Troponins and brain natriuretic peptides for the prediction of cardiotoxicity in cancer patients: a meta-analysis

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Aims
Cardiac biomarkers are a mainstay in diagnosis of cardiovascular disease but their role in cardio-oncology has not yet been systematically evaluated. This meta-analysis aims to determine whether cardiac troponins and (N-terminal pro) brain natriuretic peptide (BNP/NT-proBNP) predict cancer therapy-related left ventricular (LV) dysfunction.

Methods and results
Scientific databases were searched for studies that assessed troponins or BNP/NT-proBNP in adult patients undergoing cancer therapy. Data from 61 trials with 5691 patients were included. Cancer therapy was associated with an increase in troponin levels [odds ratio (OR) 1.43, 95% confidence interval (CI) 0.60–3.41; n = 3049]. Patients with elevated troponins receiving chemotherapy or human epidermal growth factor receptor 2 inhibitor therapy were at higher risk for LV dysfunction (OR 11.9, 95% CI 4.4–32.1; n = 2163). Troponin had a negative predictive value of 93%. Mean BNP/NT-proBNP levels were increased in patients post-treatment (standardized mean difference 0.6, 95% CI 0.3–0.9; n = 912), but the available evidence did not consistently indicate prediction of LV dysfunction (OR 1.7, 95% CI 0.7–4.2; n = 197). β-blocker and angiotensin-converting enzyme inhibitor therapy to mitigate cardiotoxicity during cancer therapy was associated with a decline in serum troponins (OR 4.1, 95% CI 1.7–9.8; n = 466).

Conclusion
Elevated troponin levels predict LV dysfunction in patients receiving cancer therapy. Assessment of troponin levels may qualify as a screening test to identify patients who require referral to cardio-oncology units and benefit from preventive strategies. Further evidence is required for both biomarkers.

Keywords
Biomarker • Brain natriuretic peptide • Cancer • Cardiotoxicity • Meta-analysis • Troponin

Introduction
Cardiac biomarkers including troponins and (N-terminal pro) brain natriuretic peptide (BNP/NT-proBNP) are a mainstay for the diagnosis of heart diseases. Elevated troponins indicate myocardial injury and myocardial infarction. Increased plasma NT-proBNP levels signal heart failure while negative BNP/NT-proBNP serves as rule-out criterion. Cancer and cancer therapy challenge the cardiovascular system in many ways. Heart failure represents the most concerning entity of cardiotoxicity, and cardio-oncology teams aim to provide a timely diagnosis for optimal treatment.

Various cancer therapies for the most common forms of cancer can induce left ventricular (LV) dysfunction. In particular, patients receiving anthracycline chemotherapy, human epidermal growth factor receptor 2 (HER2) inhibitors and radiotherapy are prone to cardiotoxic side effects. Novel targeted treatments (e.g. tyrosine kinase inhibitors) are increasingly used and may also have a significant cardiotoxic potential. Patients highly...
susceptible for cardiotoxicity have pre-existing cardiovascular risk factors (smoking, hypertension, diabetes, dyslipidaemia), older age (≥ 60 years) or clinically apparent cardiac disease. Therefore, careful and prolonged monitoring of cardiotoxicity in these collectives is crucial. Cancer therapy-related LV dysfunction is most commonly defined as ≥10% decrease in LV ejection fraction (LVEF) to values below 50% but impaired LVEF may take weeks to months to become detectable by imaging. Myocardial dysfunction as assessed by strain imaging from speckle tracking echocardiography may indicate LV dysfunction before changes in LVEF can be observed. However, this may also take weeks to become significant and early detection of cancer therapy-related cardiotoxicity is critical for the timely initiation of protective therapy with β-blockers and/or angiotensin-converting enzyme (ACE) inhibitors. Cardiac biomarkers with a high negative predictive value can be suitable for screening and have been studied in various settings in patients at risk for cancer therapy-related cardiotoxicity. In smaller cohorts, assessment of cardiac troponins has been related to cancer therapy-related cardiotoxicity when assessed as early as 72 h after chemotherapy. Prolonged troponin elevation predicted higher rates of cardiotoxicity. Limited data are available for BNP/NT-proBNP.

Systematic evaluation of cardiac biomarkers in cancer therapy-related cardiotoxicity is urgently needed for a standardized evaluation of cardiotoxicity in patients receiving cancer therapy. We therefore conducted the present systematic review and meta-analysis to assess cardiac troponins and BNP/NT-proBNP in the prediction of LV systolic dysfunction in cancer patients.

Methods

This meta-analysis was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) recommendations, the Cochrane Handbook for Systematic Reviews of Interventions, and the Preferred Reporting of Items for Systematic Meta-Analysis (PRISMA) reporting guidelines (online supplementary Tables S1 and S2). The study was registered with PROSPERO (International Prospective Register of Systematic Reviews; CRD42018106616).

Study identification

PubMed, Cochrane, Web of Science and Wiley Library databases were screened for studies that assessed conventional or high/ultra sensitivity troponin I or T, BNP, or NT-proBNP in patients undergoing cancer therapy until 1 November 2018. Only full-text articles in English language were included. Publications were screened for overlapping study populations to avoid repeated inclusion. The search was not restricted for trials by date. Trials with < 15 patients were excluded. Studies in paediatric patients or survivors of childhood cancer were also excluded. Two reviewers independently screened the literature (LM and RIM). A consensus was negotiated in case of disagreement (MT).

For the assessment of cardiac biomarker changes as a result of cancer therapy, appropriate studies assessing cardiac biomarkers before and after cancer therapy have been included. To evaluate the association of cardiac biomarkers and LV function, only studies that included systematic assessment of LV function in addition to biomarkers were included. Transthoracic echocardiography, magnetic resonance imaging (MRI) and radionuclide ventriculography were considered for an appropriate assessment of LV function. For studies equally showing both troponin I and T, only troponin I data were included for main analyses since troponin I is more commonly used for interventional studies in cardio-oncology. If applicable, both forms of troponin were included for subgroup analysis. The meta-analysis was focused on the following cancer therapies given their profound effect on LV dysfunction: anthracycline-containing chemotherapy, various high-dose chemotherapy regimens with or without anthracyclines, myeloablative therapy, HER2 inhibitor therapy, and thoracic radiotherapy. Details on high-dose regimes are listed in the online supplementary Methods S1. Studies that investigated cardioprotection from β-blockers, ACE inhibitors, or angiotensin II receptor blockers (ARB) intervention were furthermore included. The primary endpoint was a decrease in LVEF as defined by the study. Biomarker elevation over the cutoff for normal values as defined by study protocols and absolute biomarker levels were considered as secondary endpoints.

Data collection

The following data were collected: year of publication, type of cancer, type of cancer therapy and dose, biomarker details (including type of assay and cutoff values), data on LVEF and available reference values, and cardioprotective treatment. For data synthesis, mean, standard deviation and number of included patients or dichotomous values of biomarkers and LVEF were recorded. Data presented as median and interquartile or overall range were excluded due to potential lack of normal distribution.

Statistical analysis

For statistical analysis, a random effects model was used. Studies were stratified into predefined treatment groups to conduct subgroup analysis. Data are expressed as odds ratio (OR) and 95% confidence interval (CI) for dichotomous outcomes, and standardized mean difference (SMD) for continuous variables. Heterogeneity between studies was assessed using Q statistics, and inconsistencies were quantified using the I² statistical test. The list of included studies can be found in the online supplementary Methods S1. Descriptive statistics were performed using Revman 5.3 software (The Cochrane Collaboration).

Individual cohort studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) 2 revised criteria. Intervventional studies were analysed per recommendations from the Cochrane Handbook for Systematic Reviews of Interventions. Funnel plot test (Egger’s test) was used to evaluate publication bias.

Results

Article selection and baseline characteristics

Systematic search resulted in 358 potentially relevant articles. After removal of review articles, animal studies and case reports, 187 studies were included into qualitative analysis (online supplementary Figure S1). The full strategy for inclusion can be found in the online supplementary Methods S1. A total of 61 research articles studying 5691 patients met the study criteria and was included into
Troponins for the prediction of left ventricular dysfunction

The purpose of this analysis was to evaluate the association between elevated troponins and the risk for LV dysfunction. Seventeen studies (2163 patients) for dichotomous data and six studies (230 patients) for absolute troponin levels were included. Post-treatment troponins were elevated in 22.4% of patients included for the analysis. The frequency of elevated troponins did not differ between patients included for analysis of troponin during therapy and patients included for assessment of LV dysfunction (online supplementary Figure S5). Cardiotoxicity as indicated by decreased LV function was observed in 17.0% (367/2163) of all patients included for dichotomous troponin analysis with the highest risk in the high-dose chemotherapy subgroup (19.6%; 178/907). The likelihood for LVEF impairment was higher in patients with elevated troponins compared to troponin-negative patients (OR 11.9, 95% CI 4.4–32.1; n = 2163) (Figure 2). This was again most pronounced under high-dose regimens (OR 97.9, 95% CI 52.2–183.8; n = 907), but also significantly associated in patients receiving anthracyclines and/or HER2 inhibitor therapy (OR 7.0, 95% CI 1.4–34.1; n = 326 for anthracyclines and OR 10.1, 95% CI 2.1–48.9; n = 658 for HER2 inhibitor, respectively). Accordingly, the mean serum troponin levels in patients with LV dysfunction were higher compared to patients with preserved LV function (SMD 1.1, 95% CI 0.4–1.9; n = 230) (online supplementary Figure S6). Stratification for high-dose (as defined as ≥ 240 mg/m² doxorubicin equivalent dose) and low-dose anthracycline therapy revealed that the association between elevated troponins and LV dysfunction
### Meta-analysis of cardiac biomarkers in cancer therapy-related cardiotoxicity

Figure 1 Overall and individual study estimates of the odds ratio of increased troponin post-treatment compared to pre-treatment values are shown for patients receiving different cancer treatment modalities. Parallelogram boxes for odds ratio, and horizontal lines represent 95% confidence interval (CI). HER2, human epidermal growth factor receptor 2; M-H, Mantel-Haenszel; SCT, stem cell transplantation. *The included chemotherapy regimens can be found in the online supplementary Methods S1.

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### Study or Subgroup

#### 2.1.1 Anthracyclines
- Auner 2003
- Dodos 2008
- Kang 2014
- Kilickap 2005
- Shafi 2017

Subtotal (95% CI): Not estimable

Total events: 21

#### 2.1.2 HER2 Inhibitors
- Cardinale 2010
- Onitilo 2012
- Yu 2016
- Zardavas 2017

Subtotal (95% CI): Not estimable

Total events: 42

#### 2.1.3 Anthracyclines + HER2 inhibitors
- Fallah-Rad 2011
- Katsurada 2014
- Sawaya 2011
- Sawaya 2012

Subtotal (95% CI): Not estimable

Total events: 24

#### 2.1.4 Various high-dose chemotherapy regimens*
- Cardinale 2000
- Cardinale 2004

Subtotal (95% CI): Not estimable

Total events: 166

#### 2.1.5 Myeloablative for SCT
- Morandi 2001

Subtotal (95% CI): Not estimable

Total events: 0

#### 2.1.6 Radiotherapy
- Erven 2013

Subtotal (95% CI): Not estimable

Total events: 0

### 2.1.7 Total (95% CI)

Total events: 253

### Figure 2

Overall and individual study estimates of the odds ratio of decreased left ventricular ejection fraction are shown for patients with or without elevated troponin receiving different cancer treatment modalities. Parallelogram boxes for odds ratio, and horizontal lines represent 95% confidence interval (CI). HER2, human epidermal growth factor receptor 2; M-H, Mantel-Haenszel; SCT, stem cell transplantation. *The included chemotherapy regimens can be found in the online supplementary Methods S1.
was more consistently detected in studies investigating high-dose anthracycline treatment (OR 5.1, 95% CI 1.7–15.5 for high-dose anthracyclines and OR 2.7, 95% CI 0.4–20.6 for low-dose anthracyclines; n = 398) (online supplementary Figure S7). Overall sensitivity and specificity for the diagnostic value of troponins were 69% and 87%, respectively. Notably, the negative predictive value of troponins in the prediction of LV dysfunction was 93% (Table 2).

Conventional or point-of-care troponin assays were used in 12 studies (1654 subjects) while high-sensitivity troponin analysis was conducted in five studies (509 subjects). High-sensitivity troponin analysis was not superior to conventional troponin analysis (OR 22.8, 95% CI 6.6–78.4 for conventional troponin assays and OR 4.8, 95% CI 2.9–8.0 for high-sensitivity troponin assays; n = 2163) (online supplementary Figure S8) for the prediction of LV dysfunction, but this observation was limited due to unequal numbers of patients within both groups. No enhanced sensitivity (69% for high-sensitivity troponins vs. 75% for conventional troponins) or specificity (87% for high-sensitivity troponins vs. 89% for conventional troponins) in detecting decreased LVEF was found.

### BNP/NT-proBNP elevation in response to cancer therapy

To assess changes of BNP/NT-proBNP levels in response to cancer therapy-related cardiotoxicity, 11 studies (628 patients) for dichotomous (cutoff-based) analysis and 22 studies (912 patients) for analysis of absolute values were included. BNP/NT-proBNP plasma levels exceeding the cutoff were more frequent post-treatment compared to pre-treatment (OR 9.4, 95% CI 2.9–30.4; n = 628) (online supplementary Figure S9). Mean plasma BNP/NT-proBNP levels were higher in patients upon cancer therapy (SMD 0.6, 95% CI 0.3–0.9; n = 912) (online supplementary Figure S10). Anthracycline-based chemotherapy had the most consistent effect (SMD 0.6, 95% CI 0.3–0.8; n = 513).

### BNP/NT-proBNP for the prediction of left ventricular dysfunction

The following analysis aimed to determine the role of BNP/NT-proBNP in predicting LV dysfunction. Ten individual studies (462 patients; two studies included within both dichotomous analysis and analysis of absolute values) were included. Elevated mean absolute BNP/NT-proBNP levels in patients with LV dysfunction compared to patients with preserved LVEF were only present in the anthracycline-treated subgroup (SMD 0.6, 95% CI 0.1–1.1; n = 349) (Figure 3A) and presence of elevated BNP/NT-proBNP as defined by the studies’ cutoff was not consistently associated with decreased LVEF (OR 1.7, 95% CI 0.7–4.2; n = 197) (Figure 3B).

### Biomarkers in prevention of cardiotoxicity

The goal of this analysis was the evaluation of cardiac biomarkers in response to cardioprotective therapy. The impact of β-blockers or ACE inhibitors/ARB to prevent cardiotoxicity from cancer therapy has been evaluated in nine studies with four studies meeting the inclusion criteria for data synthesis (online supplementary Table S4). Of note, one trial pre-selected for troponin-positive patients before randomization. BNP/NT-proBNP was measured in only one study, which was therefore not included for meta-analysis. The median follow-up was 6 months after randomization.

Preventive β-blocker therapy and ACE inhibitor/ARB therapy was associated with less troponin elevation (OR 4.1, 95% CI 1.7–9.8; n = 466) (Figure 4). The effect was more pronounced in ACE inhibitor/ARB-treated patients compared to β-blocker-treated patients (OR 9.8, 95% CI 2.6–37.1 for ACE inhibitors/ARB; and OR 2.1, 95% CI 1.3–3.6 for β-blockers; Chi² = 4.4; P = 0.04 for subgroup differences).

### Bias and heterogeneity

High risk of bias was determined in up to 29% of selected observational studies. Patient selection applicability concerns (29%) and index test bias (24%) were most frequently detected (online supplementary Figure S11). Conduction of biomarker assessment using serial measurements (e.g. 0, 12, 24, 36 and 72 h after therapy) and selection for younger patients were commonly found as risk factors for bias. For interventional studies, the lack of a double-blind study design generated high risk for performance bias in 75% (online supplementary Figure S12).

Assessment of heterogeneity using Q statistic identified substantial heterogeneity. The analysis of cancer treatment-related biomarker dynamics revealed considerable heterogeneity for troponins (I² = 81–88%) and for BNP/NT-proBNP (I² = 84–86%). For the association between elevated troponins and LV dysfunction, anthracycline therapy (I² = 53%) showed lower heterogeneity, but the overall analysis, including all forms of cancer therapy, included considerably heterogeneous studies (I² = 84%). The level of heterogeneity was lower when high-sensitivity troponin assays were applied (I² = 0%) and when selecting high-dose anthracycline regimens ≥240 mg/m² (I² = 37%). Variations in methodology of biomarker assessment, definitions of cutoffs for biomarkers and LV function and different therapeutic regimens (e.g. anthracycline dose) within treatment groups were considered to induce heterogeneity.

Funnel plot analysis of troponins for the prediction of LV dysfunction suggested significant reporting bias indicated by asymmetric
Figure 3 (A) Overall and individual study estimates of the standardized mean difference of brain natriuretic peptide and N-terminal pro-brain natriuretic peptide (BNP/NT-proBNP) are shown in patients receiving different cancer treatment modalities with reduced and preserved left ventricular ejection fraction (LVEF). Parallelogram boxes for standardized mean difference, and horizontal lines represent 95% confidence interval (CI). (B) Overall and individual study estimates of the odds ratio of decreased LVEF are shown in patients with or without elevated BNP/NT-proBNP receiving different cancer treatment modalities. Parallelogram boxes for odds ratio, and horizontal lines represent 95% CI. HER2, human epidermal growth factor receptor 2; IV, inverse variance; M-H, Mantel-Haenszel; SCT, stem cell transplantation.
Meta-analysis of cardiac biomarkers in cancer therapy-related cardiotoxicity

Cardiac troponins were identified as a predictive marker for cancer therapy-related LV dysfunction in patients treated with anthracyclines, HER2 inhibitors, and various high-dose chemotherapy regimen subgroups. The diagnostic value of troponins for the detection of LV dysfunction was 93%, implicating a further potential benefit of troponins as a screening tool for cancer therapy-associated LV dysfunction. Of note, data on a predictive value of troponins for cardiotoxicity-related manifest heart failure or cardiotoxicity-associated mortality is not yet available. Therefore, careful interpretation of cardiac biomarkers in cancer patients is essential to obviate unnecessary changes or discontinuation of tumour therapy that may impair effectiveness of cancer treatment.

Myocardial strain analysis detects LV dysfunction earlier and with increased sensitivity compared to conventional assessment of LVEF. A combined diagnostic approach utilizing troponins and imaging (e.g. strain echocardiography) may further enhance diagnostic performance in early prediction of anthracycline cardiotoxicity; in a recent study simultaneously evaluating troponins and global longitudinal strain in anthracycline-treated patients, the combination of both parameters enhanced sensitivity for the detection of cardiotoxicity. Despite promising data, future studies are needed to elucidate how cardiac biomarkers and myocardial strain interact for the detection of cancer therapy-related cardiac dysfunction.

A predictive role of troponins for cancer therapy-related LV dysfunction was found for anthracyclines, HER2 inhibitors, anthracyclines followed by HER2 inhibitors, and various high-dose chemotherapy regimen subgroups. The diagnostic value of troponins was superior in patients receiving high-dose (> 240 mg/m²) treatment compared to patients receiving placebo or no therapy. Heart failure therapy is grouped in β-blocker therapy and angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker (ARB) therapy. Parallelogram boxes for odds ratio, and horizontal lines represent 95% confidence interval (CI). Mantel-Haenszel.

**Discussion**

The present meta-analysis evaluated the predictive value of troponins and BNP/NT-proBNP in cancer therapy-related cardiotoxicity. The main findings are: (i) cardiotoxic cancer therapy induces release of troponins and BNP/NT-proBNP; (ii) elevated troponins are associated with systolic dysfunction in patients treated with cardiotoxic cancer therapy; and (iii) preventive therapy in cancer therapy-related cardiotoxicity effectuates post-treatment cardiac troponin.

Cardiac troponins were identified as a predictive marker for the development of therapy-related LV dysfunction in patients receiving various regimens of cytotoxic chemotherapy and/or HER2 inhibitor therapy. The obtained data suggest that monitoring of troponins may be used for surveillance of adverse events in patients undergoing cancer therapy. With a sensitivity of 69%, troponins complement the cardio-oncology workup together with the assessment of risk factors, physical examination and imaging. Strikingly, the negative predictive value of troponins for the detection of LV dysfunction was 93%, implicating a further potential benefit of troponins as a screening tool for cancer therapy-associated LV dysfunction. Of note, data on a predictive value of troponins for cardiotoxicity-related manifest heart failure or cardiotoxicity-associated mortality is not yet available. Therefore, careful interpretation of cardiac biomarkers in cancer patients is essential to obviate unnecessary changes or discontinuation of tumour therapy that may impair effectiveness of cancer treatment.

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anthracycline chemotherapy compared to low-dose anthracycline therapy, but this subgroup analysis may be confounded due to an uneven distribution of studies including subsequent HER2 inhibitor therapy (all studies including subsequent HER2 inhibitor therapy were allocated to the high-dose subgroup).

Only a mild increase of troponin levels in patients with LVEF drop was observed compared to patients with preserved LVEF (SMD 1.1, 95% CI 0.4–1.9; n = 230). This observation indicates a potential benefit for high/ultra sensitivity troponin assays compared to conventional troponin assays. However, no sensitivity benefit was found for high-sensitivity troponin assessment as compared to conventional assays. Several factors may have masked a benefit for high-sensitivity troponin assays. At first, considerable heterogeneity might have confounded the conventional troponin assay subgroup (I² = 74%), while no heterogeneity was found for high-sensitivity assay subgroup (I² = 0%). Secondly, 33% of studies using conventional assays did not detect any troponin elevation limiting applicability of the assay. At last, lower number of included patients, higher rates for LV dysfunction and younger age in studies using high-sensitivity troponin assays may have determined these results. In cardio-oncology, it is likely that high-sensitivity troponin assays will still be used regarding their broad implementation in routine diagnostics. However, future studies are needed to determine whether alternative assays or alternative cutoffs for troponins in suspected cancer therapy-related cardiotoxicity enhance diagnostic performance.

Only few studies on a predictive value of BNP/NT-proBNP were available and the present meta-analysis does therefore not allow for an adequate comparison of troponins vs. BNP/NT-proBNP for the detection of cancer therapy-related cardiotoxicity. BNP/NT-proBNP plasma levels in patients with anthracycline-induced LV dysfunction were higher compared to controls but at present, there is not sufficient evidence for BNP/NT-proBNP in predicting an increased likelihood for cancer therapy-related LV dysfunction. On the basis of two individual studies simultaneously assessing troponins and BNP/NT-proBNP in detecting LV dysfunction, a predictive value of troponins was found while simultaneously a correlation between BNP/NT-proBNP and LV dysfunction was not observed. An unspecified rise of BNP/NT-proBNP in response to therapy-associated fluid overload may have limited the diagnostic value. Exemplarily, 97% of patients after high-dose stem cell mobilization therapy with intensive hydration (> 4 L/day) showed increased NT-proBNP over normal range. Future studies are needed to determine whether a standardized, prolonged interval between administration of therapy and assessment of BNP/NT-proBNP enhances diagnostic performance and to evaluate whether BNP/NT-proBNP serves for the detection of late cardiotoxicity in cancer survivors.

Recent randomized trials have assessed whether β-blocker or ACE inhibitor therapy prevents heart failure in patients receiving cardiotoxic therapy. A benefit in troponin-guided identification of high-risk patients to receive cardioprotective ACE inhibitor therapy was initially found but could not be recapitulated in a multicentre randomized trial. In anthracycline-treated patients, β-blocker or ACE inhibitor therapy was associated with a lower frequency of troponin elevation in treatment groups compared to control/placebo indicating a potential role of biomarkers as a marker for response to therapy but a correlation between biomarker response and preservation of LV function has not yet been demonstrated. Therefore, future studies will have to determine whether a decrease of troponins in cancer patients receiving cardioprotective treatment predicts response to therapy and if elevated troponins identify patients that benefit from cardioprotective treatment.

Troponins and BNP/NT-proBNP are recommended for monitoring of patients receiving anthracyclines at risk for cardiotoxicity during and after treatment for cancer within the American Society of Clinical Oncology guidelines. The European Society of Medical Oncology clinical practice guideline recommends assessment of troponins at baseline and after each cycle of cardiotoxic chemotherapy or when treated with trastuzumab. Given the lack of systemic data, the European Society of Cardiology does not generally recommend a standardized use of biomarkers for screening of cancer therapy-related cardiotoxicity. A potential benefit in identifying and monitoring patients at risk receiving anthracyclines or HER2 inhibitors is, however, acknowledged. The present study addresses this lack of standardized guideline recommendations and demonstrates systematic evidence for the benefit of troponins in screening for cardiotoxicity in patients undergoing specific forms of cancer therapy. The obtained results may serve for the standardized implementation on cardiac biomarkers in cancer therapy-related heart failure.

With regard to potential limitations of established cardiac biomarkers in cancer therapy-related cardiotoxicity, promising novel biomarkers have been evaluated in different settings (online supplementary Table S5). Myeloperoxidase (MPO) is a pro-oxidative enzyme that had been linked to adverse outcomes in myocardial infarction and heart failure. A recent study predicted that MPO might serve as a surrogate for anthracycline-induced oxidative stress and found that increased MPO levels were associated with development of cancer therapy-related cardiotoxicity. Interestingly, MPO was independent from troponin I levels and the authors hypothesized that simultaneous assessment of both markers may further enhance diagnostic performance. Several other biomarkers (e.g. microRNAs, markers of fibrosis and inflammation) have been evaluated for cancer therapy-related cardiotoxicity, but studies have generated mixed results. The identification of novel biomarkers for the specific monitoring of cardiotoxic mechanisms in cancer therapy may further enhance detection of cancer therapy-related cardiotoxicity.

Limitations
Heterogeneity in this study can most likely be related to variations in therapeutic regimens, patient cohorts and biomarker methodology. Furthermore, definitions of cardiac adverse events were not uniform throughout the assessed trials. The present patient age limit (e.g. 60–70 years) could have selected a healthier cohort that does not represent the typical cancer patient collective with advanced age. Serial troponin measurements (e.g. 0, 12, 36, and 72 h after treatment) with subsequent selection of the highest value for analysis could have induced an overestimated effect.
of cancer therapy on biomarker elevation. The small number of included studies and patients for BNP/NT-proBNP may have affected the precision of the estimated effect size. A potential association of cardiac biomarkers and heart failure with preserved ejection fraction or other forms of cancer therapy-related cardiotoxicity was not included but may be relevant for symptoms, prognosis and cardio-oncology management. Finally, fluid overload, anaemia, kidney disease or sepsis are common cancer-associated co-morbidities that may have had confounding influences on cardiac biomarkers.\textsuperscript{2,17}

**Conclusion**

Cardiac troponins and BNP/NT-proBNP may be elevated during cancer therapy. Patients with increased troponins after anthracycline-based chemotherapy or HER2 inhibitor therapy are at an increased risk for the development of LV dysfunction. Therefore, additional routine assessment of cardiac troponins during cancer therapy may be used to identify patients at risk to benefit from further cardio-oncology monitoring and preventive strategies. Particularly, patients receiving high-dose anthracyclines and subsequent HER2 inhibitor therapy are at highest risk for cardiotoxicity and may benefit most from assessment of troponin. For BNP/NT-proBNP, the available evidence does not yet consistently support a beneficial role as a marker for cancer therapy-related cardiotoxicity.

Standardized recommendations and systematic registries on the use of cardiac biomarkers in cardio-oncology are needed for best patients’ care. Prospective studies are required to evaluate if assessment of troponins prevent cardiotoxicity-associated morbidity and mortality in cancer patients.

**Supplementary Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Methods S1.** Supplementary methods.

**Figure S1.** Preferred Reporting of Items for Systematic Meta-Analysis (PRISMA) flow diagram of literature research and data collection.

**Figure S2.** Overall and individual study estimates of the standardized mean difference of absolute troponins are shown for patients receiving cancer therapy compared to pre-treatment values.

**Figure S3.** Overall and individual study estimates of the odds ratio of increased troponin I and troponin T post-treatment compared to pre-treatment values is shown for patients receiving anthracycline therapy with or without human epidermal growth factor receptor 2 inhibitor therapy. Studies with sufficient data on both forms of troponin were included for both subgroups.

**Figure S4.** Overall and individual study estimates of the odds ratio of increased troponins post-treatment compared to pre-treatment values for patients receiving anthracycline therapy <240 mg/m\textsuperscript{2} or 240–600 mg/m\textsuperscript{2} doxorubicin equivalent dose with or without human epidermal growth factor receptor 2 inhibitor therapy.

**Figure S5.** Overall and individual study estimates of the odds ratio of increased troponins post-treatment compared to pre-treatment values are shown for patients included for analysis on the association between troponins and left ventricular dysfunction and those who were not.

**Figure S6.** Overall and individual study estimates of the standardized mean difference of absolute troponin levels are shown in patients undergoing cancer therapy with decreased left ventricular ejection fraction (LVEF) compared to preserved LVEF.

**Figure S7.** Overall and individual study estimates of the odds ratio of decreased left ventricular ejection fraction are shown in patients with or without elevated troponins receiving anthracycline therapy <240 mg/m\textsuperscript{2} or 240–600 mg/m\textsuperscript{2} doxorubicin equivalent dose with or without human epidermal growth factor receptor 2 inhibitor therapy.

**Figure S8.** Overall and individual study estimates of the odds ratio of decreased left ventricular ejection fraction are shown for cancer patients with or without elevated troponin using conventional or high-sensitivity troponin assay.

**Figure S9.** Overall and individual study estimates of the odds ratio of increased brain natriuretic peptide and N-terminal pro-brain natriuretic peptide post-treatment compared to pre-treatment values are shown for patients receiving different cancer treatment modalities.

**Figure S10.** Overall and individual study estimates of the standardized mean difference of absolute brain natriuretic peptide or N-terminal pro-brain natriuretic peptide in patients receiving anthracycline-based chemotherapy compared to non-treated control patients and compared to pre-treatment values.

**Figure S11.** Summarized and individual assessment of methodologic quality of included observational studies for troponins and/or brain natriuretic peptide or N-terminal pro-brain natriuretic peptide as index test and left ventricular ejection fraction as reference standard when applicable.

**Figure S12.** Summarized and individual assessment of methodologic quality of included interventional studies for troponins and/or brain natriuretic peptide or N-terminal pro-brain natriuretic peptide as endpoint.

**Figure S13.** Funnel plot of troponin positive patients post-treatment vs. pre-treatment and frequency of left ventricular ejection fraction decrease in troponin-positive patients vs. troponin negative patients.

**Figure S14.** Funnel plot of absolute troponins and absolute brain natriuretic peptide or N-terminal pro-brain natriuretic peptide post-treatment vs. pre-treatment.

**Table S1.** MOOSE checklist.

**Table S2.** PRISMA checklist.

**Table S3.** Included studies.

**Table S4.** Interventional studies.

**Table S5.** Novel biomarkers for cancer therapy-related cardiotoxicity.

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**Conflict of interest:** none declared.
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