Scholars LITERATURE

Journal of Clinical Oncology and Therapeutics

Short Communication

DOI: https://doi.org/10.47275/2690-5663-156
Volume 8 Issue 2

Cardio-oncology: A Review of Heart Failure in Patients with Prior Malignancy and Cancer Therapy-related Cardiac Dysfunction

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Abstract

The rising population of cancer survivors, coupled with the expanding arsenal of potentially cardiotoxic cancer therapies, has made heart failure a prevalent and growing concern, necessitating a comprehensive understanding of its prevention, detection, and management within the emerging field of cardio-oncology. This review overviews current literature to provide clinicians and researchers with a cohesive overview of heart failure in patients with prior malignancy and cancer therapy-related cardiac dysfunction (CTRCD). It begins by exploring the diverse pathophysiological mechanisms of CTRCD, from oxidative stress to immune-mediated injury, and examines the prevalence and incidence of heart failure among various survivor cohorts. The review then details the clinical presentation and diagnostic challenges unique to this population, emphasizing the critical role of advanced imaging and biomarkers. Current management and treatment strategies are discussed, including pharmacological cardioprotection, lifestyle interventions, and the proven benefits of multidisciplinary cardio-oncology programmes. Finally, it summarizes key clinical trials that inform evidence-based practice, highlighting the protective effects of structured rehabilitation and integrated care models on cardiovascular outcomes. Future research must prioritize large-scale, prospective longitudinal studies to clarify the natural history of CTRCD and validate emerging risk stratification tools. The continued integration of artificial intelligence into diagnostic pathways and the embedding of cardio-oncology principles into standard oncologic care will be essential to personalize treatment and improve long-term outcomes for this vulnerable population.

Keywords: Cardio-oncology, Cancer survivors, Cancer therapy-related cardiac dysfunction, Cardiotoxicity, Heart failure, Left ventricular ejection fraction, Multidisciplinary care

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Citation: Pujitha KS, Dontiboyena S (2026) Cardio-oncology: A Review of Heart Failure in Patients with Prior Malignancy and Cancer Therapy-related Cardiac Dysfunction. J Clin Oncol Ther, Volume 8:2. 156. DOI: https://doi.org/10.47275/2690-5663-156

Received: August 07, 2026; **Accepted:** October 12, 2026; **Published:** October 16, 2026

Introduction

Cardio-oncology is an interdisciplinary field dedicated to understanding, preventing, and managing cardiovascular complications arising in patients with cancer [1-10]. It encompasses the study of how cancer therapies impact cardiac structure and function, as well as the development of strategies to mitigate these adverse effects. As highlighted by Ogilvie et al. [11], this specialty addresses the complex interplay between malignancy and cardiovascular health, emphasizing the importance of early detection and tailored interventions to improve patient outcomes. The field has evolved to include the assessment of therapy-induced cardiotoxicity, such as heart failure and other cardiac dysfunctions, which are increasingly recognized as significant contributors to morbidity and mortality among cancer survivors.

The significance of cardio-oncology has grown substantially with the advent of more effective cancer treatments that, while improving survival, also pose risks to cardiovascular health [12-21]. CTRCD, including heart failure, has emerged as a major complication that can compromise both quality of life and long-term survival [22]. As cancer survivorship increases, so does the prevalence of cardiovascular sequelae, making it imperative for clinicians to understand the mechanisms, risk factors, and management strategies for these conditions. The rising incidence of CTRCD underscores the need for integrated care models, early detection, and preventive measures to reduce the burden of heart failure in this vulnerable population [22, 23].

This review aims to provide a comprehensive overview of heart failure in patients with prior malignancy and CTRCD. It seeks to elucidate the underlying pathophysiological mechanisms, assess the prevalence and clinical presentation of heart failure among cancer survivors, and evaluate current diagnostic and management strategies. Additionally, the review highlights emerging research, risk stratification tools, and future directions to optimize cardiovascular care in oncology settings. By overviewing current literature, this review intends to inform clinicians and researchers about the critical aspects of cardio-oncology, ultimately contributing to improved patient outcomes and the development of personalized, risk-based approaches to prevent and treat cardiac dysfunction in cancer patients.

Pathophysiology of CTRCD

Cancer therapies can induce cardiac dysfunction through a variety

of molecular and cellular mechanisms [24-33]. Many agents, such as anthracyclines, generate oxidative stress by increasing reactive oxygen species, leading to mitochondrial damage and cardiomyocyte apoptosis [22]. Targeted therapies like trastuzumab interfere with the human epidermal growth factor receptor 2 (HER2) signaling pathway, which is vital for cardiomyocyte survival and repair, resulting in impaired myocardial function [34]. Additionally, immune checkpoint inhibitors can cause myocarditis through immune-mediated inflammatory responses, leading to myocardial injury [35]. The primary molecular pathways involved include oxidative stress, mitochondrial dysfunction, disrupted cellular repair mechanisms, and immune-mediated inflammation, all contributing to cardiomyocyte loss and subsequent cardiac dysfunction [22].

Several classes of cancer therapies are associated with cardiotoxicity. Anthracyclines, such as doxorubicin, are well-known for their dose-dependent cardiotoxic effects, primarily causing irreversible myocardial damage [22]. HER2-targeted therapies, including trastuzumab, can lead to reversible left ventricular dysfunction, especially when combined with anthracyclines [34]. Immune checkpoint inhibitors have been linked to myocarditis, a potentially life-threatening inflammatory condition [35]. Additionally, newer agents like tyrosine kinase inhibitors and sodium-glucose cotransporter 2 (SGLT2) inhibitors are under investigation for their cardioprotective roles, but some may also pose risks of cardiac adverse effects [36, 37]. The diversity of these therapies underscores the importance of understanding their distinct mechanisms of cardiotoxicity to optimize patient management.

The development of CTRCD is influenced by multiple patient-specific and treatment-related risk factors. Pre-existing cardiovascular disease, hypertension, and advanced age increase susceptibility to cardiotoxic effects [22]. Genetic predispositions and comorbidities such as diabetes and obesity further elevate risk [23]. The cumulative dose and duration of cardiotoxic agents, particularly anthracyclines, are significant determinants of cardiac injury [22]. Moreover, concomitant use of multiple cardiotoxic therapies amplifies the risk, necessitating careful risk stratification and monitoring [23, 34]. Identifying modifiable risk factors allows for tailored surveillance and preventive strategies to mitigate CTRCD development.

Prevalence and Incidence of Heart Failure in Cancer Survivors

Recent large-scale longitudinal studies have provided valuable insights into the prevalence and incidence of heart failure among cancer survivors [38-45]. Hou et al. [23] analyzed a cohort of 4,632 cancer patients with follow-up periods extending up to 22 years, identifying heart failure as 1 of the 5 key cardiac outcomes observed in this population. Their findings underscored that heart failure remains a significant complication in long-term cancer survivorship, with incidence rates influenced by various treatment-related and patient-specific factors. The data suggest that a substantial proportion of cancer survivors develop heart failure over time, emphasizing the importance of ongoing cardiovascular monitoring in this group.

Heart failure affects approximately 64 million people worldwide, with prevalence increasing due to aging populations and improved survival rates after myocardial infarction and heart failure treatment [46]. Among cancer survivors, the prevalence of heart failure is notably higher due to the cardiotoxic effects of cancer therapies and shared risk factors such as hypertension and obesity [47]. A systematic review and meta-analysis found that adult cancer survivors have an increased risk of heart failure, with an overall incidence rate of 2.1% compared to 1.7% in non-cancer controls, representing an absolute risk difference of 0.4% [47]. The risk is particularly pronounced in breast cancer survivors, with a relative risk of 2.57 for heart failure [47]. Among childhood cancer survivors, the cumulative incidence of heart failure over an extended period (5.0 to 72.5 years) is approximately 0.99% [48]. This highlights the long-term cardiovascular risks faced by this population, necessitating ongoing monitoring and preventive strategies. A study using Danish nationwide registries found that 5-year cancer survivors had higher rates of cardiovascular outcomes, including heart failure, compared to non-cancer controls. The incidence rate of heart failure was 6.2 per 1,000 person-years for cancer survivors, compared to 5.2 for controls [49].

Demographic factors such as age, sex, and comorbidities significantly modulate the risk of developing heart failure in cancer survivors. The longitudinal analysis by Hou et al. [23] indicated that older patients are at a higher risk, consistent with general population trends, but specific variations related to cancer types and therapies also play a crucial role. Additionally, certain subgroups, including women receiving HER2-targeted therapies like trastuzumab, exhibit elevated susceptibility to cardiac dysfunction, which can progress to heart failure if not detected early [34]. These demographic disparities highlight the need for tailored risk stratification and surveillance strategies.

Long-term follow-up studies have been instrumental in delineating the incidence and progression of heart failure post-cancer therapy. Hou et al. [23] conducted a comprehensive longitudinal analysis, revealing that the risk of heart failure persists and may even increase years after completion of cancer treatment. Their research emphasized that cancer survivors require extended cardiovascular surveillance, as the latency period for therapy-related cardiac dysfunction can be prolonged. Furthermore, emerging evidence suggests that early detection through advanced imaging and risk assessment tools can improve outcomes, underscoring the importance of integrating cardio-oncology care into survivorship programs [50, 51]. Overall, these longitudinal studies reinforce the notion that heart failure is a prevalent and evolving challenge in the long-term management of cancer survivors.

Clinical Presentation and Diagnosis

Patients with prior malignancy or undergoing CTRCD often present with symptoms indicative of heart failure, although these manifestations can be subtle or nonspecific initially [52-56]. Common clinical features include dyspnea on exertion, fatigue, peripheral edema, orthopnea, and paroxysmal nocturnal dyspnea [22]. In cancer patients, these symptoms may be confounded by other treatment-related side effects or comorbidities, making clinical suspicion crucial for early detection. Notably, the onset of symptoms can vary depending on the type and timing of cardiotoxic exposure, with some patients developing acute decompensation during therapy and others presenting months or years post-treatment [22]. Recognizing these symptoms promptly is vital, as delayed diagnosis can lead to irreversible cardiac damage and worsened prognosis.

The diagnosis of heart failure in cancer patients relies on a combination of clinical assessment and advanced diagnostic modalities [57-61]. Echocardiography remains the cornerstone imaging technique, providing real-time evaluation of cardiac structure and function, including left ventricular ejection fraction and global longitudinal strain, which can detect subclinical myocardial impairment before symptomatic heart failure develops [62]. Cardiac biomarkers such as

troponins and natriuretic peptides (B-type natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP)) are also valuable for early detection of myocardial injury and volume overload, respectively [22]. Additionally, cardiac magnetic resonance imaging offers detailed tissue characterization and can identify myocardial fibrosis or edema, further aiding in diagnosis [62]. Emerging technologies, including artificial intelligence-assisted imaging, are being explored to enhance sensitivity and predictive accuracy in detecting cardiotoxicity [63].

Diagnosing heart failure in cancer patients presents several challenges. The overlap of symptoms with cancer-related fatigue, anemia, or pulmonary issues can obscure the clinical picture [22]. Furthermore, traditional measures like left ventricular ejection fraction may lack sensitivity for early myocardial damage, necessitating the use of more sensitive parameters such as global longitudinal strain, which requires specialized expertise and equipment [62]. Variability in imaging techniques, differences in interpretation, and the absence of standardized screening protocols complicate early detection efforts (Table 1) [62]. Additionally, comorbid conditions like hypertension or coronary artery disease can confound the clinical assessment, making it difficult to attribute symptoms solely to CTRCD. These challenges underscore the need for multidisciplinary approaches and the development of validated risk stratification tools to improve diagnostic accuracy and timeliness in this vulnerable population [22].

Cardiotoxic Cancer Therapies

Exposure to cardiotoxic cancer therapies, such as chemotherapy, radiation, and targeted treatments, has significant long-term cardiovascular consequences for cancer survivors [64-72]. These therapies are associated with an increased risk of cardiovascular diseases, including heart failure, arrhythmias, ischemic heart disease, and other cardiac dysfunctions. The growing population of cancer survivors necessitates a comprehensive understanding of these risks to improve long-term health outcomes. This section details the specific cardiovascular consequences and the importance of monitoring and management strategies.

Cancer survivors exposed to cardiotoxic therapies have a 42% increased risk of heart failure compared to those not exposed to such treatments. This risk is particularly pronounced in patients treated with anthracyclines, a class of chemotherapy agents known for their cardiotoxic effects [73]. Long-term studies indicate that the risk of cardiac dysfunction, such as left ventricular dysfunction, persists and may even increase over time, with a cumulative incidence of cardiac dysfunction reaching 29.7% by 10 years post-treatment in breast cancer survivors [74]. Cardiotoxicity can manifest in various forms, including cardiomyopathy, ischemia, hypertension, and arrhythmias, which can occur during treatment or years after completion [75]. The mechanisms underlying cardiotoxicity from cancer therapies are complex and not fully understood, but they often involve direct damage to cardiac cells and accelerated atherosclerosis [75]. Risk factors such as hypertension, diabetes, and obesity significantly contribute to the development of cardiovascular complications in cancer survivors. These factors, combined with the cardiotoxic effects of treatments, necessitate careful cardiovascular risk assessment and management [73, 74].

The emerging field of cardio-oncology emphasizes the need for collaboration between oncologists and cardiologists to manage and mitigate cardiovascular risks in cancer patients. This includes comprehensive cardiovascular risk assessments and ongoing monitoring before, during, and after cancer treatment [74, 76]. Long-term cardiovascular assessment is crucial, especially in pediatric cancer survivors, to identify and manage complications early. This approach can help prevent severe outcomes and improve the quality of life for survivors.

Management and Treatment Strategies

Effective cardiac monitoring is fundamental in the management of patients undergoing cancer therapy to facilitate early detection of cardiotoxicity and prevent progression to heart failure. Advanced imaging modalities such as echocardiography, including strain imaging techniques like global longitudinal strain, are widely utilized for surveillance, as they can identify subclinical myocardial dysfunction before a decline in left ventricular ejection fraction occurs [62]. Artificial intelligence applications are increasingly being integrated into imaging practices to enhance predictive accuracy and streamline detection processes, potentially allowing for more personalized monitoring strategies [63]. Additionally, risk stratification tools, such as the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) cardiovascular toxicity risk score, are under validation to identify high-risk patients who may benefit from intensified surveillance [50]. Recognizing modifiable risk factors, including pre-existing cardiovascular conditions and lifestyle factors, is also crucial in tailoring monitoring protocols [51].

Table 1: Diagnostic modalities for heart failure in cancer patients.

Modality	Key parameters	Role in diagnosis and monitoring	Advantages	Limitations in cancer population
Echocardiography	Left ventricular ejection fraction, global longitudinal strain, diastolic function	First-line imaging for baseline assessment, surveillance, and diagnosis of CTRCD. Global longitudinal strain detects subclinical dysfunction before left ventricular ejection fraction decline.	Widely available, radiation-free, portable, provides real-time haemodynamic information.	Variability in image quality and interpretation. Global longitudinal strain requires specialized software and training.
Cardiac biomarkers	High-sensitivity troponin, BNP/NT-proBNP	Early detection of myocardial injury (troponin) and haemodynamic stress (BNP/NT-proBNP). Used for risk stratification and monitoring.	Low cost, easily repeatable, provides objective data for early injury detection.	Levels can be influenced by non-cardiac factors (e.g., renal dysfunction, sepsis). Timing of elevation varies by therapy type.
Cardiac magnetic resonance	Left ventricular ejection fraction, ventricular volumes, late gadolinium enhancement, T1/T2 mapping	Gold standard for precise assessment of cardiac structure and function. Identifies myocardial fibrosis, oedema, and inflammation.	Excellent reproducibility, tissue characterization capabilities, not limited by acoustic windows.	High cost, limited availability, long scan times. Contraindicated in patients with certain implantable devices or severe renal impairment (for gadolinium).
Artificial intelligence-assisted imaging	Automated left ventricular ejection fraction/global longitudinal strain calculation, novel imaging biomarkers	Enhances accuracy and predictive value of standard imaging. May identify subtle changes not visible to the human eye.	Potential for personalized risk prediction, improved workflow efficiency, reduced inter-observer variability.	Requires validation in large, diverse cohorts. Integration into clinical workflow is still evolving. Not widely available.

Pharmacological strategies play a pivotal role in both the prevention and treatment of CTRCD. Evidence supports the use of cardioprotective agents such as beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers to mitigate myocardial damage and improve cardiac outcomes [22]. Recent research highlights the potential of SGLT2 inhibitors as promising agents in cardio-oncology, with systematic reviews indicating their cardioprotective effects in breast cancer therapy-related cardiotoxicity [36, 37]. Statins have also demonstrated a protective effect against chemotherapy-induced heart failure, especially in patients with coronary atherosclerosis, suggesting their utility in risk management [77]. The selection of pharmacologic agents should be individualized based on patient risk profiles, type of cancer therapy, and existing comorbidities, with ongoing studies exploring novel agents and combinations to optimize cardioprotection [63].

Lifestyle modifications and non-pharmacological interventions are integral components of comprehensive management. Regular cardiovascular exercise has been shown to positively influence molecular pathways involved in cardiotoxicity and improve overall cardiac function in cancer patients [78]. Exercise programs tailored to individual capacity can enhance quality of life and potentially reduce the incidence of CTRCD. Additionally, addressing modifiable risk factors such as hypertension, obesity, and sleep apnea through behavioral interventions can further decrease the risk of cardiac dysfunction [79]. Nutritional counseling and stress management are also recommended to support cardiovascular health during and after cancer therapy. These approaches, combined with pharmacological treatments, form a holistic strategy to preserve cardiac function and improve long-term outcomes.

The complexity of cardio-oncology necessitates a multidisciplinary approach involving oncologists, cardiologists, radiologists, and other healthcare professionals. Integrated care models facilitate coordinated decision-making, ensuring timely screening, risk assessment, and intervention. Such collaboration allows for personalized treatment plans that balance effective cancer control with cardiovascular safety [51, 80]. Multidisciplinary teams can also implement surveillance protocols based on validated risk scores and emerging imaging technologies, optimizing resource utilization and patient outcomes. Furthermore, education and communication among team members are essential to adapt management strategies as new evidence and therapies evolve. These models aim to improve both survival and quality of life for cancer survivors by proactively addressing cardiac risks throughout the cancer care continuum.

Prognosis and Outcomes

The presence of heart failure in cancer survivors significantly influences overall prognosis and survival outcomes (Table 2). Studies indicate that heart failure complicates the clinical course, often leading to increased morbidity and mortality among this population [23]. The development of heart failure during or after cancer therapy can hinder ongoing oncologic treatments, potentially resulting in therapy interruptions or dose reductions, which may compromise cancer control and survival rates. Moreover, heart failure related complications, such as arrhythmias and thromboembolic events, further exacerbate the risk of adverse outcomes, underscoring the importance of early detection and management to improve both cardiac and oncologic prognoses [22].

Table 2: Prognostic factors and outcomes in cancer survivors with heart failure.

Prognostic factor	Impact on outcomes	Clinical implications
Oncologic factors	Cancer type and stage: Advanced stage or aggressive malignancies may limit treatment options for heart failure and necessitate ongoing cardiotoxic therapy, worsening prognosis.	Requires close collaboration between oncology and cardiology to balance cancer control with cardiovascular safety. May necessitate modified cancer treatment regimens.
	Cancer therapy: Prior exposure to anthracyclines, chest radiation, or HER2-targeted agents increases risk of irreversible or recurrent cardiac dysfunction.	Heightened surveillance is needed for survivors with history of high-dose or combination cardiotoxic therapies. Long-term follow-up protocols should be established.
Cardiovascular factors	Severity of heart failure: Reduced left ventricular ejection fraction, advanced New York Heart Association functional class, and elevated natriuretic peptides are associated with higher morbidity and mortality.	Aggressive guideline-directed medical therapy for heart failure is warranted. Early referral to advanced heart failure services may be beneficial.
	Timing of CTRCD: Late-onset heart failure (occurring years after therapy) may be associated with a different trajectory than acute-onset heart failure, but both confer increased long-term risk.	Survivors require lifelong cardiovascular surveillance, even if they remain asymptomatic years after treatment completion.
	Concurrent cardiovascular disease: Presence of coronary artery disease, hypertension, or valvular disease exacerbates heart failure progression and complicates management.	Comprehensive cardiovascular risk factor modification is essential. Multidisciplinary management addressing all cardiovascular conditions is recommended.
Patient-specific factors	Age at exposure: Younger age at time of cancer therapy (especially childhood cancer survivors) is associated with a longer duration of risk exposure and higher lifetime risk of heart failure.	Pediatric and adolescents and young adults' survivors need transition of care to adult cardio-oncology services with clear survivorship care plans.
	Comorbidities: Diabetes, obesity, and chronic kidney disease increase heart failure progression and mortality risk.	Integrated management of comorbidities is crucial. Lifestyle interventions (diet, exercise) should be emphasized.
	Genetic predisposition: Certain genetic variants may increase susceptibility to therapy-related cardiac dysfunction and influence long-term outcomes.	Family history should be assessed. Emerging role for genetic counseling and testing in selected high-risk patients.
Quality of life and functional status	Symptoms and functional capacity: Persistent dyspnea, fatigue, and exercise intolerance diminish daily functioning, independence, and overall well-being.	Rehabilitation programs (cardiac-oncology rehabilitation) should be offered to improve functional capacity and symptom management.
	Psychological burden: Concurrent cancer and heart failure are associated with increased rates of anxiety, depression, and reduced health-related quality of life.	Routine screening for psychological distress is needed. Integration of psychosocial support services into survivorship care is recommended.
Long-term prognosis	Mortality: Heart failure significantly increases all-cause and cardiovascular mortality in cancer survivors compared to those without heart failure.	Early detection and optimal heart failure management are critical to improve survival outcomes.
	Recurrent cardiac events: Survivors with heart failure are at elevated risk for recurrent heart failure exacerbations, arrhythmias, and thromboembolic events.	Ongoing monitoring and prompt intervention for acute decompensations are necessary. Patient education on symptom recognition is important.
	Progressive cardiac dysfunction: Despite treatment, many survivors experience progressive ventricular remodeling and decline in cardiac function over time.	Long-term cardiology follow-up with serial imaging is required. Advanced heart failure therapies (e.g., device therapy, transplantation) may be considered in eligible patients.

Heart failure markedly impacts the quality of life in cancer survivors, contributing to symptoms such as fatigue, dyspnea, and exercise intolerance that diminish daily functioning and well-being [78]. The psychological burden associated with concurrent cancer and cardiac dysfunction can lead to increased anxiety and depression, further impairing quality of life. Effective management strategies, including pharmacological therapy, lifestyle modifications, and multidisciplinary care, are essential to mitigate these effects and enhance quality of life in this vulnerable population [51]. Addressing heart failure symptoms proactively can help maintain functional independence and improve overall patient satisfaction with their care.

Long-term outcomes for cancer survivors who develop heart failure are generally guarded, with many experiencing persistent cardiac dysfunction despite therapeutic interventions [23]. Longitudinal studies reveal that survivors with therapy-related heart failure face an elevated risk of recurrent cardiac events, progressive ventricular remodeling, and reduced survival rates [23]. The chronic nature of heart failure necessitates ongoing surveillance and tailored treatment approaches to prevent deterioration. Emerging therapies, such as cardioprotective agents and personalized risk stratification tools, hold promise for improving long-term cardiac outcomes and survival in this population [36, 81]. Nonetheless, comprehensive, multidisciplinary management remains critical to optimize prognosis and enhance longevity among cancer survivors affected by heart failure.

Clinical Studies

Cardio-oncology randomized controlled trials are crucial for understanding and mitigating the cardiovascular risks associated with cancer therapies. These trials aim to balance the efficacy of cancer treatments with the management of potential cardiotoxic effects, a growing concern as cancer survival rates improve. The current landscape of cardio-oncology randomized controlled trials reveals a focus on both pharmacological and non-pharmacological interventions to prevent or manage cardiotoxicity, with varying degrees of success and challenges in trial design and implementation.

The MANTICORE 101–breast trial by Pituskin et al. [82] investigated the effectiveness of perindopril and bisoprolol in preventing trastuzumab-associated cardiotoxicity in patients with HER2-positive early breast cancer. A total of 94 patients were included in the study, with 33 receiving perindopril, 31 receiving bisoprolol, and 30 receiving placebo. Baseline demographic, cancer, and cardiovascular profiles were comparable across all 3 groups. The study drugs, perindopril and bisoprolol, were well tolerated by patients. No serious adverse events were reported in connection with the study drugs. After 17 cycles of trastuzumab, indexed left ventricular end diastolic volume increased in all groups: perindopril group: +7 ± 14 mL/m^2; bisoprolol group: +8 ± 9 mL/m^2; placebo group: +4 ± 11 mL/m^2. The difference in left ventricular end diastolic volume change among the groups was not statistically significant (p = 0.36), indicating that perindopril and bisoprolol did not prevent trastuzumab-mediated left ventricular remodeling, which was the primary outcome. In secondary analyses, a decline in left ventricular ejection fraction mediated by trastuzumab was attenuated in patients treated with bisoprolol compared to the other groups: bisoprolol group: −1 ± 5%; perindopril group: −3 ± 4%; placebo group: −5 ± 5%. This difference was statistically significant (p = 0.001), suggesting a protective effect of bisoprolol on left ventricular ejection fraction. Both perindopril and bisoprolol use were identified as independent predictors of maintained left ventricular ejection fraction in a multivariable analysis. In summar, while perindopril and bisoprolol were well tolerated and protected against declines in left ventricular ejection fraction caused by cancer therapy, they did not prevent the primary outcome of trastuzumab-mediated left ventricular remodeling.

The CORE trial by Viamonte et al. [83] demonstrated that center-based cardiac rehabilitation (CBCR) is more effective than community-based exercise training (CBET) for improving cardiorespiratory fitness, controlling cardiovascular risk factors, enhancing physical activity, quality of life, and health literacy, and promoting higher exercise adherence among cancer survivors with high cardiovascular risk (Figure 1). A total of 75 participants successfully completed the study. The mean age of these participants was 53.6 years, with a standard

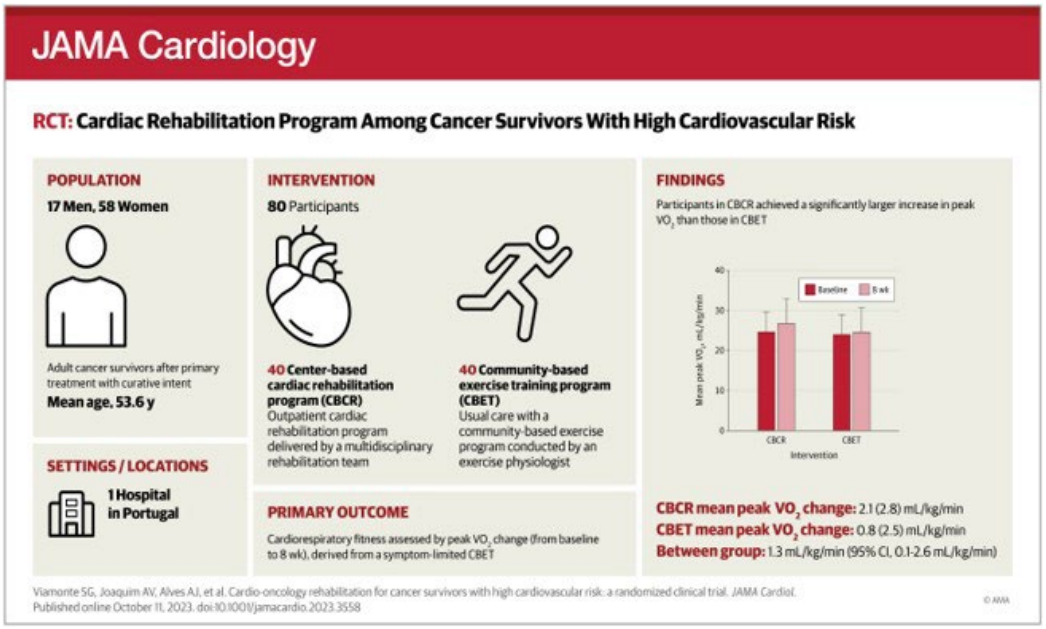


Figure 1: Cardiac rehabilitation program among cancer survivors with high cardiovascular risk [83].

deviation (SD) of 12.3 years. The majority of participants were female, accounting for 77.3% of the total (58 individuals). The participants were divided into 2 groups: 38 in the CBCR group and 37 in the CBET group. The CBCR group demonstrated a significantly greater mean increase in peak oxygen consumption (VO_2) compared to the CBET group. The CBCR group's mean increase was 2.1 mL/kg/min (SD: 2.8), while the CBET group's mean increase was 0.8 mL/kg/min (SD: 2.5). This resulted in a statistically significant between-group mean difference of 1.3 mL/kg/min (95% confidence interval (CI), 0.1 to 2.6 mL/kg/min; p = 0.03), indicating the superiority of CBCR for cardiorespiratory fitness improvement. The CBCR group achieved a substantially greater reduction in both systolic and diastolic blood pressure. Systolic blood pressure decreased by −12.3 mm Hg (SD: 11.8) in the CBCR group versus −1.9 mm Hg (SD: 12.9) in the CBET group (p < 0.001). Diastolic blood pressure decreased by −5.0 mm Hg (SD: 5.7) in the CBCR group versus −0.5 mm Hg (SD: 7.0) in the CBET group (p = 0.003). Participants in the CBCR group experienced a greater mean reduction in body mass index (−1.2, SD: 0.9) compared to the CBET group (0.2, SD: 0.7), with p < 0.001. The CBCR group showed significantly greater improvements in physical activity levels, with an increase of 1035.2 METs/min/wk (SD: 735.7) compared to 34.1 METs/min/wk (SD: 424.4) in the CBET group (p < 0.001). Quality of life scores improved more in the CBCR group (14.0 points, SD: 10.0) than in the CBET group (0.4 points, SD: 12.9), with p < 0.001. Health literacy scores also saw greater improvements in the CBCR group (2.7 points, SD: 1.6) compared to the CBET group (0.1 points, SD: 1.4), with p < 0.001. Exercise adherence was markedly higher in the CBCR group, with participants completing 90.3% (SD: 11.8%) of sessions, as opposed to 68.4% (SD: 22.1%) in the CBET group (p < 0.001).

The ONCORE randomized controlled trial by Díaz-Balboa et al. [84] investigated the effectiveness of an exercise-based Cardio-Oncology Rehabilitation (CORe) program in preventing cardiotoxicity during breast cancer chemotherapy (Figure 2). The study included 122 early-stage breast cancer women receiving cardiotoxic treatments, randomized to either CORe (n = 60) or usual care with exercise recommendation (n = 62). The average intervention duration was 5.8 months. No cases of CTRCD were identified in either group during the study. CTRCD was defined as a left ventricular ejection fraction drop ≥10% to a value <53% or a decrease >15% in global longitudinal strain. While left ventricular ejection fraction decreased in both groups, the decline was significantly attenuated in the CORe group, showing a reduction of −1.5% (−2.9, −0.1) with a p-value of 0.006. No significant changes were detected in global longitudinal strain or cardiac biomarkers in either group. The CORe intervention led to a significant reduction in body mass index (p = 0.037), particularly in obese patients, where the reduction was 3.1 kg/m² (1.3, 4.8). Physical performance and quality of life remained stable in both groups. Physical activity levels increased in both the CORe and usual care groups. No adverse events were detected throughout the study in either group. In summary, the study indicates that exercise-based CORe programs are safe and can help mitigate the decline in left ventricular ejection fraction in breast cancer patients undergoing cardiotoxic therapy. Additionally, these programs were effective in reducing body mass index, especially in obese individuals. While no CTRCD cases were observed, the attenuation of left ventricular ejection fraction decline suggests a protective effect.

A randomized controlled trial by Li et al. [85] evaluating digital therapeutics-based CORe for lung cancer survivors yielded several significant findings regarding participation, exercise adherence, efficacy, and safety. A high percentage of participants completed the trial, with 40 out of 47 (85%) patients finishing. This included 22 patients in the telerehabilitation group and 18 in the usual care group. Patients in the telerehabilitation group engaged in exercise an average of 3.3 times per week. The average weekly exercise duration was 151.4 min, with an effective exercise duration (when the required heart rate was reached) of 92.3 min per week. The average prescription compliance rate, calculated as effective exercise duration divided by

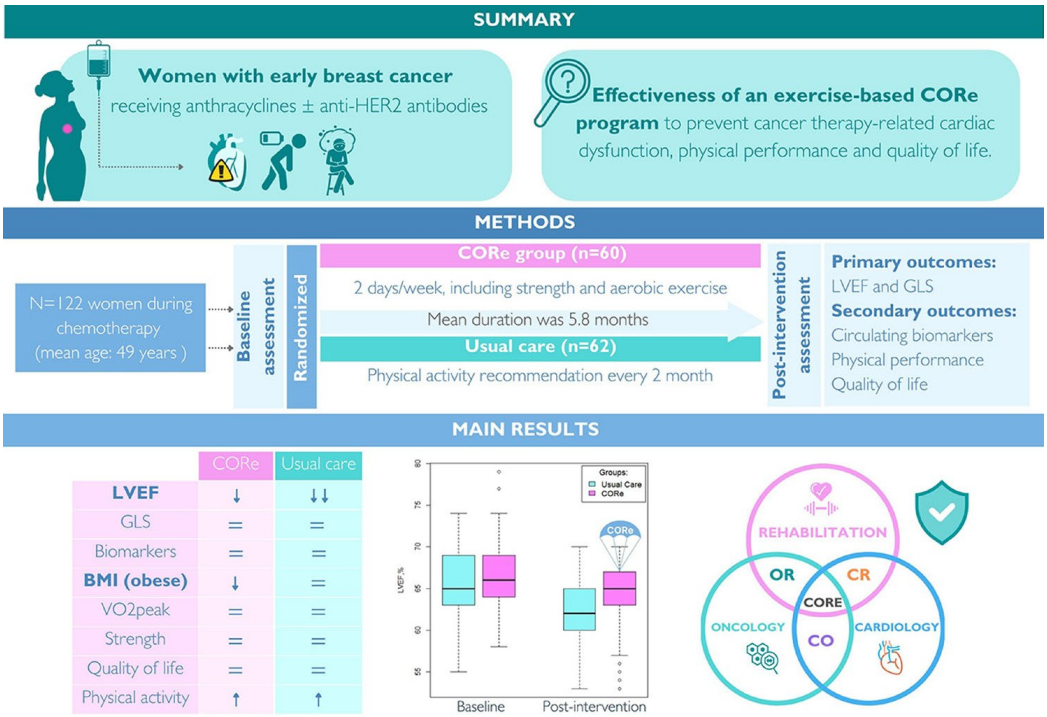


Figure 2: Exercise-based CORe for cardiotoxicity prevention during breast cancer chemotherapy: The ONCORE randomized controlled trial [84].

the lower limit of prescription duration, was notably high at 101.2%. The telerehabilitation group showed a significantly higher average improvement in maximal oxygen uptake peak (VO_2 PEAK) (3.660 ± 3.232 mL/Kg/min) compared to the usual care group (1.088 ± 3.230 mL/Kg/min), with a p-value of 0.023. Cardiac telerehabilitation was associated with several significant improvements: Better alleviation of affective interference (−0.883 ± 1.500 vs 0.208 ± 1.222, p = 0.048). Higher quality of life improvement (16.250 ± 23.017 vs 1.042 ± 13.903, p = 0.027). Reduction in fatigue (−0.889 ± 15.960 vs 1.389 ± 12.087, p = 0.024). Improvement in daytime dysfunction (−0.550 ± 0.686 vs 0.000 ± 0.516, p = 0.015). More anxiety relief (−0.314 ± 0.444 vs −0.054 ± 0.295, p = 0.048). Other measured efficacy outcomes, such as FEV1, DLCO, and cardiac function, did not show significant differences between the 2 groups. No exercise-related adverse events were reported during the entire intervention period, indicating a high safety profile for the digital therapeutics-based program. In summary, the study demonstrated that digital therapeutics-based CORe is a safe and highly compliant intervention that significantly improves cardiorespiratory fitness, psychological well-being, and quality of life in early-stage lung cancer survivors' post-lobectomy.

A study investigated by Chang et al. [86] the impact of a multidisciplinary cardio-oncology program on cardiovascular outcomes in breast cancer patients undergoing anthracycline therapy (Figure 3). The results highlight significant improvements in patient care and outcomes within the cardio-oncology group compared to a non-cardio-oncology group. The ages of patients in both the non-cardio-oncology and cardio-oncology programme groups were similar (53.8 ± 11.5 vs 53.7 ± 10.1 years old, p = 0.87). There was no significant difference in the prevalence of background cardiovascular risks, such as hypertension (7.1% vs 6.5%; p = 0.52), diabetes (2.2% vs 1.9%; p = 0.43), hyperlipidaemia (6.2% vs 5.2%; p = 0.21), and chronic kidney disease (1.3% vs 1.3%; p = 0.68) between the 2 groups. Both groups had similar average single and accumulating doses of anthracycline. In the non-cardio-oncology programme, echocardiography screening ratios were significantly lower (36% before, 18% during, and 10% after anthracycline therapy). In contrast, the post-cardio-oncology program achieved screening ratios close to 100% at each stage (before, during, and after therapy). The non-cardio-oncology group experienced a continuous drop in left ventricular ejection fraction as anthracycline doses accumulated (74.8 ± 8.6% before, 72.3 ± 12% during, and 67.3 ± 10.1% after). Conversely, the cardio-oncology program mitigated this decline, showing an insignificant trend in left ventricular ejection fraction reduction (74.6 ± 7.2% before, 71.7 ± 8.3% during, and 70.3 ± 8.1% after). Only 3.2% (5 patients) in the cardio-oncology program fulfilled the criteria for CTRCD, and none developed heart failure symptoms or cardiovascular complications. These 5 patients, mostly young with few traditional cardiovascular risks, saw their myocardial function return to baseline with lifestyle modifications and medical interventions. Before the cardio-oncology program, there was a 1% incidence of new-onset heart failure, 1.7% new-onset hypertension, 0.9% myocardial infarction, 0.9% ischemic stroke, and 16.6% all-cause mortality. After the program, new-onset hypertension dropped to 0.6%, and no other cardiovascular complications were reported. Although high-sensitivity troponin I and NT-proBNP initially increased after anthracycline therapy, they gradually returned to baseline. Similarly, the 6-minute walking distance and quality of life (EuroQol-5D index and visual analogue scale) initially declined but improved to or even surpassed baseline levels within a year for patients in the cardio-oncology program. In summary, the multidisciplinary cardio-oncology program in Taiwan demonstrated significant benefits, including improved left ventricular ejection fraction preservation, reduced cardiovascular complications, and better quality of life outcomes for breast cancer patients undergoing anthracycline therapy, primarily due to enhanced monitoring and timely intervention.

Future Directions and Research Gaps

The landscape of cardio-oncology is rapidly evolving with the development of novel therapeutic strategies aimed at preventing and mitigating CTRCD. Recent systematic reviews highlighted the potential of agents such as SGLT2 inhibitors, which have demonstrated cardioprotective effects in preclinical and early clinical studies [36, 37]. These agents may offer a promising avenue for reducing the incidence and severity of heart failure in patients undergoing cardiotoxic cancer treatments. Additionally, ongoing research into targeted pharmacologic interventions, including the use of statins, shows a protective effect against the development of heart failure, especially in patients with underlying coronary atherosclerosis [77]. The integration of artificial intelligence into cardio-oncology imaging also holds promise for early detection and personalized intervention, potentially enabling clinicians to identify high-risk patients more accurately and tailor

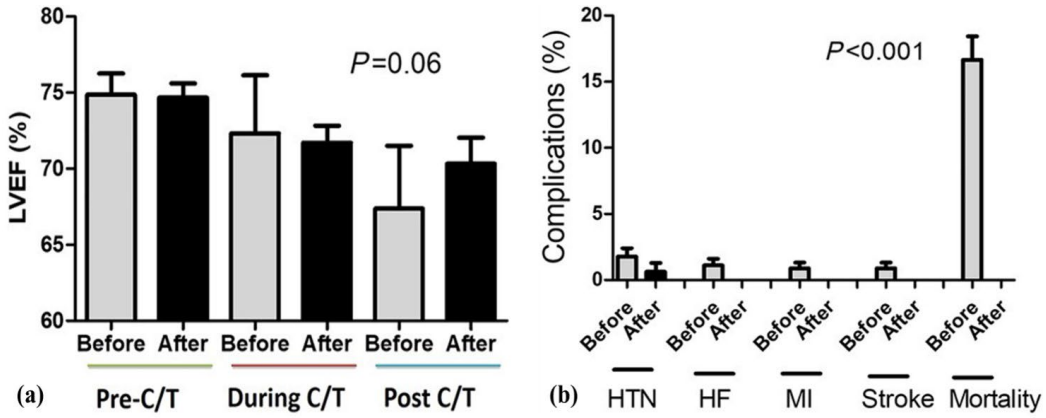


Figure 3: (a) The decrease in left ventricular ejection fraction was attenuated in patients managed within a cardio-oncology program, contrasting with the continuous decline seen in those receiving standard care. **(b)** In the period preceding the cardio-oncology program, patients experienced new-onset hypertension (1.7%), heart failure (1.0%), myocardial infarction (0.9%), and ischemic stroke (0.9%), alongside a mortality rate of 16.8%. After the program was established, hypertension rates fell to 0.6%, and all other major cardiovascular complications were effectively eliminated [86].

therapies accordingly [63]. Future research should focus on large-scale, prospective clinical trials to validate these emerging therapies and establish standardized protocols for their implementation in routine clinical practice.

Despite increasing recognition of CTRCD, there remains a significant gap in long-term data tracking the progression of cardiac dysfunction in cancer survivors. Most existing studies are retrospective or cross-sectional, limiting understanding of the temporal relationship between cancer therapies and cardiac outcomes [22, 23]. Longitudinal studies with extended follow-up periods are essential to elucidate the natural history of heart failure post-therapy, identify early biomarkers of subclinical dysfunction, and assess the long-term efficacy of preventive and therapeutic interventions. Such studies would also help clarify the impact of emerging therapies on cardiac health over time and inform optimal surveillance strategies. The need for comprehensive, prospective cohort studies is underscored by the current lack of data on long-term outcomes, especially in diverse patient populations and those receiving novel cancer treatments [51, 53].

To improve cardiovascular outcomes in cancer patients, there is a pressing need to embed cardio-oncology principles into standard oncologic care pathways. This integration involves routine risk stratification, early screening for cardiotoxicity, and multidisciplinary collaboration between oncologists and cardiologists [34, 50, 81]. Developing standardized guidelines and risk assessment tools, such as the HFA-ICOS cardiovascular toxicity risk score, can facilitate early identification of high-risk individuals and enable timely intervention [50]. Furthermore, incorporating advanced imaging modalities and artificial intelligence driven diagnostic tools into routine practice can enhance early detection of subclinical cardiac dysfunction, allowing for personalized management plans [62, 63]. Education and training programs aimed at oncologists and cardiologists are also vital to foster a collaborative approach. Ultimately, integrating cardio-oncology into standard cancer care will require concerted efforts in research, guideline development, and healthcare policy to ensure comprehensive, patient-centered management of cardiovascular health throughout the cancer treatment continuum.

Conclusion

Heart failure has emerged as a significant and growing complication among the increasing population of cancer survivors, driven by the cardiotoxic effects of modern anticancer therapies. As this review highlights, the pathophysiological mechanisms underlying CTRCD are diverse, ranging from direct cardiomyocyte injury to immune-mediated inflammation, and their clinical presentation can be subtle, often overlapping with cancer-related symptoms. The elevated prevalence of heart failure in this population, particularly among those exposed to anthracyclines, HER2-targeted agents, or chest radiation, underscores the critical need for heightened clinical awareness and proactive surveillance. The integration of advanced diagnostic modalities, such as global longitudinal strain and cardiac biomarkers, has improved the capacity for early detection of subclinical dysfunction, enabling timely intervention before irreversible damage occurs. Furthermore, evidence from clinical studies, including randomized controlled trials and real-world programme evaluations, demonstrates that structured CORe and multidisciplinary care models can significantly attenuate left ventricular ejection fraction decline, reduce cardiovascular complications, and improve quality of life.

The management of heart failure in cancer patients necessitates a paradigm shift from reactive treatment to proactive, integrated care throughout the cancer continuum. Pharmacological strategies, including the use of cardioprotective agents, alongside lifestyle modifications and close monitoring, form the cornerstone of effective management. The demonstrated benefits of multidisciplinary cardio-oncology programmes—such as improved screening adherence, better preservation of cardiac function, and reduced incidence of major adverse cardiovascular events—provide a compelling rationale for their widespread adoption. As the field continues to evolve, future efforts must focus on embedding these principles into standard oncologic care, fostering collaboration between cardiologists and oncologists, and generating robust long-term data to refine risk stratification and therapeutic approaches. Ultimately, a comprehensive, patient-centred approach that balances effective cancer treatment with cardiovascular safety is essential to optimize both the quantity and quality of life for cancer survivors.

Acknowledgements

None.

Conflict of Interest

None.

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