaire was performed for the included studies interventional studies. Most of the studies were fair to good in quality, and few studies had missing data, smaller sample sizes, dropouts, and differences in baseline characteristics. Among seven studies, one was a single-arm pre-post intervention design; four were randomized controlled trials (RCTs); two were non-RCT. In all included studies, the patients were diagnosed with breast cancer; however, only few authors reported their stage. Most of the participants included in the studies were those aged above 18. The outcome measure of all included studies was cardiac function using echocardiography- LVEF, Global longitudinal strain (GLS), and circulating cardiac biomarkers (troponins and N terminal-pro brain natriuretic peptide (NT-proBNP). Most of the patients received anthracycline class drugs such as doxorubicin and trastuzumab as adjuvant therapy.

Exercise intervention for the included participants comprised either aerobic or resistance training or a combination of both. Supervised treadmill walking, unsupervised home-based walking, and cycle ergometry were the modalities used in aerobic exercise, and for resistance training, Theraband, dumbbell, and medicine ball were used. Out of seven studies, three studies30–32 used aerobic, and resistance training as their intervention, and the other four studies33–36 used only
<table>
<thead>
<tr>
<th>Author</th>
<th>Cancer site/Stage</th>
<th>Age/Gender</th>
<th>Study design</th>
<th>Sample size</th>
<th>Adjuvant treatment</th>
<th>Exercise intervention</th>
<th>Quality assessment measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foulkes et al., 2019</td>
<td>Breast cancer</td>
<td>female/46-66</td>
<td>non-RCT</td>
<td>28</td>
<td>Usual care; n = 14 Exercise; n = 14</td>
<td>chemotherapy +radiotherapy</td>
<td>Fair</td>
</tr>
<tr>
<td>Katarzyna Hojan et al., 2020</td>
<td>Breast cancer IB,</td>
<td>female/18-75</td>
<td>RCT</td>
<td>68</td>
<td>Usual care; n = 34 Exercise; n = 34</td>
<td>trastuzumab therapy +radiotherapy</td>
<td>Good</td>
</tr>
<tr>
<td>Erin J Howden et al., 2019</td>
<td>Breast cancer</td>
<td>female(47-53) ±9</td>
<td>non-RCT</td>
<td>28</td>
<td>Usual care; n = 14 Exercise; n = 14</td>
<td>anthracycline</td>
<td>Fair</td>
</tr>
<tr>
<td>Amy A. Kirkham et al., 2018</td>
<td>stage I–III Breast cancer</td>
<td>female/50 ± 9</td>
<td>RCT</td>
<td>24</td>
<td>Usual care; n = 11 Exercise; n = 13</td>
<td>doxorubicin</td>
<td>Good</td>
</tr>
<tr>
<td>Haykowsky et al., 2009</td>
<td>HER2 positive Breast cancer</td>
<td>53 ± 7 years</td>
<td>single group design (pre-post)</td>
<td>Exercise; n = 17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhijun Ma et al., 2018</td>
<td>Breast cancer</td>
<td>43.1±5 years</td>
<td>RCT</td>
<td>64</td>
<td>Usual care; n = 33 Exercise; n = 31</td>
<td>anthracycline</td>
<td>Good</td>
</tr>
<tr>
<td>A.A. Kirkham et al., 2017</td>
<td>Breast cancer</td>
<td>above 18</td>
<td>RCT</td>
<td>24</td>
<td>Usual care; n = 11 Exercise; n = 13</td>
<td>doxorubicin</td>
<td>Good</td>
</tr>
</tbody>
</table>

RCT-randomized control trial, HER-human epidermal receptor.
### Table 2. Intervention characteristics, Outcomes, Result of included studies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Exercise details</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
</table>
| Foulkes et al. (2019) | AEROBIC 2 session/week moderate to vigorous intensity for 12 weeks aerobic-cycle ergometer 30 minutes 1 session/week unsupervised 30-60 min home aerobic exercise with moderate intensity | RESISTANCE TRAINING 30 min, moderate to vigorous intensity for 12 weeks | Exercise Training  
LVEF %  
PRE AC 63.8 ± 5.4  
4 Months -3.3 (-0.4, 6.9)  
16 Months -6.9 (-11.1, -2.0)  
BNP, ng/L  
Pre-AC 39.4 ± 50.0  
4 Months -4.1 (-48.2, 39.9)  
16 Months -14.5 (-63.8, 34.9)  
Troponin I, ng/L Pre-AC 2.57 ± 0.79  
4 Months 33.43 (1.87, 64.99)  
16 Months 2.57 (0.50, 5.72)  
GLS, %  
Pre-AC -19.9 ± 2.3  
4 Months 0.9 (-1.4, 1.4)  
16 Months 2.4 (-1.2, 3.5) |
| Katarzyna Hojan et al. (2020) | endurance 5 session/week for 9 weeks 2 forms of exercise (walking/running, cycling) 45-50 min | strength 5 session/week for 9 weeks isometric, concentric, eccentric training consisted of one to three sets of 8-10 repetitions | LVEF (%)  
Baseline 63.9 ± 2.72  
After 59.82 ± 4.02 (0.143)  
RVEF (%)  
Baseline 53.3 ± 6.5  
After 54.2 ± 5.2 (0.488)  
GLS (%)  
Baseline 17.3 ± 2.5  
After 16.8 ± 2.5 |
| Erin J Howden et al. (2019) | AEROBIC 2 session/week for 12 weeks 30 minutes one unsupervised 30-60 minute | RESISTANCE TRAINING 2 session/week for 12 weeks 30 minutes | LVEF (%)  
Pre-treatment 62.8 ± 4.9  
post-treatment 59.1 ± 4.1  
GLS (%) pre 204.2 ± 21 post 195.6 ± 20  
BNP (ng/L) pre 35.8 ± 39.6 post 36.2 ± 19.7  
Troponin I (ng/L) pre-2.6 ± 1.0 post 35.6 ± 27.2 |

**LVEF**: Left Ventricular Ejection Fraction  
**BNP**: Brain Natriuretic Peptide  
**GLS**: Global Longitudinal Strain
<table>
<thead>
<tr>
<th>Author</th>
<th>Exercise details</th>
<th>Outcome measure</th>
<th>Result</th>
</tr>
</thead>
</table>
| Amy A. Kirkham et al. (2018) | prior to 24 hrs. treatment supervised treadmill 10-min warm-up 30 min vigorous intensity (70% of heart rate reserve (HRR)), and a 5-min cool-down | Echocardiograms and circulating biomarkers 0–14 days (baseline) and 7–14 days after treatment | Longitudinal strain (%)  
Baseline – 19.6 ± 1.9  
End of T – 20.3 ± 1.6  
Cardiac troponin T (pg./mL)  
Baseline 1.5 ± 2.3  
End of T 11.6 ± 8.3  
NT-proBNP (pg./mL)  
Baseline 59 ± 35  
End of T 77 ± 39  
LVEF (%)  
Baseline 58 ± 3  
After 58 ± 3  
Cardiac troponin T (pg./mL)  
Baseline 1.9 ± 2.6  
After 2.6 ± 3.2  
NT-proBNP (pg./mL)  
Baseline 59 ± 35  
After- 323 ± 15  
LVEF (%)  
Baseline 58 ± 3  
After- 59 ± 4  
Cardiac troponin T (pg./mL)  
Baseline 19.6 ± 1.9  
After- 21.5 ± 1.6  |
| Haykowsky et al. (2009) | 3D/week for 4 months (30-60 min) cycle ergometry (60%-90%) peak oxygen consumption | nil                                                                                | LVEF (%)  
Baseline (pre: 64% ± 4%)  
After 4 months  
Post: (55% ± 4%)  |
| Zhijun Ma et al. (2018) | 3D/week for 16 weeks 50 min treadmill 60%-70% HR max                              | nil                                                                                | LVEF (%)  
Baseline= (pre: 51 ± 5.6)  
After-post: 47 ± 2.6  
NT-proBNP (ng/L)  
Baseline-72.1 ± 13.6  
After-348.2 ± 25.4  
LVEF (%)  
Baseline-55 ± 3.5  
After-60 ± 2.9  
NT-pro BNP (ng/L)  
Baseline-84.2 ± 21.5  
After-90.6 ± 18.4  |
| A.A. Kirkham et al. (2017) | prior to 24 hrs. treatment supervised treadmill 10-min warm-up 30 min vigorous intensity (70% of heart rate reserve (HRR)), and a 5-min cool-down | nil                                                                                | Cardiac troponin T (pg./mL)  
Baseline- 1.5 ± 2.3  
After- 1.9 ± 2.6  
NT-proBNP (pg./mL)  
Baseline- 59 ± 35  
After- 323 ± 15  
LVEF (%)  
Baseline- 58 ± 3  
After- 59 ± 4  
Cardiac troponin T (pg./mL)  
Baseline-19.6 ± 1.9  
After-21.5 ± 1.6  |

RVEF- right ventricular ejection fraction, LVEF- left ventricle ejection fraction, GLS- global longitudinal strain, BNP-B-type natriuretic peptide, AC- Anthracycline class.
aerobic training for their patients. The duration of these exercises was around 30-60 min performed in about 9-16 weeks. Two out of seven studies 33,34 incorporated exercise bout just 24-hours before the chemotherapy and observed the changes in echocardiographic findings and cardio biomarkers.

The dropouts were as follows: 11 from Foulkes et al., 21 from Katarzyna Hojan et al., two from Howden et al., three from Kirkham et al., two from Haykowsky et al., six from Zhijun Ma et al., and three from Kirkham et al.

One study among seven has been published twice in a different journal, and their relevant data has been extracted and presented in Tables 1 and 2.

Discussion
Patients with cancer with underlying cardiovascular complications have reduced life expectancy compared to those with cancer alone. It is expected that the survival rate of the cancer population will increase by 30% by 2022 in the United States alone.37 Modern treatment strategies for cancer have improved their survival rate and costed adverse cardiovascular injury as side effects in their long-term survival period. This study aimed to look for therapeutic strategies to alleviate the side effects.38 A growing body of evidence supports the role of exercise in preventing and managing various treatment-related complications in cancer survivors. Hence, this review was conducted to summarize the available literature and thus evaluate the effects of exercise training on cardiotoxicity in cancer survivors. The studies included in this review used outcome measures that directly measure cardiotoxicity in cancer survivors. The effect of exercise interventions has been discussed in detail under each outcome measure.

Left ventricular ejection fraction
Cancer therapy-induced cardiac dysfunction is a long-term complication in cancer survivors, with some being symptomatic and others asymptomatic. Heart failure is defined as pump failure, measured in LVEF.39 Exercise training potentially induces ventricular remodeling in patients with heart failure40 by restoring abnormal neurohormonal, autonomic and hemodynamic functions. Among the included studies, five studies30–32,35,36 measured LVEF as a primary outcome measure, and the other two studies33,34 evaluated it as a secondary measure. One36 among seven studies, showed clinically significant improvements in LVEF (P<0.05). In contrast, six other showed negligible changes in left ventricular ejection from baseline to post-chemotherapy. This study incorporated only aerobic exercises for their patients for 16 weeks (3d/week).36

Global longitudinal strain (GLS)
It is one of the echocardiographic findings and a potential predictor of subclinical cancer therapy-related cardiac dysfunction. It analyzes the subtle changes or deformation occurring in the left ventricle.39,41 Based on research evidence, a greater than 15% change is a strong predictor of cardiotoxicity.41 There a is lack of evidence supporting the role of exercise training in GLS; however, in a trial conducted by Valzania, Cinzia et al., improvements have been seen in GLS values in patients receiving cardio resynchronization therapy during exercise.42 Among seven studies included in this review, two studies35,36 didn’t assess GLS as an outcome measure, while most studies showed slight changes in GLS value. However, a clinical trial conducted by Foulkes et al. demonstrated a considerable decline in GLS value over 16 months (P = 0.015).30 despite providing a combination of aerobic and resistance training.

Cardiac biomarkers
Biomarkers are one of the best diagnostic predictors of early cardiotoxicity. The test performed during or after the chemotherapy helps anticipate the presence of cardiotoxicity. Troponins and Natriuretic peptides are the significant biomarkers in determining subclinical cardiotoxicity. These biomarkers imply a certainty of cardiac damage due to chemotherapy.39,43 Based on the research literature, it is evident that even prolonged exercise training in healthy individuals can cause an acute elevation in these biomarkers, which are transient.44 However, a trial conducted by Braith et al. on heart failure patients showed that 16-weeks of endurance training helped reduce the baseline values of natriuretic peptides.45 Only five studies30,32–34,36 investigated biomarkers as their outcome and revealed that there is a significant elevation of troponins and natriuretic peptides post-chemotherapy in acute time. Interestingly these values recovered after 12 months in two studies.30,36 Thus, exercise training as an intervention to reduce biomarkers level is unclear and poorly understood.

Strength and limitation
Thus, this systematic review summarizes the effect of exercise training on cardiotoxicity in cancer survivors. Although previous studies summarize the impact of exercise as an intervention on cardiotoxicity measured by VO2 max in cancer survivors, no review synthesizes evidence regarding the direct measure of cardiotoxicity. The inclusion of studies published in English and exclusion of the grey literature are the limitation of this review. Aerobic exercise training was
limited to treadmill modality in most of the studies. Recent advances in exercise training like high-intensity interval training have shown clinical benefits in reduced ejection fraction patients suggesting ventricular remodeling, thus improving their functional capacity.\textsuperscript{46} So, there is a need for an alternate form of exercise to counteract the chemotherapy-induced dysfunction.

In this review, one out of seven studies\textsuperscript{36} showed statistically significant improvement in cardiotoxicity-related outcome measures. In comparison, three studies\textsuperscript{30,32,33} showed that there was no deterioration of the cardiotoxicity related outcome measures. In contrast, the remaining three studies\textsuperscript{30,32,35} showed a decline in the outcome measures, which was statistically significant.

Individualized exercise prescription, based on the frequency, intensity, type, and time (FITT) principle, can be recommended based on patients’ baseline characteristics or comorbidities limiting their physical performance. Cancer patients also suffer from sarcopenia,\textsuperscript{47–49} which reduces their strength; there is a clinical need for resistance training.

The timing of exercise intervention used before, concomitant, or after chemotherapy has a significant role in providing protective effects. A gap has to be explored for further strengthening of evidence in optimal timing. In most of the included studies, the intervention duration was short, about four months; other studies can implement exercises for the long run and see the clinical changes.

Childhood cancer survivors with Hodgin’s lymphoma, and adult cancer survivors with prostate and colorectal cancer, are common and may also suffer from chemotherapy-related side effects. Predominantly early childhood cancer survivors with a longer life span have to sustain chemotherapy-induced cardiovascular injury affecting their quality of life in the long run. Despite evidence regarding exercise training, no studies are measuring the clinical changes in LVEF, GLS, and biomarkers, which are the direct measures of cardiotoxicity. Therefore, exploring the role of exercises in other cancer survivors is crucial to gather more evidence regarding the direct measurement of cardiotoxicity.

**Conclusion**

This review concludes that exercise has a potential role as an intervention in preventing deterioration of outcome measures that measure cardiotoxicity and improve the same. We recommend further research to ascertain the dose, volume of exercise, and optimal timing to further understand the role of exercise in cardiotoxicity.

**Data availability**

**Underlying data**


This project contains the following underlying data:

- Review protocol.docx. (It has information on search strategy, databases, search terms used, and inclusion and exclusion criteria.)
- Systematic review.xlsx. ( Patients’ characteristics such as site/stage, adjuvant treatments, intervention, results, dropouts)
- Risk of bias.docx. (It includes the tables for which risk of bias for studies was done using NIH tool)

Data are available under the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

**Reporting guidelines**


Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

**Author contributions**

Conceptualization, R.R. AND S.R.S; Methodology, R.R. Investigation, R. R AND S.R.S.


4. Table 1 | Chemotherapy-Induced Cardiotoxicity: Overview of the Risks of Oxidative Stress. [cited 2021 May 11]. Reference Source


7. 2015 Strategic Priorities Symptom Management & Quality of Life Steering Committee (SxQoL SC).


27. Study Quality Assessment Tools | NHLBI, NIH; [cited 2021 May 23]. Reference Source


38. Blackwell: Cardiotoxicity of Anticancer Treatments: Epidemiology, Detection, and Management CONTINUING MEDICAL EDUCATION ACCREDITATION AND DESIGNATION STATEMENT.


Sharon F. Kramer
Faculty of Health, School of Nursing and Midwifery, Deakin University, Geelong, Vic, Australia

Thank you for the opportunity to review this manuscript of a systematic review investigating the effect of exercise on cardiotoxicity outcomes in cancer patients receiving chemotherapy and/or radiotherapy.

The rationale for the review is clearly stated. The background is missing some details regarding definitions of the main concepts addressed in this review for example: cardiotoxicity and details about how this is measured (this information is reported in the discussion and could be moved to the background and methods) and exercise and what is the potential underlying mechanisms of exercise on cardiotoxicity.

Methods:
- Several sections are missing in the methods.
- What criteria are used regarding study design? i.e., randomised controlled trail, non-randomised controlled trials, pre-post studies?
- What was the process of screening title and abstract?
- What comparisons were of interest? i.e., exercise A vs exercise B, exercise vs no exercise etc.
- I suggest providing more background about why these tools were developed as I was not aware of these tools and maybe other readers might not be either. For example, it is not clear that there are several tools that were developed for different study types. Specify which tools were used.
- Add a section to the methods about the outcomes of interest including; timing of outcome measurement of interest (post intervention and FU), how these outcomes are/should be measures, and how the outcome measure should be interpreted higher value is greater toxicity? (some of the details are reported in discussion and could be moved to methods.
Although no meta-analyses were performed, the methods still need a section about how the data was summarised/synthesised. Please provide information about how the results were structured by study design, by population, by outcome.

**Results:**
- The main results regarding toxicity are reported in the discussion and should be moved to the results section. I suggest restructuring or adding a table with just the results outcomes and consider how this could be structured (see suggestions above by study design, outcome or population).
- Avoid vote counting i.e. 1 out of seven studies showed a significant result. Reporting 95% CI is more informative and helps the reader to interpret data better instead of reporting just the p-value.

**Conclusion:**
- The conclusion currently doesn't reflect what is reported in the results. Currently there doesn't seem to be any strong evidence to suggest that exercise mitigates the cardiotoxic effects of chemo/radiotherapy in cancer patients.

I suggest revisiting the PRISMA guidelines to help with structuring the manuscript and adding missing information/sections.

**Are the rationale for, and objectives of, the Systematic Review clearly stated?**
Yes

**Are sufficient details of the methods and analysis provided to allow replication by others?**
No

**Is the statistical analysis and its interpretation appropriate?**
No

**Are the conclusions drawn adequately supported by the results presented in the review?**
No

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Systematic review methods including meta-analyses and data synthesis, risk of bias assessment; clinical trials and exercise

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com