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Biomarkers to diagnose ventricular dysfunction in childhood cancer survivors: a systematic review

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ABSTRACT

Objective To systematically review the literature and assess the diagnostic value of biomarkers in detection of late-onset left ventricular (LV) dysfunction in childhood cancer survivors (CCS) treated with anthracyclines.

Methods We systematically searched the literature for studies that evaluated the use of biomarkers for detection of LV dysfunction in CCS treated with anthracyclines more than 1 year since childhood cancer diagnosis. LV dysfunction definitions were accepted as an ejection fraction <50% or <55% and/or a fractional shortening <28%, <29% or <30%. Contingency tables were created to assess diagnostic accuracies of biomarkers for diagnosing LV dysfunction.

Results Of 1362 original studies screened, eight heterogeneous studies evaluating four different biomarkers in mostly asymptomatic CCS were included. In four studies, an abnormal N-terminal pro-B-type natriuretic peptide (NT-proBNP, cut-off range 63–125 ng/L) had low sensitivity (maximally 22%) and a specificity of up to 97% for detection of LV dysfunction. For troponin levels, in five studies one patient had an abnormal troponin value as well as LV dysfunction, while in total 127 patients had LV dysfunction without troponin elevations above cut-off values (lowest 0.01 ng/mL). Two studies that evaluated brain natriuretic peptide and nitric oxide were underpowered to draw conclusions.

Conclusions In individual studies, the diagnostic value of NT-proBNP for detection of LV dysfunction in CCS is limited. Troponins have no role in detecting late-onset LV dysfunction with cut-off values as low as 0.01 ng/mL. Further study on optimal NT-proBNP cut-off values for rule out or rule in of LV dysfunction is warranted.

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INTRODUCTION

Every year, an estimated total of 20 000 children are diagnosed with cancer in Europe.[1] Due to better treatment options for childhood cancer, the 5-year survival rate has increased dramatically over the last decades and currently exceeds 80%.[2] As a result of this improved prognosis, a considerable proportion of these children become long-term survivors. It is estimated that 1 in 680 people is a childhood cancer survivor (CCS) in the USA.[3] Along with this growing number of CCS, there is an increase in late effects of cancer therapies.[4]

Anthracycline derivatives are used in 60% of all children with cancer[5] and are well known for their dose-dependent cardiotoxic side effects with the most important one being left ventricular (LV) dysfunction ultimately leading to congestive heart failure.[6–8] Three types of anthracycline-related LV dysfunction are defined in time.[9] (1) Acute cardiotoxicity leading to a reversible decline in LV function within 2 weeks after anthracycline infusion. (2) Early onset progressive cardiotoxicity occurs during or within the first year after treatment. This cardiotoxicity is thought to be irreversible, related to cardiomyocyte damage resulting in progressive LV dysfunction. (3) Late-onset cardiotoxicity occurs more than 1 year after treatment and is thought to be caused by initial damage to cardiomyocytes resulting in harmful compensation mechanisms leading to LV dysfunction up to decades after anthracycline exposure.[9] This review will focus on late-onset LV dysfunction starting more than 1 year after anthracycline treatment in CCS.

Late-onset LV dysfunction 10–15 years after anthracycline treatment occurs in nearly 30% of this relatively young population of CCS, defined as a fractional shortening (FS) <30%.[7] Moreover, in 30 years, one in eight has overt heart failure which requires treatment.[8] In the general population, early treatment of patients with asymptomatic LV dysfunction with ACE inhibitors reduces mortality and incidence of heart failure.[10] Detecting LV dysfunction following anthracycline chemotherapy in the asymptomatic phase may reduce long-term morbidity and mortality as overt heart failure may be prevented by providing treatment with ACE inhibitors, although more evidence is still needed on the benefit of ACE inhibitors in the presence of LV dysfunction in this specific population.[6]

Echocardiography is the imaging modality of choice to detect LV dysfunction in long-term CCS. The current guidelines for the screening of LV dysfunction in CCS recommend echocardiography with a screening interval of 5 years or shorter, depending on risk factors for LV dysfunction such as cumulative anthracycline dose (CAD), age during treatment, gender and concomitant radiotherapy.[6 11]

In the general population, screening for asymptomatic LV dysfunction has been performed using natriuretic peptides (N-terminal pro-B-type natriuretic peptide (NT-proBNP) and brain natriuretic peptide (BNP)).[12] Biomarkers such as natriuretic peptides show potential in early detection of LV dysfunction in CCS.[13–15] In children and adults, a rise in cardiac troponins during or shortly after anthracycline treatment, indicating cardiomyocyte damage, may serve as a predictor for future LV dysfunction.[16 17] In late-onset cardiotoxicity, the utility of biomarkers such as natriuretic peptides and troponins in detection of LV dysfunction is still evolving.[6 14] In this systematic review, we aimed to evaluate the diagnostic value of biomarkers to detect late-onset LV systolic dysfunction as measured by ejection fraction (EF) or FS, in long-term CCS treated with anthracyclines.

METHODS

Literature search and eligibility criteria

Pubmed, EMBASE and the Cochrane library were systematically searched for original studies on biomarkers and LV dysfunction in survivors of childhood cancer treated with anthracyclines more than 1 year after treatment. The full search strategy is provided in the online Supplementary file 1. The reference list of included articles was manually screened for additional studies.

Two reviewers (SJV and WEMK) independently screened these studies. Excluded were reviews, animal studies, studies with patients having their primary cancer diagnosis above 21 years of age, studies that lacked or did not define LV dysfunction by an EF or FS cut-off (see the Definitions section below) and studies with an unknown number of patients with LV dysfunction. Further excluded were studies that did not perform biomarker sampling and echocardiography within 1 month and studies with a duplicated patient cohort. Studies combining early (<1 years) and late onset (>1 year) detections of LV dysfunction were included but were described separate in the tables.

Quality assessment

Critical appraisal of the included studies was performed by two reviewers using the Standards for Reporting Diagnostic Accuracy 2015 (STARD 2015) checklist[18] (online Supplementary file 2). Uncertainties were discussed with a third person. This review was conducted following the criteria from the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline[19] (online Supplementary file 3).

Definitions

Late-onset cardiotoxicity was defined as LV systolic dysfunction occurring more than 1 year after treatment. LV systolic dysfunction in studies was accepted as such when defined as an EF <50% or <55% and/or a FS <28%, <29% or <30% measured by echocardiography. Biomarker cut-off values were noted and defined as abnormal if stated in the study.

Data extraction

From the included studies, number of patients, age at time of childhood cancer diagnosis, age at time of study, time since last treatment, gender, type of chemotherapy, CAD, radiotherapy exposure, cardiac symptoms or medication, LV dysfunction definition and prevalence, evaluated biomarkers, biomarker cut-off values and number of patients with an abnormal biomarker were manually collected by two investigators independently (JML and SJV).

Statistical analysis of the data

To measure the diagnostic accuracy of each biomarker to detect LV dysfunction, contingency tables were created and sensitivity (true positives/true positives+false negatives), specificity (true negatives/true negatives+false positives), positive predictive value (PPV, true positives/true positives+false positives), negative predictive value (NPV, true negatives/true negatives+false negatives) were calculated. Likelihood ratios (LR+ and LR−) were calculated using the formulas: LR+=sensitivity/1−specificity and LR−=1 sensitivity/specificity. For an thorough overview on these metrics, we refer the reader to one of the following articles.[20–22] Accompanying 95% CIs were calculated by the efficient-score method.[23]

RESULTS

By searching the literature, we identified 1494 studies (figure 1). In addition, three studies were manually found by searching the references. After removing 105 duplicate records, 1392 studies underwent title and abstract screening. Full-text screening was intended in 25 studies. However, of one study, a translation was requested but not received[24] and another study only had an abstract available.[25] Main reasons for exclusion of full-text studies were: an absence or different LV dysfunction definitions not defined by an EF or FS cut-off, exclusion of patients with LV dysfunction, an unknown number of patients with LV dysfunction or time since anthracycline treatment of less than 1 year in all patients. Finally, eight cohort studies with in total 691 CCS at a median of 0.9–18.2 years since anthracycline treatment were included (median dose 165–480 mg/m^2) evaluating four different biomarkers (table 1). Applying the STARD 2015 checklist, it was notable that none of the studies were identified as a diagnostic accuracy study and no diagnostic accuracies of biomarkers for the diagnosis of LV dysfunction were reported. Also, three studies did not report biomarker cut-off values impairing the use of contingency tables in these studies[26–28] (online Supplementary file 2). Three studies did not exclude symptomatic patients and patients on heart failure medication[15 26 29] and one study excluded patients with CAD <400 mg/m^2 (table 1).[30]

N-terminal pro-B-type natriuretic peptide

Five studies with a total of 575 patients measured NT-proBNP levels in anthracycline-exposed patients (table 2). Significant heterogeneity was present in median follow-up duration (between 7.1 and 18.2 years) and in median CAD (ranged from 180 to 225 mg/m^2). LV dysfunction was present in 0%–37% of the study populations with one study having no patients with LV dysfunction.[28] Cut-off values for NT-proBNP levels varied from 63 ng/L in males and 116 ng/L in females[29] to 125 ng/L in males and females.[15] Cut-off values for children were defined in the studies as age-specific and sex-specific values previously reported by Nir *et al*[29 31 32] and Albers *et al*.[13 33] Also, sex-specific and age-specific cut-off values defined by Fradley *et al*[34] (ranging from 42.5 to 106.4 ng/L in males and 111.0–215.9 ng/mL in females depending on age) were used.[32] Abnormal NT-proBNP values were seen in 5.3% up to 13% of the patients; we did not observe a relation with NT-proBNP cut-off values (table 2). In four of five studies, patients with LV dysfunction were present and these studies were used for diagnostic accuracy analysis.[13 15 29 32] Sensitivities (14%–22%) and PPVs (13%–50%) were low in the four studies, while demonstrating higher specificities (88%–97%) and NPVs (65%–90%). LRs for having LV dysfunction with an abnormal NT-proBNP value (LR+) were 1.70–6.67 and LRs for having LV dysfunction with a normal

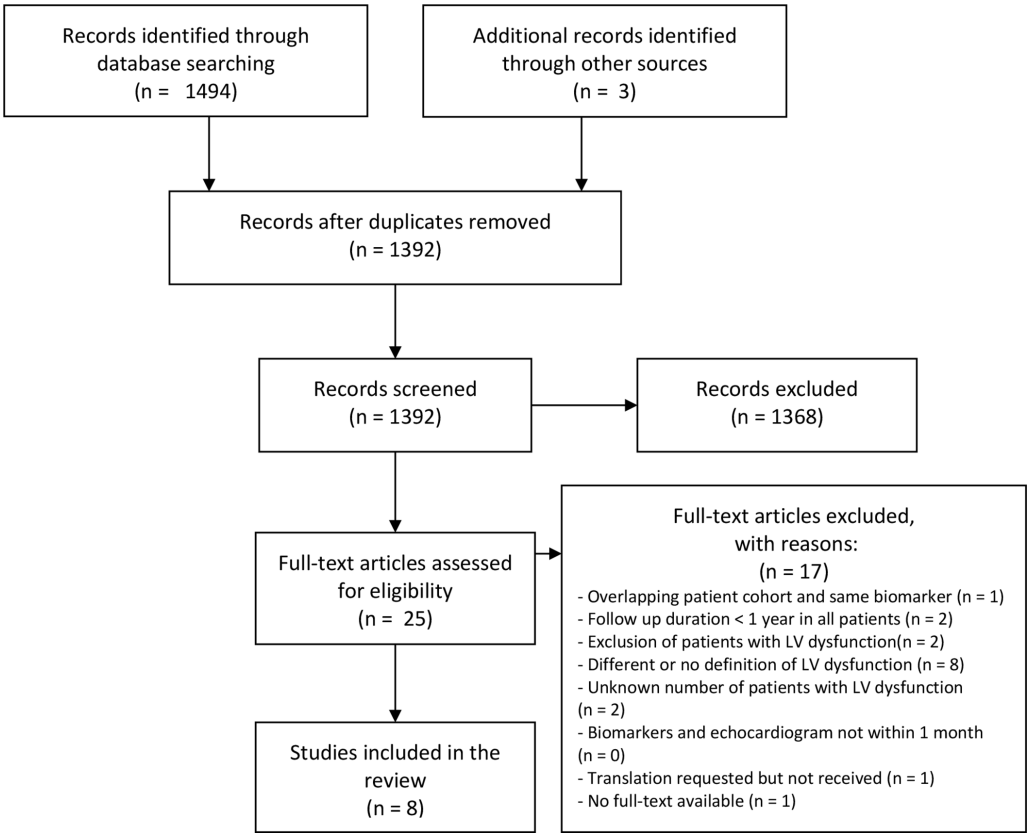

Figure 1 Study inclusion flow chart. LV, left ventricular.

NT-proBNP level (LR−) were 0.83–0.93 (table 2). Of note, CIs of the diagnostic accuracy estimates were wide in all four studies (table 2). A meta-analysis was not performed because of heterogeneity in the presented studies.

Troponins

Five studies with a total of 423 patients were included using various troponin assays in the detection of LV dysfunction in CCS (table 3). Median CAD ranged from 180 to 480 mg/m^2 and time since last treatment varied between 1 and 18.2 years. LV dysfunction prevalence ranged between 7.4% and 36.5%. Abnormal troponins (cut-off values for troponin T between 0.01 and 0.014 ng/mL, and for troponin I 0.03–0.04 ng/mL) were seen in only five of all 423 patients. Only one of these five patients showed LV dysfunction[30] and a troponin T>0.01 ng/mL, while in the total population LV dysfunction was present in 128 patients. Troponin testing in this single study had very limited sensitivity (50%; 95% CI 3 to 97%) and PPV (33%; 95% CI 2 to 87) with higher specificity (91%; 95% CI 69 to 98) and NPV (95%; 95% CI 74 to 99). The LR+ and LR− for this study were 5.49 (95% CI 0.81 to 37.32) and 0.55 (95% CI 0.14 to 2.22), respectively. Two studies used high-sensitive troponin T measurements[29 32] with the lowest cut-off value of 0.0135 ng/mL, but no abnormal troponins were present in these studies.

Brain natriuretic peptide

Only one study was included studying BNP in 63 patients.[26] Higher BNP values were present in CCS with a FS <29% compared with CCS with a FS >29% (32.4±34.9 vs 15.6 ± 12.4 pg/mL, p<0.008) but no cut-off values or contingency tables were provided.[26]

Nitric oxide

One study[27] measured plasma total nitrite levels, a stable product of nitric oxide, 10.5 months (range 2–37.4) since last anthracycline treatment in 29 children. LV dysfunction defined as an EF <55% and/or FS <30% was present in 10.3% of the patients, and this was related to significantly higher nitrite levels compared with matched healthy controls (92.35±50.36 vs 59.26±13.56 μmol/L, p=0.038).

DISCUSSION

In this systematic review, we show that the diagnostic value of biomarkers to detect LV dysfunction in CCS is limited at the presented cut-off values and are overall not yet suited for either excluding (rule out) or confirming (rule in) LV dysfunction. Although biomarker screening has been advocated by some,[35] we show that the current literature does not yet provide evidence to implement routine biomarker screening in the surveillance of CCS at risk for LV dysfunction.

N-terminal pro-B-type natriuretic peptide

In our review, NT-proBNP is the best studied biomarker for the detection of LV dysfunction in CCS with a limited diagnostic accuracy (table 2). Our finding of low sensitivities and PPVs and higher specificities and NPVs for detection of LV dysfunction in long-term CCS is in line with previous reviews.[6 14] Considering the consequences of missing patients with LV dysfunction, the NPV of NT-proBNP must be at least 98% to rule out LV dysfunction and defer an echocardiogram.[36] Therefore, with the presented cut-off values, NT-proBNP is not useful to rule out LV dysfunction. At the same cut-off values, NT-proBNP is not

Table 1 Summary of the included studies on biomarkers for the detection of late-onset LV dysfunction

	n	Male, n (%)	Anthracyline type	CAD, median (range)	Chest radiotherapy, n (%)	Heart failure, n; heart failure medication, n	Age at diagnosis, years (range or SD)	Age at study, years (range or SD)	Time since last treatment, years (range or SD)	LV dysfunction definition	LV dysfunction, %	Evaluated biomarker(s)
Early and late onset												
Guler *et al*[27]	29	17 (59%)	DOX	310 (180–480)	6 (21%)	–	–	9.1±3.7	0.9 (0.2–3.1)	EF<55 FS<30	10.3%	NO
Kismet *et al*[24 30]	24	14 (58%)	DOX	480 (400–840)	4 (17%)	–	–	14 (3-31)	1.0 (0.1–14)	EF<55 FS<29	8.3%	cTnT
Late onset												
Aggarwal *et al*[26]	63	37 (59%)	ANT	165 (45–520)	–	3; 5	–	13.1 (6.5–26.5)	5.4±4.1	FS<29	14.3%	BNP
Brouwer *et al*[15]	277	155 (56%)	DAU, DOX	183 (50–600)	69 (25%)	11; 17	8.8 (0–20.1)	27.5 (18–48)	18.2 (5.4–30.8)	FS<29	36.8%	cTnI, cTnT, NT-proBNP
Mavinkurve-Groothuis *et al*[13]	122	62 (51%)	DAU, DOX	180 (50–542)	7 (6%)	–	5.7 (0–14.4)	21 (5.0–39.4)	13.8 (5.0–28.7)	EF<55 FS<29	7.4%	cTnT, NT-proBNP
Mladosievicova *et al*[28]	36	19 (53%)	DAU, DOX, EPI	221	1 (3%)	–	8 (1–17)	22 (18–31)	11 (5–22)	EF<50	0%	NT-proBNP
Pourier *et al*[32]	64	38 (59%)	ANT	225 (85–450)	15 (23%)	–	5.8 (0.3–17.3)	16.7 (7.2–39.8)	8.3 (4.5–34.1)	EF<55 FS<29	10.9%	hs-cTnT, NT-proBNP
Ylänen *et al*[29]	76	34 (45%)	ANT	224 (80–454)	10 (13%)	–-; 4	3.8 (0–13.8)	14.3 (7.2–20.0)	7.1 (5–18)	3DEF<50 FS<28	13.3%	cTnI, cTnT, hs-cTnT, NT-proBNP

3DEF, ejection fraction measured by three-dimensional echocardiography; ANT, any anthracycline not further specified; CAD, cumulative anthracycline dose in mg/m^2; cTnT, cardiac troponin T; cTnI, cardiac troponin I; DAU, daunorubicin; DOX, doxorubicin; EPI, epirubicin; hs-cTnT, high-sensitivity cTnT, NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Table 2 Diagnostic value of NT-proBNP for detection of LV dysfunction

	n	Time since last treatment, years (range)	LV dysfunction, %	NT-proBNP cut-off, ng/L	Abnormal NT-proBNP, n (%)	LV dysfunction and abnormal NT-proBNP, n	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR+ (95% CI)	LR– (95% CI)
Late onset												
Brouwer *et al*[15]	277	18.2 (5.4–30.8)	36.8%	125	32/262 (12.2%)	16	17% (10 to 26)	90% (84 to 94)	50% (32 to 68)	65% (58 to 71)	1.70 (0.89 to 3.25)	0.93 (0.85 to 1.01)
Mavinkurve-Groothuis *et al*[13]	122	13.8 (5.0–28.7)	7.4%	M 84.6 F 152.2 C *Albers	16/122 (13.1%)	2	22% (4 to 60)	88% (80 to 93)	13% (2 to 40)	93% (60 to 98)	1.79 (0.48 to 6.69)	0.89 (0.62 to 1.26)
Mladosievicova, 2012[28]	36	11 (5–22)	0%	M 75 F 105	4/36 (11.1%)	0	–	–	–	–	–	
Pourier *et al*[32]	64	8.3 (4.5–34.1)	10.9%	M/F *Fradley C *Nir	5/64 (7.8%)	1	14% (1 to 58)	93% (82 to 98)	20% (1 to 70)	90% (79 to 96)	2.04 (0.26 to 15.75)	0.92 (0.68 to 1.25)
Ylänen *et al*[29]	76	7.1 (5.0–18.0)	13.3%	M 63 F 116 C *Nir	4/76 (5.3%)	2	20% (4 to 56)	97% (88 to 99)	50% (9 to 91)	89% (78 to 95)	6.50 (1.03 to 41.07)	0.83 (0.60 to 1.13)

*Albers *et al*[33]: age-specifc and sex-specific values in children; Fradley *et al*[34]: age-specific and sex-specific values in adults; Nir *et al*[31]: age-specific values in children.
C, children; F, female; LV, left ventricular; LR+, poitive likelihood ratio; LR–, negative likelihood ratio; M, male, NPV, negative predictive value; NT-proBNP, N-terminal pro B-type natriuretic peptide; PPV, positive predictive value.

Table 3 Diagnostic value of troponins for detection of LV dysfunction

	n	Time since last treatment, years (range)	LV dysfunction, %	Evaluated troponin(s)	Troponin cut-off (ng/mL)	Abnormal troponin, %	LV dysfunction and abnormal troponin (n)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	LR+ (95% CI)	LR– (95% CI)
Early and late onset													
Kismet *et al*[24 30]	24	1 (0.1–14)	8.3%	cTnT	0.010	2/24 (8.3%)	1	50% (3 to 97)	91% (69 to 98)	33.3% (2 to 87)	95% (74 to 99)	5.49 (0.81 to 37.32)	0.55 (0.14 to 2.22)
Late onset													
Brouwer *et al*[15]	277	18.2 (5.4–30.8)	36.8%	cTnI, cTnT	0.04, 0.01	3/268 (1.1%)	0	–	–	–	–	–	–
Mavinkurve-Groothuis *et al* [1314]	122	13.8 (5.0–28.7)	7.4%	cTnT	0.01	0	0	–	–	–	–	–	–
Pourier *et al*[32]	64	8.3 (4.5–34.1)	10.9%	hs-cTnT	0.0135	0	0	–	–	–	–	–	–
Ylänen *et al*[29]	76	7.1 (5.0–18.0)	13.3%	cTnI, cTnT, hs-cTnT	0.0095, 0.03, 0.014	0	0	–	–	–	–	–	–

cTnI, cardiac troponin I; cTnT, cardiac troponin T; hs-cTnT, high-sensitivity cTnT; LR+, positive likelihood ratio; LR–, negative likelihood ratio; LV, left ventricular; NPV, negative predictive value; PPV, positive predictive value; Unk, unknown.

yet suited for rule in purposes, as specificity ranges from 88% to 97%, implying significant rates of false positives.

The limited diagnostic accuracy of NT-proBNP for detection of LV dysfunction might be partly explained by the LV dysfunction definitions used in the included studies, similar to findings in the general population.[12] In the general population of <65 years of age, the diagnostic accuracy of NT-proBNP for detection of an EF <50% is very limited compared with the detection of an EF <40% (area under the curve of 0.88 and 0.56, respectively).[12] NT-proBNP might also prove more useful in diagnosing an EF <40% in CCS treated with anthracyclines. This is an interesting subject for future studies because diagnosing an EF <40% in CCS is meaningful as this has implications for initiating treatment with heart failure therapies.[37] Also, in the general population of <65 years of age, the optimal NT-proBNP cut-off value of 59 ng/L for diagnosing an EF <50%[12] is lower than the cut-off values used in the included studies and corresponded to a higher sensitivity of 62.2%, at the cost of a lower specificity of 61.3% compared with sensitivities and specificities reported in our review. In future studies, separate optimal age and sex-adjusted cut-off values for rule out and rule in of LV dysfunction in CCS should be tested, as is also done for the diagnosis of acute heart failure in the emergency department.[36]

Optimal NT-proBNP cut-off values to rule out and rule in LV dysfunction may not only vary by age and sex but also by individual pretest probabilities of LV dysfunction because predictive values of a diagnostic test are dependent on the prevalence of disease.[20] We noticed a wide spread in the prevalence of LV dysfunction in the included studies ranging from 7.4% to 36.8%, probably due to patient selection, differences in CAD and differences in definitions of LV dysfunction (table 2). Indeed, NPVs were high (89%–93%) in three of the four studies with the lowest prevalence of LV dysfunction (7.4%–13.3%)[13 29 32] and lower (NPV 65%) in the study with the highest prevalence (36.8%).[15] To account for such heterogeneity in the populations, individual pretest probabilities for LV dysfunction should be taken into consideration when using NT-proBNP to diagnose LV dysfunction in CCS and can be estimated by traditional risk factors for anthracycline-related cardiotoxicity such as sex, age at diagnosis, follow-up duration and CAD and radiotherapy dose.[38] Subsequently, the LR can be used to calculate individual post-test probabilities of LV dysfunction. LRs above 10 or below 0.1 may be regarded as strong.[22] The LRs we report for NT-proBNP are therefore moderate and need improvement before NT-proBNP testing can play a role in the surveillance for late-onset LV dysfunction in CCS.

Troponins

Troponins are markers for cardiomyocyte damage and may predict heart failure and cardiovascular death in the population using very low cut-off values.[39] Troponin measurements during or shortly after anthracycline treatment may be useful for prediction of future LV dysfunction.[16] For detection of late-onset LV dysfunction in CCS, the position of troponins in detection of cardiotoxicity is less clear. In the five included studies, troponins in the presence or absence of LV dysfunction are rarely elevated, even though cut-off values in these studies were as low as 0.01 ng/mL or 0.013 ng/mL with the newest high sensitivity assays. Therefore, there appears to be no potential in detecting LV dysfunction with the present troponin assays. This is in line with the previous reports.[6 14] Possibly, troponins may be of use for risk stratification using very low cut-off values of troponin for development of LV dysfunction in long-term CCS.[39]

Other biomarkers

The few studies on BNP and nitric oxide were too limited in patient number to draw conclusions. Identification of new biomarkers for detection of late-onset LV dysfunction in an early stage in CCS treated with anthracyclines is an interesting subject for future studies. Especially, biomarkers that relate to the mechanisms of late-onset anthracycline-induced LV dysfunction.

Strengths and limitations

Our systematic review provides a new overview of the literature in an emerging field of biomarkers with respect to the detection of LV dysfunction in CCS. However, some limitations must be mentioned. Based on the heterogeneity of the included studies regarding LV dysfunction definitions and biomarker cut-off values performing a meta-analysis was not appropriate. An individual patient data analysis is needed to define optimal biomarker cut-off values with a uniform LV dysfunction definition and will be performed by us for NT-proBNP in the near future. The aim of our review was to compare biomarkers levels with the presence of LV systolic dysfunction as measured by EF or FS, while other parameters indicating milder forms of LV dysfunction such as diastolic function parameters, myocardial strain parameters and interstitial fibrosis measurements derived from cardiac MRI may also be compared with biomarker tests. However, we chose to compare biomarkers to the LV systolic dysfunction parameters EF and/or FS because these are the most widely used parameters for detection of cardiotoxicity in CCS[6 11] with consequences for initiating heart failure therapies.[6 37]

Implications for clinical practice and future research

Our results showing that none of the biomarkers at present cut-off values can safely rule in or rule out LV dysfunction in CCS and discourages the routine use of biomarkers in the surveillance of CCS treated with anthracyclines. Furthermore, our review serves as an incentive for more research on optimal biomarker cut-off values and for the identification of new biomarkers that can accurately exclude or confirm LV dysfunction.

Key messages

What is already known on this subject?

- Long-term childhood cancer survivors (CCS) treated with anthracyclines are at risk for developing heart failure up to four decades after anthracycline exposure and are therefore periodically screened for left ventricular (LV) dysfunction by guideline recommended echocardiograms. At present, biomarkers are not recommended for screening of LV dysfunction in long-term CCS.

What might this study add?

- In this systematic review of eight studies, we show that the biomarkers N-terminal pro-B-type natriuretic peptide and troponins have a limited diagnostic value for detection of late-onset LV systolic dysfunction in CCS treated with anthracyclines. Other biomarkers are insufficiently studied to draw conclusions.

How might this impact on clinical practice?

- The results of our systematic review should discourage the routine use of biomarkers in the screening for late-onset LV systolic dysfunction in CCS treated with anthracyclines.

CONCLUSIONS

The biomarkers NT-proBNP and troponins have limited diagnostic value to detect late-onset LV dysfunction in CCS at the presented cut-off values and are not useful in the screening of long-term CCS treated with anthracyclines. Other biomarkers have not been sufficiently studied in long-term CCS to draw conclusions regarding their diagnostic value.

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