

Cardiac biomarkers for the detection of cardiotoxicity in childhood cancer – a meta-analysis

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Supplementary methods

Search strategy

Cancer AND cardiotoxicity AND pediatric AND troponin

Cancer AND cardiotoxicity AND pediatric AND BNP

Cancer AND cardiotoxicity AND pediatric AND brain natriuretic peptide

Cancer AND cardiotoxicity AND children AND troponin

Cancer AND cardiotoxicity AND children AND BNP

Cancer AND cardiotoxicity AND children AND brain natriuretic peptide

Cancer AND cardiotoxicity AND childhood AND troponin

Cancer AND cardiotoxicity AND childhood AND BNP

Cancer AND cardiotoxicity AND childhood AND brain natriuretic peptide

Assessment of bias

Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) revised criteria

All included studies were assessed according to Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) revised criteria (1). The risk of bias regarding patient selection, index test, reference standard, and flow and timing was judged based on the available information from the respective manuscripts. Risk of bias and applicability concerns were judged as “low risk”, “unclear risk” and “high risk”. Assessment of biomarkers was defined as index test, and determination of left ventricular (LV) function (left ventricular ejection fraction or fractional shortening) was defined as reference standard. No assessment of reference standard bias and applicability concerns was conducted when studies were not included for analyses regarding LV dysfunction.

Predefined criteria were applied as depicted below. Two investigators (LM, RIM) evaluated additional concerns regarding risk of bias or applicability that were found in individual studies and not listed within the predefined criteria individually.

Patient selection

- Use of pirarubicin: *Unclear or high risk/applicability concerns*
- Administration of dexrazoxane (only when data was insufficient to exclude patients):
Unclear or high risk/applicability concerns
- Non-prospective design: *Unclear risk of bias*
- Exclusion of patients with symptomatic heart failure: *High risk of bias*
- Inappropriate exclusion criteria: *High risk of bias*

Index test

- Serial biomarker measurements: *Unclear or high risk of bias*

Reference standard

- No definition of LV dysfunction stated: *High risk of bias*

Flow and timing

- Exclusion of patients with symptomatic heart failure: *High risk of bias*
- Five years or more after therapy: *Unclear applicability concerns*
- Inappropriate exclusion criteria: *High risk of bias*

Newcastle-Ottawa Scale

The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses was applied to facilitate assessment of study quality (2). Studies received a maximum of 9 stars for eight questions (two stars can be allotted to question 5). Predefined criteria were applied as depicted below. Two investigators (LM, RIM) judged all studies individually and evaluated criteria that were not included within the list of predefined criteria.

Question 1: Is the selected cohort representative? (all of the following criteria)

- Use of anthracyclines other than pirarubicin
- No administration of dexrazoxane or sufficient data to exclude patients that received dexrazoxane
- No exclusion of patients with symptomatic heart failure

- No inappropriate exclusion criteria

Question 2: Is the selection of controls appropriate? (One or more of the following criteria)

- Studies that included a control group
- Studies that compared patients with a specific outcome (presence of LV dysfunction or presence of elevated biomarker) to patients without this outcome

Question 3: Is the ascertainment of exposure appropriate?

- Studies that included at least 100 mg/kg body weight doxorubicin or doxorubicin-equivalent dose

Question 4: Was demonstrated that the outcome of interest was not present at the start of the study?

- Prospective studies that assessed pre-treatment status

Question 5: Are the selected and control groups comparable concerning age/other controlled factors? (Maximum 2 stars)

- Studies that included a control group: +1 star
- Studies that included evaluation of LV function: +1 star
- Control collective of cancer patients receiving other-than anthracycline cancer therapy (instead of healthy individuals): +1 star

Question 6: Is the independent or blind assessment stated in the paper?

- Studies that stated blind assessment of LV function

Question 7: Was follow-up long enough for outcomes to occur?

- Studies that included at least 6 months follow-up after anthracycline therapy

Question 8: Was follow-up adequate?

- Studies that included at least 6 months follow-up after anthracycline therapy

Supplementary methods references

1. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 2011;155(8):529-36.
2. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in metaanalyses.

Supplementary tables

Online supplementary table 1. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, figure 1, online

			suppl. material
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6, figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	online suppl. material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, figure 6, online suppl. figure 4, online

			suppl. table 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8, figures
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, figure 6, online suppl. figure 4, online suppl. table 6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

Suppl., supplementary.

Modified from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Online supplementary table 2. MOOSE checklist.

Recommendation	Reported on Page No
Reporting of background should include	
Problem definition	3
Hypothesis statement	3-4
Description of study outcome(s)	4
Type of exposure or intervention used	4-5
Type of study designs used	4
Study population	4
Reporting of search strategy should include	
Qualifications of searchers (eg, librarians and investigators)	Not stated
Search strategy, including time period included in the synthesis and key words	4, online suppl. material
Effort to include all available studies, including contact with authors	4
Databases and registries searched	4
Search software used, name and version, including special features used (eg, explosion)	Not stated
Use of hand searching (eg, reference lists of obtained articles)	online suppl. material
List of citations located and those excluded, including justification	figure 1
Method of addressing articles published in languages other than English	4, figure 1
Method of handling abstracts and unpublished studies	4, figure 1
Description of any contact with authors	None.
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	4-5
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	4-5
Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	4-5
Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	5
Assessment of heterogeneity	5
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	5
Provision of appropriate tables and graphics	5
Reporting of results should include	

Graphic summarizing individual study estimates and overall estimate	Figure 2-5
Table giving descriptive information for each study included	Online suppl. table 3
Results of sensitivity testing (eg, subgroup analysis)	Table 2, online suppl. table 4-5
Indication of statistical uncertainty of findings	6-8
Reporting of discussion should include	
Quantitative assessment of bias (eg, publication bias)	8
Justification for exclusion (eg, exclusion of non-English language citations)	Figure 1
Assessment of quality of included studies	8, figure 6, online suppl. figure 4
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	10
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	11
Guidelines for future research	11
Disclosure of funding source	12

Suppl., supplemental.

Modified from 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;283:2008–12. Copy righted © 2000, American Medical Association. All rights reserved.

Online supplementary table 3. Study characteristics.

Study	Pro-spective	Age of patients	Cancer entity	Drug, cumulative dose	Biomarker	Troponin cutoff	BNP/NT-proBNP cutoff	Timing of biomarker assessment	Definition LV dysfunction	Form of analysis
Aggarwal 2007	No	13	Various, 46% ALL	Drug N/A, \bar{x} = 165 mg/m ²	BNP			3.8 years after ANT	FS <29% EF <64%	b)
Arslan 2013	No	8	Various, 70% lymphoma	Drug N/A, \bar{x} = 150 mg/m ²	Trop. I	>0.16µg/mL		1.9 years after last ANT		
Asselin 2016	Yes	10	Various hematological	Doxorubicin, 360 mg/m ²	Trop. T	>0.01 ng/mL		Immediately before ANT, 3 weeks after completion of ANT		
Cetin 2018	No	11	Various, 50% lymphoma	Doxorubicin ± daunorubicin, dose N/A	BNP		>100 pg/mL	<1.8 years after ANT		
Clark 2007	Yes	10	Various, 50% ALL	Doxorubicin and/or daunorubicin \bar{x} = 150 mg/m ²	Trop. T	>10 pg/mL		<48 h after ANT		
Ekstein 2007	Yes	10	Various, 40% leukemia	Various drugs, \bar{x} = 180 mg/m ²	NT-proBNP		>350 pg/mL	Before each ANT cycle	FS <28%	a)
Erkus 2007	Yes	7	Leukemia	Doxorubicin, daunorubicin and/or idarubicin \bar{x} = 181.64 mg/m ²	Trop. I, BNP	>0.04 ng/mL		After ANT, not further specified	FS <29% EF <55%	c)
Fink 1995	Yes	7	Various, 45% leukemia	Adriamycin, daunorubicin, idarubicin, \bar{x} = 180 mg/m ²	Trop. T	>0.14 µg/L		>72 h after ANT cycles		
Gupta 2018	Yes	9	Various hematological	Drug N/A \bar{x} = 268.40 mg/m ²	Trop. I, NT-proBNP	>0.02 ng/mL	>100 pg/mL	6 months after start of ANT	EF relative decline ≥20%	
Hayakawa 2001	No	12	N/A	Doxorubicin, \bar{x} = 314 mg/m ²	BNP		>13 pg/mL	>1 month after last ANT	FS <30% EF <60%	a) b)

Kismet 2004	No	14	Various solid	Doxorubicin, \bar{x} = 480 mg/m ²	Trop. T	≥0.01 ng/ml		12 months after last ANT	FS <29% EF <55%	c)
Kremer 2002	Yes	10	Various hematological	Various, including mitoxantrone \bar{x} = 255 mg/m ²	Trop. T	>0.01 ng/mL		24 h after ANT	FS <30%; FS decline >15%	c)
Kunarahah 2017	Yes	8	Various, 29% ALL	Doxorubicin, \bar{x} = 95 mg/m ²	Trop. I	≥0.04 µg/L		5 min-120 h after ANT		
Leger 2017	Yes	11	Various, 33% AML	Various including mitoxantrone, \bar{x} = 102 mg/m ²	Trop. T	≥14 ng/L; ≥5 ng/L higher than pre-treatment		6-24 h after one ANT cycle		
Lipshultz 2012	Yes	8	ALL	Doxorubicin, 300 mg/m ²	Trop. T, NT-proBNP	Any detectable amount	Age <1 year: ≥150 pg/mL; age ≥1 year: ≥150 pg/mL	Day 1-7 after ANT induction; 7 day 7 after ANT consolidation; end of ANT therapy		
Mavinkurve-Groothuis 2009	No	21	Various, 30% ALL	Doxorubicin, daunorubicin \bar{x} = 180 mg/m ²	Trop. T, NT-proBNP	≥0.01 ng/mL	Age-dependent*	13.8 years after cancer diagnosis	FS <29% EF <55%	a)
Mavinkurve-Groothuis 2013	Yes	6	ALL	Various, including mitoxantrone \bar{x} = 300 mg/m ²	Trop. T, NT-proBNP	>0.01 ng/mL	Age-dependent*	3 month; 1 year after diagnosis		
Pinarli 2005	No	12	Various, 65% lymphoma	Doxorubicin, ± epirubicin or daunorubicin \bar{x} = 259.26 mg/m ²	BNP		>9.27 pg/mL	3.8 years after diagnosis		
Pongprot 2012	No	10	Various, 63% leukemia	Doxorubicin, \bar{x} = 300 mg/m ²	Trop. T, NT-proBNP	>0.01 ng/mL	Age-dependent***	Shortly before, or >1 month after ANT	FS <29% EF <55%	a) b) c)
Pourier 2015	No	16	Leukemia	Drug N/A \bar{x} = 225 mg/m ²	Trop. T, NT-proBNP	>13.5 ng/L	Age-dependent**	8.3 years after cancer diagnosis	FS ≤27% EF ≤55%	a) c)
Ruggiero 2013	Yes	6	ALL	Doxorubicin, 240 mg/m ²	Trop. T, NT-proBNP	>0.01 ng/mL	Age-dependent*	2 h, 24 h after ANT cycle	EF decline >20%;	

									EF decline >10% to <55%	
Shimomura 2011	No	15	ALL	Pirarubicin, Doxorubicin \bar{x} = 207 mg/m ²	BNP			8.1 years after cancer diagnosis	FS <28% EF <54%	
Soker 2005	No	8	Various hematological	Doxorubicin, \bar{x} = 227.26 mg/m ²	Trop. I, NT-proBNP	≥0.5 ng/mL		9.39 month after last ANT	FS <30% EF <60%	b)
Tragiannidis 2012	Yes	7	Various hematological	Drug N/A, Dose N/A	BNP			After completion of ANT	FS <29% EF <64%	
Urbanova 2010	No	23	Leukemia	Doxorubicin and daunorubicin \bar{x} = 221 mg/m ²	Trop. T, BNP	>0.01 ng/mL		10.5 years after completion of ANT		
Yildirim 2013	No	17	ALL	Doxorubicin, \bar{x} = 200 mg/m ²	NT-proBNP		>100 pg/mL	10.5 years after completion of ANT		
Ylänen 2015	No	14	Various, 55% leukemia	Drug N/A, 224 mg/m ²	Trop. T, I, NT-proBNP	Trop. T: >0.03 µg/L hsTrop. T: >14 ng/L Trop. I: N/A	males: >63 pg/mL females: >116 pg/mL	9.0 years after cancer diagnosis	Echo: EF <50% excluded: FS <28% MRI: EF <55%	a)

Control groups are not included within number of patients. Studies including sufficient data on cardiac biomarkers and LV function were included to one or more of the following forms of analysis as indicated:

- Analysis of LV dysfunction in patients with elevated BNP/NT-proBNP compared to patients with non-elevated troponin.
- Analysis of absolute BNP/NT-proBNP levels in patients with LV dysfunction compared to patients with preserved LV function.
- Analysis of LV dysfunction in patients with elevated troponin compared to patients with non-elevated troponin.

ALL, acute lymphoblastic leukemia, AML, acute myeloid leukemia, ANT, anthracycline; BNP, brain natriuretic peptide; echo, echocardiography; EF, ejection fraction; FS, fractional shortening; hs, high sensitivity; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro brain natriuretic peptide; N/A, not available (not stated within the manuscript of the respective study); Trop., troponin.

* Albers S, Mir TS, Haddad M, Laer S. N-Terminal pro-brain natriuretic peptide: normal ranges in the pediatric population including method comparison and interlaboratory variability. *Clinical chemistry and laboratory medicine*. 2006;44(1):80-85.

**Fradley MG, Larson MG, Cheng S, McCabe E, Coglianese E, Shah RV, Levy D, Vasan RS, Wang TJ. Reference limits for N-terminal-pro-B-type natriuretic peptide in healthy individuals (from the Framingham Heart Study). *The American journal of cardiology*. 2011 Nov 1;108(9):1341-1345.

Nir A, Lindinger A, Rauh M, Bar-Oz B, Laer S, Schwachtgen L, Koch A, Falkenberg J, Mir TS. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. *Pediatric cardiology*. 2009 Jan;30(1):3-8.

***Nir A, Lindinger A, Rauh M, Bar-Oz B, Laer S, Schwachtgen L, Koch A, Falkenberg J, Mir TS. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. *Pediatric cardiology*. 2009 Jan;30(1):3-8.

Online supplementary table 4: Diagnostic accuracy of BNP/NT-proBNP for acute/subacute LV dysfunction

	LV dysf.	no LV dysf.		
Positive test	10	6	PPV	0.625
Negative test	9	63	NPV	0.875
	Sensitivity	Specificity		
	0.526	0.913		

BNP, brain natriuretic peptide; LV dysf., left ventricular dysfunction; NT-proBNP, N-terminal pro brain natriuretic peptide; NPV, negative predictive value; PPV, positive predictive value.

Online supplementary table 5: Diagnostic accuracy of BNP/NT-proBNP for LV dysfunction in survivors of childhood cancer

	LV dysf.	no LV dysf.		
Positive test	5	20	PPV	0.200
Negative test	21	216	NPV	0.911
	Sensitivity	Specificity		
	0.238	0.915		

BNP, brain natriuretic peptide; LV dysf., left ventricular dysfunction; NT-proBNP, N-terminal pro brain natriuretic peptide; NPV, negative predictive value; PPV, positive predictive value.

Online supplementary table 6: Assessment of bias using the Newcastle-Ottawa Scale

Study	Is the selected cohort representative?	Is the selection of controls appropriate?	Is the ascertainment of exposure appropriate?	Was demonstrated that the outcome of interest was not present at the start of the study?	Are the selected and control groups comparable concerning age/other controlled factors?	Is the independent or blind assessment stated in the paper?	Was follow-up long enough for outcomes to occur?	Was follow-up adequate?	Total number of stars
Aggarwal 2007		*	*		**	*	*	*	6
Arslan 2013	*	*	*		*		*	*	8
Asselin 2016	*		*	*		*	*	*	5
Cetin 2018	*	*			*	*	*	*	9
Clark 2007	*		*	*			*	*	4
Ekstein 2007	*	*	*	*	**	*		*	7
Erkus 2007	*	*	*	*	**	*		*	5
Fink 1995	*		*	*		*		*	4
Gupta 2018	*		*	*		*	*	*	8
Hayakawa 2001		*	*		**	*			6
Kismet 2004		*	*		**	*	*		7
Kremer 2002	*	*	*	*	**	*		*	5

Kunarajah 2017	*			*		*	*	*	5
Leger 2017		*	*	*	**	*			5
Lipshultz 2012	*		*	*		*	*	*	8
Mavinkurve- Groothuis 2009		*	*		**	*	*	*	7
Mavinkurve- Groothuis 2013	*	*	*	*	*	*	*		7
Pinarli 2005	*	*	*		*	*	*		7
Pongprot 2012	*	*	*		**	*			5
Pourier 2015	*	*	*		**	*	*	*	6
Ruggiero 2013	*		*	*		*	*	*	6
Shimomura 2011		*	*		*	*	*	*	8
Soker 2005	*	*	*		**			*	7
Tragiannidis 2012	*			*		*		*	5
Urbanova 2010	*	*	*		*	*	*	*	9
Yildirim 2013	*	*	*		*		*	*	8
Ylänen 2015		*	*		**		*	*	5

Supplementary figure legends

Online supplementary figure 1. BNP/NT-proBNP for the detection of LV dysfunction in young and old studies. Frequency of BNP/NT-proBNP elevation post-treatment compared to pre-treatment or control cohort for studies prior to 2011 and studies from 2011 and younger separately. Parallelogram boxes denote the odds ratio, and horizontal lines represent the 95% confidence interval. BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro BNP.

Online supplementary figure 2. BNP/NT-proBNP for the detection of LV dysfunction within high-dose and low-doses anthracycline treatment subgroups. A, frequency of LV dysfunction in patients with elevated BNP/NT-proBNP compared to patients without elevated BNP/NT-proBNP post-treatment in patients receiving 240-600 mg/m² compared to patients receiving <240 mg/m² cumulative doxorubicin or doxorubicin-equivalent dose. B, absolute BNP/NT-proBNP levels in patients with LV dysfunction compared to patients without LV dysfunction post-treatment in patients receiving 240-600 mg/m² compared to patients receiving <240 mg/m² cumulative doxorubicin or doxorubicin-equivalent dose. Parallelogram boxes denote the odds ratio or standardized mean difference, and horizontal lines represent the 95% confidence interval. Std, standardized.

Online supplementary figure 3. BNP and NT-proBNP subgroups for the detection of LV dysfunction. Absolute BNP levels and NT-proBNP levels separately in patients with LV dysfunction compared to patients without LV dysfunction post-treatment. Parallelogram boxes denote the standardized mean difference, and horizontal lines represent the 95% confidence interval. Std., standardized.

Online supplementary figure 4. Absolute troponin I levels compared to troponin T levels post-treatment. Absolute troponin I levels and troponin T levels separately in patients with LV dysfunction compared to patients without LV dysfunction post-treatment. Parallelogram boxes denote the standardized mean difference, and horizontal lines represent the 95% confidence interval. Std., standardized.

Online supplementary figure 5. Individual bias assessment. Risk of bias and applicability concerns judgement for single studies.

Online supplementary figure 6. Analysis of heterogeneity. Funnel plot of dichotomous analysis of BNP/NT-proBNP in children with cancer or survivors of childhood cancer post-treatment compared to pre-treatment or control cohort when pre-treatment values were not available. BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro BNP; SE, standard error; SMD, standardized mean difference.

Supplemental references: Included studies

1. Gupta V, Kumar Singh S, Agrawal V, Bali Singh T. Role of ACE inhibitors in anthracycline-induced cardiotoxicity: A randomized, double-blind, placebo-controlled trial. *Pediatr Blood Cancer* 2018;65:e27308.
2. Cetin S, Babaoglu K, Basar EZ, Deveci M, Corapcioglu F. Subclinical anthracycline-induced cardiotoxicity in long-term follow-up of asymptomatic childhood cancer survivors: Assessment by speckle tracking echocardiography. *Echocardiography* 2018;35:234-240.
3. Leger KJ, Leonard D, Nielson D, de Lemos JA, Mammen PP, Winick NJ. Circulating microRNAs: Potential Markers of Cardiotoxicity in Children and Young Adults Treated With Anthracycline Chemotherapy. *J Am Heart Assoc* 2017;6.
4. Kunarajah K, Hennig S, Norris RLG et al. Population pharmacokinetic modelling of doxorubicin and doxorubicinol in children with cancer: is there a relationship with cardiac troponin profiles? *Cancer Chemother Pharmacol* 2017;80:15-25.
5. Asselin BL, Devidas M, Chen L et al. Cardioprotection and Safety of Dexrazoxane in Patients Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic Non-Hodgkin Lymphoma: a Report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404. *J Clin Oncol* 2016;34:854-862.
6. Ylanen K, Poutanen T, Savukoski T, Eerola A, Vettenranta K. Cardiac biomarkers indicate a need for sensitive cardiac imaging among long-term childhood cancer survivors exposed to anthracyclines. *Acta Paediatr* 2015;104:313-9.
7. Pourier MS, Kapusta L, van Gennip A et al. Values of high sensitive troponin T in long-term survivors of childhood cancer treated with anthracyclines. *Clin Chim Acta* 2015;441:29-32.
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