Heart failure in childhood cancer survivors—a systematic review protocol

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Abstract

Background: Over the past decades, the survival rate for childhood cancer has greatly improved. However, the risk of late cardiac complications after cancer treatment remains high. Previous studies have shown that the risk for heart failure among childhood cancer survivors is significantly higher than that observed in varying control populations. The aim of this systematic review is to identify, critically appraise, and synthesize existing population-based studies reporting on the frequency of heart failure, both the incidence and prevalence, that may develop after treatment for childhood cancer.

Method: The following databases will be searched from their inception date until May 17, 2021: MEDLINE, Embase, Scopus, CINAHL, CAB International, AMED, Global Health, PsycINFO, Web of Science, and Google Scholar. Population-based studies reporting on the incidence and/or prevalence of heart failure after the treatment of any type of childhood cancer will be included. The screening of articles, data extraction, and quality assessment will be performed independently by two reviewers. The quality and risk of bias in the included studies will be assessed by using the Effective Public Health Practice Project tool. A narrative synthesis of the extracted data will be carried out, and for studies that are sufficiently homogenous, a meta-analysis using random-effects models will be performed.

Discussion: This systematic review will provide a clearer picture of the epidemiology of heart failure after the treatment of childhood cancer. The collected data will be of value for future childhood cancer treatment protocols and will offer guidance for posttreatment cardiac surveillance among survivors.

Systematic review registration: PROSPERO CRD42021247622. Registered on April 28, 2021. This protocol follows the structure of the recommendation of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).

Keywords: Childhood cancer, Anthracyclines, Survivors, Cardiomyopathy, Heart failure protocol and guidelines, Meta-analysis, Protocol and guidelines, Systematic review

Background

The survival rate for childhood cancer has greatly improved over the past decades and is currently above 80%. As a result, the cohort of adult childhood cancer survivors is steadily growing [1–3]. Correspondingly, the risk of debilitating and sometimes fatal long-term side effects of cancer treatment is high, with a cumulative incidence of approximately 40% after 30 years of follow-up [4]. The most common forms of severe late complications and causes of death among childhood cancer survivors include secondary malignancies, cardiovascular diseases, and pulmonary disorders [5, 6]. Reports from the US Childhood Cancer Survivor Study have reported up to seven times higher risk of premature death due to cardiac complications among childhood cancer survivors compared to that among the general population [5, 6].
wide variation in heart diseases in childhood cancer survivors has been reported [7–10]. The most common cardiac condition in this population is heart failure, which has previously been reported in a wide range, with up to a 15-fold higher risk compared to that of varying control populations [4, 7, 11, 12].

According to the 2013 American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) guidelines for the management of heart failure (HF), HF is largely a clinical diagnosis based on a careful history and physical examination and cannot be characterized by a single diagnostic test. The cardinal clinical manifestations of HF are dyspnea, fatigue, and fluid retention [13]. The severity of HF was initially defined by the New York Heart Association (NYHA) functional classification, in which patients are assigned to one of four groups based on how much they are limited during physical activity (Table 1) [14]. In addition, the ACCF/AHA has developed a classification including four stages that complements the NYHA system (Table 2) [13]. Both classifications provide useful information about the presence and severity of HF and have valuable prognostic implications. The ACCF and AHA have defined HF as a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or the ejection of blood [13]. Accordingly, the European Society of Cardiology (ESC) states that HF is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by clinical signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality [15].

Previous echocardiography investigations in childhood cancer survivors who did not experience any symptoms have reported a variety of structural and/or functional cardiac abnormalities, referred to as subclinical cardiotoxicity. Nevertheless, the observed frequency of such echocardiographic aberrations is highly inconsistent and ranges from 0 to 57% [16]. Furthermore, it is unclear to what degree subclinical cardiotoxicity in childhood cancer survivors may evolve into overt heart failure over time [16, 17].

Treatment with anthracyclines (ACs) has greatly improved survival rates in children with cancer [18]. A drawback is that ACs are cardiotoxic, and the risk for developing heart failure increases in parallel with the cumulative dose of these chemotherapeutics [8, 16, 19, 20]. A dose of anthracyclines below 250 mg/m² has been reported to be associated with a low risk for cardiotoxicity, but for susceptible persons, no dose is safe [11, 20–22]. However, published data on which doses of different ACs are safe with respect to cardiotoxicity and the risk for subsequent heart failure are contradictory [23, 24]. In addition, other types of chemotherapeutic drugs have been seen to contribute to the cardiotoxic effect of ACs, including tyrosine kinase inhibitors, alkylating agents, and cisplatin [9]. Chest radiation is also a considerable risk factor for heart failure after treatment for childhood cancer, especially in combination with ACs, and may also contribute to coronary artery disease and valvular heart disease [8, 11, 25].

**Table 1** The NYHA functional classification

| Classification | Definition |
|----------------|------------|
| I              | No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF. |
| II             | Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF. |
| III            | Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF. |
| IV             | Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest. |

NYHA New York Heart Association, HF heart failure

**Table 2** The ACCF/AHA stages of heart failure

| Stage | Definition |
|-------|------------|
| A     | At high risk for HF but without structural heart disease or symptoms of HF |
| B     | Structural heart disease but without signs or symptoms of HF |
| C     | Structural heart disease with prior or current symptoms of HF |
| D     | Refractory HF requiring specialized interventions |

ACCF American College of Cardiology Foundation, AHA American Heart Association, HF heart failure
A synthesis of population-based studies reporting on the frequency of heart failure after childhood cancer treatment and examining whether the incidence and prevalence of this condition change over time is important. The acquisition of such epidemiological knowledge is likely to be of value when generating future treatment protocols for childhood cancer and organizing posttreatment cardiac surveillance programs.

Objectives
The primary aim of this systematic review is to identify, critically appraise, and synthesize existing population-based studies reporting on the incidence and/or prevalence of heart failure in persons who have survived for a minimum of 5 years after treatment for childhood cancer. The incidence and prevalence of heart failure will be compared regarding different time periods, including the 1970s, 1980s, 1990s, 2000s, and 2010s. The secondary aims are to identify and study the impact of different risk factors on the development of heart failure after childhood cancer treatment, including the type and dose of cancer therapy, and to examine the potential impact of demographic factors and comorbidities. The participants, Interventions, Comparators, and Outcomes (PICO) framework we used to formulate the research questions is provided below. There are no specific groups of comparison.

- Participants: patients who have survived for at least 5 years after being treated for cancer before the age of 18
- Interventions: childhood cancer treatment
- Comparators: no comparison group
- Outcomes: heart failure incidence and/or prevalence; risk factors for the development of heart failure

Primary question
What is the incidence and/or prevalence of heart failure in 5-year survivors of childhood cancer posttreatment?

Secondary question
Can we identify any individual and/or treatment-related risk factors for the development of heart failure in this patient group?

Methods
This systematic review protocol follows the structure of the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) [26]. The protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) on April 28, 2021, with the registration number CRD42021247622. The reporting of this systematic review will be in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines and in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [27, 28]. Any amendments to the protocol and rationale during the systematic review will be accounted for in the final report.

Ethical considerations
The present study will be based solely on previously reported data and will not involve any contact with patients. Hence, there are no concerns that require ethical vetting.

Eligibility criteria
This systematic review will include population-based studies that reported the incidence and/or prevalence of heart failure after the treatment of any type of childhood cancer. Randomized controlled trials will not be included, since clinical studies of this kind are not expected to address our research questions. Case reports, case series, and other studies not reporting on population-based data will also be excluded since we are interested in the incidence and prevalence of heart failure in populations of CCS compared to the general population. The subjects of interest are patients who received cancer treatment before the age of 18 years and have survived for a minimum of 5 years. The international definition of childhood cancer is a cancer diagnosis for a child aged 0–14 years. However, in many countries in Europe, pediatric health care covers patients until age 18; thus, we decided to include patients treated for cancer before the age of 18. Patients with any cancer type who have received any form of cancer treatment will be included. Animal studies will be excluded from the literature search.

Study identification/information sources
The following databases will be searched from their inception date to May 17, 2021: MEDLINE, Embase, Scopus, CINAHL, CAB International, AMED, Global health, PsycINFO, Web of Science, and Google Scholar. Grey literature will also be screened to identify studies that were not published in mainstream journals. The reference lists of retrieved papers will be screened to identify possible additional articles of relevance. There will be no language restrictions, and efforts will be made to translate studies reported in languages other than English.

Search strategy
Our MEDLINE search strategy is provided in Additional file 1, and this will be adapted in searching the other databases.
Study selection
Retrieved papers will be exported to EndNote, and further screening will be performed using the software program Rayyan. The titles and abstracts of all articles retrieved from the database searches will be screened independently by two reviewers according to the eligibility criteria. After the screening is finished, the reviewers will compare their results, and a third reviewer will arbitrate in case of any disagreements that cannot be resolved by discussion between the two reviewers. Papers that are potentially eligible at this stage will proceed to the next step, which will involve full-text screening, again performed independently by two reviewers, with a third reviewer arbitrating any disagreements. The screening process will be reported in a PRISMA flow diagram and will include the total number of abstracts assessed, as well as the complete number of all full texts retrieved.

Data extraction and management
A standardized data extraction form for the study will be developed in Excel to retrieve data and applied independently by two reviewers (TB and JB). The extracted information will be based on the PICO structure and include the following:

- Participant characteristics: e.g., sources of subjects, inclusion criteria, and characteristics of the cohort group (age, sex, geographical region, socioeconomic status, ethnicity, comorbidities, ICD cancer diagnosis)
- Exposure to childhood cancer treatment: e.g., anthracyclines, tyrosine kinase inhibitors, alkylating agents, cisplatin, and chest radiation
- Primary outcomes: e.g., heart failure diagnosis (definitions of heart failure from each study will be recorded, and in those with multiple definitions, the proportion of patients will be classified by each method), year of diagnosis, age at diagnosis, incidence or prevalence of heart failure in the cohort, and the frequency of heart failure-related death
- Secondary outcomes: identification of risk factors for the development of heart failure in the population

General information (e.g., reviewer, date of data extraction, record number, author, article title), study characteristics (e.g., study design, study aim), the methods of follow-up, missing data, analyses, and quality assessments will also be collected. The ability of this process to capture the intended data will be piloted with a few studies before a complete data extraction from all included studies is carried out.

When data extraction is completed, the reviewers will compare their results, and a third reviewer (MJ) will arbitrate in cases of any disagreement. If relevant information is missing in a significant article, an effort will be made to contact the authors of the paper so that missing data may be retrieved.

Quality assessment
The quality and risk of bias in all included studies will be assessed by using the Effective Public Health Practice Project tool (EPHPP) [29]. The EPHPP tool enables the detailed assessment of the strengths and weaknesses of individual studies, as it provides individual ratings for six domains of study quality assessment. For each study, the risk of bias will be categorized as low, moderate, or high. Two independent reviewers will perform the quality appraisal, and a third reviewer will arbitrate in cases of any disagreement.

Analysis/data synthesis
The descriptive data and characteristics for all included studies will be presented in tables. We will conduct a narrative synthesis of the extracted data and describe the key characteristics and findings of each study. We will search, compare, and contrast the concepts and findings across studies to determine the prevailing concept of the underlying evidence. For studies that are sufficiently homogeneous with respect to their methods, populations, designs, interventions/exposures, outcomes, and assessments, we will implement the random-effects meta-analysis using the method of DerSimonian and Laird [30]. We will use the $I^2$ statistic, which provides an indication of study heterogeneity due to chance in the effect estimates between studies. Furthermore, we will perform subgroup analysis after dividing the study population into groups of age, country of residence, comorbidities, and sex, as well as time period, type of cancer treatment, and years since diagnosis. If a sufficient number of studies is retrieved, we will perform a meta-regression to explore the potential reasons for the heterogeneity in the estimates between studies. We will also undertake a sensitivity analysis to explore any potential scenarios that can change the conclusion of our findings, e.g., by excluding all low-quality studies from the meta-analysis and evaluating whether the results from high-quality studies differ from all studies included together. Finally, the Begg and Egger tests will be used to evaluate the funnel plot asymmetry for the secondary aim of the study in which we evaluate the risk
Discussion
Heart failure is a late complication after treatment for childhood cancer, which is common, serious, and sometimes fatal. Nevertheless, there are many uncertainties surrounding the epidemiology of this condition. The frequency of heart failure in different subgroups of childhood cancer survivors varies greatly. Although the risk for the development of heart failure increases with the dose of ACs, some patients develop impaired cardiac function even after receiving low doses. This underlines the fact that features other than the cumulative AC dose are important.

In the present review, we will only focus on population-based studies. Thus, we will avoid bias caused by wide variations in the frequency of heart failure due to the differences in specific subpopulations. To our knowledge, there are no previous systematic reviews on heart failure after childhood cancer treatment based on population-based studies. We intend to provide a clearer picture of the epidemiology of heart failure after any childhood cancer treatment. Data on the type and dose of cancer treatment will be collected to study the impact of these factors on the development of heart failure. In addition, we will gather information on demographic features and comorbidities to study to what degree such characteristics may constitute risk factors.

Despite improved survival after treatment for childhood cancer, the incidence of late cardiac complications remains high, especially heart failure. Therefore, it is of great importance to systematically collect data from available studies to generate knowledge about the long-term cardiotoxicity of chemotherapy and radiation that is applied when treating childhood cancer. This systematic review will provide valuable information for future treatment protocols for children with cancer and will also offer guidance for posttreatment cardiac surveillance. Early detection of cardiac abnormalities may allow for early intervention, which is likely to improve the outcomes in this patient population.

Abbreviations
ACCF: American College of Cardiology Foundation; AHA: American Heart Association; HF: Heart failure; NYHA: New York Heart Association; ESC: European Society of Cardiology; ACs: Anthracyclines; PROSPERO: International Prospective Register of Systematic Reviews; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; MOOSE: Meta-Analysis of Observational Studies in Epidemiology; EPPH: Effective Public Health Practice Project tool; PICO: Participants, Interventions, Comparators, and Outcomes.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13643-022-01929-0.

Additional file 1. MEDLINE search strategies (to be adapted in searching other databases).

Additional file 2. PRISMA-P 2015 Checklist.

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Authors’ contributions
This study was conceived by TB, MJ, and JB. The protocol was developed by all authors. TB wrote the first draft of the protocol manuscript, and all authors gave input for the final draft. TB and JB will independently perform the study screening, data extraction, and quality assessment of the articles, whereas MJ and KK will arbitrate any disagreements and provide field expertise. BN is an epidemiologist who has substantial experience in performing systematic reviews and will provide knowledge of the systematic review structure and statistical analysis expertise. MJ is the guarantor of the review. The authors read and approved the final manuscript.

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Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Gatta GB, Rossi S, Aareleid T, Belksa-Lasota M, Clavel J, et al. Child- hood cancer survival in Europe 1999–2007: results of EUROCARE-5—a population-based study. Lancet Oncol. 2014;15(1):35–47.

2. Gustafsson G, Heyman M, Kogner P, et al. Childhood cancer incidence and survival in Sweden. 1985–2010. http://www.forskavserien.se/wpcontent/uploads/ChildhoodCancerIncidenceandSurvivalInSweden1984-2010.pdf. From the Swedish Childhood Cancer Registry; 2013.

3. Olle Bergman LF, Hont G, Johansson E, Ljungman P, Munck-Wikland E, Nahi H, Zedensius J. Cancer in infants 2018, Populärvetenskapliga fakta om cancer. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikkelkatalog/statistik/2018-610.pdf. Socialstyrelsen, Cancerfonden; 2018.

4. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355(15):1572–82.

5. Armstrong GT, Liu Q, Neglia JP, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol. 2009;27(14):2328–38.

6. Mertens AC, Liu Q, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2008;100(19):1368–79.

7. Gudmundsdottir T, Winther JF, de Fine LS, Bonneseen TG, Asdahl PH, Tryggvadottir L, et al. Cardiovascular disease in adult life after childhood cancer therapy: a population-based cohort study of 32,308 one-year survivors. Int J Cancer. 2015;137(5):1176–86.

8. van der Pal HJ, van Dalen EC, van Delden E, van Dijk IW, Kok WE, Geskus R, et al. Cardiovascular disease in adult survivors of childhood cancer: a systematic review. Isr Med. 2006;355(15):1572–82.

9. Armstrong GT, Liu Q, Yasgur JP, Leisenring W, Robison LL, et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol. 2009;27(14):2328–38.

10. Atkinson FG, Warner AM, Moodley Y, et al. The role of cardiac exercise training in children treated for cancer: a systematic review and meta-analysis. Pediatr Blood Cancer. 2014;67(3):502–9.

11. van der Pal HJ, van Dalen EC, van Delden E, van Dijk IW, Kok WE, Geskus R, et al. Cardiovascular disease in adult survivors of childhood cancer: a systematic review. Isr Med. 2006;355(15):1572–82.

12. Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ. 2009;339:b4606.

13. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Dzau VM, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147–299.

14. Committee NYHAC. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston: Little Brown & Co; 1994.

15. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Rev Esp Cardiol (Engl Ed). 2016;69(12):1167.

16. Kremer LC, van der Pal HJ, Ofriniga M, van Dalen EC, Voute PA, Frequency and risk factors of subclinical cardiotoxicity after anthracycline therapy in children: a systematic review. Ann Oncol. 2002;13(6):819–29.

17. Lipshultz SE, Karnik R, Sambatakos P, Franco VI, Ross SW, Miller TL. Anthracycline-related cardiotoxicity in childhood cancer survivors. Curr Opin Cardiol. 2014;29(1):103–12.

18. Armenian SH, Hudson MM, Mulder RL, Chon MH, Constine LS, Dwyer M, et al. Recommendations for cardiomypathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2015;16(3):e123–36.

19. Ramos A, Meyer R, Korfhagen J, Wong K, Kaplan S. Echocardiographic evaluation of adriamycin cardiotoxicity in children. Cancer Treat Rep. 1976;60(9):1281–4 Available from: https://www.cochranelibrary.com/central/display/doi/10.1002/central/CN-00308576/full.

20. Volkova M, Russell R 3rd. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev. 2011;7(4):214–20.

21. Jarfelt M, Kujacic V, Holmgren D, Bjarnsson R, Lannering B. Exercise echocardiography reveals subclinical cardiac dysfunction in young adult survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2007;49(6):835–40.

22. Sadurska E. Current views on anthracycline cardiotoxicity in childhood cancer survivors. Pediatr Cardiol. 2013;36(6):1112–9.

23. van Dalen EC, Michiels EM, Caron HN, Kremer LC. Different anthracycline derivatives for reducing cardiotoxicity in cancer patients. Cochrane Database Syst Rev. 2010;2010(5):CD005006. https://doi.org/10.1002/14651858.CD005006.pub4. PMID: 2046735; PMCID: PMC457588.

24. Feijen EA, Leisenring WM, Stratton KL, Niss KK, van der Pal HJ, Caron HN, et al. Equivalence ratio for daunorubicin to doxorubicin in relation to late heart failure in survivors of childhood cancer. J Clin Oncol. 2015;33(32):3774–80.

25. Tukenova M, Guibout C, Oberlin O, Doyon F, Moysan A, Haddy N, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. J Clin Oncol. 2010;28(8):1308–15.

26. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

27. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama. 2000;283(15):2008–12.

28. Page MJ, McKenzie JE, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed). 2021;372:n71.

29. Effective Public Health Practice Project. Quality Assessment Tool for Quantitative Studies. http://www.ephpp.ca/PDF/Quality%20Assessment%20Tool_2010_2.pdf. 2009

30. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88.

31. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test detcted by a simple, graphical test. Bmj. 1997;315(7109):629–34.

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