https://doi.org/10.31925/farmacia.2024.5.1 **REVIEW**

CARDIAC SURVEILLANCE IN ONCOLOGY: A REVIEW OF CIRCULATING BIOMARKERS AND DIAGNOSIS METHODS IN CHEMOTHERAPY-INDUCED CARDIOTOXICITY

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Abstract

Cancer survivors are at a much greater risk of developing cardiovascular diseases due to cardiotoxic chemotherapy. Anthracyclines, antimetabolites and alkylating agents are known to have damaging side effects on the cardiovascular system. Cancer treatment-related cardiac dysfunction (CTRCD) or cardiotoxicity (CTOX) is defined by the development of acute or chronic heart dysfunction following chemotherapy. It is commonly associated with heart failure (HF) symptoms and left ventricle (LV) dysfunction. Despite extensive research efforts aimed at finding early diagnostic methods, the outcomes remain inconclusive. Currently, CTRCD is commonly diagnosed by imaging techniques in conjunction with blood troponins and natriuretic peptides assessments. Blood biomarkers are non-invasive, cost-effective means of screening for a wide range of diseases and present great potential utility in CTOX risk assessment and diagnosis. Some biomarkers, such as troponin and natriuretic peptides, are already recommended for screening this type of patient, but a battery of specific biomarkers is intensely needed to accurately diagnose or even predict cardiac risk in oncologic patients.

Rezumat

Supraviețuitorii de cancer au risc mult mai mare de a dezvolta boli cardiovasculare datorită chimioterapiei cardiotoxice. Este bine-cunoscut faptul că antraciclinele, antimetaboliții și agenții alchilanți au efecte secundare dăunătoare asupra sistemului cardiovascular. Disfuncția cardiacă datorată terapiei împotriva cancerului, sau cardiotoxicitatea, se definește prin dezvoltarea afecțiunilor cardiace acute sau cronice după administrarea chimioterapiei. Aceasta este frecvent asociată cu insuficiența cardiacă și disfuncția ventriculului stâng. În ciuda eforturilor ample de cercetare care vizează identificarea unor metode de diagnostic precoce, rezultatele rămân neconcludente. În prezent, disfuncția cardiacă datorată terapiei împotriva cancerului este diagnosticată printr-o combinație de tehnici imagistice cu determinări ale peptidelor natriuretice și ale troponinelor sangvine. Biomarkerii sangvini sunt o modalitate neinvazivă și eficientă din punct de vedere al costurilor de screening pentru multiple afecțiuni și au un potențial ridicat pentru urmărirea pacienților supuși chimioterapiei. Deși biomarkerii menționați sunt deja utilizați în procesul de screening, o baterie de biomarkeri specifici este extrem de necesară pentru diagnosticarea și predicția riscului cardiac la acești pacienți.

Keywords: cancer treatment-related cardiac dysfunction, cardiotoxicity, cardiotoxic chemotherapy

Introduction

Cancer and cardiovascular diseases (CVD) persist as the primary causes of mortality worldwide [1]. The number of cancer diagnoses is on the rise each year in the European Union. Breast cancers are the most commonly diagnosed, followed by colorectal, prostate and lung cancer, the latter being the primary leading cause of cancer-related death [2]. Despite the alarming rise in new cancer cases, significant advances are continuously made in the development of early diagnostic methods and more efficient treatment discovery, thus leading to increases in positive treatment outcomes, cancer survivability and increases in the quality of life for this population.

The short- to medium-term side effects of cancer systemic treatment are well studied, and several strategies have been developed to counteract them. However, as the population of cancer survivors continues to increase, more attention should be given to the long-term implications of cancer treatments. This is due to the fact that most efficient treatment options often lead to the development of comorbidities, which already represent one of the burdens of older individuals [3].

Every year, around 1 million cancer patients are undergoing anthracycline-based chemotherapy regimens in North America [4]. From 2002 to 2021, the Web of Science Core Collection accumulated 3504 research publications on anthracyclines [5]. This suggests that high research efforts are directed towards optimising anthracycline-based chemotherapy regimens, which are proven to be highly effective, yet their use is limited by their cardiotoxic side effects.

The prevalence of anthracycline-induced CTOX is hard to estimate, given the difficulty of diagnosis. Firstly, judging by cumulative dose, it is estimated that CTOX affects around 5% of patients treated with 400 mg/m^2 and up to 48% in patients reaching 700 mg/m^2 [6]. Even at lower doses, classified as safe (200 - 250 mg/m2), CTOX risk is still evaluated at 10% [4]. A thorough analysis of the patients enrolled in the CARDIOTOX registry (NCT02039622), which included a heterogeneous group of cancer patients undergoing therapies with high CTOX risk, reported a 37.5% incidence of CTOX and found strong correlations between more severe forms of the disease and all-cause mortality [7].

Over the last decade, there have been remarkable improvements regarding cancer treatment, with overall survival, progression-free survival and life expectancy constantly increasing. Despite this, CTRCD affects a high number of patients undergoing cancer treatment. In a recent meta-analysis conducted by Deng *et al*., the overall incidence of patients affected by CTRCD was found to be 63.21 *per* 1000 person-years [8].

Currently, two biomarkers are used to diagnose and monitor heart disease: cardiac troponins and natriuretic peptides, which have also been shown to be useful in the early identification of CTOX [9]. However, as the European Institute for Oncology points out, the use of these two biomarkers for the subclinical identification of CTOX is limited by the lack of standardization [10]. The studies carried out so far were conducted on an insufficient number of subjects with heterogeneous chemotherapy regimens, and the results are almost impossible to reproduce because different variants of these biomarkers were assessed using different immunoassays and samples collected at variable time points. Moreover, the CTOX diagnosis cannot be established based on a small number of biomarkers due to their non-specificity. Troponins may indicate, in addition to CTOX, the presence of a pulmonary embolism or rhabdomyolysis [11] and high natriuretic peptide values are often associated with renal failure or hyperthyroidism [12].

The use of the most suitable set of biomarkers for the early identification of cardiotoxicity has several advantages, the most notable ones being simple analysis and quantification, minimal invasiveness and ease of use in any medical laboratory. Another advantage is that this could have an important economic impact, improving the cost-to-benefit ratio by excluding oncologic patients without CTOX from long-term cardiac monitoring that requires expensive imaging studies.

The scope of this review is to summarize current knowledge regarding CTRCD diagnosis methods, with a focus on anthracycline-induced CTRCD, to aid in the identification of a complete, specific set of biomarkers capable of detecting subclinical signs of this disease. Figure 1 summarizes the proposed biomarkers and some of their targets.

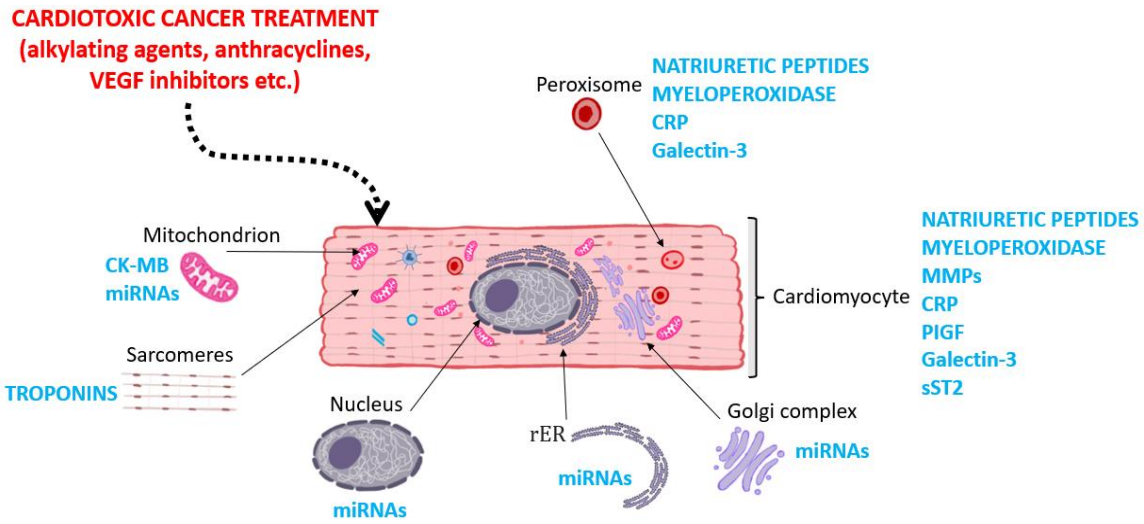

Figure 1.

Overview of the targets for the biomarkers discussed in the review

Natriuretic peptides – volume/pressure overload; myeloperoxidase, metalloproteinases (MMPs), C-reactive protein (CRP), placental growth factor (PIGF), Galectin-3, soluble suppression of tumorigenicity 2 (sST2) – oxidative stress, inflammation, cell injury and necrosis, apoptosis; troponins – contraction mechanism; miRNAs – cell proliferation, differentiation and maturation, inflammation and metabolism reprogramming; creatine kinase – myocardial band (CK-MB) – energy homeostasis

Current knowledge of cancer treatment-related cardiac dysfunction

CTRCD is one of the most important adverse events associated with anticancer therapy. While there are many definitions proposed for CTRCD, in the clinical setting, it is mostly defined as a decrease in LVEF (left ventricle ejection fraction) by over 10% below baseline level, with or without a decrease of over 15% in global longitudinal strain (GLS) [13].

The cause and incidence of CTRCD are not yet completely understood, mainly because of their complexity. There are many chemotherapeutic agents found to be associated with CTRCD development, out of which the most notable ones belong to the anthracycline and HER2 inhibitor classes of medications [14]. A summary of the main classes of cardiotoxic cancer therapies, along with a summary of disease-related information, is listed in Table I.

CTOX is manifested as heart failure, hypertension, valvular disease, thromboembolism and other CVDs and is classified into three categories: acute, chronic and late CTOX (Figure 2). In acute CTOX, patients develop signs of the disease in the first weeks of cancer treatment, while chronic CTOX has a debut at 1-year post-treatment. Late CTOX can occur years after treatment completion and is commonly seen in childhood cancer survivors at later stages in life [14]. The first two stages are often reversible with dose adjustments to the cancer therapy and with the administration of cardioprotective drugs [32]. Late-stage CTOX cannot be reversed, and the diagnosis is difficult to establish due to the presence of comorbidities that predispose survivors to CVD. In this case, treatment is reduced to ameliorating cardiac failure symptoms. In the Childhood Cancer Survivor study, patients had a median follow-up time of 24.5 years, and the results showed that cancer treatment led to an increase in CVD among these individuals. By 50 years of age, half of the survivors followed in the study experienced debilitating adverse effects or died as a result of the adverse effects of chemotherapy coupled with life factors [33].

Table I

Summarised list of cancer therapies that are correlated to CTOX development

	Main mechanisms of action	CVD system toxicity	Uses	Source
Alkylating agents (cyclophosphamide, ifosfamide, cisplatin, mitomycin, busulfan)	Suppression of protein synthesis by inhibiting DNA transcription	Toxic metabolites directly cause cell injury, tissue necrosis	Haematological cancers, solid tumours	[15, 16]
Anthracyclines: DOX, daunorubicin, epirubicin, idarubicin	Direct damage to DNA, TOP2 poisoning, ROS generation, stimulation of apoptosis	By ROS over-production	Solid tumours (breast, uterine, stomach, lung, ovarian, sarcomas), haematological cancers	[17, 18]
Anti-HER2 monoclonal antibodies (trastuzumab, pertuzumab)	Suppression of cell growth and proliferation	By ROS over-production, HER-2 mediated cardiomyocyte apoptosis	HER2-positive breast/gastric cancers	[19, 20]
Fluoropyrimidines (5-fluorouracil, capecitabine, tegafur, TAS-102)	Inhibition of DNA synthesis	ROS production, toxic metabolites, endothelial injury and coronary vasospasm	Breast, gastric, colorectal, pancreatic, oesophageal cancers	[21, 22]
Immunotherapy checkpoint inhibitors (ipilimumab, pembrolizumab, nivolumab	Lowering immune tolerance of T cells to cancer cells	Immune cell tissue infiltration leading to myocarditis	Colorectal cancer, melanoma, non-small cell lung cancer, lymphoma, cervical cancer	[23, 24]
Proteasome inhibitors (bortezomib, carfilzomib, ixazomib)	Proteotoxic stress induction	ROS production, proteasome dysfunction	Multiple myeloma, lymphoma	[25]
Radiotherapy	Direct DNA damage, ROS production	ROS production, proinflammatory environment, direct tissue damage	Solid tumours, haematological cancer	[26, 27]
Microtubule inhibitors (taxanes, epothilones)	Suppression of tumour growth by inhibition of cell migration	Impaired vascular endothelial cell function, inflammation	Non-small cell lung cancer, breast & ovarian cancer, lymphoma	[28, 29]
Tyrosine kinase inhibitors (ponatinib, sunitinib, sorafenib, ibrutinib)	Proliferation inhibition	ROS production, down-regulation of PI3K-Akt pathway, hypoxia	Solid tumours, haematological cancer	[30, 31]

	Main mechanisms of action	CVD system toxicity	Uses	Source
Vascular endothelial growth factor (VEGF) inhibitors (bevacizumab, ramucirumab)	Inhibition of angiogenesis	Decreasing nitric oxide production, inhibition of cell proliferation	NSCLC, thyroid cancer, melanoma, renal cell carcinoma	[30, 31]

CVD – cardiovascular disease, DNA - deoxyribonucleic acid, DOX - doxorubicin, TOP2 – topoisomerase 2, HER2 – human epidermal growth factor receptor 2, NSCLC – non-small cell lung cancer

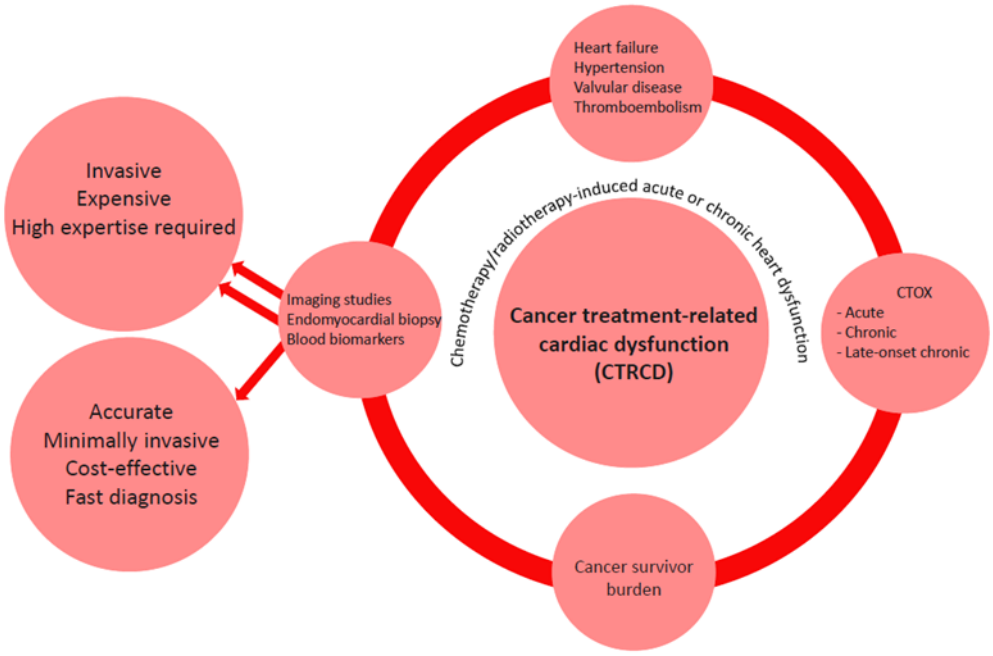

Figure 2.
Summary of CTRCD manifestation and diagnosis methods

Biomarkers for the diagnosis of CTRCD

Troponin

Troponin is a protein complex with three subunits (T, I, C) that plays an important role in the contraction of skeletal and cardiac muscles. Each subunit has a different function: troponin T acts as an anchor for the troponin complex to the actin filament, troponin C has a calcium-binding role and allows for the initiation of the contraction process, and troponin I inhibits the actin-myosin interaction in the absence of calcium ions [34].

The detection of cardiac troponin (cTn), especially T and I isoforms (cTnT and cTnI, respectively), is considered the "gold standard" in the diagnosis of heart-related conditions, especially myocardial infarction (MI) [35]. Out of both, cTnI seems to be preferred because it is less affected by the circadian rhythm, and its variation could be taken out of consideration in clinical settings [36-38].

In the context of anthracycline-induced cardiotoxicity, the cardiac isoforms of troponin have been widely investigated for their biomarker potential in both animal models and clinical studies. A significant elevation of serum cTnT and cTnI was observed in oncology patients who underwent anthracycline-based treatments in both small studies [39, 40, 41] and larger cohorts [10, 42].

It is well known that troponin can be elevated in other non-cardiac conditions, such as rhabdomyolysis, renal disease, sepsis, or pulmonary embolisms [43]. Because of the non-specific nature of this biomarker and the lack of sufficient long-term studies involving large cohorts of patients, it should not be used alone as a diagnostic or prevention tool. Moreover, the heterogeneity of assay types for the detection of these molecules makes the standardisation of results very difficult [44]. A low cut-off value of 7 ng/L was identified as acceptable for the identification of high-risk patients [42].

Natriuretic peptides

Natriuretic peptides are hormones with multiple physiological roles in the organism, with cardio-vascular system regulation being the most important. The main members of this hormone family are atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) [45].

BNP and the N-terminal pro-B-type natriuretic peptides (NT-proBNP) are currently recommended by the European Society of Cardiology as biomarkers for the heart failure screening of anthracycline-treated oncologic patients, along with other cardiac function tests [46]. Murtagh *et al*. [47] reviewed multiple studies that reported an increase in BNP within patients treated

with anthracycline-based chemotherapy regimens and concluded that even though these biomarkers are useful in the cardiotoxicity risk stratification of patients, their predictive power is low, mainly due to the assay heterogeneity and multitude of different thresholds, as well as the small sample sizes of patients. Other recent, less extended studies that evaluated NT-proBNP levels at different time points in the chemotherapy regimen did not find any significant changes in the serum levels of these biomarkers [48, 49].

Creatine Kinase-Myocardial Band (CK-MB)

CK-MB is a creatine kinase (CK) isoenzyme mostly in cardiac tissue. Because CK-MB values quickly rise and peak 24 hours post-event, it used to be a good indicator of acute MI. Due to the discovery of better biomarkers, such as troponin, it stopped being classified as the biomarker of choice for the diagnosis of heart injury [50].

In recent years, CK-MB was investigated as a potential DOX-induced cardiac dysfunction (CD) biomarker in murine models. Current research shows that CK-MD increases with DOX administration, and the efficacy of cardioprotective treatments could be monitored by assessing CK-MB serum levels [51-53]

Myeloperoxidase (MPO)

MPO is a heme peroxidase enzyme expressed predominantly by neutrophils. Its main role is in the phagocytosis process, where it contributes to hypochlorous acid production and is, therefore, essential in pathogen breakdown. The link between MPO and cardiotoxicity is oxidative stress and, subsequently, the inflammation produced by cardiotoxic chemotherapy administration. Moreover, MPO levels are also elevated in non-chemotherapy-related CVD [54]. This enzyme was proposed as a CTRCD marker in recent years, and its efficacy in comparison to other biomarkers for risk evaluation is about to be proven [55, 56, 57]. In a study conducted using patients recruited in the CECCY (Carvedilol Effect in Preventing Chemotherapy-Induced Cardiotoxicity) trial, blood MPO levels failed to show a correlation to CTOX development but helped identify patients that could benefit from cardioprotective treatment [58]. However, most of the studies that investigated the potential of MPO as a biomarker for CTRCD were done on breast cancer and haematological cancer patients undergoing DOX-based chemotherapy regimens, so the results cannot be generalised for other types of neoplastic diseases. More studies with larger cohorts are needed to evaluate the prediction and patient stratification values of this biomarker correctly.

Matrix metalloproteinases (MMPs)

MMPs are a group of zinc- and calcium-dependent proteolytic enzymes that contribute to extracellular matrix (ECM) remodelling after tissue injury, inflammation and cancer [59]. Anthracyclines and other cardiotoxic chemotherapeutic agents increase oxidative stress, which stimulates ECM remodelling and cardiac tissue degradation by MMPs. Several members of this family, such as MMP-2, MMP-8 and MMP-9, were found to be associated with cardiovascular disease development and were studied as potential biomarkers and therapeutic targets [60, 61].

In DOX-induced CD animal models, MMP-2 was found to be the MMP with the highest association with left ventricular systolic dysfunction, elevated blood pressure and myocardial passive stiffness [61-63]. Human studies involving patients treated with DOX-based chemotherapeutic regimens demonstrated that MMP-2, MMP-8 and MMP-9 can be used as prognostic biomarkers for CTRCD at both the transcript level and by assessing their serum concentration [64, 65].

Myoglobin (MB)

MB is a member of the globin family of proteins that serves as oxygen storage for the organism mainly found in cardiac and skeletal muscle [66]. While MB is not an accurate biomarker for cardiac disease risk monitoring, it could potentially be used as a diagnostic tool in CTRCD due to its rapid release in the blood-stream following a cardiac event [66, 67]. High MB is also seen in skeletal muscle injuries, such as rhabdomyolysis and renal insufficiency. For increased accuracy, the use of MB as a CTRCD biomarker should be done in conjunction with troponin and CK (creatine kinase) [68, 69].

C-reactive protein (CRP)

CRP is an acute-phase protein synthesised by the liver and found in high amounts in plasma in response to inflammation. Although not a specific biomarker, it is commonly screened in routine clinical practice. High sensitivity (hs) assays are mostly used to identify CVD risk [70].The efficacy of hs-CRP as a marker for treatment-related cardiotoxicity is still debatable, with research showing no connection between serum levels and echocardiographic studies [71] or not finding any significant changes in the early post-treatment period [72], but it is generally considered a good candidate for identifying cardio-toxicity with high accuracy [73, 74]. The ASCEND-HF trial concluded that an increase in hs-CRP 30 days post-admission is associated with a high 180-day mortality risk [75].

Placental growth factor (PIGF)

PIGF is a protein that belongs to the vascular endothelial growth factor (VEGF) family. It is a pleiotropic factor involved in angiogenesis during embryonic development, neoplastic progression and inflammation [76]. PIGF was also found to be a predictor of CVD and cancer mortality [77], and thus has been studied for its biomarker potential in CTRCD. However, an analysis conducted by Chen *et al*. showed that PIGF has a protective role in CVD, and its upregulation is, in fact, due to tissue repair and remodelling processes [78]. Patients treated with either DOX, trastuzumab, or a combination of the two had higher levels of blood PIGF that mostly returned to baseline over time [55, 79]. Due to a limited understanding of

PIGF and its association with CRTCD, the biomarker potential of this cytokine is currently low.

Galectin-3 (GAL-3)

GAL-3 is a protein from the lectin family that binds ligands presenting β-galactoside structures and is a well-established biomarker due to its implications in inflammatory, fibrotic, infectious and cardiac diseases [80]. Over the years, GAL-3 has been intensely investigated in the context of CTRCD in patients treated with anthracyclines, and the results are conflicting. In patients from the CECCY trial, GAL-3 was not able to indicate the development of CTOX, as patients that had a reduction in LVEF had similar levels of this biomarker compared to the control group at later time points [58]. Similarly, in a study involving patients treated with other cardiotoxic medications alongside DOX, raises in GAL-3 were not observed long-term [81]. In less extended studies, the rise in GAL-3 levels preceded changes in GLS and predicted LVEF reduction [82].

Soluble suppression of tumorigenicity 2 (sST2)

sST2 belongs to the interleukin 1 (IL-1) receptor family and mediates inflammatory responses to mechanical myocardium strain. It is recommended to be used for its predictive value of disease severity and outcome in CVD [83] [84]. High levels of sST2 are found to be correlated with myocardial fibrosis, commonly seen in patients undergoing cardiotoxic oncologic treatments [85]. However, its use as a predictive biomarker for CTRCD is limited because high serum levels of this biomarker are associated with breast cancer progression [86].

Studies investigating sST2 in patients undergoing anthracycline chemotherapy failed to show its efficacy in predicting cardiac events in childhood cancer survivors [87], and in hematologic and solid tumour patients [88].

MicroRNAs (miRNAs)

miRNAs are non-coding RNAs that regulate gene expression by interacting with different regions of targeted mRNAs. miRNAs are required for various biological processes, including organism development, metabolic homeostasis, immune responses and pathogenesis [89]. Due to their ubiquitous presence in biological fluids, some extracellular miRNAs are intensely studied for their use as biomarkers in many diseases [90]. In the context of CTRCD, animal studies were used to identify potential miRNAs of interest. In contrast, human studies, mostly including breast cancer patients and survivors, were conducted to validate their efficacy in predicting and assessing cardiac injury. As for the more researched biomarkers, most of the results for miRNAs vary from study to study due to method heterogeneity. Some of the most studied miRNAs are listed in Table II.

Despite intensive research efforts, the data that is currently available is not yet sufficient in order to suggest a clear, definitive battery of biomarkers suitable for each step of disease assessment. However, based on current information about these biomarkers, troponins, MMPs, PIGF and sST2 show some potential as predictive biomarkers. CK-MB and MPO levels could be assessed in order to monitor the effectiveness of cardioprotective treatments and natriuretic peptides, MB and CRP could serve as biomarkers for assessing cardiac function. For accurate use of biomarkers in CTRCD management, there is a major need to evaluate all the promising biomarkers at the beginning of treatment to obtain baseline values and monitor them along the course of treatment.

Table II

List of miRNAs studied as biomarkers for CTRCD

Species	miRNA	Findings	Representative studies
Human	miR-133a	Upregulated by DOX and affects ErbB2 signalling.	[91]
Rat	miR-140-5p	Upregulated by DOX. Contributes to cardiac damage *via* Nrf2 and Sirt2 signalling.	[92]
Human	miR-1	Upregulated by DOX. Better predictive power than cTnI by association with LVEF changes. Downregulated by DOX.	[93, 94]
Rat	miR-29b	Downregulated by DOX, leading to apoptosis-related dysfunctions. Potential therapeutic target.	[95]
Human	let-7f	Downregulated by DOX. Can predict CTOX risk independently.	[96]
Human	miR-126	Downregulated by DOX. Increased predictive accuracy if associated with let-7f.	[96]
Human	miR-210	Downregulated by DOX. Negatively correlated to cTnI.	[96]
Rat	miR-34a	Upregulated by DOX. Besides acting as a biomarker, it has a potential therapeutic target role.	[97]

Classical methods for the diagnosis of CTRCD

Cardio-oncology is the field involved in the detection, monitoring and treatment of CVD arising as a result of cancer therapies. In the early stages of the diagnosis process, imaging studies *via* echography and electro-cardiography, along with blood tests for heart disease biomarkers, are preferred as non-invasive and cost-effective methods, to the detriment of specificity and accuracy. However, these traditional methods often fail to show subclinical evidence of CTRCD. More accurate methods with increased reliability are often recommended only when these widely available techniques fail to show any evidence of the disease, but clinical evaluations show signs of cardiac dysfunction.

CTOX is assessed by imagistic methods when the symptoms are already present and, in some cases, can be identified by observing changes in the LV GLS. Thus, an attractive strategy for identifying discrete, subclinical changes associated with this disease is the concurrent use of multiple biomarkers, which can individualise multiple aspects of the pathophysiological process. Monitoring cardiac function during cancer treatment is insufficient, and the development of a fast and effective method of screening in all stages of the treatment journey is of utmost importance since patients can develop CTOX long after treatment completion [98].

Echocardiography imaging is one of the most commonly used techniques in the diagnosis and management of cardiac diseases. For LVEF evaluation, 2D, 3D and M-mode imaging are used, especially in children. This method can also be used to calculate the Tei index, which can be used as an outcome predictor [99]. Speckle tracking echocardiographic assessment of left ventricular GLS is very important for early diagnosis, especially in conjunction with blood-based biomarkers [100].

Electrocardiography (ECG) is used in conjunction with echocardiography. A study that involved long-term screening of lymphoma patients treated with DOX showed that QT prolongation and T-wave flattening appear in the pre-onset stage of CTRCD [101]. Waveform analysis *via* artificial intelligence (AI) methods can significantly improve the detection of patients at risk for developing CTRCD, as demonstrated in multiple studies [102-104]. AI-based methods, if officially validated, could be an extremely important tool in detecting CTRCD due to their ability to deliver results rapidly, high efficacy and reduced cost compared to other means of diagnosis. Another very notable aspect is the ease of use, as this could spare patients from undergoing invasive and lengthy procedures, especially children. Paediatric patients often require sedation for such procedures, which can affect imaging quality and induce diagnostic errors [105].

Cardiovascular magnetic resonance imaging (CMRI) is a method used to obtain non-invasive imaging of the heart. Echocardiography can be used to diagnose various cardiac diseases by assessing tissue structure, function and heart-related parameters such as LVEF and extracellular volume fraction (ECVF) [106]. Images obtained by CMRI are of greater quality than previous methods described, without subjecting patients to additional radiation [107].However, like other MRI scans, besides being costly, it involves preparation time and may require the administration of gadolinium-based contrast agents that can pose severe side effects in oncology patients [108, 109].

A multi-gated acquisition scan (MUGA) is a nuclear imaging technique that uses radioactive tracers. It is considered the gold standard for assessing CTOX in patients undergoing cancer therapy [110]. These scans require labels such as Technetium-99m that target red blood cells and produce images that create a 2D film of the cardiac cycle, which is then used to evaluate heart structures in both stress and resting conditions. Even though the radiation exposure is low, it should be taken into consideration for patients undergoing adjuvant therapy [111].

Endomyocardial biopsy is performed only if other means of diagnosis fail to show signs of CTRCD despite clinical presentation suggestive of the disease or if the administration of a higher dose of the cardiotoxic agent could be more beneficial for the patient. Evaluation using electron microscopy is the most sensitive method for the diagnosis of CTRCD [112]. This procedure is not widely available as it requires high expertise in both biopsy collection and analysis [113].

Conclusions

While the potential of multiple biomarkers for the diagnosis and early prediction of CTRCD have been studied, their clinical applicability should still be evaluated. The exploration of biomarkers capable of predicting, as well as diagnosing CTRCD and DOX-induced CTOX, highlights the hardships involved in establishing biomarkers for complex diseases. Conflicting findings across similar studies, assay variability and non-specific modifications unrelated to CTRCD emphasise the need for additional research involving larger cohorts and longer follow-up periods.

To establish a complete, accurate laboratory test-based diagnostic method for CTRCD, the research effort should be orientated towards finding a small set of biomarkers that are highly specific for changes encountered in this disease at the molecular level. In addition to efforts towards uniformising study methods for decreasing assay variability, another way of improving biomarker research is by establishing specific batteries of tests that cater to each step of clinical care. Predictive biomarkers could be used to assess CTRCD development risk, and patients showing no changes in biomarker levels can be excluded from further testing. Diagnosis-specific biomarkers can be used along with imaging methods to establish the stage of CTRCD and to find the best cardioprotective strategy for the patient. Monitoring biomarkers could provide insights related to disease evolution and the effectiveness of cardioprotective treatments.

Conflict of interest

The authors declare no conflict of interest.

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