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Cancer treatment-related cardiovascular disease - real world data in cardio-oncology

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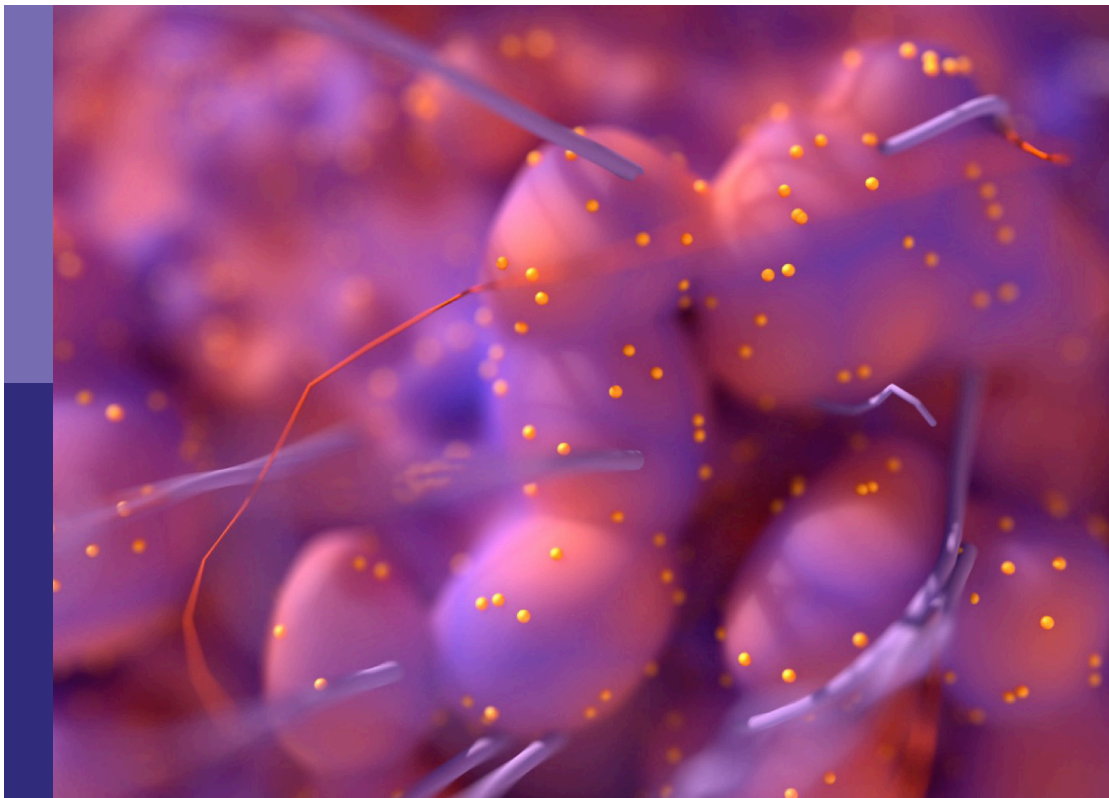

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Cancer treatment-related cardiovascular disease - real world data in cardio-oncology

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Editorial: Cancer treatment-related cardiovascular disease - real world data in cardio-oncology

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Editorial on the Research Topic
Cancer treatment-related cardiovascular disease - real world data in cardio-oncology

Modern anti-cancer therapies have revolutionized cancer treatment. With improving outcomes and survival and cure rates, the significance of cancer treatment-related cardiovascular disease (CTRCD) or toxicity (CTR-CVT) is also being realized (1, 2). The crux of cardio-oncology is to understand such interactions better, to reduce their morbidity and mortality, and to develop protocols and guidelines to manage CTRCD through collaborative efforts in the clinic and research (2, 3). The Global Cardio-oncology Registry has initiated multinational collaboration and has prioritized research on CTRCD in the setting of breast cancer, hematological cancers, and immune-checkpoint inhibitors (ICI) (4). The spectrum of CTRCD, however, is not limited to these alone. Recently published ESC guidelines focus on the definition and management of the entire spectrum of CTRCD (5).

Multiple myeloma is mostly diagnosed in elderly patients with pre-existing cardiovascular (CV) comorbidities (5, 6). Anti-myeloma combination therapy, including immunomodulators (IMiDs), dexamethasone, proteasome inhibitors, and monoclonal antibodies (MABs), has demonstrated an increased risk of serious cardiovascular adverse events (CVAEs), necessitating simple and quick clinical tools for risk stratification (5). Yuan et al., in a retrospective study of 253 newly diagnosed multiple myeloma (NDMM) patients, developed and validated a risk score prognostic and predictive model for CVAEs in this patient population. Patients were divided into training and validation cohorts randomly. Univariate and multivariate analysis identified three independent factors associated with CVAEs – age > 61 years, high baseline blood pressure (BP), and left ventricular (LV) hypertrophy. Age was assigned 2 points and others 1 point each to

construct a prognostic model that differentiated NDMM patients into three risk groups - 3–4 points, high risk; 2 points, intermediate risk; 0–1 point, low risk. These groups exhibited significant differences in 1-year and 2-year CVAEs in both the training and validation cohorts. Statistical analysis using C-index values, ROC curves, and decision curve analysis showed that this model had good calibration and provided greater net benefit than the default strategies of CV risk assessment for all patients. This study successfully showed that NDMM patients at increased risk of CVAEs can be identified at baseline, permitting the introduction of CV protective strategies. This model merits further validation in a large prospective cohort for its widespread application and acceptability.

Allogeneic hematopoietic cell transplantation (allo-HCT) has significantly improved cure rates in relapsed refractory hematological malignancies. While the associated long-term impact of increasing CV morbidity and mortality amongst survivors is well known, the short-term CV effects are less studied (7). Dillon et al., in a 3-month prospective study, evaluated the short-term CV impact of allo-HCT in 17 high-risk hematological cancer patients compared to an age-matched non-cancer control group of 12. This was done through pre- and post-transplant cardio-pulmonary exercise testing, to quantify the VO2peak, along with exercise cardiac MRI (for cardiac reserve), resting echocardiography (ECHO), dual-energy x-ray absorptiometry (for lean and fat mass), BP assessment, hemoglobin sampling, and arterio-venous oxygen difference estimation via Fick's equation. They found significant reductions in the absolute VO2peak, body weight-indexed VO2peak, lean mass, and cardiac reserve in the allo-HCT group, indicating rapid CV aging in this population and the need for early preventive measures. This study also increases our awareness of these early changes and raises the question of whether we should be searching for them in clinical practice.

Hubbert et al. evaluated the long-term incidence, risks, and predictors of CTR-CVT and all-cause mortality in a retrospective Swedish registry study, which included 433 lymph node-positive early breast cancer (EBC) patients considered for adjuvant chemotherapy, who were aged 18-60 years and diagnosed between 1998 and 2002. The CTR-CVT events included hypertension (HT), coronary artery disease (CAD), heart failure (HF), or atrial fibrillation (AF) after the diagnosis of BC. Patients were followed until November 2021 or death. A total of 910 CTR-CVT events were diagnosed in 311/433 women (71.8%), with a median of 19.3 years follow-up - HT 281 (64%); CAD 198 (46%); HF 206 (47%); and AF 225 (51%). Older age (51-60 years) and anthracycline exposure increased the risk of CTR-CVT. Among CTR-CVTs, HF showed the strongest association with anthracycline use (HR 2.0), followed by CAD (HR 1.7) and AF (HR 1.5). At the end of the 24-year study period, 227 of the 433 women were alive, with a 47.6% cumulative mortality. The study demonstrated the high prevalence of CTR-CVT and all-cause mortality after BC diagnosis and treatment, particularly in older patients and those receiving anthracyclines. These findings support the need for CV risk stratification prior to starting anti-cancer therapy and long-term annual screening for CV risk factors and CTR-CVT among BC survivors.

Wu et al. conducted a retrospective study of 2060 consecutive patients with stage 0 – III BC undergoing pre-treatment ECHO (n=1032) or MUGA (n=1028) from 2010 to 2019 at a tertiary cancer care center in Canada. The primary end point was a composite of all-cause mortality and incidence of HF. Follow-up cardiac imaging scans were obtained in 39.3% of patients with MUGA and 38.0% with ECHO. At a median follow-up of 6.7 years, there were 194 deaths, including 7 CV deaths, and 28 heart failure events, with no difference in events between the MUGA and ECHO groups. Patients without follow-up imaging had a similar adjusted risk for the composite outcome compared to those with imaging follow-up, with a hazard ratio of 0.8 (95% CI 0.5-1.3, p=0.457). This study demonstrated that CV deaths and HF event rates were low in a real-world setting and uninfluenced by follow-up CV imaging. Further research is needed to determine the potential benefit of CV imaging surveillance in high-risk patients who have completed anti-cancer therapy.

Head and neck squamous cell carcinoma (HNSCC) patients have a high incidence of CVD and stroke due to common CV risk factors (e.g., tobacco) and cancer treatment-related risk factors such as neck radiotherapy (RT), platinum chemotherapy, and neck surgery (8). Mukherjee et al. assessed the association of HNSCC-related factors [subsite, stage, treatment, human papillomavirus (HPV) status] and traditional CV risk factors [HT, diabetes, dyslipidemia, tobacco, obesity] with 1- and 5-year CVD risk (CAD, ischemic stroke, HF) in a retrospective cohort of 1829 HNSCC patients. Patients treated with RT, HPV +, diabetes, and older age were reported to have a higher risk of CVD. The use of anti-hypertensives at baseline significantly reduced the 1-year and 5-year risk of CVD. The findings are similar to a recently published cohort study of 35897 HNSCC patients that had a high incidence of CV events and HT as the most prevalent CV risk factor (9). These studies highlight the importance of risk-directed primary preventive measures in HNSCC patients to reduce the incidence of CVAEs.

ICIs have improved the clinical outcomes of several types of early and advanced cancer. However, they can cause non-specific activation of the immune system, leading to immune-related adverse events (IRAEs). Moreover, the CV system is not spared. Zhang et al. prospectively analyzed the incidence of CVAEs in 106 ICI-treated cancer patients in a single-center study from China. They found that 38% of patients developed various ECG abnormalities, 36% LV diastolic dysfunction, and 8% LV ejection fraction (LVEF) decline, while 8% saw increased cardiac biomarkers and 2% pericardial effusion. Baseline HT and lower peak early diastolic mitral annulus velocity (e') predicted a higher incidence of LV dysfunction in ICI-treated patients. Others have reported a higher risk of myocarditis, stress cardiomyopathy, and even an increased risk of atherosclerosis (5). ICI-associated myocarditis, though rare, can often occur early with high fatality (30-50%). Such eventualities may be higher in patients with pre-existing cardiac disease. Hence, a high index of suspicion is required. Put together, there is increasing evidence that the CV IRAEs are likely underestimated. Besides regular CV monitoring including ECG, ECHO, and cardiac biomarkers, cardio-oncologists will have to identify and utilize novel strategies to prevent such acute and long-term sequelae.

Vascular Endothelial Growth Factor (VEGF)-targeting MABs and oral tyrosine kinase inhibitors (TKIs) have shown remarkable

efficacy in a variety of cancers, but their associated CVAEs remain poorly elucidated in a real-world setting. Wang et al. looked at the CV toxicity profile associated with all VEGF inhibitors in a comprehensive pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) database from 2014 to 2021. Bevacizumab was reported to have the highest CVAEs (31.8%), followed by Sunitinib (12.4%), amongst all VEGF inhibitors. Amongst CVAEs, HT showed the strongest association, with the shortest time to onset (median 23 days) but the least proportion of death or life-threatening events, whereas thromboembolism had the longest time to onset (median 51 days) but the highest risk of fatality.

QTc prolongation, a known risk factor for fatal ventricular arrhythmias, is seen in 2.5 – 12.5% of patients on anti-cancer treatments, more specifically due to oral TKIs, arsenic trioxide, anti-emetics, and antimicrobials, with some having black-box warnings (10). Risk stratification scores for QTc prolongation have been developed, but they are more applicable to the inpatient and acute care setting. There is a paucity of real-world data in the ambulatory oncology setting. Reeves et al. conducted a single-center retrospective study to describe the incidence and risk factors of QTc prolongation in 49 outpatients on oral TKIs with available baseline and follow-up ECGs. They found a 24% incidence, with 3 patients (6%) having significant QTc prolongation (Bazett formula) - QTc >500 ms or >60 ms increase from baseline. These patients, however, remained asymptomatic, and there was no discontinuation of TKI. Concomitant therapy with a loop diuretic (41% vs 11%, p=0.029) was a risk factor for QTc prolongation. This study showed that real-world incidence of QTc prolongation is higher, and frequent ECG and electrolyte monitoring is needed for patients on oral TKIs, especially those on concomitant loop diuretics.

Takotsubo Syndrome (TTS), a transient and reversible LV systolic dysfunction due to different specific triggers, is known to be more common among cancer patients. However, the relationship between its triggers and cancer outcomes is not well studied. Safdar et al. published a retrospective study from the MD Anderson Cancer Center to determine whether different triggering events for TTS—"cancer-specific triggers" (e.g., chemotherapy, immunomodulators, or RT) or "traditional triggers" (e.g., medical, procedural, and emotional stress)—modified outcomes in 81 identified patients with TTS among 373 cancer patients presenting with acute coronary syndrome over a period of 12 years. This study showed a high prevalence of TTS in cancer patients. A total of 47 out of the 81 TTS patients died, all of these being cancer-related deaths, and there was no CV mortality, with a median survival of 11.9 months. Immunomodulator and RT-related TTS showed higher mortality. Medical triggers showed the least recovery in LVEF and global longitudinal strain (GLS), while patients with emotional and chemotherapy triggers showed the most improvement.

This Research Topic covers a wide spectrum of CTR-CVT and fulfills its aim of collecting meaningful and impactful real-world data in this field.

Author contributions

VA: Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. AGh: Writing – review & editing. AGu: Writing – review & editing. PP: Writing – review & editing. SD: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Cardiovascular toxicity associated with angiogenesis inhibitors: A comprehensive pharmacovigilance analysis based on the FDA Adverse Event Reporting System database from 2014 to 2021

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Background: The profiles of cardiovascular toxicity associated with angiogenesis inhibitors, including intravenous monoclonal antibodies (mAbs) and oral tyrosine kinase inhibitors (TKIs), targeting vascular endothelial growth factor (VEGF) remain poorly elucidated in real-world settings. This pharmacovigilance analysis aimed to comprehensively investigate the frequency, spectrum, timing, and outcomes of cardiovascular toxicities associated with angiogenesis inhibitors and to explore the differences in such patterns between mAbs and TKIs.

Methods: Disproportionality analysis was performed by leveraging reports from the FDA Adverse Event Reporting System (FAERS) database from 2014 to 2021. Cardiovascular adverse events (AEs) were grouped into nine narrow categories using the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs). Reporting odds ratio (ROR) and information components (ICs) were calculated with statistical shrinkage transformation formulas and a lower limit of 95% confidence interval (CI) for ROR (ROR_{025}) > 1 or IC (IC_{025}) > 0, with at least three reports being considered statistically significant.

Results: A total of 757,577 reports of angiogenesis inhibitors and 70,668 (9.3%) reports of cardiovascular AEs were extracted. Significant disproportionality was detected in angiogenesis inhibitors for cardiovascular AEs ($IC_{025}/ROR_{025} = 0.35/1.27$). Bevacizumab (31.8%), a mAb, presented the largest number of reports, followed by sunitinib (12.4%), a TKI. Hypertension (SMQ) was detected with the strongest signal value ($IC_{025}/ROR_{025} = 1.73/3.33$), followed

by embolic and thrombotic events (SMQ) (IC_{025}/ROR_{025} = 0.32/1.26). Hypertension showed the shortest time to onset with a median (interquartile range) value of 23 (8, 69) days, while embolic and thrombotic events had the longest value of 51 (16, 153) days. Notably, hypertension presented the lowest proportions of death and life-threatening events (10.9%), whereas embolic and thrombotic events posed the highest (29.3%). Furthermore, both mAbs (IC_{025}/ROR_{025} = 0.47/1.39) and TKIs (IC_{025}/ROR_{025} = 0.30/1.23) showed increased cardiovascular AEs. Hypertension was detected in both agents (IC_{025}/ROR_{025} = 1.53/2.90 for mAbs and IC_{025}/ROR_{025} = 1.83/3.56 for TKIs) with a shorter time to onset of 17 (6, 48) days for TKIs than mAbs of 42 (14, 131) days. By contrast, embolic and thrombotic events were detected for mAbs (IC_{025}/ROR_{025} = 0.90/1.87) without TKI (IC_{025}/ROR_{025} = −0.08/0.95).

Conclusion: Angiogenesis inhibitors were associated with increased cardiovascular toxicity with a discrepancy between intravenous mAbs and oral TKIs, deserving distinct monitoring and appropriate management.

KEYWORDS

cardiovascular toxicity, angiogenesis inhibitors, FAERS database, real-world study, disproportionality analysis, pharmacovigilance analysis

Introduction

Angiogenesis plays a critical role in tumor growth and metastasis, and vascular endothelial growth factor (VEGF) has been confirmed to be the main proangiogenetic factor (1, 2). Targeting VEGF-induced angiogenesis to establish an anti-neoplastic effect was first proposed by Folkman in 1971 (3). Since bevacizumab, an anti-VEGF monoclonal antibody (mAb), was first approved in 2004 by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic colorectal carcinoma in combination with chemotherapy (4), four main classes of agents targeting the VEGF signaling pathway have been developed: anti-VEGF mAb, anti-VEGF receptor (VEGFR) mAb, VEGF soluble decoy receptor capturing free available VEGF (VEGF-trap), and tyrosine kinase inhibitors (TKIs), that is, oral small-molecule agents that act on the intracellular tyrosine kinase domains of VEGFRs to inhibit their activation (1, 2). In contrast to mAbs, small-molecule TKIs target multiple tyrosine kinases other than VEGFs. In addition, recombinant human endostatin is another agent with an antiangiogenic effect, which was developed mainly in China (5).

Despite the remarkable anti-tumor effects of angiogenesis inhibitors in a variety of cancer cases, emerging evidence has shown cardiovascular toxicity associated with angiogenesis inhibitors (6–8). Although hypertension has received the most attention, a wider range of cardiovascular toxicity, including left ventricular systolic dysfunction, heart failure, myocardial ischemia, thromboembolic events, QT interval prolongation, and arrhythmia, has also been increasingly recognized (1, 2, 6–20). However, the majority of these data were from clinical trials, conducted in selected populations, which may underestimate the real burden of cardiovascular toxicity. Moreover, it is unclear whether the differences in the mechanism of action and route of administering between intravenous mAbs (including anti-VEGF mAb, anti-VEGFR mAb, and VEGF-trap) and oral TKIs with anti-VEGF(R) activity translate into clinically relevant differences in the incidence of cardiovascular toxicity.

Therefore, this pharmacovigilance analysis aimed to systematically investigate real-world patterns of total and class-specific cardiovascular toxicity associated with angiogenesis inhibitors and to explore the potential differences in such profiles between mAbs and TKIs with anti-VEGF(R) activity.

Materials and methods

Data sources

The U.S. FDA Adverse Event Reporting System (FAERS) database is a free post-marketing safety surveillance database that contains millions of real-world spontaneous adverse event (AE) reports submitted by healthcare professionals, individual patients, and drug manufacturers around the world (21). The large quantity of data collected at a national level from a large population and under conditions that may have been overlooked in controlled clinical trials makes FAERS particularly

TABLE 1 Cardiovascular adverse events grouped into 9 narrow categories of Standardized MedDRA Queries (SMQs) according to MedDRA 24.0.

SMQ name	SMQ code	Algorithm
Cardiac arrhythmias	20000049	Narrow
Cardiac failure	20000004	Narrow
Cardiomyopathy	20000150	Narrow
Embolic and thrombotic events	20000081	Narrow
Hypertension	20000147	Narrow
Ischaemic heart disease	20000043	Narrow
Noninfectious myocarditis/pericarditis	20000239	Narrow
pulmonary hypertension	20000130	Narrow
torsade de pointes/QT prolongation	20000001	Narrow

robust to conduct a pharmacovigilance study in the real-world setting.

In FAERS, AEs are coded using preferred terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA) (version 24.0). A specific PT can be assigned to several high-level terms (HLTs), high-level group terms (HLGTs), and system organ classes (SOCs). In addition, all PTs representing symptoms, signs, investigations, or diagnoses likely to be relevant can be grouped into meaningful categories using the Standardized MedDRA Queries (SMQs) to define a medical condition of interest. In this study, cardiovascular AEs were grouped into nine narrow categories of SMQs (cardiac arrhythmia, cardiac failure, cardiomyopathy, embolic and thrombotic events, hypertension, ischemic heart disease, noninfectious myocarditis/pericarditis, pulmonary hypertension, and torsade de pointes/QT prolongation) (Table 1) (see Supplementary Tables S1–S9) (22).

Data extract

This retrospective analysis enrolled data in the FAERS database from the first quarter of 2014 to the fourth quarter of 2021. Of note, there are inevitably duplicates (the same report submitted by different sources) and multiple reports (a follow-up of the same case with additional and updated information) in the spontaneous reporting database. Therefore, a two-step data cleaning was conducted before analysis. First, as for the reports with the same "safetyreportid," only the last version of the reports was used. Second, reports with the same variables, such as "patientsex," "patientonsetage," "reportercountry," "receiptdate," "reaction meddra pt," and "medicinal product," were considered duplicated and removed.

TABLE 2 Disproportionality analysis based on two-by-two contingency table.

	Target adverse events	Other adverse events	Total
Target drug	a ($N_{observed}$)	b	N_{drug} =a+b
Other drugs	c	d	c+d
Total	N_{event} =a+c	b+d	N_{total} =a+b+c+d

Furthermore, since time to onset was defined as the period between the start date of angiogenesis inhibitors and the onset date of cardiovascular AEs, reports without any information on the "drug start date" or "case event date" or start date of the drug later than the onset date of AEs were regarded as aberrant and excluded from the analysis of time to onset.

Notably, the drugs are reported as free text in FAERS, either generic names or brand names even research codes can be reported; and misspelling can also be present. Thus, a thorough drug name archive including all generic names, brand names, and research codes of angiogenesis inhibitors approved by the U.S. FDA or the National Medical Products Administration (NMPA) in China (formerly known as the China Food and Drug Administration, CFDA) was applied (see Supplementary Table S10).

Statistical analysis

Currently, disproportionality analysis (also known as case–noncase analysis) is a widely used signal detection method in the pharmacovigilance study based on a two-by-two contingency table (Table 2) (23, 24).

Reporting odds ratio (ROR) and information components (ICs) are two specific indices calculated to detect potential associations between drugs and AEs. Notably, statistical shrinkage transformation was applied to obtain robust results, and the corresponding calculation formulas for ROR and IC are as follows (25):

$$\begin{aligned} ROR &= (N_{observed} + 0.5)/(N_{expected} + 0.5) \\ IC &= \log_2[(N_{observed} + 0.5)/(N_{expected} + 0.5)] \\ N_{expected} &= N_{drug} * N_{event}/N_{total}, \end{aligned}$$

where $N_{observed}$ (a) is the observed number of reports of target drug AEs, $N_{expected}$ is the expected number of reports of target drug AEs, N_{drug} (a+b) is the total number of reports of target drug, N_{event} (a+c) is the total number of reports of target AEs, and N_{total} (a+b+c+d) is the total number of reports in the whole database.

Moreover, the calculation formulas for the 95% confidence interval (CI) of the ROR and IC are as follows:

$$\begin{aligned} \text{ROR 95\%CI} &= e^{ln(ROR) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}} \\ IC_{025} &= IC - 3.3^{*}(N_{observed} + 0.5)^{-0.5} \\ &\quad - 2^{*}(N_{observed} + 0.5)^{-1.5} \\ IC_{075} &= IC + 2.4^{*}(N_{observed} + 0.5)^{-0.5} \\ &\quad - 0.5^{*}(N_{observed} + 0.5)^{-1.5} \end{aligned}$$

The lower limit of the 95% CI for ROR (ROR_{025}) >1 or the lower limit of the 95% CI for IC (IC_{025}) exceeding 0 with at least three reports was considered statistically significant and deemed a potential signal.

All the analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, United States).

Results

Descriptive analysis

From the first quarter of 2014 to fourth quarter of 2021, a total of 42,874,609 reports were extracted from the FAERS database and 32,916,895 reports were included in the final analysis, of which 757,577 reports on angiogenesis inhibitors and 70,668 (9.3%) reports of cardiovascular AEs were extracted (Figure 1).

Characteristics of cardiovascular AE reports are presented in Table 3. The median [interquartile range (IQR)] age of patients with angiogenesis inhibitors was 66 (57, 73) years, which was older than those of 61 (47, 72) years with other drugs. Among cardiovascular reports associated with angiogenesis inhibitors, older patients (aged of ≥ 65 years vs. 18–64 years: 40.5% vs. 33.1%) and male patients (49.1% vs. 41.3%) accounted for a greater proportion than younger patients and female patients, respectively. In addition, cardiovascular AEs with angiogenesis inhibitors were chiefly submitted by health professionals (65.0%) and mainly from the United States (46.3%). As for the outcomes of AEs, caused or prolonged hospitalization, other serious events and death were the most frequently reported.

Disproportionality analysis of cardiovascular AEs for angiogenesis inhibitors

Of note, most cardiovascular AEs were reported in cases using TKIs (N = 45 475, 62.4%), among which sunitinib was the most common reported agent (N = 9 061, 12.4%). By contrast, bevacizumab (N = 23 177, 31.8%), an anti-VEGF mAb, presented the largest number of reported AEs as a single agent (Table 4).

Using angiogenesis inhibitors was significantly associated with a higher reporting frequency of cardiovascular AEs than the whole database corresponding to an ROR (ROR_{025}, ROR_{975}) of 1.29 (1.27, 1.30) and an IC (IC_{025}, IC_{975}) of 0.36 (0.35, 0.37) (Table 4).

Notably, significant signals were detected in the majority of agents, except for erdafitinib, fruquintinib (China), vatalanib, anlotinib (China), and recombinant human endostatin (China). Since these agents accounted for a very small proportion of AEs reported with no significant signals detected as a consequence, these agents were not included in the further analysis as single agents.

As for the signal strength, TKIs as a class of agents demonstrated the weakest signal value (IC_{025}/ROR_{025} = 0.30/1.23) compared with anti-VEGF mAb (IC_{025}/ROR_{025} = 0.43/1.35), anti-VEGFR mAb (IC_{025}/ROR_{025} = 0.48/1.40), and VEGF-Trap (IC_{025}/ROR_{025} = 0.69/1.62).

In addition, with respect to single agent, cediranib held the strongest signal value (IC_{025}/ROR_{025} = 0.98/2.01), despite a very small proportion reported (N = 71, <0.1%), while regorafenib (N = 3 184, 4.4%) showed the weakest signal value (IC_{025}/ROR_{025} = 0.01/1.01).

Spectrum of cardiovascular AEs based on PTs for angiogenesis inhibitors

Overall, hypertension (N = 10 654, 15.1%) contributed to the most frequently reported cardiovascular PTs associated with angiogenesis inhibitors, followed by dyspnea (N = 7 739, 11.0%) and increased blood pressure (N = 6 404, 9.1%).

According to IC_{025} >0, a total of 112 PTs were observed to be significantly associated with angiogenesis inhibitors as a whole. For single agent, bevacizumab presented the broadest spectrum of cardiovascular AEs with a total of 106 PTs detected as signals, while cediranib held the least PTs (N = 3) (see Supplementary Table S11).

Of note, hypertension was detected as signals in 13 agents, except apatinib (China) and tivozanib, which were the most frequently reported PTs. Furthermore, blood pressure increased, ejection fraction decreased, and ascites with another three PTs detected as signals among 11 agents (see Supplementary Table S12).

Spectrum of cardiovascular AEs based on SMQs for angiogenesis inhibitors

As seen in Table 5, among the nine narrow categories of SMQs, cardiomyopathy (SMQ) (N = 22 186, 22.7%) comprised the most frequently reported

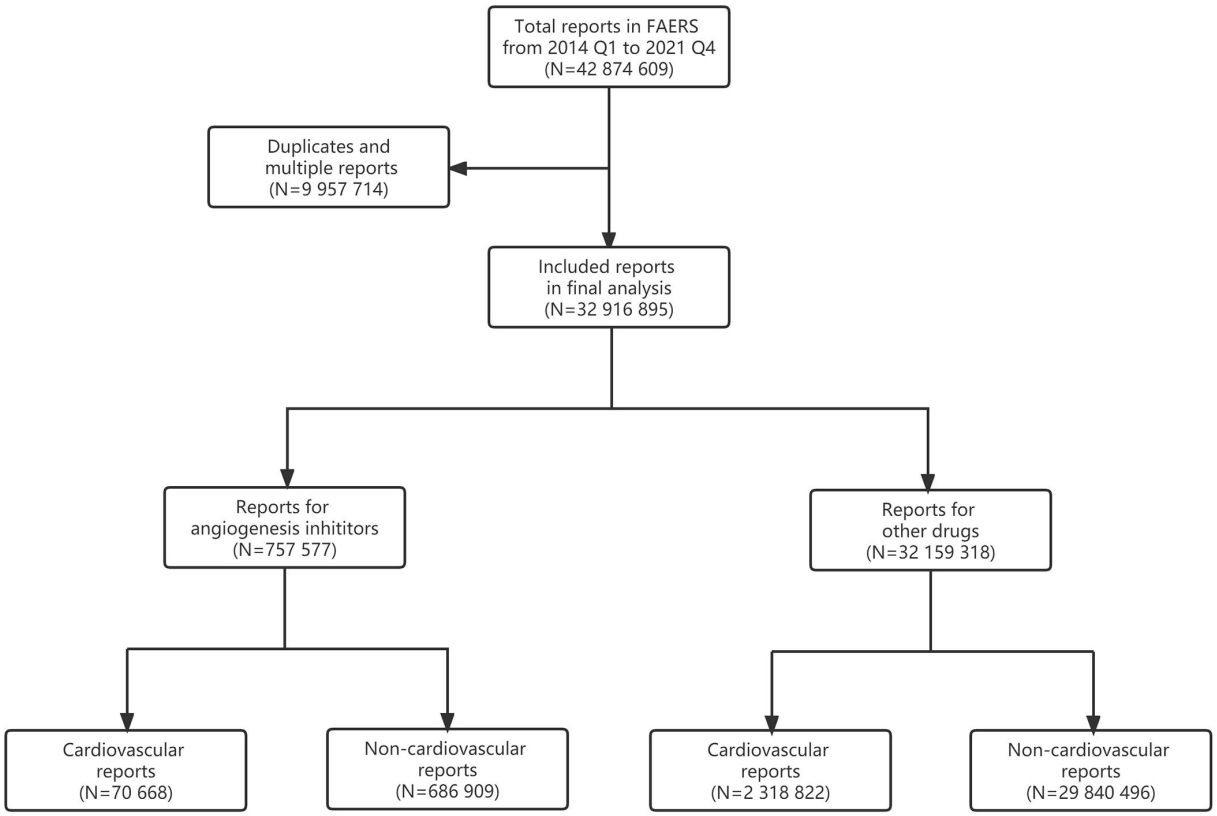

FIGURE 1
Flowchart of report selection.

cardiovascular AEs, followed by hypertension (SMQ) (N = 19 385, 19.8%) and embolic and thrombotic events (SMQ) (N = 15 365, 15.7%).

Specifically, hypertension (SMQ) held the strongest signal value (IC_{025}/ROR_{025} = 1.73/3.33), followed by embolic and thrombotic events (SMQ) (IC_{025}/ROR_{025} = 0.32/1.26), cardiac failure (SMQ) (IC_{025}/ROR_{025} = 0.13/1.10), cardiomyopathy (SMQ) (IC_{025}/ROR_{025} = 0.12/1.09), and pulmonary hypertension (SMQ) (IC_{025}/ROR_{025} = 0.11/1.08). However, cardiac arrhythmias (SMQ), ischemic heart disease (SMQ), noninfectious myocarditis/pericarditis (SMQ), and torsade de pointes/QT prolongation (SMQ) were not observed as significantly associated with angiogenesis inhibitors as a whole.

Based on MedDRA, embolic and thrombotic events (SMQ) can be subcategorized into embolic and thrombotic events, arterial thromboembolic events (ATEs) (SMQ), embolic and thrombotic events, venous thromboembolic events (VTEs) (SMQ), and embolic and thrombotic events, vessel type unspecified, and mixed arterial and venous (SMQ). Further analysis showed that both ATEs (IC_{025}/ROR_{025} = 0.01/1.01) and VTEs (IC_{025}/ROR_{025} = 1.03/2.06) were significantly associated with angiogenesis inhibitors.

Importantly, analysis based on a single agent showed varied patterns of cardiovascular AEs among different angiogenesis inhibitors, as depicted in Figure 2. Of note, aflibercept was the only agent significantly associated with ischemic heart disease (SMQ) (IC_{025} = 0.61). Furthermore, cardiac arrhythmias (SMQ) were observed to be significantly associated with vandetanib (IC_{025} = 0.87) and cediranib (IC_{025} = 0.62). Similarly, torsade de pointes/QT prolongation (SMQ) is also associated with vandetanib (IC_{025} = 1.57) and cediranib (IC_{025} = 0.07). In addition, nintedanib (IC_{025} = 1.65), tivozanib (IC_{025} = 0.60), and cediranib (IC_{025} = 0.94) were the only three agents related to pulmonary hypertension (SMQ). By contrast, cardiac failure (SMQ), cardiomyopathy (SMQ), and noninfectious myocarditis/pericarditis (SMQ) were detected as signals in nine agents, embolic and thrombotic events (SMQ) was detected in 10 agents, and hypertension (SMQ) was detected as signals in 14 agents, except apatinib (China), which was the most frequently reported PTs.

TABLE 3 Baseline characteristics of cardiovascular reports associated with angiogenesis inhibitors and other drugs from 2014 to 2021.

Characteristics	Angiogenesis inhibitors ($n = 70\ 668$)	Other drugs ($n = 2\ 318\ 822$)	Total ($n = 2\ 389\ 490$)
Patient's age, years, median (Q1-Q3)	66 (57, 73)	61 (47, 72)	61 (48, 72)
Data available, *n* (%)	52,859 (74.8)	1,603,471 (69.2)	1,656,882 (69.3)
Age group, *n* (%)			
<18 years	847 (1.2)	62,446 (2.7)	63,293 (2.7)
18∼65 years	23,401 (33.1)	863,660 (37.3)	887,061 (37.1)
≥ 65 years	28,611 (40.5)	677,365 (29.2)	706,528 (29.6)
Unknown	17,809 (25.2)	715,351 (30.8)	732,608 (30.7)
Patient's gender, *n* (%)			
Male	34,731 (49.1)	886,247 (38.2)	920,978 (38.6)
Female	29,183 (41.3)	1,223,706 (52.8)	1,252,889 (52.4)
Unknown	6,754 (9.6)	208,869 (9.0)	215,623 (9.0)
Type of reporter, *n* (%)			
Health professional	45,906 (65.0)	1,278 704 (55.2)	1,324,610 (55.4)
Non-health professional	23,572 (33.3)	972,435 (41.9)	996,007 (41.7)
Unknown	1,190 (1.7)	67,683 (2.9)	68,873 (2.9)
Outcome of adverse events, *n* (%)			
Death	13,300 (18.8)	286,691 (12.4)	299,991 (12.6)
Life-threatening	3,117 (4.4)	141,776 (6.1)	144,893 (6.1)
Caused/prolonged hospitalization	24,975 (35.3)	816,713 (35.2)	841,688 (35.2)
Disabling/incapacitating	384 (0.5)	29,124 (1.2)	29,508 (1.2)
Congenital anomaly	1 (0)	4,041 (0.2)	4,042 (0.2)
Other serious events	19,391 (27.4)	664,311 (28.6)	683,702 (28.6)
Reported countries, *n* (%)			
United States	32,755 (46.3)	1,242,146 (53.6)	1,274,901 (53.4)
Canada	3,606 (5.1)	189,636 (8.2)	193,242 (8.1)
Great Britain	1,915 (2.7)	100,385 (4.3)	102,300 (4.3)
Germany	3,404 (4.8)	93,682 (4.0)	97,086 (4.1)
France	3,611 (5.1)	88,021 (3.8)	91,632 (3.8)
Italy	2,094 (3.0)	53,081 (2.3)	55,175 (2.3)
Japan	7,085 (10.0)	79,696 (3.4)	86,781 (3.6)
China	1,610 (2.3)	21,911 (0.9)	23,521 (1.0)
Other countries	12,519 (17.8)	355,163 (15.4)	367,682 (15.4)
Unknown	2,069 (2.9)	95,101 (4.1)	97,170 (4.0)
Reported year, *n* (%)			
2014	7,966 (11.3)	296,750 (12.8)	304,716 (12.8)
2015	9,418 (13.3)	357,180 (15.4)	366,598 (15.3)
2016	6,392 (9.1)	221,264 (9.6)	227,656 (9.5)
2017	7,076 (10.0)	229,409 (9.9)	236,485 (9.9)
2018	9,587 (13.6)	287,918 (12.4)	297,505 (12.5)
2019	8,917 (12.6)	271,430 (11.7)	280,347 (11.7)
2020	9,548 (13.5)	290,083 (12.5)	299,631 (12.5)
2021	11,764 (16.6)	364,788 (15.7)	376,552 (15.8)

TABLE 4 Disproportionality analysis results associated with different angiogenesis inhibitors.

Drug class	Agent	*N* (%)	ROR	ROR025	ROR975	IC	IC025	IC975
Anti-VEGF mAb	Bevacizumab	23,177 (31.8)	1.37	1.35	1.39	0.45	0.43	0.47
Anti-VEGFR mAb	Ramucirumab	1,193 (1.6)	1.49	1.40	1.58	0.57	0.48	0.64
VEGF-Trap	Aflibercept	1,596 (2.2)	1.71	1.62	1.80	0.77	0.69	0.83
Tyrosine kinase inhibitors	Sunitinib	9,061 (12.4)	1.06	1.04	1.08	0.08	0.05	0.11
	Lenvatinib	7,131 (9.8)	1.74	1.70	1.79	0.80	0.76	0.83
	Nintedanib	6,824 (9.4)	1.40	1.36	1.43	0.48	0.44	0.51
	Pazopanib	6,277 (8.6)	1.25	1.22	1.28	0.32	0.28	0.35
	Cabozantinib	4,827 (6.7)	1.05	1.02	1.08	0.07	0.02	0.10
	Sorafenib	4,473 (6.1)	1.13	1.10	1.16	0.18	0.13	0.21
	Axitinib	3,402 (4.7)	1.36	1.31	1.40	0.44	0.38	0.48
	Regorafenib	3,184 (4.4)	1.04	1.01	1.08	0.06	0.01	0.10
	Apatinib (China)	947 (1.3)	1.23	1.15	1.31	0.30	0.19	0.37
	Vandetanib	487 (0.7)	1.48	1.35	1.63	0.57	0.42	0.68
	Tivozanib	104 (0.1)	1.42	1.16	1.74	0.51	0.18	0.74
	Cediranib	71	2.60	2.01	3.37	1.38	0.98	1.66
	Erdafitinib	45	0.47	0.35	0.64	−1.08	−1.57	−0.72
	Fruquintinib (China)	5	0.75	0.30	1.85	−0.41	−1.98	0.57
	Vatalanib	2	N	N	N	N	N	N
	Anlotinib (China)	1	N	N	N	N	N	N
	All TKIs	45,475 (62.4)	1.24	1.23	1.26	0.32	0.30	0.33
Other	Recombinant human endostatin (China)	26	1.34	0.89	2.00	0.42	−0.24	0.88
Total		70,668	1.29	1.27	1.30	0.36	0.35	0.37

VEGF, vascular endothelial growth factor; mAb, monoclonal antibody; VEGFR, vascular endothelial growth factor receptor, TKI, tyrosine kinase inhibitors; ROR, reporting odds ratio; IC, information components.

TABLE 5 Disproportionality analysis for angiogenesis inhibitors based on specific SMQs.

Cardiovascular reports	*N* (%)	ROR	ROR025	ROR975	IC	IC025	IC975
Cardiac arrhythmias (SMQ)	8,607 (8.8)	0.65	0.63	0.66	−0.63	−0.67	−0.60
Cardiac failure (SMQ)	9,031 (9.2)	1.12	1.10	1.14	0.16	0.13	0.19
Cardiomyopathy (SMQ)	22,186 (22.7)	1.10	1.09	1.12	0.14	0.12	0.15
Embolic and thrombotic events (SMQ)	15,365 (15.7)	1.28	1.26	1.30	0.35	0.32	0.37
Hypertension (SMQ)	19,385 (19.8)	3.38	3.33	3.43	1.76	1.73	1.78
Ischaemic heart disease (SMQ)	3,672 (3.7)	0.79	0.76	0.82	−0.34	−0.40	−0.30
Noninfectious myocarditis/pericarditis (SMQ)	5,849 (6.0)	1.01	0.98	1.03	0.01	−0.03	0.04
Pulmonary hypertension (SMQ)	10,009 (10.2)	1.10	1.08	1.12	0.14	0.11	0.16
Torsade de pointes/QT prolongation (SMQ)	3,524 (3.6)	0.68	0.66	0.71	−0.55	−0.60	−0.51

SMQ, standardized MedDRA queries; ROR, reporting odds ratio; IC, information components.

Time to onset of specific SMQs with significant signals

As displayed in Figure 3A, hypertension (SMQ) demonstrated the shortest time to onset with the median (IQR) value of 23 (8, 69) days, while embolic and thrombotic events (SMQ) had the longest time to onset of 51 (16, 153) days. Nonetheless, cardiac failure (SMQ), cardiomyopathy (SMQ), and pulmonary hypertension (SMQ) presented similar median values (IQR) of time to onset. Furthermore, the cumulative proportions of time to onset within the first 30 days and 90 days after treatment with angiogenesis inhibitors were 57.8% and 78.3% for hypertension (SMQ), which was the greatest, whereas they were 38.7% and 63.4% for embolic and thrombotic events (SMQ), which was the lowest (Figure 3B).

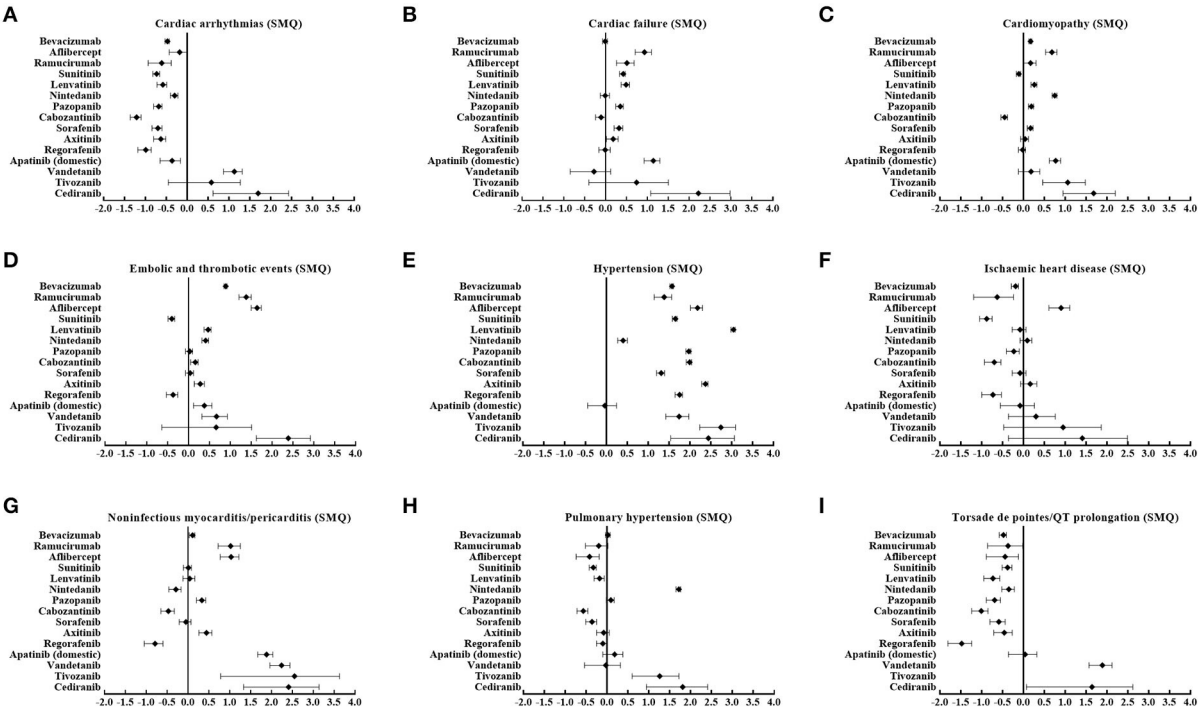

FIGURE 2
(A–I) Cardiovascular toxicity profiles based on nine narrow categories of (SMQs) according to ICs among different angiogenesis inhibitors. SMQs, Standardized MedDRA Queries; IC, information components.

Outcome of adverse events

Of note, death accounted for 18.8% of all cardiovascular AEs associated with angiogenesis inhibitors, which was higher than that with other drugs (12.4%) (Table 3). Specifically, higher risk level outcomes, namely, death, life-threatening events, and caused or prolonged hospitalization proportions according to specific SMQs with significant signals are shown in Figure 4. Notably, hypertension (SMQ) presented the lowest proportions of death and life-threatening events (10.9%) and caused or prolonged hospitalization (30.7%), whereas embolic and thrombotic events (SMQ) posed the highest proportions of death and life-threatening events (29.3%) and a similar proportion of caused or prolonged hospitalization (36.5%) compared with cardiac failure (SMQ), cardiomyopathy (SMQ), and pulmonary hypertension (SMQ).

Comparison of cardiovascular AEs between intravenous mAbs and oral TKIs with anti-VEGF(R) activity

Both mAbs and TKIs with anti-VEGF(R) activity were significantly associated with an increased risk of cardiovascular AEs, with a relatively stronger signal strength for mAbs (IC_{025}/ROR_{025} = 0.47/1.39) than TKIs (IC_{025}/ROR_{025} = 0.30/1.23).

As for PTs, Supplementary Table S13 showed the top 20 PTs with the strongest signal values between mAbs and TKIs. There was a great difference in the distribution of these PTs with only six PTs overlapping between these two classes with consistently stronger signals for mAbs.

According to SMQs, Figure 5 demonstrates that significant signals were detected in hypertension (SMQ), cardiac failure (SMQ), and cardiomyopathy (SMQ) for both classes, embolic and thrombotic events (SMQ) and noninfectious myocarditis/pericarditis (SMQ) only for mAbs, and pulmonary hypertension (SMQ) only for TKIs. However, cardiac arrhythmias (SMQ), ischemic heart disease (SMQ), and torsade de pointes/QT prolongation (SMQ) were not detected as signals in both classes.

With respect to hypertension (SMQ), analysis of timing revealed a remarkably shorter time to onset for TKIs than mAbs, with a median (IQR) value of 17 (6, 48) days vs. 42 (14, 131) days. In addition, the cumulative proportions of time to onset within the first 30 days and 90 days were 65.8 and 84.7% for TKIs, which were higher than those of 42.0 and 65.8% for mAbs.

With regard to embolic and thrombotic events (SMQ), a total of 59 PTs were detected to be significantly associated with mAbs, whereas 23 PTs were found to be related to TKIs. Furthermore, 16 PTs overlapped between mAbs and TKIs, and

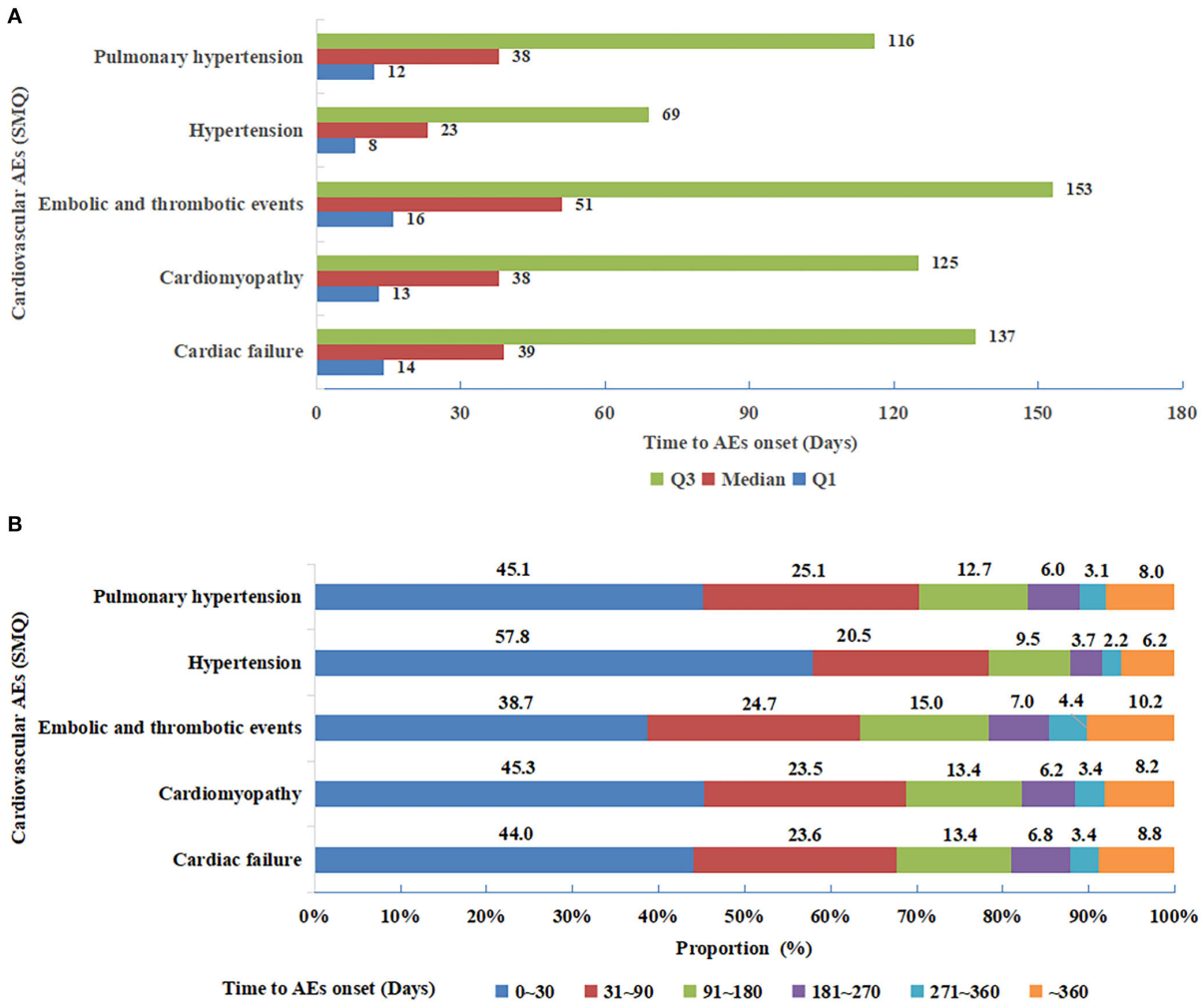

FIGURE 3
(A) Median (interquartile range) of time to onset for five cardiovascular adverse events (SMQs) detected as significant signals. SMQs, Standardized MedDRA Queries. **(B)** Time to onset groups for five cardiovascular adverse events (SMQs) detected as significant signals. SMQs, Standardized MedDRA Queries.

the majority with stronger signal values (IC_{025}) for mAbs except for two PTs with a stronger signal strength for TKIs (see Supplementary Table S14) were observed.

Both ATEs (IC_{025}/ROR_{025} = 0.53/1.46) and VTEs (IC_{025}/ROR_{025} = 1.79/3.47) held a significantly higher reporting frequency for mAbs. On the contrary, the signal was detected only in VTEs (IC_{025}/ROR_{025} = 0.80/1.76), and no signal was detected in ATEs (IC_{025}/ROR_{025} = −0.12/0.93) for TKIs.

Discussion

Although the application of angiogenesis inhibitors has revolutionized the therapy and substantially improved the outcomes for patients with a variety of malignancies, their side effects, especially cardiovascular toxicity, have been increasingly recognized along with their curative effects (1, 2, 6–20). Nevertheless, the real profiles of cardiovascular toxicity associated with angiogenesis inhibitors are still unclear due to scarce evidence in the real-world setting (20). To the best of our knowledge, this is the first comprehensive pharmacovigilance study on cardiovascular toxicity associated with angiogenesis inhibitors by leveraging the FAERS database, involving the frequency, spectrum, timing, and outcomes of cardiovascular toxicity, as well as the extensive comparison of such patterns between mAbs and TKIs with anti-VEGF(R) activity. Importantly, the main findings of our study are as follows.

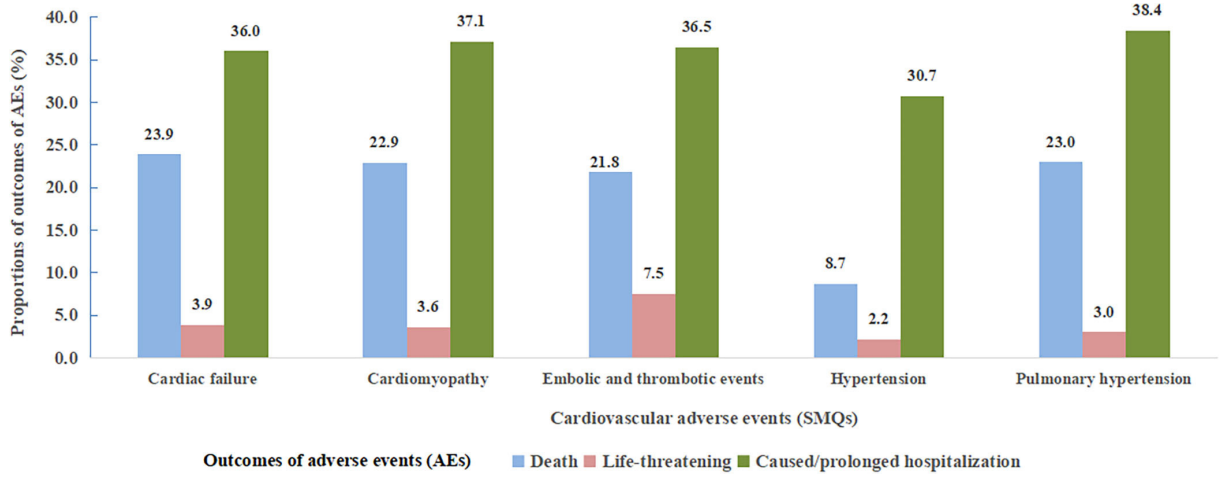

FIGURE 4
Proportions of cardiovascular adverse event outcomes according to five cardiovascular adverse events (SMQs) detected as significant signals. SMQs, Standardized MedDRA Queries; AEs, adverse events.

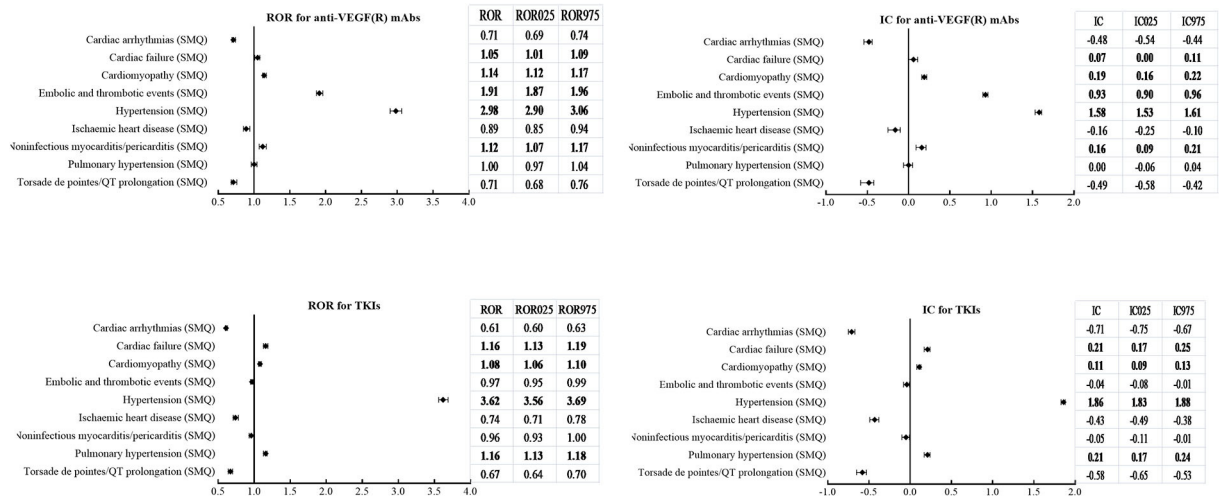

FIGURE 5
Comparison of cardiovascular adverse events (SMQs) according to ROR (ROR_{025}, ROR_{975}) and IC (IC_{025}, IC_{975}) between mAbs and TKIs with anti-VEGF(R) effects. SMQs, Standardized MedDRA Queries; ROR, reporting odds ratio; ROR_{025}, lower limit of ROR; ROR_{975}, upper limit of ROR; IC, information components; IC_{025}, lower limit of IC; IC_{975}, upper limit of IC; mAbs, monoclonal antibodies; TKIs, tyrosine kinase inhibitors; VEGF(R), vascular endothelial growth factor or receptor.

Cardiovascular toxicity burden and profile of angiogenesis inhibitors

First, our study revealed that cardiovascular reports accounted for a proportion of 9.3% of all reports related to angiogenesis inhibitors. Notably, using angiogenesis inhibitors was significantly associated with an increased risk of cardiovascular AEs according to the markedly higher signal values of IC_{025}/ROR_{025} = 0.36/1.27. In addition, all the four main classes of agents targeting the VEGF signaling pathway and the majority of single agents demonstrated this trend, except for few agents, which may be due to a very small number of reported AEs. To sum up, these findings indicated that cardiovascular toxicity may be a class effect of angiogenesis inhibitors. Given its continuous development and wide application, the incidence of angiogenesis inhibitor-related cardiovascular toxicity is expected to increase constantly, which necessitates more attention to be paid.

Noteworthily, our study found that cardiovascular toxicity profiles varied among different agents of angiogenesis inhibitors,

such as different agents and different AEs. On the one hand, regarding specific agent, bevacizumab was first approved for clinical use; accordingly, its cardiovascular toxicity has been first and extensively studied over the past years (10, 13). Similarly, bevacizumab presented the largest number of reported AEs with relatively stronger signal strength as a single agent and held the broadest spectrum of cardiovascular AEs in our study. On the contrary, despite a very small proportion reported, cediranib held the strongest signal value for total cardiovascular AEs and some specific cardiovascular AEs, including cardiac failure (SMQ), cardiomyopathy (SMQ), and embolic and thrombotic events (SMQ). On the other hand, as for specific cardiovascular AEs, hypertension, to date, is the most frequently reported and best characterized cardiovascular toxicity associated with angiogenesis inhibitors targeting VEGF (9, 16, 17, 26, 27). Similar to previous studies, the present study demonstrated that hypertension was the most frequently reported cardiovascular AE based on PTs (15.1%) and SMQs (19.8%). Moreover, hypertension was the most frequently detected signal among the agents observed (13/15), with the strongest signal value of IC_{025}/ROR_{025} = 1.73/3.33 based on SMQs and a relatively higher value of IC_{025}/ROR_{025} = 2.06/4.19 based on PTs.

Especially, as a single agent, lenvatinib presented the strongest signal strength for hypertension (SMQ) (IC_{025} =2.98), indicating the most frequently reported PT, which was similar to a recent report (28) showing the highest incidence of any grade hypertension of 68% and grade 3 or 4 hypertension of 42% for lenvatinib. In addition, two meta-analyses revealed a higher incidence of torsade de pointes/QT prolongation for vandetanib (29, 30). Our present study demonstrated similar results.

Taken together, all these findings suggested a great discrepancy of cardiovascular AEs with specific agents, which deserves some individual AE monitoring strategies for angiogenesis inhibitors in the treatment of cancer types.

Timing and outcomes of cardiovascular AEs with angiogenesis inhibitors

As for the time to onset of cardiovascular AEs, in Österlund's study (31), the median time to the onset of hypertension was 1 month (range of 1–15 months and within 6 months in 95%), as calculated from the start of bevacizumab treatment. In addition, a real-life study on the TKI cohort showed that the cumulative incidence of thrombotic events kept increasing all along the first year of treatment (20). Nevertheless, no study to date has investigated the disparity of timing according to different types of cardiovascular AEs associated with angiogenesis inhibitors. Our present study first compared the time to onset of specific cardiovascular AEs based on SMQs, which provided some valuable information. We found that hypertension occurred fairly early, whereas embolic and thrombotic events occurred relatively late. Of note, virtually almost every patient experiences a rapid increase in blood pressure within days after initiation of therapy (26), whether or not leading to hypertension. Therefore, recognition of the variance in time to onset among different cardiovascular AEs may be worthwhile at clinical practice to guide distinct monitoring strategies.

With regard to the outcomes of AEs, the present study showed that cardiovascular AEs associated with angiogenesis inhibitors presented more death than other drugs, suggesting a greater impact on patients' prognosis. In addition, we compared the differences in outcomes among specific cardiovascular AEs based on SMQs and found that hypertension posed the lowest risk of mortality, despite being most frequently reported in comparison to other cardiovascular AEs. It may be due to the less severity of hypertension *per se* as well as appropriate management with anti-hypertensive medications to some extent. However, the prognostic value of hypertension induced by angiogenesis inhibitors, namely, whether or not it was a biomarker for the efficacy of anti-cancer treatment, remains the subject of investigation (32–35). Furthermore, we found that embolic and thrombotic events (SMQ) posed the highest proportions of death and life-threatening events among the reported cardiovascular AEs (SMQs).

Differences in cardiovascular AEs between intravenous mAbs and oral TKIs

To our knowledge, no head-to-head study so far has compared the differences in cardiovascular AEs between mAbs and TKIs with anti-VEGF(R) activity. A systematic review and meta-analysis showed no significant interaction between the two subgroups for cardiovascular outcomes (12). Noteworthily, our study made the foremost and extensive comparison between mAbs and TKIs and thus provided several new insights into cardiovascular AEs associated with angiogenesis inhibitors. First, both mAbs and TKIs as class agents significantly increased cardiovascular AE risk with greater extent for mAbs. Second, there was a discrepancy in the distribution of cardiovascular AEs based on PTs or SMQs. Third, for hypertension (SMQ), TKIs demonstrated a relatively stronger signal strength and remarkably shorter time to onset than mAbs. Last, we also observed the variance in embolic and thrombotic events (SMQ), including ATEs and VTEs. Explanations for these discrepancies may be multifarious, mainly including the following two aspects: (1) difference in action mechanism, namely, unlike mAbs with high affinity to VEGF(R) (on-target mechanism), TKIs typically target multiple tyrosine kinases other than VEGFs, which, consequently, may induce some "off-target" toxicities besides the "on-target" effects; (2) difference in the administering route, that is, mAb is usually administered intravenously, while TKI is used

orally, which theoretically can generate some variances in AEs. Anyway, these findings again underscore the necessity to pay more attention to agent-specific AEs.

Limitations

There are some limitations in this study to be acknowledged. First, as a spontaneous reporting database, the FAERS database has some intrinsic limitations, such as multiple data sources, non-uniform data format, multi-reporting, under-reporting, and incomplete information. Second, the causal relationship of AEs and drug application cannot be confirmed in the retrospective study. Third, it is difficult to evaluate the effect of patients' baseline characteristics including cardiovascular risk factor profiles on the subsequent occurrence of cardiovascular AEs after application of angiogenesis inhibitors since no relevant variables other than age and sex were reported in the FAERS database. Finally, the majority of the reporting data in the FAERS database are from North America (particularly the United States), European countries, and Japan, while few reports come from China, which might result in geographic bias of the results. Therefore, further prospective studies may be warranted to confirm the findings in our study.

Conclusion

Treatment with angiogenesis inhibitors was significantly associated with an increased risk in cardiovascular toxicity as a class effect mainly involving cardiac failure, cardiomyopathy, hypertension, embolic and thrombotic events, and pulmonary hypertension with varied profiles in terms of frequency, spectrum, timing, and outcomes among specific agents and special AEs. Moreover, there was a great discrepancy in cardiovascular toxicity patterns between mAbs and TKIs with anti-VEGF(R) activity. These findings provide valuable evidence for precise management of cardiovascular toxicity associated with angiogenesis inhibitors in the treatment of cancer cases.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

YW: conception, design, and manuscript reviewing and revising. WC: administrative support. XR and XD: data collection and analysis. YW and CC: data interpretation. CC: manuscript writing. All authors contributed to the article and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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Trigger related outcomes of takotsubo syndrome in a cancer population

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Background: Takotsubo syndrome (TTS) occurs more frequently in cancer patients than in the general population, but the effect of specific TTS triggers on outcomes in cancer patients is not well studied.

Objectives: The study sought to determine whether triggering event (chemotherapy, immune-modulators vs. procedural or emotional stress) modifies outcomes in a cancer patient population with TTS.

Methods: All cancer patients presenting with acute coronary syndrome (ACS) between December 2008 and December 2020 at our institution were enrolled in the catheterization laboratory registry. Demographic and clinical data of the identified patients with TTS were retrospective collected and further classified according to the TTS trigger. The groups were compared with regards to major adverse cardiac events, overall survival and recovery of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) after TTS presentation.

Results: Eighty one of the 373 cancer patients who presented with ACS met the Mayo criteria for TTS. The triggering event was determined to be "cancer specific triggers" (use of chemotherapy in 23, immunomodulators use in 7, and radiation in 4), and "traditional triggers" (medical triggers 22, and procedural 18 and emotional stress in 7). Of the 81 patients, 47 died,

all from cancer-related causes (no cardiovascular mortality). Median survival was 11.9 months. Immunomodulator (IM) related TTS and radiation related TTS were associated with higher mortality during the follow-up. Patients with medical triggers showed the least recovery in LVEF and GLS while patients with emotional and chemotherapy triggers, showed the most improvement in LVEF and GLS, respectively.

Conclusion: Cancer patients presenting with ACS picture have a high prevalence of TTS due to presence of traditional and cancer specific triggers. Survival and improvement in left ventricular systolic function seem to be related to the initial trigger for TTS.

KEYWORDS

takotsubo stress cardiomyopathy, chemotherapy, immunomodulators, cardio-oncology, takotsubo syndrome, triggers

Introduction

Takotsubo syndrome (TTS) is a condition characterized by transient and reversible left ventricular (LV) systolic dysfunction frequently preceded by stressors, either emotional or physical; however, 28% of patients have no correlating evident trigger (1–4). Identifying the preceding event is important, as different triggers have been shown to influence TTS outcome (5, 6). A new classification of TTS was proposed recently to acknowledge these triggers: (1) primary TTS (TTS triggered by psychological stress) and (2) secondary TTS (related to physical factors such as surgery, trauma, and medical complications). Patients with secondary TTS have significantly worse prognosis than patients with primary TTS (6).

The trigger and underlying mechanisms of TTS are of particular importance in vulnerable populations, such as cancer patients in whom it is not only more prevalent but portrays a prognosis similar to true non-ST-elevation myocardial infarction (NSTEMI) (7–9). Among those with a history of TTS, cancer is the major cause of death, making cancer survivors with TTS an especially vulnerable population (9).

Patients with TTS often have increased tendencies to have thromboembolic events (10, 11) and often portray a worse prognosis in the setting of atrial fibrillation, malignant ventricular arrhythmias, and cardiogenic shock (12–14). A substantial number of TTS patients show an association with malignancy and some studies suggest that an appropriate screening for malignancy should be considered in these patients (15). Patients with TTS have more often malignant diseases than patients with MI and cancer patients with TTS have a worse clinical outcome (16). The underlying mechanism is unclear yet, but the results point at TTS being the syndrome of an extracardiac disease rather than a disease of cardiac origin (8). Positive emotional trigger related TTS has been described as "happy heart syndrome" (17). It is a rare type of TTS characterized by a higher prevalence of male patients and atypical, non-apical ballooning and similar outcomes compared to patients with negative stressors in short term studies (17).

The possible triggers of TTS in cancer patients can be both "cancer specific triggers" (use of chemotherapy, immunomodulators, and radiation) and "traditional triggers" (medical, procedural and emotional triggers). Several chemotherapeutic agents have been associated with TTS with varying hypothesized mechanisms but they have not been fully explored, and while a temporal relationship has been established, a causal relationship between chemotherapeutic/immune-modulating agents and TTS is yet to be confirmed (18). Due to aforementioned reasons, we hypothesize that a trigger-driven study may help improve understanding, guide treatment, and predict outcomes in a cancer patient population presenting with TTS.

Materials and methods

Study population

All cancer patients presenting with ACS who met the modified Mayo criteria for TTS (19, 20) and underwent quantitative coronary angiography and left ventriculogram between December 2008 and December 2020 at The University of Texas MD Anderson Cancer Center catheterization laboratory were entered into the laboratory registry. Demographic and clinical data was collected retrospectively. This study was approved by the Institutional Review Board. Patient informed consent was waived due to the retrospective nature of data analysis.

Baseline demographic information (age and sex), cardiovascular risk factors (coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus, and smoking status), type of malignancy, cancer stage, and past and current anticancer therapeutic regimens were reviewed. Patients with multiple cancers were categorized according to the malignancy being actively treated at the time of TTS.

Potential sources of "traditional triggers" including emotional, procedural, or medical stress during the week prior to TTS onset were systematically reviewed. This review included terms referring to medical complications, any type of invasive procedure or surgery, and emotional challenges (anger, anxiety, or grief) as documented in the clinical notes before/during the TTS event.

Based on this information, patients were classified according to the predominant trigger as having chemotherapy-induced TTS (CI-TTS; chemotherapy), immunomodulator-induced TTS (IM-TTS: Immune checkpoint inhibitors, Notch Inhibitors, Colony stimulating factors, Anti CD-20) and procedural/emotional TTS (PE-TTS).

TTS was regarded as being chemotherapy/immunotherapy/radiation-induced if the episode occurred within one week after exposure to the trigger and no significant medical complication, invasive procedure, or significant emotional stress was noted during this time. This cut-off point is based on a recent review specifically on CI-TTS (21). Moreover, CI-TTS and IM-TTS were considered if cardiac symptoms were documented when chemotherapy and immunotherapy were administered respectively.

Imaging data including electrocardiograms (ECG), transthoracic echocardiograms, and coronary angiograms/left ventriculography as well as laboratory data including cardiac troponin, complete blood count/complete metabolic panel (CBC/CMP) etc. were reviewed. We characterized cancer patients in terms of ECG patterns, cardiac biomarkers, and echocardiographic findings, including apical vs. midcavitary TTS morphology. Patients with stenosis on quantitative coronary angiography (>50% of left main or >70% of any major coronary artery) or with definite evidence of myocardial infarction were excluded. Additionally, follow-up echocardiography was performed and recovery time to normal left ventricular ejection fraction (LVEF) or, if available, baseline LVEF, was noted.

We compared the overall incidence of major adverse cardiac events, defined as cardiac death or arrest, myocardial infarction, or re-hospitalization for unstable or progressive angina, and overall survival (OS) in cancer patients with TTS, as well as grouped based on triggering event, CI-TTS vs. PE-TTS vs. IM-TTS. The cause of death was classified as cardiac- or cancer-related. Cancer was considered the cause of death if the patient's demise was secondary to cancer therapy–related complications (e.g., sepsis) or to progression of disease with a patient-requested do not resuscitate/intubate order and/or care transferred to a hospice team.

Additionally, we assessed the impact of the clinical measures of TTS severity, such as LVEF at presentation, cardiac biomarkers or thrombocytopenia, on the prognosis of these groups.

Statistical analysis

Patient characteristics were summarized with descriptive statistics for the entire group by survival status. Overall survival (OS) was defined as the time interval from the TTS event to death. For survival analysis up to 72 months, patients who were alive were censored at last follow-up or 72 months, whichever was earlier. Patients who died more than 72 months after the TTS event were censored at 72 months. Univariable Cox proportional hazards regression was used to identify factors that were significantly associated with risk of death. Factors identified by this analysis with a p-value less than 0.15 were initially included in a multivariable Cox regression model and reduced by backward elimination. Factors with p-value less than 0.05 were retained in the multivariable model. A p-value of less than 0.05 was regarded as indicating statistical significance. The SAS 9.4 software (SAS Institute INC., Cary, NC) was used for data analysis.

Results

Baseline characteristics

Of 373 patients presenting with ACS, 81 (21.7%) patients met the Mayo criteria for diagnosis of TTS and were included in the study. The majority of patients were women (64/81; 79%). Baseline demographics and results of clinical evaluation of TTS patients in the study are shown in **Table 1**.

Furthermore, for CI-TTS patients, information on primary cancer type, ECG findings, peak troponin I and BNP values, LVEF, angiography findings, TTS morphology (apical/midcavitary), and survival at 72 months are summarized (**Supplementary Table 1** and **Supplementary Figures 1, 2**). Clinical features were further analyzed according to proposed TTS mechanism between (PE-TTS and CI-TTS groups) in **Table 2**.

Results based on triggers

We observed 23 out of 81 patients (28.5%) had CI-TTS, 22 due to medical condition (27.2%), 18 procedure related (22.2%), 7 (8.6%) due to emotional trigger, 7 (8.6%) due to immunomodulators and 4 (4.9%) due to chest radiation.

TABLE 1 Baseline characteristics of the studied population.

		Count (%) or Mean ± SD, Median (range)
Age (years)		65.8 ± 9.3
Creatinine (mg/dl)		0.93 ± 0.35
Platelet count (K/μl)		212.71 ± 151.61
Age (years)	<65	34 (42%)
	≥65	47 (58%)
Sex (*n*)	F	64 (79%)
	M	17 (21%)
Hypertension (*n*)		56 (69.1%)
Dyslipidemia (*n*)		35 (43.2%)
Diabetes mellitus (*n*)		19 (23.4%)
Stroke (*n*)		7 (8.6%)
Coronary artery disease (*n*)		10 (12.3%)
Smoking (*n*)		21 (25.9%)
Heart failure with reduced ejection fraction (*n*)		3 (3.7%)
Malignancy (*n*)	Hematologic	21 (25.9%)
	Solid	60 (74.1%)
Triggering event (*n*)	Chemotherapy	23 (28.5%)
	Medical	22 (27.2%)
	Procedure	18 (22.2%)
	Emotional	7 (8.6%)
	Immunomodulators	7 (8.6%)
	Radiation to Chest	4 (4.9%)
Mechanism (*n*)	Adrenergic	26 (65%)
	Vasospastic	14 (35%)
Morphology (*n*)	Apical	53 (65.4%)
	Midcavitary	27 (33.3%)
Left ventricle ejection fraction on presentation	<30%	15 (18.5%)
	30–39%	24 (29.7%)
	40% and above	42 (51.8%)

TABLE 2 Demographic information for the study group organized by proposed TTS mechanism (PEM-TTS vs. CI-TTS).

		PE-TTS (*N* = 26) mean ± SD or count (%)	CI-TTS (*N* = 14) mean ± SD or count (%)
Age (years)		64.23 ± 9.4	66.93 ± 10.25
Creatinine level (mg/dl)		0.8 ± 0.23	0.87 ± 0.45
Platelet count (K/μl)	Mean ± SD	219.54 ± 131.21	222.57 ± 196.13
Age (years)	<65	13 (50%)	6 (42.9%)
	≥65	13 (50%)	8 (57.1%)
Sex (*n*)	F	18 (69.2%)	13 (92.9%)
	M	8 (30.8%)	1 (7.1%)
Hypertension (*n*)	No	8 (30.8%)	4 (28.6%)
	Yes	18 (69.2%)	10 (71.4%)
Dyslipidemia (*n*)	No	12 (46.2%)	5 (35.7%)
	Yes	14 (53.8%)	9 (64.3%)
Diabetes mellitus (*n*)	No	21 (80.8%)	11 (78.6%)
	Yes	5 (19.2%)	3 (21.4%)
History of myocardial infarction (*n*)	No	25 (96.2%)	12 (85.7%)
	Yes	1 (3.8%)	2 (14.3%)
Coronary artery disease (*n*)	No	24 (92.3%)	12 (85.7%)
	Yes	2 (7.7%)	2 (14.3%)
Smoking (*n*)	No	14 (53.8%)	10 (71.4%)
	Yes	12 (46.2%)	4 (28.6%)
Malignancy (*n*)	Hematologic	6 (23.1%)	3 (21.4%)
	Solid	20 (76.9%)	11 (78.6%)
TTS Type (*n*)	Apex	14 (53.8%)	12 (85.7%)
	Mid	12 (46.2%)	2 (14.3%)
Echo LVEF	<30%	3 (15.8%)	3 (30%)
	30–39%	7 (36.8%)	3 (30%)
	40–49%	5 (26.3%)	2 (20%)
	≥50%	4 (21.1%)	2 (20%)

CI-TTS, chemotherapy-induced Takotsubo syndrome; PE-TTS, procedural/emotional Takotsubo syndrome; LVEF, left ventricular ejection fraction.

Majority of the patients were women (79%). The median follow-up time was 31.3 month and median survival was 11.9 months (Figure 1A). All deaths were secondary to cancer and no major adverse cardiac events were recorded during the follow-up period.

Compared to patients not receiving active chemotherapy, the overall survival of patients receiving chemotherapy was worse at 72 months (log-rank test $p = 0.0405$) (Figure 1B). Survival of patients not receiving any kind of cancer therapy (chemo, radiation, etc.) was also significantly better at 72 months (log-rank test $p = 0.0061$) (Figure 1C).

Using emotional trigger as reference, Immunomodulator triggered IM-TTS (immune checkpoint inhibitors, notch inhibitors, colony stimulating factors, Anti CD 20, mTOR inhibitor) was associated with HR of 9.7 compared to emotional trigger (CI 1.92–49.1 $p = 0.0060$). Radiation triggered TTS also had HR of 10.369 (1.845–58.264) ($p = 0.0079$). Kaplan-Meier curve comparing the overall survival of patients showed significantly worse prognosis for radiation exposure and immunomodulators with 100% mortality before 24 months ($p = 0.0004$) (Figure 2).

Using paired-*t*-test, the mean ejection fraction prior to TTS event, at the time and during recovery were compared. The mean difference between ejection fraction during TTS and

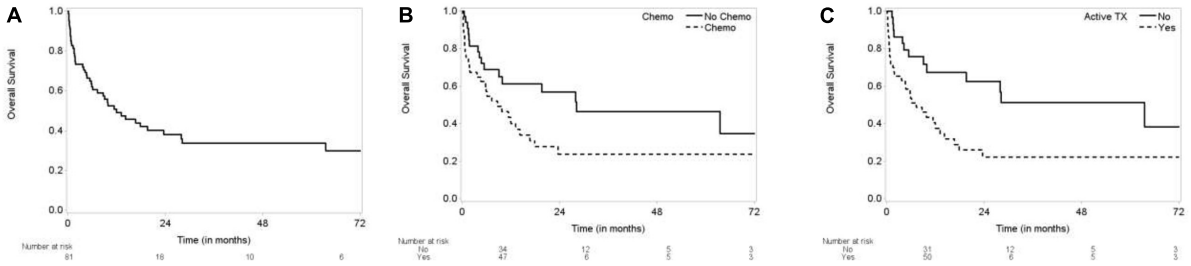

FIGURE 1
Kaplan-Meier curves for overall survival. **(A)** Overall survival (OS) of TTS patients. **(B)** OS by chemotherapy. **(C)** OS by active treatment.

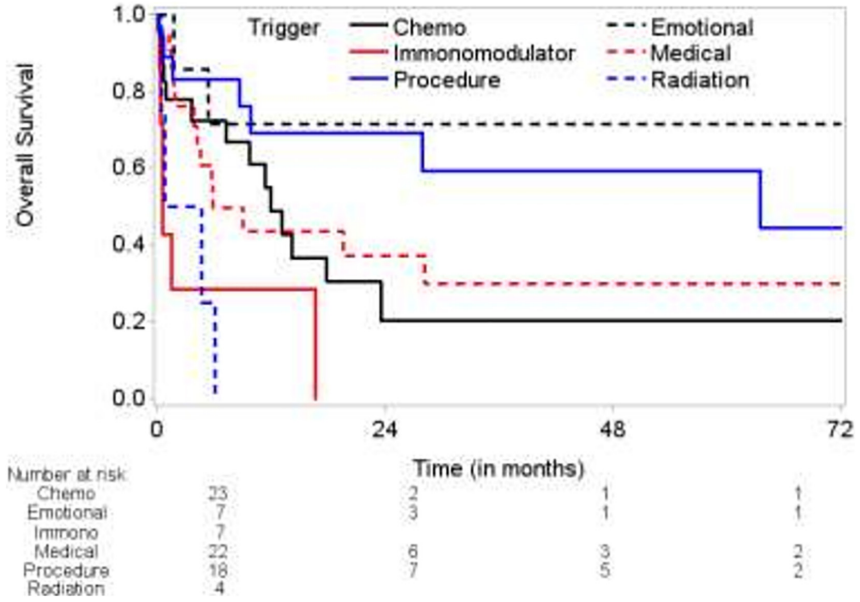

FIGURE 2
Kaplan-Meier curves for survival based on individual triggers.

baseline ejection fraction was −21.73 ± 12.93 ($p < 0.0001$), and the mean ejection fraction recovery was 14.83 ± 14.60 ($p < 0.0001$). Despite recovery of ejection fraction, the recovered ejection fraction was −8.93 ± 11.83 ($p < 0.0001$) compared to baseline (**Figure 3A** and **Table 3**). Similarly, global longitudinal strain (GLS) was −19.6 ± 3.18% at baseline. During TTS, the mean strain was −11.94 ± 4.21% with a mean difference of 9.04 ± 4.14% ($P < 0.0001$). GLS recovered by a mean difference of −3.63 ± 5.16% following TTS episode ($p = 0.0420$) (**Figure 3B** and **Table 4**).

Time to EF recovery was dependent on trigger. Chest radiation induced TTS patients showed 50% recovery at 3 month, compared to 80% recovery for emotionally triggers TTS. TTS due to the patient's medical condition showed the worst recovery (5% at 9 months), followed by chemotherapy induced TTS (25% at 12 months) (**Figure 3C**). Similarly, time to GLS recovery varied base on trigger. At 12 months, 50% IM-TTS, 70% CI-TTS, 50% emotionally triggered TTS, and 40% of TTS due to patient's medical condition showed GLS recovery (**Figure 3D**).

Discussion

The important findings of this study include, (1) There is a high prevalence (21.7%) of TTS in cancer patients presenting with ACS due to presence of "cancer specific triggers" (use of chemotherapy, immunotherapy and radiation) in addition to traditional triggers (procedure, emotional and medical triggers), (2) In cancer patients with TTS, the survival differed based on inciting trigger with emotional trigger having best survival and immunomodulators and chest radiation triggers having worst survival. (3) Recovery

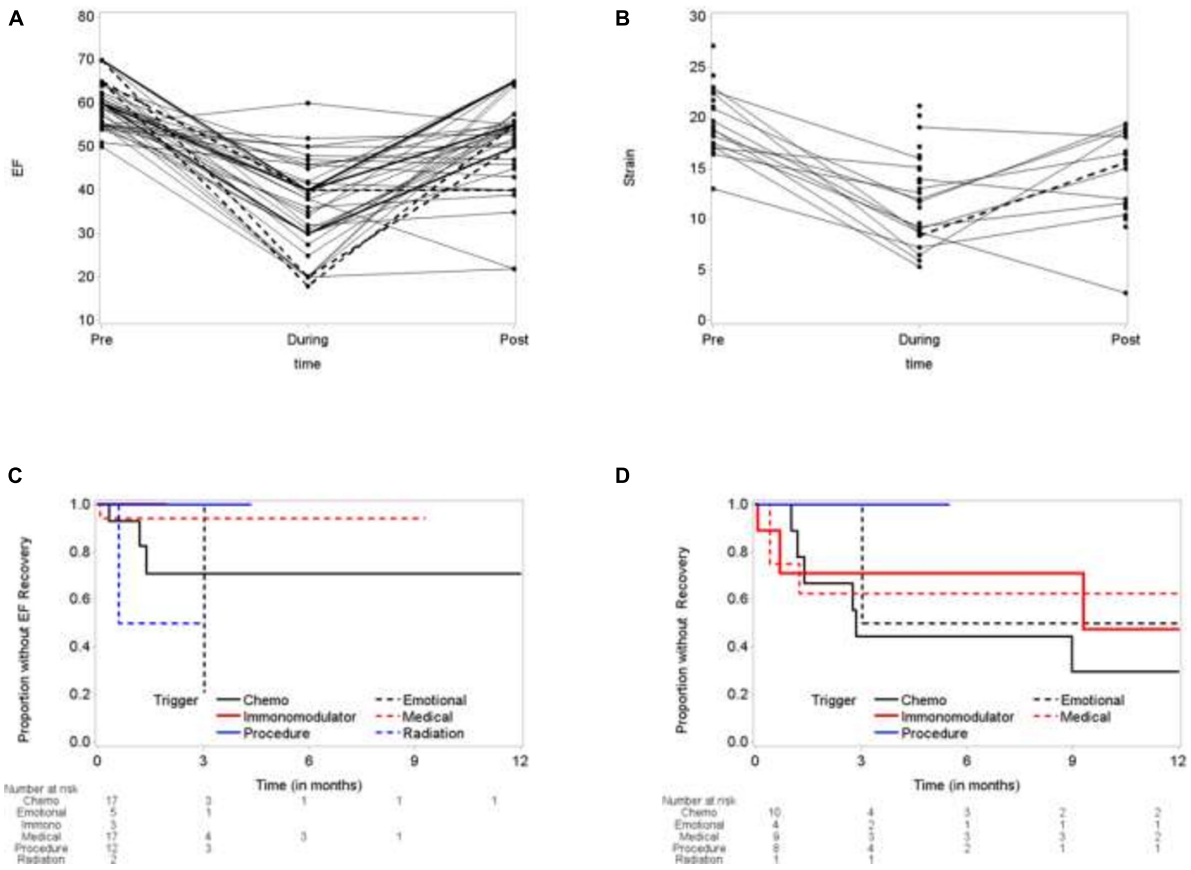

FIGURE 3
Time to recovery of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS). **(A)** Election fraction (EF) comparing baseline, during TTS episode and following recovery. **(B)** Global longitudinal strain (GLS) at baseline, during TTS episode and following recovery. **(C)** Time to EF recovery. **(D)** Time to GLS Recovery.

TABLE 3 Ejection fraction prior to TTS, during episode and following recovery.

Time	N	Mean ± SD	Comparison	*n*	*P*-value	Diff Mean ± SD
Pre	49	59.41 ± 5.5	During vs. Pre	49	<0.0001	−21.73 ± 12.93
During	81	39.03 ± 11.88	Post vs. During	57	<0.0001	14.83 ± 14.60
Post	57	52.72 ± 10.47	Post vs. Pre	36	<0.0001	−8.93 ± 11.83

TABLE 4 Global longitudinal strain during episode and following recovery.

Time	*N*	Mean ± SD	Comparison	*n*	*P*-value	Diff Mean ± SD
Pre	21	−19.6 ± 3.18	During vs. pre	13	<0.0001	9.04 ± 4.14
During	31	−11.94 ± 4.21	Post vs. during	10	0.0420	−3.63 ± 5.16
Post	25	−14.56 ± 4.13	Post vs. pre	7	0.0564	4.83 ± 5.42

of LVEF also varied based on the event leading to TTS with emotional trigger showing best improvement while medical triggers followed by chemotherapy triggers showing least recovery in LVEF. (4) Recovery of GLS was best with chemotherapy related TTS while medical triggers showing least recovery.

The prevalence of TTS in all patients presenting with ACS has been reported to be 4.4% in one study and around 1–2.5% in a systematic review (22). Prior studies have reported a higher prevalence of malignancy in TTS patients (23). While explicitly studying cancer patients presenting with ACS, a higher prevalence of TTS was observed in our study (21.7%) than previously reported for general patient population (24). Various potential explanations for this observation include emotional turmoil of cancer diagnosis, physical distress from cancer and its treatment and importantly the well-known cardiotoxic effects of various anticancer therapies (24).

In previous large scale studies of TTS patients, physical/medical triggers are more common compared to emotional triggers and independent predictor of in-hospital complications. Our study is unique since we

included only cancer patients and concluded that cancer treatment related TTS, particularly immunotherapy or radiation therapy, portrays a worse prognosis when compared to emotional triggers (23). Another important observation was that patients who developed TTS while on treatment with anticancer therapy including chemotherapy, had a worse survival when compared with those who were not receiving active treatment. This may be due to selection bias where more sick patients were exposed to anticancer therapies including chemotherapy that lead to a worse survival.

Two prevailing theories to explain the pathophysiology of TTS include an "excess catecholamine release" and a "transient vasospastic state" (24–27). Among cancer patients with TTS, PE-TTS can be due to various physical stressors like cancer surgery, increased predisposition to infection and sepsis from an immunocompromised state, via an "excess catecholamine release" (24, 25). Vascular endothelial dysfunction in the setting of malignancy and its treatment can explain the CI and IM-TTS via the "transient vasospastic state" (28). Many chemotherapeutics and immunomodulators have been associated with TTS but 5-FU is frequently involved trigger in CI-TTS (29, 30). Recent evidence suggests that inflammation of the coronary adventitial vasa vasorum and perivascular adipose tissue is associated with coronary spasm (31). These results have not yet been replicated in a cancer population; however, cancer is known to be a pro-inflammatory state. Future studies should further evaluate a possible pathophysiological interconnection between cancer—inflammation—vasospasm—TTS. Some other contributing factors including a protective effect of estradiol on the electric disturbances seen in TTS patients and hyperthyroidism seen in TTS patients can be worthwhile targets in treating and preventing TTS in all patients including cancer patients (32, 33).

Another important finding from our study was regarding recovery of LV systolic function. It is now well known from various studies that despite normal or recovered LVEF, patients with TTS can have subclinical LV dysfunction in form of reduced apical or global longitudinal strain (34, 35). In our study CI-TTS patients showed best recovery of GLS while medical triggers had the least recovery of GLS. This could either be due to choosing alternative therapies with minimal cardiotoxic affects in patients developing CI-TTS, as well as meticulous surveillance, and prophylactic use of cardio-protective medications in such patients while on chemotherapy, rendering a better improvement in GLS. Despite a small sample size and being underpowered for this outcome, the improvement in GLS did not correlate with improvement in LVEF during the follow-up.

Having a large population of patients with chemotherapy-induced TTS was useful for noting features of chemotherapy-induced TTS (**Supplementary Table 1**). We found that patients can present with certain ECG findings. T-wave inversion was the most common ECG pattern in our population, which is consistent with our previous study (23, 24). Among patients with exposure to chemotherapy, the apical morphology was found in the vast majority of cases, while the distribution between apical and midcavitary morphology was more equal in the PE-TTS group. Unfortunately, our study was not powered to detect statistical significance of these features in CI-TTS. Moreover, limited data exists regarding rechallenging patients with cancer therapy induced TTS with the same therapy. Rechallenging should be avoided if possible, particularly if the LVEF or GLS does not completely normalize (21). If it is inevitable or if the LVEF and GLS have normalized, rechallenging can be considered while maintaining patients on the cardioprotective treatments and with close surveillance (36).

Strengths and limitations

Several aspects of our study contribute to its strength. First, we had access to a large population of cancer patients with TTS and the largest population of patients with CI-TTS known to date. Second, patients included in our study who are not classified as having CI-TTS are, nonetheless, cancer patients, eliminating a potential confounding factor if CI-TTS were to be compared with the TTS population in general. Third, the cardiac catheterization laboratory at The University of Texas MD Anderson Cancer Center allowed for on-site documentation of absence of prior cardiac disease and TTS morphology with angiography during the acute TTS episode. This advantage allowed our unique patient population to undergo state-of-the-art cancer treatment as well as cardiac assessment within the same facility. An important aspect for future studies can involve studying involvement of right ventricle (RV) function including RV strain to assess for subset of patients who present with biventricular TTS. Data regarding RV function during the episode of TTS at follow-up was not obtained in this study but prior studies have indicated a higher prevalence of biventricular TTS in cancer patients (37).

On the other hand, our study suffers from the known limitations of retrospective study. Additionally, a causal relationship between various TTS triggers and survival is extremely difficult to establish due to multiple confounding factors in this complex patient population. Despite the higher incidence of TTS in cancer patients, the sample size of patients is simply not large enough to produce a study with matching that may point to chemotherapy as the only factor causing worse outcomes in these patients. Nonetheless, we believe it

is important for clinicians to note that patients with TTS who have recent exposure to chemotherapy are at higher risk for death extending beyond the duration of cancer treatment. Identification of the triggering event in cancer patients with TTS also presents the challenge of separating pure emotional stress from the psychological and physical stress that parallels diagnosis, treatment, and follow-up of malignancies. Also, distinguishing LV dysfunction from myocardial toxicity from CI-TTS can be challenging in the absence of endomyocardial biopsy and is strictly based on the left ventriculogram and echocardiographic appearance (cardiotoxicity with a global and more patchy appearance, vs. CI–TTS with the typical subtypes: apical, midcavitary, or reversed). Our classification of the mechanism of TTS in this study is empirical, since it is possible that both catecholamine excess and vasospasm are involved in the pathogenesis of both CI-TTS and PE-TTS. Unfortunately, the number of patients who qualify for a study on CI-TTS will always be low, and thus the study suffers from limitations in terms of the power of its findings. It is important to note that the distribution of cancers involved in this study could differ significantly from that of another population of patients. Different malignancies can have significantly varied prevalence, treatments, and outcomes.

Conclusion

TTS can present in cancer patients after a wide spectrum of triggering events. CI-TTS presents mainly in women and is predominantly segmental and apical in morphology on echocardiography. PE-TTS appears to be better tolerated and to have better outcomes at 2 years. Underlying mechanisms of TTS could possibly predict outcomes in a cancer population. These results suggest that identifying a physical or emotional stressor as a cause of TTS among cancer patients may indicate a better prognosis than TTS induced by immunotherapy, radiation therapy and chemotherapy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the MD Anderson Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AS and TA contributed to conception or design of the work and the acquisition, analysis or interpretation of data for the work, and drafting the work or revising it critically for important intellectual content. VL and AAd contributed to the acquisition, analysis or interpretation of data for the work, and drafting the work. AAg contributed to revising it critically for important intellectual content. DG and DB did analysis of the data and provided approval for publication of the content. TDo, TDa, JL-M, PK, SH, KK, NP, JT, GI, EY, JH, KM, and PA contributed to revising it critically for important intellectual content and final approval. CI contributed to revising it critically, provided final approval of publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past collaboration with several of the authors JL-M, PK, and EY.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1019284/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Diagnostic studies for chemotherapy induced apical takotsubo syndrome.

SUPPLEMENTARY FIGURE 2
Diagnostic studies for procedural/emotional trigger induced midcavitary takotsubo syndrome.

SUPPLEMENTARY TABLE 1
Showing characteristics of various chemotherapy regimen induced takotsubo syndrome.

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Rapid cardiovascular aging following allogeneic hematopoietic cell transplantation for hematological malignancy

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Introduction: Allogeneic hematopoietic cell transplantation (allo-HCT) offers a potential cure for high-risk hematological malignancy; however, long-term survivors experience increased cardiovascular morbidity and mortality. It is unclear how allo-HCT impacts cardiovascular function in the short-term. Thus, this 3-month prospective study sought to evaluate the short-term cardiovascular impact of allo-HCT in hematological cancer patients, compared to an age-matched non-cancer control group.

Methods: Before and ∼3-months following allo-HCT, 17 hematological cancer patients (45 ± 18 years) underwent cardiopulmonary exercise testing to quantify peak oxygen uptake (VO_2peak)—a measure of integrative cardiovascular function. Then, to determine the degree to which changes in VO_2peak are mediated by cardiac vs. non-cardiac factors, participants underwent exercise cardiac MRI (cardiac reserve), resting echocardiography (left-ventricular ejection fraction [LVEF], global longitudinal strain [GLS]), dual-energy x-ray absorptiometry (lean [LM] and fat mass [FM]), blood pressure (BP) assessment, hemoglobin sampling, and arteriovenous oxygen difference (a-vO_2diff) estimation *via* the Fick equation. Twelve controls (43 ± 13 years) underwent identical testing at equivalent baseline and 3-month time intervals.

Results: Significant group-by-time interactions were observed for absolute VO_2peak ($p = 0.006$), bodyweight-indexed VO_2peak ($p = 0.015$), LM ($p = 0.001$) and cardiac reserve ($p = 0.019$), which were driven by 26, 24, 6, and 26% reductions in the allo-HCT group (all $p \leq 0.001$), respectively, as no significant changes were observed in the age-matched control group. No significant group-by-time interactions were observed for LVEF, GLS, FM, hemoglobin, BP or a-vO_2diff, though a-vO_2diff declined 12% in allo-HCT ($p = 0.028$).

Conclusion: In summary, allo-HCT severely impairs VO_2peak, reflecting central and peripheral dysfunction. These results indicate allo-HCT rapidly accelerates cardiovascular aging and reinforces the need for early preventive cardiovascular intervention in this high-risk group.

KEYWORDS

cardiac function, cardiopulmonary fitness, hematological cancer, exercise testing, cardiotoxicity, cardiovascular disease

Introduction

Hematological malignancies accounted for 1.28 million (6.6%) and 711, 840 (7.1%) cancer diagnoses and deaths globally in 2020 (1). Accordingly, allogeneic hematopoietic cell transplantation (allo-HCT) rates to manage these malignancies have more than doubled between 2006–2016 (2). This increase in allo-HCT, combined with advances in human leukocyte antigen-matched donor selection, graft-vs.-host disease (GvHD) prevention and management, and supportive care have contributed to a progressive growth in long-term cancer survivors (3, 4). However, the curative potential of allo-HCT continues to be offset by significant cardiovascular morbidity and mortality. Indeed, compared to age-matched non-cancer controls, long-term allo-HCT survivors (≥2 y) experience elevated rates of cardiovascular disease (CVD) (5–9) and serious cardiovascular events (9–11), culminating in a 2-to-4-fold increased risk of premature cardiovascular mortality (11, 12). These data provide compelling evidence of an accelerated cardiovascular aging phenotype among allo-HCT survivors and have sparked a call for studies aimed at understanding allo-HCT-induced CVD in order to inform efficacious preventive intervention (13).

The paradigm explaining the deterioration in cardiovascular health among allo-HCT survivors suggests there are multiple contributing factors including: the cancer itself (14); anti-cancer therapies (15); prolonged bedrest resulting in muscle loss and physical deconditioning (16); and the inflammatory perturbations of allografting which is exacerbated by GvHD and its prophylaxis/treatment (17, 18). Importantly, evidence extrapolated from studies with overlapping exposures suggests these insults are particularly deleterious to the heart (15–17), but also impact the entire cardiovascular-hematological-skeletal muscle axis (15–21). However, despite evidence of accelerated cardiovascular aging in long-term allo-HCT survivors (e.g., premature onset of overt CVD and related mortality), few studies have prospectively characterized the short-term cardiovascular impact of allo-HCT. Further, the cardiovascular impact of allo-HCT has been minimally characterized using sensitive biomarkers or state-of-the-art, high-resolution physiological testing at any point of the allo-HCT survivorship continuum. Therefore, the clinical trajectory and pathogenesis of allo-HCT related CVD remains unclear—two factors integral for informing the design (e.g., type and timing) of efficacious cardiovascular intervention.

Early detection of cancer treatment-related cardiac dysfunction is critical to facilitate prompt intervention and more effectively prevent irreversible damage and long-term morbidity. Accordingly, the application of exercise stress for the quantification of cardiovascular reserve (defined as the increase in cardiovascular function from rest to peak exercise) has emerged as an efficacious approach in unmasking subclinical cardiovascular pathology (22–24), and predicting all-cause, cardiovascular, and cancer-specific mortality (25–27). Cardiovascular reserve can be evaluated *via* a specific approach using exercise cardiac magnetic resonance imaging (exercise CMR) to directly quantify cardiac reserve (ability to augment cardiac output during exercise), or an integrative approach using cardiopulmonary exercise testing (CPET) for the assessment of peak oxygen uptake (VO_2peak). Importantly, beyond capturing cardiac reserve, VO_2peak also encapsulates the integrative function of non-cardiac, "peripheral" organ systems (hematological, vascular, skeletal muscle), which play an important role in the pathogenesis and pathophysiology of CVD (28–31), and are postulated to be impaired by allo-HCT. Hence, early cardiovascular follow-up with exercise-based measures that can provide a more accurate and comprehensive characterization of central and peripheral organ functioning may aid in guiding improved diagnostic and therapeutic approaches necessary to prevent long-term cardiovascular morbidity in this high-risk patient group.

Therefore, this 3-month prospective study sought to evaluate the short-term cardiovascular impact of allo-HCT, assessed primarily as VO_2peak and cardiac reserve, with direct comparison to an untreated age-matched non-cancer control group.

Methods

Study population and design

We performed a prospective cohort study comparing adults with hematological cancer scheduled for allo-HCT and age-matched non-cancer controls. Allo-HCT patients were recruited *via* direct referral from the Alfred Health HCT coordinators in Melbourne, Australia. Controls were recruited from the community who responded to advertisements seeking ostensibly healthy adults. Exclusion criteria for both groups included: (1) age <18 years, (2) inability to speak/understand English, and (3) known contraindications to CPET or CMR (i.e., injury, pacemaker, implanted metallic foreign body or device). Additional exclusion criteria for controls included: (1) BMI ≥35 $kg.m^{-2}$, (2) presence of a significant underlying medical condition(s), and (3) participation in ≥150-min of moderate intensity or ≥75-min of vigorous intensity aerobic physical activity per week.

Study protocol and experimental measurements

Participants underwent a comprehensive battery of physiological testing on two occasions. The allo-HCT group underwent testing prior to [median [IQR], 16 (11–27) days],

and ∼3-months following allo-HCT, while controls underwent identical testing, on two time-points, ∼3-months apart. Participants were asked to refrain from moderate to vigorous intensity physical activity in the 24-h preceding testing and abstain from alcohol and caffeine on the day of testing.

Participant medical history

A complete medical history of the allo-HCT patients was obtained from the Alfred Health Clinical Database and information relating to diagnosis, cardiovascular risk profile, prior treatment history, allo-HCT (donor, graft source, conditioning intensity, GvHD prophylaxis, GvHD status) and current medication use were recorded. A general lifestyle questionnaire was administered to controls to obtain information relating to current health status and relevant medical history including use of any medications.

Cardiopulmonary fitness

An incremental ramp protocol CPET was conducted on an electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, the Netherlands) for the measurement of VO_2peak. Briefly, participants cycled at 10–25 Watts for 1-min, after which, the workload increased at a progressive rate of 10–30 Watts.min^{-1} until volitional fatigue. The ramp protocol was individualized according to participant age, weight, self-reported exercise capacity, and physical activity history, with the intention of achieving volitional fatigue within 8-to-12-min. Breath-by-breath expired air gas analysis was performed continuously throughout testing using a calibrated metabolic cart (Vyntus CPX, Carefusion, San Diego, USA). Blood pressure (BP) was measured at 2-min intervals using an ECG-gated electrosphygmomanometer BP cuff (Tango M2 Stress Test Monitor and Orbit-K Blood Pressure Cuff, SunTech Medical Inc. Morrisville, USA). Heart rate (HR) and electrical activity were monitored continuously with a 12-lead electrocardiogram (Vyntus^{TM} ECG 12-lead PC-ECG, Vyaire Medical, Mettawa, USA). VO_2peak was defined as the average of the six consecutive highest 5-sec VO_2 values, and percent of age-, height-, weight and sex-predicted VO_2peak was calculated according to the FRIEND reference equation (32). V_E/VCO_2 was assessed from linear regression of V_E and VCO_2 values as it has been validated as an important prognostic marker in patients with heart failure, independent of VO_2peak (33). Contraindications to CPET adhered to the American Thoracic Society recommendations (34). In addition, a lower limit of 80 g.L^{-1} of hemoglobin was employed in line with clinical hemoglobin transfusion thresholds.

Resting cardiac function

Resting cardiac function was evaluated *via* echocardiogram (Vivid E95, General Electric Medical Systems, Milwaukee, Wisconsin). Images were collected, saved in a digital format, and analyzed offline (Echopac v13.0.00, GE, Norway) by a trained sonographer. A three-dimensional full-volume dataset was acquired to measure left-ventricular ejection fraction (LVEF). Two-dimensional speckle tracking echocardiography-derived global longitudinal strain (GLS) was quantified from three apical views at a temporal resolution of 60–90 frames.sec^{-1} with GLS defined as the average negative value of the strain rate curves.

Peak cardiac function and cardiac reserve

The biventricular response to exercise was evaluated using a validated real-time CMR method (35). Exercise was performed within the CMR bore using an electronically braked supine cycle ergometer (MR Ergometer Pedal, Lode, Groningen, the Netherlands). Cardiac images were acquired using a Siemens MAGNETOM Prisma 3.0T CMR with a five-element phased array coil at rest and during exercise at 60% of the maximal power output achieved during CPET as this approximates maximal exercise capacity in supine (35). Real-time steady-state free-precession cine MR imaging was performed without cardiac or respiratory gating at a temporal resolution of 36–38 ms and a three-dimensional stack of 10–18 adjoining 8-mm image slices, encapsulating both ventricle and atria, were acquired in the short axis (SAX) and horizontal long-axis (HLA) planes.

Real-time cine images were analyzed offline in RightVol (KUL, Leuven, Belgium). End-diastole and end-systole were retrospectively marked at end-expiration, and the left- and right-ventricular endocardia (papillary muscles and trabeculations included in the blood pool) were manually contoured on the SAX images, with reference to the atrioventricular valve plane in the HLA. Ventricular volumes were quantified at rest and peak exercise *via* the summation of disc method. Stroke volume index (SVI) was calculated as the difference between end-diastolic volume and end-systolic volume, indexed to body surface area (BSA), while cardiac index (CI) was calculated as stroke volume multiplied by HR, indexed to BSA. Left- and right-ventricular ejection fractions (LVEF, RVEF) were calculated as SV/end-diastolic volume, multiplied by 100. Cardiac (CI, SVI, HR) and contractile (LVEF, RVEF) reserve were defined as the ability to augment cardiac function from rest to peak exercise (peak values—rest values). Arteriovenous oxygen difference (a-vO_2diff) was estimated *via* the Fick equation using CPET-derived VO_2peak and exercise CMR-derived peak cardiac output.

Biochemistry

Blood samples were collected in the morning after an overnight fast to measure hemoglobin concentration, cardiac Troponin-I (cTn-I) and B-natriuretic peptide (BNP).

Anthropometry and body composition

Height (m) and body mass (kg) were assessed and used to calculate BMI and BSA. Total lean mass (LM, kg), fat mass (FM, kg) and percentage body fat (%BF) were quantified using dual-energy X-ray absorptiometry (GE Lunar iDXA, GE Healthcare, Little Chalfont, UK), with scans manually analyzed using enCore software (version 14.10.022).

Blood pressure

After resting in the supine position for 10-min in a quiet room, resting BP and HR were measured in triplicate at the brachial artery using an automated oscillometric BP monitor (OMRON HEM-907, OMRON Corporation, Tokyo, Japan). The average of three measurements was used for analysis.

Definitions of cardiotoxicity and functional disability

Cardiotoxicity was defined using standard echocardiography criteria (15): (1) an absolute reduction in LVEF of >15%, to a value >50%, (2) an absolute reduction in LVEF of >10%, to a value <50% and (3) a >12% relative reduction in GLS. Functional disability was defined as VO_2peak <18 ml.kg^{-1}.min^{-1} as per the American Heart Association Scientific Statement (36).

Sample size

The sample size calculation for the allo-HCT group was based on the reported reduction in VO_{2peak} following 4-weeks of bedrest in healthy individuals (37). Indeed, the pooling of 19 bedrest investigations suggests %Δ VO_2peak can be explained by the linear regression = 1.4–0.85 (days), r = −0.73 (37). Considering the average hospital stay for allo-HCT patient is 28 days, a ∼22.4% reduction in VO_2peak was expected. To account for normal variation in test-retest reproducibility (4.4%), the study was powered to detect an 18% difference between allo-HCT and non-cancer control groups. With estimated standard deviation of 12% (obtained from our study in women treated for breast cancer), 15 allo-HCT and 8 non-cancer control completions were deemed necessary (SD = 12%; 90% power; alpha = 0.05). Sample size was increased ∼20% to account for possible drop-out.

Statistical analysis

Analysis was performed using SPSS software (version 24.0, Statistical Package for the Social Sciences, IBM, Chicago, USA). Continuous data were inspected for normality, linearity and homoscedasticity and presented as mean ± SD or mean (95% CI). Categorical data are presented as *n* (%). Independent *t*-tests or Fishers exact tests were performed to assess baseline group differences for continuous and categorical variables, respectively. Treatment effects were assessed *via* generalized linear mixed modeling with covariance structure informed by the Akaike information criteria. The model included time as the repeated measure, group and group-by-time as fixed effects, and participants as random effects. Findings remained unchanged when adjusting for sex, thus, unadjusted results are presented. Within-group changes after 3-months are expressed as mean (95% CI) change from baseline and between-group differences for the mean changes after 3-months [net difference (95% CI)] were calculated by subtracting the within-group changes from baseline for controls from the within-group changes for allo-HCT. CTn-I was transformed to yield a normal distribution before analysis. Two-sided $p < 0.05$ indicated significance.

Results

Participant characteristics and transplant-related information

Twenty-six individuals scheduled for allo-HCT (17 men, 9 women) and 12 age-matched non-cancer controls (5 men, 7 women) were recruited and completed all baseline assessments. After 3-months, all controls (100%) and 17 (65%; 12 men, 5 women) allo-HCT participants completed follow up ($n = 7$ deceased, $n = 1$ declined due to perceived incapacity, $n = 1$ lost-to-follow-up) and were included in analyses. There were no significant differences in baseline participant characteristics or transplant-related factors between allo-HCT recipients who did and did not complete follow-up (see Supplementary Table S1).

Characteristics of the allo-HCT and control participants who completed follow-up are summarized in Tables 1, 2. There were no significant differences in demographic, anthropometric or traditional cardiovascular risk factors between allo-HCT recipients and controls (Table 1). However, allo-HCT recipients had a significantly lower VO_2peak ($p < 0.001$), cardiac reserve ($p = 0.004$), LVEF ($p = 0.043$), and GLS ($p = 0.018$), relative to controls (Table 1). Acute myeloid leukemia was the most common transplant indication (65%) among allo-HCT recipients, and treatment history was diverse (A more detailed summary of prior treatments is provided in Supplementary Table S1). Sixteen participants (94%) had previous chemotherapy exposure, with anthracycline and anti-metabolite agents most frequently administered (both 82%). With regard to transplant related factors, the most common donor type, graft source, conditioning intensity and GvHD prophylaxis were unrelated, peripheral blood, reduced intensity, and methotrexate/ciclosporine, respectively (Table 2).

Exercise capacity

As shown in Figures 1A,B, a significant between-group difference existed for the net change over 3-months for absolute (-0.4 L.min^{-1} [95% CI -0.7, -0.1]; group-by-time-interaction, $p = 0.006$) and bodyweight-indexed VO_2peak (-4.5 ml.kg^{-1}.min^{-1} [95% CI -8.1, -0.9]; group-by-time interaction, $p = 0.015$), due to a 26% (-0.5 L.min^{-1} [95% CI -0.7, -0.3]; $p < 0.001$) and 24% (-5.4 ml.kg^{-1}.min^{-1} [95% CI -7.7, -3.1]; $p < 0.001$) decline in allo-HCT recipients, respectively, and no significant change in controls. Consequently, allo-HCT recipients achieved a follow-up VO_2peak that was, on average, 49% below predicted (-16% from baseline; $p < 0.001$), with 53% considered functionally disabled. As shown in Table 3, significant between-group differences (group-by-time interactions) were also observed for peak power output ($p < 0.001$) and percentage of age-predicted HR_{peak} ($p = 0.005$), which was driven by a 30% and 11% reduction from baseline in the allo-HCT recipients (both $p < 0.001$) as no significant change was observed in controls. A similar significant group-by-time interaction was noted for V_E/VCO_2 slope ($p = 0.008$), which was due to a 17% increase in allo-HCT recipients ($p < 0.001$) as there was no change in controls. Peak a-vO_2diff declined 12% in allo-HCT recipients ($p = 0.028$), but a significant between-group difference for the net change from baseline was not observed (interaction, $p = 0.23$), due to a slight, non-significant downward shift in controls.

Resting cardiac function and cardiac biomarkers

Echocardiographic measures of resting cardiac function and cardiac biomarkers were unchanged in both groups at 3-months (Table 4). No participants developed overt CVD or met LVEF cardiotoxicity criteria, but one allo-HCT recipient commenced treatment for arrhythmia, and three allo-HCT recipients and two controls had clinically significant GLS declines. One allo-HCT recipient had a post-treatment troponin >15 ng.L^{-1} and two had a post-treatment BNP >100 ng.L^{-1}, totalling a 35% incidence of subclinical cardiac pathology in allo-HCT and 17% in controls (between-group difference, $p = 0.41$).

Peak cardiac function and cardiac reserve

As shown in Table 4, allo-HCT was associated with a 13% reduction in CI_{peak} ($p < 0.001$) and a 9% reduction in SVI_{peak} ($p = 0.003$), but no change in HR_{peak}. CI_{peak}, SVI_{peak} and HR_{peak} remained unchanged in controls, resulting in a net group difference for the change at 3-months for CI_{peak} (interaction, $p = 0.042$), a trend toward a significant net group difference for SVI_{peak} (interaction, $p = 0.058$), but not HR_{peak} (interaction, $p = 0.37$). With respect to peak biventricular contractility, $LVEF_{peak}$ and $RVEF_{peak}$ remained unchanged in controls but decreased (absolute) 1.9% ($p = 0.033$) and 3.2% ($p = 0.004$),

TABLE 1 Baseline characteristics for Allo-HCT and Control participants who completed baseline and follow-up assessments.

	Allo-HCT ($n = 17$)	Control ($n = 12$)
Sex, % male	70%	42%
Age, years	45 ± 18	43 ± 13
Weight, kg	80.7 ± 18.0	74.3 ± 14.4
Body mass index, kg.m^{-2}	27.4 ± 6.2	24.6 ± 3.7
Cardiovascular function		
LVEF, %	54.7 ± 5.5*	59.5 ± 5.7*
GLS, %	−17.8 ± 2.0*	−20.0 ± 2.4
CI Reserve, L.min^{-1}.m^{-2}	3.8 ± 1.4**	5.9 ± 1.7
VO_2peak, ml.kg^{-1}.min^{-1}	22.9 ± 8.0***	34.8 ± 8.1
VO_2peak, % predicted	67 ± 12***	104 ± 16
Functional disability, *n* (%)	5 (29)	0 (0)
Cardiovascular risk factors, *n* (%)		
Hypertension	4 (24)	0 (0)
Hyperlipidaemia	2 (12)	0 (0)
Diabetes	1 (6)	0 (0)
Body mass index ≥25 kg.m^{-2}	9 (53)	5 (42)
Previous cardiovascular event	2 (12)	0 (0)
≥1 cardiovascular risk factor	10 (59)	5 (42)
Cardiovascular medications, *n* (%)		
Statin/Cholesterol absorption inhibitor	1 (6)	0 (0)
Antihypertensives	2 (12)	0 (0)
Beta–blocker	1 (6)	0 (0)
Antidiabetic	1 (6)	0 (0)
Non–steroidal anti–inflammatory	3 (18)	1 (8)
Diagnosis, *n* (%)		
Acute myeloid leukemia	11 (65)	n/a
Non–Hodgkin lymphoma	3 (18)	n/a
Acute lymphoblastic leukemia	2 (12)	n/a
Myelodysplasia	1 (6)	n/a
Prior cancer treatment, *n* (%)		
No prior treatment	1 (6)	n/a
Chemotherapy	16 (94)	n/a
Cumulative anthracycline dose, mg.m^{-2}	180 (100–270)	n/a
Targeted Therapy	5 (29)	n/a
Immunotherapy	3 (18)	n/a
Radiation	2 (12)	n/a
Autologous stem cell transplant	1 (6)	n/a

Data are mean ± SD, median (IQR) or n (%). CI, cardiac index; GLS, global longitudinal strain; LVEF, left-ventricular ejection fraction; VO_2peak, peak oxygen uptake. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. control.

TABLE 2 Transplant related information for Allo-HCT participants that completed baseline and follow–up assessments.

	N (%)
Donor type	
Related	8 (47)
Unrelated	9 (53)
Graft source	
Bone marrow	3 (18)
Peripheral blood stem cell	14 (82)
Conditioning intensity	
Myeloablative	7 (41)
Reduced Intensity	10 (59)
Conditioning regimen	
Ciclosporin/TBI	6 (35)
Flu/Mel	6 (35)
Flu/Mel/Campath	3 (18)
ETP/TBI	1 (6)
LACE	1 (6)
GvHD prophylaxis	
MTX/Ciclosporin ± ATG	10 (59)
PTCy/Ciclosporin	4 (24)
Ciclosporin	2 (12)
TAC	1 (6)
Acute GvHD grade	
No GvHD	10 (59)
Grade I	6 (35)
Grade II	1 (6)
Hospital length of stay, days	31 (21–39)

Data are n (%) or median (range). ATG, ATGAM thymoglobulin; ETP, Etoposide; Flu, Fludarabine; GvHD, Graft–vs.–host disease; LACE, Lomustine, Cytarabine, Cyclophosphamide, Etoposide; Mel, Melphalan; MTX, Methotrexate; PTCy, Post–transplant Cyclophosphamide; TAC, Tacrolimus; TBI, Total body irradiation.

respectively, following allo-HCT, leading to a significant group-by-time interaction for $RVEF_{peak}$ ($p = 0.010$), but not $LVEF_{peak}$ ($p = 0.14$).

Results pertaining to changes in cardiac and contractile reserve (ability to augment function above resting) are shown in Figures 2A–E. CI, SVI and HR reserve were unchanged in controls at 3-months, but were further blunted in allo-HCT recipients ($p = 0.001$, $p = 0.010$, $p = 0.020$, respectively), resulting in a net group difference for the change at 3-months for CI reserve (interaction, $p = 0.019$) and trends toward significant net group differences for SVI reserve and HR reserve (interaction, $p = 0.081$ and $p = 0.056$, respectively). A significant interaction was observed for RVEF reserve ($p = 0.010$), due to a blunted augmentation from rest to peak exercise in allo-HCT ($p = 0.001$) and no change in controls. There were no within- or between-group differences for LVEF reserve.

Body composition and indices of vascular and hematological function

Weight declined 3.8 kg in allo-HCT recipients ($p = 0.002$), but this was not significantly different from the change in controls (−0.6 kg, $p = 0.65$; interaction, $p = 0.082$) (Table 5). Conversely, allo-HCT recipients experienced a significant net loss of 3.2 kg in LM relative to controls after 3-months (interaction, $p = 0.001$). No significant changes existed in either group for FM, %BF, hemoglobin, or BP. Three allo-HCT recipients and one control developed new-onset hypertension at 3-months, totaling a 35 and 8% prevalence, respectively (between-group difference, $p = 0.19$).

Discussion

To our knowledge, this is the first study to prospectively evaluate the short-term cardiovascular impact of allo-HCT among early transplant survivors, with comparison to an age-matched control group. Utilizing novel, state-of-the-art, non-invasive measures of cardiac function, this study demonstrated that, relative to matched controls, patients scheduled for allo-HCT presented with marked impairment in VO_2peak and cardiac reserve. Importantly, we extend these findings and demonstrate that VO_2peak and cardiac reserve deteriorate further in the 3-months following allo-HCT. Moreover, such impairments coincided with a reduction in a-vO_2diff which makes an important contribution to the symptomatology of cardiovascular disorders such as heart failure (30). Collectively, these findings provide evidence of an accelerated cardiovascular aging phenotype that is present prior to transplant but is further exacerbated by the transplant and hospitalization process.

The inverse relationship between VO_2peak and risk of cardiovascular morbidity, cardiovascular mortality, all-cause mortality, and cancer-specific mortality has been well established (25–27). In the present study, we observed a 26 and 24% reduction in absolute and bodyweight-indexed VO_2peak in allo-HCT recipients over 3-months, which was ∼9-fold greater than that observed in age-matched controls and approximates the degree of cardiovascular aging expected over 24 years of normal aging (38). While the 5.4 $ml.kg^{-1}.min^{-1}$ decline in VO_2peak in allo-HCT recipients is profound, the true vulnerability of this population becomes especially evident when viewed in the context of the already diminished cardiovascular function prior to undergoing allo-HCT. Indeed, evidence from large prospective studies in ostensibly healthy non-cancer populations demonstrates that for each 1 MET (3.5 $ml.kg^{-1}.min^{-1}$) decrement in VO_2peak, the risk of incident heart failure and all-cause mortality increases 16–21 and 25%, respectively (25, 39). In the present study, allo-HCT recipients achieved a VO_2peak at follow-up that was 50% (16.4 $ml.kg^{-1}.min^{-1}$ or 4.7 METs) lower than controls,

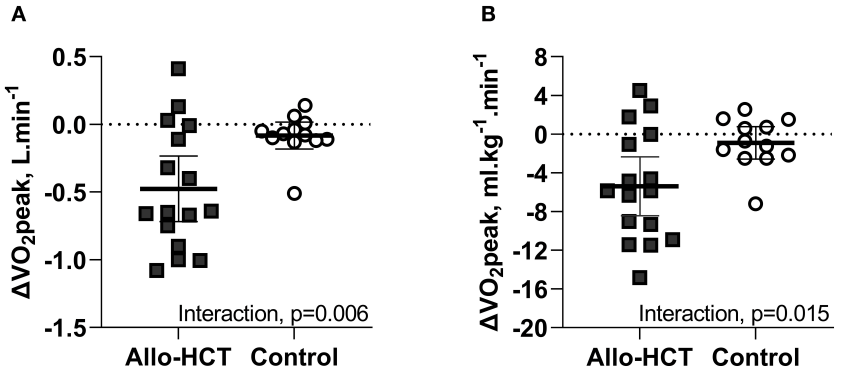

FIGURE 1
(A,B) Mean (95% CI) 3-month change from baseline in absolute and bodyweight-indexed VO_2peak in Allo-HCT and Control assessed by cardiopulmonary exercise testing. There was a significant between-group difference for the net change from baseline for absolute and bodyweight-indexed VO_2peak ($p = 0.006$ and $p = 0.015$, respectively), which was due to a significant decrease in allo-HCT and no change in controls.

but of clinical relevance is that 53% of allo-HCT recipients were classified as being functionally disabled (VO_2peak $<18\ ml.kg^{-1}.min^{-1}$) at 3-months. This threshold has been associated with a reduced capacity to independently perform activities of daily living (40), and serves as a strong prognostic threshold, below which, the risk of incident heart failure and all-cause mortality are heightened 7-to-9-fold (26, 36). Notably, cross-sectional evaluation of VO_2peak among long-term allo-HCT survivors (median time since allo-HCT, 9.8 years [range, 3—20]) indicates that these deleterious impairments in VO_2peak do not fully recover over time, remaining substantially lower than predicted (22% below predicted) (7). Taken together, and consistent with the increased cardiovascular burden reported among long-term survivors (5–7, 9–12), these findings infer that allo-HCT recipients face a substantially greater risk of developing CVD relative to controls and provide novel insight into the potential trajectory of cardiovascular dysfunction in this cohort.

Dissecting the cardiac contribution to these reductions in VO_2peak is critical given the potential role for pharmacological and non-pharmacological (i.e., lifestyle) interventions to attenuate cardiotoxicity. Using state-of-the-art exercise CMR, we provide the first evidence that treatment with allo-HCT significantly blunts cardiac reserve. Indeed, compared to pre-transplant, allo-HCT recipients experienced a blunted increase in SVI and HR from rest to peak exercise, resulting in a reduced augmentation in CI during exercise. These changes are indicative of myocardial injury/maladaptation—likely ascribed to both direct (i.e., cardiotoxic conditioning regimens) and indirect (i.e., physical inactivity, sedentary behavior) pathological perturbations (15, 16). The exact pathological mechanisms of allo-HCT induced cardiotoxicity are incompletely understood, but growing evidence suggests chemotherapy, radiotherapy, physical inactivity, and the allograft itself (by way of alloreactive donor T cell mediated immune and pro-inflammatory cytokine activation) can perturb the redox and inflammatory balance, which would theoretically lead to DNA damage, mitochondrial dysfunction, impaired sarcoplasmic reticulum calcium uptake activity, and extracellular matrix remodeling (i.e., fibrosis), and ultimately contractile dysfunction and cardiomyocyte apoptosis (41–44). The "mechanical unloading" associated with physical inactivity and bedrest may further compromise cardiac output *via* deconditioning of the cardiac muscle or *via* reductions in venous return and therefore stroke volume (45, 46). Moreover, it is important to highlight these declines in cardiac reserve induced by allo-HCT occurred on top of a reserve that was already diminished at baseline, such that following allo-HCT, CI_{peak}, $LVEF_{peak}$ and $RVEF_{peak}$ were 26%, 7% (absolute), and 3% (absolute) lower than age-matched controls. Given that an inability to generate sufficient cardiac output during periods of high metabolic demand is an early hallmark of heart failure (24, 47), extrapolating these results over the years following allo-HCT—wherein normal age-related decline in cardiac function continues—may offer a possible explanation for the heightened prevalence of premature CVD and associated cardiovascular events and mortality in long-term survivors. Another intriguing finding from our study was that these allo-HCT induced reductions in cardiac reserve ensued whereas standard resting measures of cardiac function (LVEF, GLS, cardiac biomarkers) were unchanged. Indeed, echocardiographic parameters remained, on average, within normal ranges, and interpreted as an isolated assessment, would not flag an increased risk of CVD. These results are consistent with that observed among long-term allo-HCT survivors (normal LVEF despite impaired VO_2peak at a median of 9.8 years after allo-HCT) (7) but are in contrast to Moriyama et al. (48) whom detected significant left-ventricular systolic dysfunction (characterized as a decrease

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TABLE 3 Mean baseline values, within-group changes after 3–months and the net between-group differences for the change for peak CPET parameters in Allo-HCT and Control groups.

Measure	Allo-HCT	Control	Δ net difference (HCT vs. Con)	Group, p	Time, p	Group x Time, p
VO_2peak, L.min^{-1}						
Baseline	1.8 ± 0.6	2.6 ± 0.7				
3–months	1.3 ± 0.4	2.5 ± 0.7				
Δ	−0.5 (−0.7, −0.3)***	−0.1 (−0.2, 0.1)	−0.4 (−0.7, −0.1)	< 0.001	< 0.001	0.006
VO_2peak, ml.kg^{-1}.min^{-1}						
Baseline	22.9 ± 8.0	34.8 ± 8.1				
3–months	17.5 ± 5.7	33.9 ± 8.0				
Δ	−5.4 (−7.7, −3.1)***	−0.9 (−3.6, 1.8)	−4.5 (−8.1, −0.9)	< 0.001	0.001	0.015
VO_2peak, % predicted						
Baseline	67 ± 12	104 ± 16				
3–months	51 ± 13	101 ± 17				
Δ	−16 (−23, −10)***	−3 (−11, 4)	−13 (−23, −3)	< 0.001	< 0.001	0.012
Peak Power Output, Watts						
Baseline	154 ± 62	254 ± 68				
3–months	108 ± 44	258 ± 69				
Δ	−46 (−59, −32)***	4 (−12, 19)	−50 (−70, −29)	< 0.001	< 0.001	< 0.001
HR_{peak}, % predicted						
Baseline	96 ± 8	102 ± 4				
3–months	85 ± 11	101 ± 4				
Δ	−11 (−15, −6)***	−1 (−6, 5)	−10 (−17, −3)	< 0.001	0.002	0.005
Peak RER						
Baseline	1.38 ± 0.09	1.33 ± 0.15				
3–months	1.31 ± 0.14	1.33 ± 0.07				
Δ	−0.07 (−0.13, −0.01)*	0.00 (−0.07, 0.07)	−0.07 (−0.16, 0.02)	0.79	0.13	0.15
V_E/VCO_2 slope						
Baseline	27.8 ± 3.4	26.8 ± 2.9				
3–months	32.5 ± 5.5	26.5 ± 4.0				
Δ	4.7 (2.3, 7.1)***	−0.3 (−3.0, 2.4)	5.0 (1.4, 8.6)	0.011	0.017	0.008
Peak a–vO_2diff, %						
Baseline	12.0 ± 2.6	14.7 ± 1.7				
3–months	10.5 ± 2.7	14.4 ± 1.9				
Δ	−1.5 (−2.8, −0.2)*	−0.3 (−1.7, 1.0)	−1.1 (−3.0, 0.7)	< 0.001	0.06	0.23

All baseline and 3–month values are unadjusted means ± SDs; all within-group changes are unadjusted mean (95% CI) and expressed as absolute change from baseline. Mean net differences were calculated by subtracting the within–group changes from baseline in the control group from the within–group change from baseline in the allo-HCT group after 3 months. *$p < 0.05$, ***$p < 0.001$ vs. baseline. VO_2peak, peak oxygen uptake; HR_{peak}, peak heart rate; RER, respiratory exchange ratio; peak a–vO_2diff, peak arteriovenous oxygen difference.

in LVEF of ≥10% or LVEF ≤53%) in 17% of patients within 100 days after allo-HCT. These discrepant echocardiographic observations may be explained by differences in study design and potential selection bias. Indeed, we conducted a prospective echocardiographic assessment of all allo-SCT recipients whereas Moriyama et al. (48) conducted a retrospective review of allo-SCT recipients who underwent echocardiographic assessment at physician discretion (136/416 patients), biasing the likelihood of a cardiac finding. Nonetheless, the results of our study are consistent with the pattern of cardiac impairment seen among heart failure and anthracycline-treated cancer patients, wherein reductions in cardiac reserve often precede impairment in resting function (22–24, 47). Therefore, whilst not the primary aim of this study, our results also highlight the added utility of exercise cardiac reserve assessment in unmasking early treatment induced cardiac dysfunction in vulnerable populations.

Importantly, given non-cardiac factors also make important contributions to VO_2peak (28) and the CVD phenotype (29–31), we explored whether the reduction in VO_2peak

TABLE 4 Mean baseline values, within-group changes after 3–months and the net between-group differences for the change for cardiac parameters in Allo-HCT and Control groups.

Measure	Allo-HCT	Control	Δ net difference (HCT vs. Con)	Group, p	Time, p	Group x Time, p
Cardiac biomarkers						
cTn–I, ng.L^{-1}						
Baseline	4.6 ± 4.2	2.8 ± 1.2				
3–months	5.4 ± 5.7	2.9 ± 1.1				
Δ	0.8 (−1.8, 3.4)	0.1 (−2.8, 3.0)	0.71 (−3.2, 4.6)	0.14	0.63	0.72
BNP, ng.L^{-1}						
Baseline	40.5 ± 32.0	33.2 ± 22.9				
3–months	54.3 ± 35.6	31.7 ± 28.5				
Δ	13.8 (−3.2, 30.8)	−1.6 (−21.2, 18.1)	15.4 (−10.6, 41.3)	0.22	0.34	0.24
Resting echocardiography						
LVEF, %						
Baseline	54.7 ± 5.5	59.5 ± 5.7				
3–months	56.1 ± 3.8	57.6 ± 4.4				
Δ	1.4 (−1.3, 4.1)	−1.8 (−4.9, 1.3)	3.2 (−0.9, 7.3)	0.065	0.84	0.12
GLS, %						
Baseline	−17.8 ± 2.0	−20.0 ± 2.4				
3–months	−17.3 ± 1.5	−19.4 ± 1.9				
Δ	0.5 (−0.6, 1.6)	0.6 (−0.7, 2.0)	−0.1 (−1.8, 1.6)	0.001	0.18	0.90
Resting CMR						
HR, beats.min^{-1}						
Baseline	81 ± 12	66 ± 9				
3–months	84 ± 6	63 ± 9				
Δ	3 (−5, 10)	−3 (−11, 5)	6 (−5, 16)	< 0.001	0.98	0.30
SVI, ml.m^{-2}						
Baseline	50.0 ± 7.4	54.2 ± 9.2				
3–months	47.6 ± 9.0	53.7 ± 8.3				
Δ	−2.4 (−5.2, 0.3)	−0.5 (−3.4, 2.4)	−1.9 (−5.9, 2.1)	0.14	0.14	0.33
CI, L.min^{-1}.m^{-2}						
Baseline	4.0 ± 0.8	3.6 ± 0.6				
3–months	4.0 ± 0.9	3.4 ± 0.5				
Δ	0.0 (−0.4, 0.4)	−0.2 (−0.6, 0.2)	0.2 (−0.4, 0.7)	0.032	0.42	0.58
LVEF, %						
Baseline	53.4 ± 5.5	56.5 ± 2.6				
3–months	53.2 ± 4.3	56.2 ± 3.2				
Δ	−0.2 (−3.2, 2.8)	−0.3 (−3.4, 2.8)	0.1 (−4.2, 4.4)	0.026	0.80	0.96
RVEF, %						
Baseline	55.5 ± 3.7	52.4 ± 4.7				
3–months	55.6 ± 2.9	52.8 ± 4.3				
Δ	0.1 (−1.9, 2.1)	0.5 (−1.6, 2.6)	−0.3 (−3.2, 2.5)	0.054	0.67	0.81
Exercise CMR						
HR_{peak}, beats.min^{-1}						
Baseline	136 ± 16	147 ± 13				
3–months	130 ± 16	146 ± 14				
Δ	−6 (−12, 1)	−2 (−8, 6)	−4 (−14, 5)	0.029	0.14	0.37
SVI_{peak}, ml.m^{-2}						
Baseline	57.9 ± 10.0	63.8 ± 11.6				
3–months	52.9 ± 11.0	63.2 ± 9.6				
Δ	−5.0 (−8.1, −1.9)**	−0.6 (−3.9, 2.7)	−4.4 (−8.9, 0.2)	0.063	0.017	0.058

(Continued)

TABLE 4 (Continued)

Measure	Allo-HCT	Control	Δ net difference (HCT vs. Con)	Group, p	Time, p	Group x Time, p
CI_{peak}, $L.min^{-1}.m^{-2}$						
Baseline	7.8 ± 1.5	9.4 ± 2.1				
3–months	6.8 ± 1.3	9.2 ± 1.7				
Δ	−1.0 (−1.5, −0.5)***	−0.2 (−0.8, 0.2)	−0.8 (−1.6, 0.0)	0.004	0.002	0.042
$LVEF_{peak}$, %						
Baseline	59.2 ± 4.3	64.1 ± 3.7				
3–months	57.3 ± 5.4	64.1 ± 3.6				
Δ	−1.9 (−3.6, −0.2)*	0.0 (−1.8, 1.8)	−1.9 (−4.4, 0.6)	0.001	0.13	0.14
$RVEF_{peak}$, %						
Baseline	62.4 ± 3.0	61.9 ± 5.5				
3–months	59.2 ± 4.5	62.8 ± 5.0				
Δ	−3.2 (−5.3, −1.1)**	0.9 (−1.3, 3.1)	−4.1 (−7.2, −1.0)	0.37	0.14	0.01

All baseline and 3–month values are unadjusted means ± SDs; all within-group changes are unadjusted mean (95% CI) and expressed as absolute change from baseline. Mean net differences were calculated by subtracting the within–group changes from baseline in the control group from the within–group change from baseline in the allo-HCT group after 3 months. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. baseline. BNP, brain natriuretic peptide; CI, cardiac index; cTn-I, troponin I; CMR, cardiac magnetic resonance imaging; GLS, global longitudinal strain; HR, heart rate; LVEF, left-ventricular ejection fraction; RVEF, right-ventricular ejection fraction; SVI, stroke volume index.

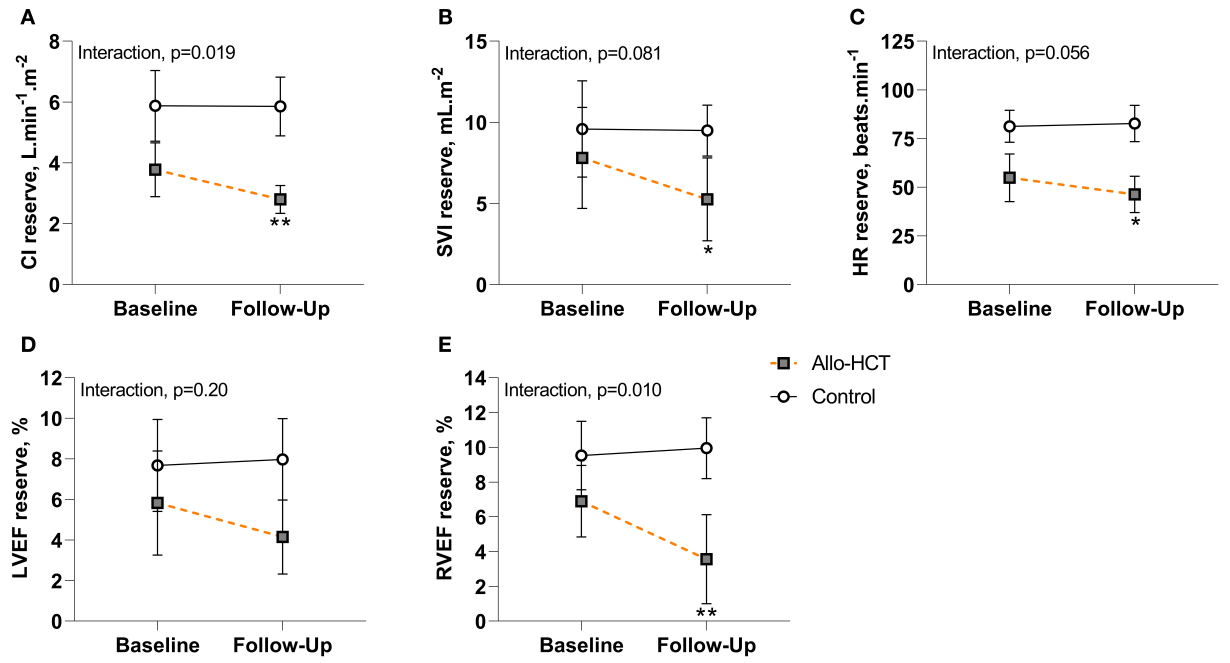

FIGURE 2
(A–E) Cardiac and contractile reserve at baseline and 3-month follow-up for Allo-HCT ($n = 12$) and Control ($n = 11$). After 3-months, cardiac and contractile reserve were maintained in controls, but allo-HCT experienced a blunted CI, SVI, HR, and RVEF reserve, resulting in a significant between-group difference for the net change from baseline for CI reserve and RVEF reserve and a trend toward a significant between-group difference for the net change from baseline for SVI reserve and HR reserve. *$p < 0.05$ and **$p < 0.01$ for within-group change in reserve. Data are unadjusted mean (95% CI). CI, cardiac index; HR, heart rate; LVEF, left-ventricular ejection fraction; RVEF, right-ventricular ejection fraction; SVI, stroke volume index.

observed among allo-HCT recipients could also reflect impairment in non-cardiac factors that determine peripheral muscle O_2 delivery and utilization. In the present study, deficits in O_2 carrying capacity as a result of anemia due to disease and prior therapies likely contributed to the baseline deficit in VO_2peak among allo-HCT recipients

TABLE 5 Mean baseline values, within-group changes after 3–months and the net between-group differences for the change for body composition and indices of vascular and hematological function in Allo-HCT and Control groups.

Measure	Allo-HCT	Control	Δ net difference (HCT vs. Con)	Group, p	Time, p	Group x Time, p
Weight, kg						
Baseline	80.7 ± 18.2	74.3 ± 14.4				
3–months	76.9 ± 18.1	73.6 ± 15.2				
Δ	−3.8 (−6.0, −1.5)**	−0.6 (−3.3, 2.1)	−3.2 (−6.7, 0.4)	0.48	0.016	0.082
Body mass index, kg.m^{-2}						
Baseline	27.4 ± 6.2	24.6 ± 3.7				
3–months	26.2 ± 6.3	24.4 ± 3.7				
Δ	−1.2 (−2.0, −0.5)**	−0.2 (−1.1, 0.7)	−1.0 (−2.2, 0.2)	0.26	0.014	0.090
Total LM, kg						
Baseline	51.7 ± 12.9	49.5 ± 10.1				
3–months	48.5 ± 11.9	49.5 ± 10.3				
Δ	−3.2 (−4.3, −2.0)***	0.0 (−1.4, 1.4)	−3.2 (−5.0, −1.3)	0.001	0.88	0.001
Total FM, kg						
Baseline	25.9 ± 10.3	21.8 ± 8.8				
3–months	25.3 ± 9.6	21.3 ± 8.1				
Δ	−0.6 (−2.7, 1.5)	−0.5 (−3.0, 2.0)	−0.1 (−3.4, 3.2)	0.25	0.48	0.95
Body fat percentage, %						
Baseline	31.8 ± 8.9	29.0 ± 8.8				
3–months	32.5 ± 8.5	28.6 ± 7.5				
Δ	0.7 (−1.4, 2.9)	−0.4 (−3.0, 2.2)	1.1 (−2.2, 4.5)	0.28	0.84	0.50
SBP, mmHg						
Baseline	129 ± 19	118 ± 15				
3–months	127 ± 20	118 ± 14				
Δ	−2 (−10, 6)	0 (−10, 10)	−2 (−14, 11)	0.071	0.78	0.80
DBP, mmHg						
Baseline	77 ± 15	70 ± 11				
3–months	77 ± 13	70 ± 11				
Δ	0 (−5, 5)	−1 (−7, 6)	1 (−7, 8)	0.11	0.90	0.90
Hemoglobin, g.L^{-1}						
Baseline	114.5 ± 20.0	138.9 ± 10.5				
3–months	107.2 ± 13.3	142.3 ± 9.7				
Δ	−7.3 (−16.5, 1.9)	3.4 (−8.6, 15.4)	−10.7 (−25.8, 4.4)	< 0.001	0.61	0.16

All baseline and 3–month values are unadjusted means ± SDs; all within-group changes are unadjusted mean (95% CI) and expressed as absolute change from baseline. Mean net differences were calculated by subtracting the within–group changes from baseline in the control group from the within–group change from baseline in the allo–HCT group after 3 months. $^{**}p < 0.01$, $^{***}p < 0.001$ vs. baseline. DBP, diastolic blood pressure; FM, fat mass; LM, lean body mass; SBP, systolic blood pressure.

(relative to controls) (49), but any further reductions in hemoglobin induced by allo-HCT had recovered at 3-months, and is therefore unlikely to explain the allo-HCT induced decline in VO_2peak. We did, however, observe a significant reduction in peak a-vO_2diff among allo-HCT recipients at 3-months. This is an important and novel finding as the impact of allo-HCT on skeletal muscle oxygenation has not been fully appreciated but may also contribute to the premature development of CVD and functional impairment in this population. Delineating the contribution of vascular and skeletal muscle factors to this decline in a-vO_2diff will provide important insight into its clinical significance.

Premature vascular aging in allo-HCT patients may have been expected based on evidence from small cross-sectional and prospective studies which have evaluated vascular structure and function in the allo-HCT setting. Indeed, allo-HCT recipients have been shown to exhibit increased endothelial damage and dysfunction (evidenced by elevated circulating endothelial cells and soluble markers of endothelial damage, and lower

endothelial dependent flow-mediated dilation) (50–53), central arterial stiffening (evidenced by increased aortic pulse wave velocity and reduced carotid distensibility, compliance and incremental elastic modulus) (54–56), and carotid intima-media thickening (54) compared to age-matched healthy controls or pre-transplant values. Consequently, hypertension is a common early (1-month incidence: 38–61%) (57, 58) and persistent complication of allo-HCT (odds ratio: 3.65 [95% CI, 1.82–7.32] at 8.6 years after allo-SCT) (59). It was therefore somewhat unexpected that the baseline prevalence and 3-month incidence of hypertension was similar between allo-HCT recipients and controls. This discrepancy could reflect the comparatively lower occurrence of grade II-IV GvHD and subsequent immunosuppressant exposure in our study (17, 18). Beyond this, it is important to note that subclinical vascular damage (i.e., endothelial dysfunction, arterial stiffness, intimal thickening) often precedes the development of hypertension and can remain "silent" for years before manifesting clinically, and therefore cannot be excluded as a possible mediator of allo-HCT-induced impairments in a-vO_2diff and subsequently VO_2peak. Moreover, there is emerging evidence that impairments in a-vO_2diff, and subsequent exercise capacity following allo-HCT are explicable by concomitant skeletal muscle atrophy and mitochondrial dysfunction (60, 61). Indeed, as per-stated, generation of reactive oxygen species is a common effect of allo-HCT conditioning (41), allografting (43), and associated physical inactivity which can perturb homeostatic control of energy balance, upregulate muscle proteolytic and apoptotic signaling pathways, downregulate mitochondrial biogenesis and quality control pathways, and induce mitochondrial dysfunction (62). These deleterious processes may be further exacerbated by indirect treatment effects such as reductions in physical activity and dietary intake (63). Mitochondrial function was not directly assessed in the present study, but we did observe a significant reduction in LM which is a key determinant of VO_2peak and risk factor for CVD (29). Taken together, with the cardiac insults, our results draw attention to the global nature of allo-HCT induced cardiovascular toxicity and highlights the need for cardiovascular preventive therapies capable of preserving and/or augmenting both central and peripheral determinants of VO_2peak.

The strengths of this study include the prospective design, inclusion of a control group and the comprehensive cardiovascular evaluations employed which facilitated a more detailed characterization of the global cardiovascular consequences of allo-HCT than previously documented. A key limitation of the present study is the small cohort size which increases the possibility of type II error and precluded analyses of treatment-related and demographic modifiers of VO_2peak and organ-specific function in our allo-SCT group. Such factors, particularly the impact of conditioning intensity (myeloablative vs. reduced intensity) which presumably impact the degree of cardiovascular damage incurred, warrant investigation in larger studies. Additionally, whilst we may speculate on the evolution of these changes in the years following allo-HCT, the short-term nature of this study limits our ability to explicitly discern the degree to which the observed changes depict persistent cardiovascular dysfunction that may culminate in overt CVD. Longitudinal assessment of these effects over subsequent years will be integral to understand their clinical trajectory and potential clinical significance. The selection of a cancer-free control group may be considered a limitation, however, the challenges associated with recruiting a suitable comparator should be acknowledged. Indeed, whilst ideal, it is implausible to compare to patients with similar hematological malignancies without allo-SCT due to the severity of the underlying illness and need for active treatment. From an alternate perspective, the inclusion of a cancer-free control group effectively highlights the pathological nature of the observed changes seen among allo-SCT recipients and provides important context of the true vulnerability of this high-risk patient group. Finally, we cannot exclude the possibility of subclinical allo-SCT induced vascular toxicity. A more detailed characterisation of effects of allo-HCT on subclinical vascular damage (e.g., endothelial dysfunction, arterial compliance) is required to provide a more complete understanding of the mechanisms underscoring the reduced VO_2peak.

In summary, treatment with allo-HCT was associated with a marked reduction in VO_2peak, reflecting a deterioration in both exercise cardiac reserve and a-vO_2diff. Considering the inverse association between VO_2peak and CVD risk, our results suggest that allo-HCT is a potent accelerator of cardiovascular aging, and provides valuable insight into the potential trajectory and pathogenesis of CVD in allo-HCT survivors. Combining these results with the existing cardiovascular dysfunction identified pre-allo-HCT, our study highlights the urgent need for preventive interventions—initiated early in, or even prior to, the allo-HCT process and capable of targeting the heart and periphery—to mitigate cardiovascular dysfunction in this high-risk patient group.

Data availability statement

The reported data will be shared upon reasonable request to the corresponding author.

Ethics statement

This study was reviewed and approved by the Alfred Hospital Ethics Committee. All experimental procedures conformed to the ethical standards set by the Helsinki Declaration. The patients/participants provided their written informed consent to participate in this study.

Author contributions

EH, BK, DD, ALG, and SA contributed to the conceptualization and design of the study. HD, SF, YH-O, EH, and DK were responsible for participant recruitment. HD, SF, YH-O, and EH conducted data collection. HD, ALG, SF, and EH were responsible for image analyses (DXA, Echo, and CMR). HD and RD conducted the statistical analysis. HD drafted the original manuscript. All authors critically revised the manuscript and approved the final version.

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Conflict of interest

BK was employed by CSL Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.926064/full#supplementary-material

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Traditional risk factors and cancer-related factors associated with cardiovascular disease risk in head and neck cancer patients

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Background: Risk of incident cardiovascular disease (CVD) in head and neck squamous cell carcinoma (HNSCC) patients is under-reported. We assessed the association of HNSCC-related factors and traditional risk factors with 1- and 5-year CVD risk in HNSCC patients without prevalent CVD at cancer diagnosis.

Methods: A clinical cohort of 1,829 HNSCC patients diagnosed between 2012 and 2018, at a National Cancer Institute (NCI)-designated cancer center was included. Information on HNSCC-related factors [HNSCC anatomical subsite, stage at diagnosis, treatment, and tumor human papillomavirus (HPV) status] were extracted from the tumor registry. Data on traditional risk factors (hypertension, dyslipidemia, diabetes, tobacco smoking status, and obesity) were extracted from the electronic health records system (EHR) at baseline (HNSCC diagnosis). A composite of ischemic heart disease, heart failure, and ischemic stroke was the outcome of interest in time to event analysis. Hazard ratio (HR) (95% CI) were reported with death as a competing risk.

Results: In patients diagnosed with HNSCC, 10.61% developed incident CVD events by 1-year post cancer diagnosis. One-year CVD risk was lower in patients using antihypertensive medications at baseline, compared to patients without baseline hypertension [HR (95% CI): 0.41 (0.24–0.61)]. One-year CVD risk was high in patients receiving HNSCC surgery. Patients receiving radiation therapy had a higher 5-year CVD risk than surgery patients [HR (95% CI): 2.17 (1.31–3.04)]. Patients using antihypertensive medications had a lower 5-year CVD risk than patients without baseline hypertension [HR (95% CI): 0.45 (0.22–0.75)]. Older age and diabetes were associated with increased 1- and 5-year CVD risk. HPV-negative patients were older (p 0.006) and had a higher 5-year cumulative incidence of CVD (p 0.013) than HPV-positive patients.

Conclusion: Traditional risk factors and cancer-related factors are associated with CVD risk in HNSCC patients. Future research should investigate the role of antihypertensive medications in reducing CVD risk in HNSCC patients.

KEYWORDS

head and neck cancer, cardiovascular disease, traditional risk factors, hypertension, electronic health records

Introduction

Head and neck cancer (HNC) accounts for approximately 14,600 deaths in the United States (US) annually (1). With advances in cancer screening and use of multimodality treatment, survival has improved in HNC patients (2). However, with increased survival, the disease burden of comorbidities and cancer treatment related side-effects have also increased. Cancer patients and survivors have a higher burden of cardiovascular disease (CVD) than the age-adjusted general population (3–5). Cardiotoxic effects of cancer therapies, especially the usage of anthracyclines, platinum-based agents, targeted kinase inhibitors and 5-fluorouracil in aggravating left ventricular (LV) dysfunction, heart failure, stroke, or myocardial infarction have been reported in cancer patients, including patients with HNC (6–9). Increased risk of cerebrovascular events in HNC patients receiving radiation therapy is also established (10–12). Inflammation, vascular damage, and accelerated atherosclerosis following cancer radiation are responsible for increased risk of stroke or transient ischemic attacks (13). Peri- and post-operative CVD complications in HNC surgery are not uncommon (14–17).

Cancer and CVD share common risk factors including obesity, smoking, and diabetes. Older age and inflammation also play important roles in the pathophysiology of CVD in cancer patients (18). Modifiable risk factors like hypertension, dyslipidemia, and obesity are associated with increased CVD risk in adult survivors of childhood cancer (19). While several studies have reported on CVD morbidity and mortality in cancer patients (19–22), association of traditional risk factors with CVD risk vary by cancer type (22). Literature assessing CVD risk in HNC patients is limited (10) and studies are mostly restricted to older HNC patients who had prevalent CVD events (23, 24).

Our objective was to assess association of head and neck squamous cell carcinoma (HNSCC)-related factors and traditional risk factors with incident CVD events (ischemic heart disease, heart failure, and ischemic stroke) in patients without a prior history of CVD at HNSCC diagnosis.

Materials and methods

Study population

In this clinical cohort, 1,829 consecutive HNSCC patients diagnosed between January 2012 and December 2018, at the University of Alabama at Birmingham (UAB) hospital system and O'Neal comprehensive cancer center (CCC) were included (**Figure 1**). HNSCC patients were identified from the UAB CCC tumor registry and electronic health records (EHR) system using ICD 9/10 diagnosis codes. HNSCC diagnosis codes and histology were confirmed by physician notes and ICD-O-3 histology codes. Patients were included if they met the following inclusion criteria:

a) Confirmed ICD9/10 codes for HNC diagnosis [ICD9 codes: 140.–149., 160. (except 160.1), 161.; ICD10 codes: (C00–C14, C30.0, C31, and C32.)] and histologically confirmed squamous cell carcinoma of head and neck (ICD-O-3 histology codes: 805–808).
b) Had HNSCC diagnosis date.
c) 18 years or above at HNSCC diagnosis (baseline).
d) Did not have any prevalent CVD (ischemic heart disease, heart failure, or ischemic stroke) at baseline.
e) Did not have missing data.

Follow-up data from the EHR were extracted until 31st December, 2020 (end of study period). De-identified data were analyzed. The study was approved by the UAB Institutional Review Board (IRB) and CCC, and a waiver of written informed consent was granted. The first author (AM) had full access to all the data in the study and takes responsibility for its integrity and data analyses.

Outcome of interest

Our outcome of interest was a composite of incident ischemic heart disease, heart failure, and ischemic stroke, whichever occurred first. CVD outcomes were identified and recorded from the EHR at each clinic visit using the following ICD 9/10 codes:

a) ICD-9 codes: 410.–414. (ischemic heart disease), 428. (heart failure), 433.–434. (ischemic stroke if cerebral infarction present).
b) ICD-10 codes: I20.–I25. (ischemic heart disease), I50. (heart failure), and I63.–I64. (ischemic stroke if cerebral infarction present).

For a sub-sample of the study population (n = 200), CVD outcomes were validated by reviewing medical charts (kappa 0.78).

HNSCC-related factors

Data on HNSCC anatomical subsite, stage at diagnosis, treatment, and tumor human papillomavirus (HPV) status were extracted. HNSCC anatomical subsite was categorized as: oral cavity, oropharynx, hypopharynx, nasopharynx-nasal cavity, larynx, and

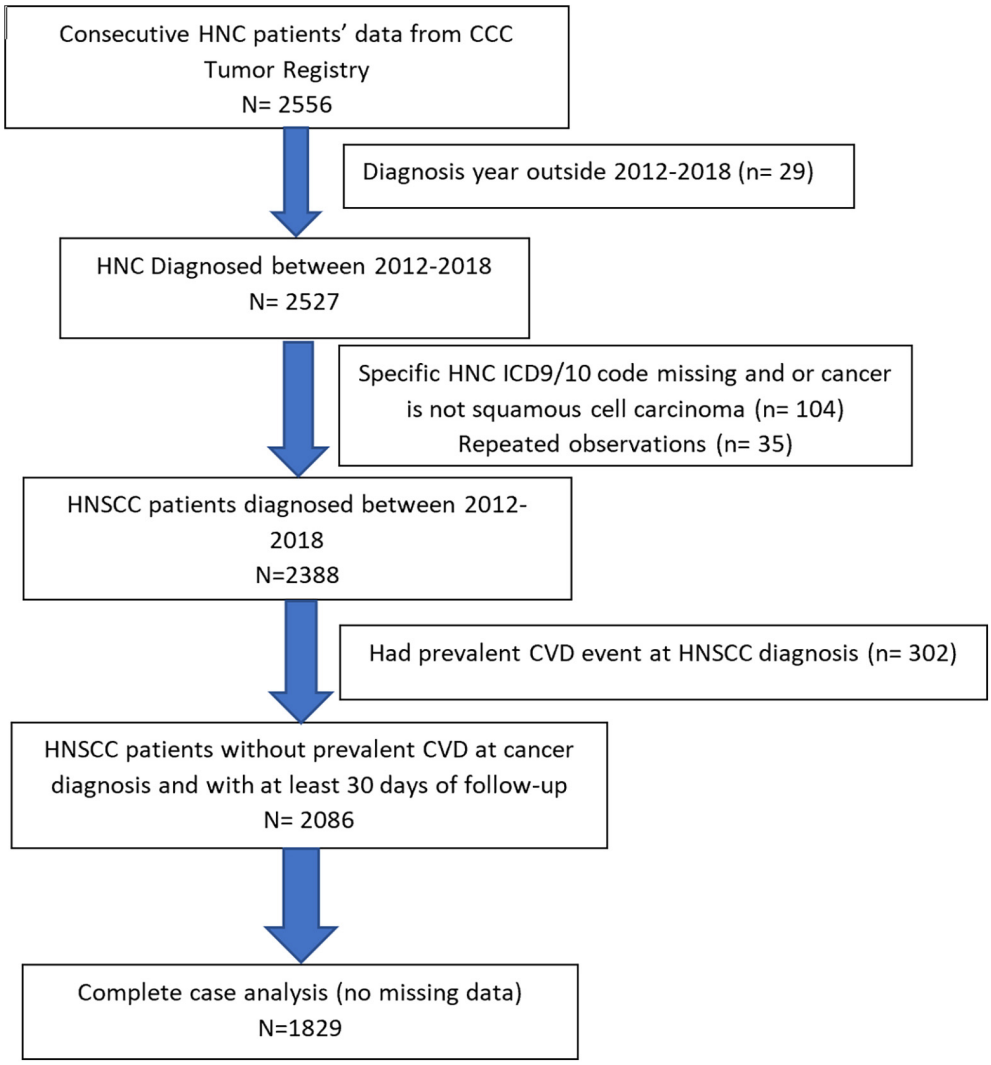

FIGURE 1
Flowchart of head and neck squamous cell carcinoma (HNSCC) study population based on inclusion/exclusion criteria is presented.

major salivary. HNSCC clinical stage at diagnosis was categorized as: early (stages 0/I/II)/advanced (stages III/IV)/other, based on the American Joint Committee on Cancer TNM classification, 7th edition (25). Patients with "incomplete/unstageable/not defined" TNM classification records were grouped in the "other" category. HNSCC treatment had the following categories: only surgery, only chemotherapy, only radiation therapy, chemoradiation, surgery with chemo/radiation, and no HNSCC treatment. Patients in the "no HNSCC treatment" category did not receive surgery, chemotherapy, or radiation for HNSCC, but might have received palliative care or alternate therapy. Data on type of surgery (local excision/wide excision/radical surgery) were also extracted. Information on tumor HPV status was available for a subsample of the study population (n = 567) in the tumor registry. Patients were categorized as HPV positive/negative, based on presence of high-risk HPV types.

Traditional risk factors

Baseline tobacco and alcohol use were categorized into three groups based on patients' self-reports- current users, former users and never. Body mass index (BMI) categories included- non-obese (BMI < 30.0 kg/m^2) and obese (BMI ≥ 30.0 kg/m^2). For clinically diagnosed CVD risk factors- hypertension, dyslipidemia, and diabetes mellitus, a combination of ICD 9/10 codes and medication use/pharmacy records was used (**Supplementary Table 1**). Baseline CVD clinical risk factors were included as categorical variables and had the following categories- absent, present with medication use, and present without medication use.

Other covariates

Information on self-reported socio-demographic variables- age, sex, race, marital status, and geographic location/residence were extracted from the EHR at baseline. Age was included as a continuous variable, as well as a categorical variable- ≤ 45 years, 46 to < 65 years, and 65 years or above. Geographic residence was categorized as rural or urban, based on patients' residential zip-codes. Rural and urban counties were defined based on 2010 United States Census Bureau's urban-rural classification (26).

TABLE 1 Distribution of baseline demographic characteristics, traditional risk factors, and head and neck squamous cell carcinoma (HNSCC)-related variables by incident cardiovascular disease (CVD) status at 1-year post cancer diagnosis, in patients without prevalent CVD at cancer diagnosis.

	All HNSCC patients—no prevalent CVD (*N* = 1,829)	HNSCC patients—no incident CVD at 1-year (*N* = 1,635)	HNSCC patients -incident CVD at 1-year (*N* = 194)	*p*-value
Age at HNSCC diagnosis				
[Median (IQR) years]	61.0 (54.0–68.0)	60.0 (53.0–67.0)	67.0 (61.0–74.0)	**<0.001**
Sex				
Female	464 (25.37)	415 (25.38)	49 (25.26)	0.97
Male	1,365 (74.63)	1,220 (74.62)	145 (74.74)	
Race				
White	1,549 (84.68)	1,378 (84.28)	171 (88.14)	0.25
Black	235 (12.85)	214 (13.09)	21 (10.82)	
Other	45 (2.46)	43 (2.63)	2 (1.03)	
Marital status				
Married/with partner	1,059 (57.90)	950 (58.10)	109 (56.19)	0.24
Divorced/separated/widowed	381 (20.83)	332 (20.31)	49 (25.26)	
Single	389 (21.27)	353 (21.59)	36 (18.56)	
Geographic location (rurality)				
Urban	1,126 (61.56)	1,013 (61.96)	113 (58.25)	0.32
Rural	703 (38.44)	622 (38.04)	81 (41.75)	
Alcohol use				
Current	757 (41.39)	686 (41.96)	71 (36.60)	0.23
Former	141 (7.71)	128 (7.83)	13 (6.70)	
Never	931 (50.90)	821 (50.21)	110 (56.70)	
Tobacco use				
Current	602 (32.91)	546 (33.39)	56 (28.87)	0.43
Former	688 (37.62)	609 (37.25)	79 (40.72)	
Never	639 (29.47)	480 (29.36)	59 (30.41)	
BMI category				
Non-obese	1,339 (73.21)	1,197 (73.21)	142 (73.20)	0.99
Obese	490 (26.79)	438 (26.79)	52 (26.80)	
Hypertension at baseline				
Absent	841 (45.98)	716 (43.79)	125 (64.43)	**<0.001**
Present, use medications	966 (52.82)	901 (55.11)	65 (33.51)	
Present, no medication record	22 (1.20)	18 (1.10)	4 (2.06)	
Dyslipidemia at baseline				
Absent	1,340 (73.26)	1,215 (74.31)	125 (64.43)	**<0.013**
Present, use medications	443 (24.22)	380 (23.24)	63 (32.47)	
Present, no medication record	46 (2.52)	40 (2.45)	6 (3.09)	
Diabetes at baseline				
Absent	1,584 (86.60)	1,429 (87.40)	155 (79.90)	**<0.012**
Present, use medications	226 (12.36)	191 (11.68)	35 (18.04)	
Present, no medication record	19 (1.04)	15 (0.92)	4 (2.06)	
HNSCC anatomical subsite				**<0.014**
Oral cavity	615 (33.62)	536 (32.78)	79 (40.72)	
Oropharynx	602 (32.91)	541 (33.09)	61 (31.44)	
Nasopharynx/nasal cavity	88 (4.81)	80 (4.89)	8 (4.12)	

(Continued)

TABLE 1 (Continued)

	All HNSCC patients—no prevalent CVD (*N* = 1,829)	HNSCC patients—no incident CVD at 1-year (*N* = 1,635)	HNSCC patients -incident CVD at 1-year (*N* = 194)	*p*-value
Hypopharynx	60 (3.28)	56 (3.43)	4 (2.06)	
Larynx	431 (23.56)	397 (24.28)	34 (17.53)	
Salivary	33 (1.80)	25 (1.53)	8 (4.12)	
Clinical stage at diagnosis				
Early (stages 0/I/II)	644 (35.21)	572 (34.98)	72 (37.11)	0.54
Advanced (III/IV)	906 (49.54)	817 (49.97)	89 (45.88)	
Other	279 (15.25)	246 (15.05)	33 (17.01)	
HNSCC treatment category				
Surgery only	725 (39.64)	628 (38.41)	97 (50.00)	**<0.003**
Chemo only	64 (3.50)	63 (3.85)	1 (0.52)	
Radiation only	148 (8.09)	133 (8.13)	15 (7.73)	
Chemoradiation	275 (15.04)	253 (15.47)	22 (11.34)	
Surgery + chemo/rad	347 (18.97)	306 (18.72)	41 (21.13)	
No treatment	270 (14.76)	252 (15.41)	18 (9.28)	
High-risk HPV status				
Positive	324 (17.71)	301 (18.41)	23 (11.86)	**<0.018**
Negative	243 (13.29)	223 (13.64)	20 (10.31)	
Not tested/reported	1,262 (69.00)	1,111 (67.95)	151 (77.84)	

CVD outcomes = composite of ischemic heart disease, heart failure, and ischemic stroke, whichever occurred first; bold = p-value ≤ 0.05.

Statistical analysis

Distribution of baseline demographic characteristics, traditional CVD risk factors, and HNSCC-related variables were reported using median (IQR) or frequency (percentage), as appropriate. For time to event analysis, follow-up started after 30 days post HNSCC diagnosis to make sure that prevalent CVD cases were not included. Patients were followed until they developed the first CVD event (a composite of incident ischemic heart disease, heart failure, and ischemic stroke, whichever occurred first), death, loss to follow-up, or end of study, whichever occurred first.

Proportional hazard assumptions were checked using variable*time interactions and Kolmogorov–Supremum test. Parametric accelerated failure time (AFT) survival models with Weibull distribution were used to assess 1- and 5-year risk of incident CVD events, as the proportional hazards assumptions were not met. Death was treated as a competing risk and the AFT models were censored for death, loss to follow-up, or end of study (follow-up), whichever occurred first. Hazard ratio (HR) was calculated from AFT-Weibull models by exponentiating $-\alpha\beta$, where α is Weibull shape and β is the parameter estimate ($HR = e^{-\alpha\ \beta}$). In the adjusted models, variables with clinical/biological relevance and variables with unadjusted p-value ≤ 0.10 were included. Cumulative incidence of CVD events was plotted.

In sensitivity analysis, separate AFT models were analyzed for association of traditional CVD risk factors and HNSCC-related factors with incident CVD in patients aged < 65 years and in patients ≥ 65 years. Cutoff for age was set at 65 years, as the average age for first CVD event in US men is ~65 years (27). Association of HPV status with CVD, along with CVD cumulative incidence plots by HPV status were reported. Level of statistical significance was set at 0.05. Hazard ratio (HR, 95% CI) and two-sided p-values were reported. All statistical analyses were performed in SAS 9.4 (Cary, NC, USA).

Results

Eighteen hundred twenty-nine HNSCC patients were included in the study. By 1-year post HNSCC diagnosis, 10.61% of all HNSCC patients developed incident CVD events. In patients with incident CVD by 1-year, 83.51% patients had ischemic heart disease, 11.34% had heart failure and 5.15% patients had ischemic stroke as their first CVD event. Baseline demographic characteristics, traditional risk factors, and HNSCC-related factors of all patients and patients by incident CVD status at 1-year post HNSCC diagnosis are reported in **Table 1**. Patients who developed CVD by 1-year were older than patients who did not [median age 67.0 (61.0–74.0) vs. 60.0 (53.0–67.0) years, $p < 0.001$]. Hypertension was the most common CVD clinical risk factor at baseline (54.02%), followed by dyslipidemia (26.74%) and diabetes (13.04%). Nearly half of the HNSCC patients (49.54%) were diagnosed at an advanced AJCC clinical stage. Surgery was the most common HNSCC treatment category (39.64%). Overall, 17.71% of patients had high-risk HPV positive status.

Figure 2 shows adjusted association of traditional CVD risk factors and HNSCC-related factors with risk of incident CVD at 1-year post HNSCC diagnosis. Per 10-year increase in HNSCC diagnosis age was associated with 57% higher 1-year risk of CVD [HR, 95% CI: 1.57 (1.41–1.68)], after adjusting for hypertension, dyslipidemia, diabetes, HNSCC anatomical subsite, clinical stage at diagnosis, and treatment. Hypertensive patients who used

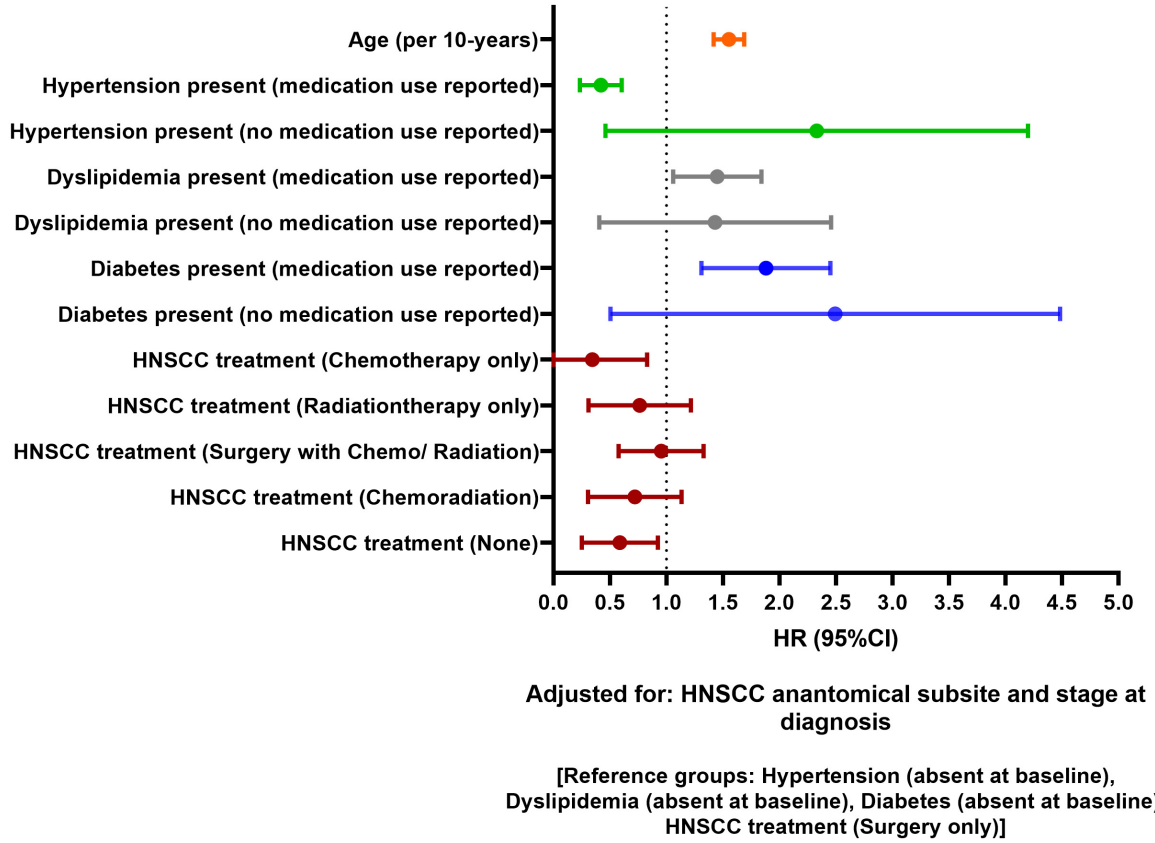

FIGURE 2
Forest plot showing adjusted association of head and neck squamous cell carcinoma (HNSCC)-related factors and traditional risk factors with 1-year cardiovascular disease (CVD) risk in HNSCC patients.

antihypertensive medications at baseline had a lower 1-year risk of incident CVD than patients without hypertension [HR, 95% CI: 0.41 (0.24–0.61)]. Patients with dyslipidemia and diabetes at baseline had higher 1-year CVD risk than patients without the respective CVD risk factors. Compared to patients receiving HNSCC surgery, patients receiving only chemotherapy and no HNSCC treatment had lower 1-year CVD risk in the adjusted model [HR, 95% CI: 0.12 (0.01–0.90) and 0.55 (0.27–0.94), respectively]. No statistically significant association was observed for stage at HNSCC diagnosis and anatomical subsite in the adjusted model. No race or sex-based differences were observed. Unadjusted and adjusted association for 1-year CVD risk is presented in **Supplementary Table 2**.

Cumulative incidence of CVD at 1-year post HNSCC diagnosis varied by HNSCC surgery category (Gray's $p < 0.001$) (**Figure 3A**), with a sharp rise in cumulative incidence observed in the first 90 days in the radical surgery group. Cumulative incidence of CVD at 1-year also varied by baseline hypertension (Gray's p 0.022) (**Figure 3B**). Baseline hypertensive patients who used antihypertensive medications had the lowest cumulative incidence of CVD.

Data on 5-year follow-up was available for 1,054 HNSCC patients. **Figure 4** shows adjusted model for 5-year CVD risk post HNSCC diagnosis. After adjusting for age, race, marital status, baseline tobacco use, stage at diagnosis, hypertension, and diabetes status, HNSCC patients receiving only radiation had 117% higher 5-year risk of CVD than patients receiving only surgery [HR, 95% CI: 2.17 (1.31–3.04)]. Per 10-year increase in age was associated with 79% increase in 5-year risk of CVD [HR, 95% CI: 1.79 (1.54–1.96)]. Tobacco use at baseline (current) was associated with increased 5-year risk of CVD [HR, 95% CI: 2.54 (1.45–3.69)]. Patients who used antihypertensive medications at baseline had lower 5-year CVD risk than patients without hypertension [HR, 95% CI: 0.45 (0.22–0.75)]. Hypertensive patients who did not use antihypertensive medications had higher 5-year CVD risk than patients without hypertension [HR, 95% CI: 5.35 (2.04–10.12)]. Baseline diabetes was associated with increased 5-year CVD risk. Baseline dyslipidemia and stage at HNSCC diagnosis were not associated with 5-year CVD risk. No race or sex-based differences in 5-year risk of CVD were observed. Unadjusted and adjusted association for 5-year CVD risk is presented in **Supplementary Table 3**.

In sensitivity analysis, per 10-year increase in HNSCC diagnosis age was associated with higher 1-year CVD risk, but not with 5-year risk of CVD, in patients aged < 65 years at baseline (data not shown). Cumulative incidence of CVD events at 5-years post HNSCC diagnosis varied by HNSCC treatment category in both HPV-positive and HPV-negative patients (Gray's p 0.019 in both HPV groups) (**Figure 5**). While patients receiving only radiation had higher cumulative incidence irrespective of HPV status, overall cumulative incidence of CVD at 5-years was higher in the HPV-negative group than in HPV-positive patients (Gray's p 0.013). Differences in demographics, traditional risk factors, and HNSCC-related factors by HNSCC treatment category are presented in **Supplementary Table 4**.

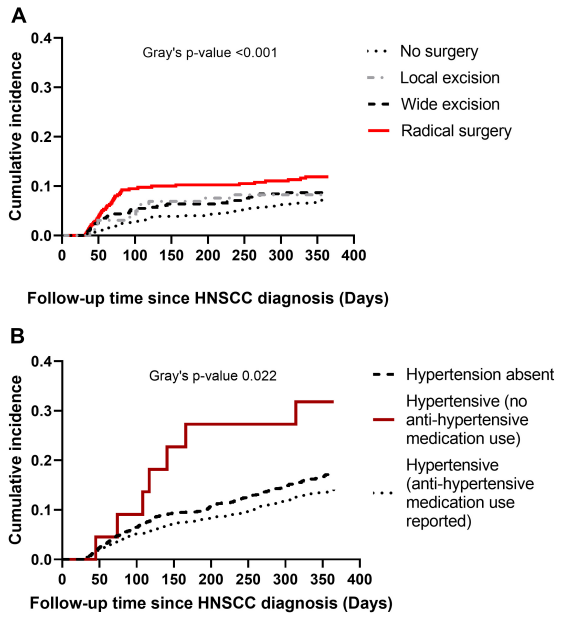

FIGURE 3
Cumulative incidence plots of cardiovascular disease (CVD) at 1-year post head and neck squamous cell carcinoma (HNSCC) diagnosis. Panel **(A)** shows cumulative incidence of CVD by type of HNSCC surgery. Panel **(B)** shows cumulative incidence of CVD by baseline hypertension.

Discussion

This clinical cohort study provides insight into the association of traditional risk factors and cancer-related factors with risk of CVD in patients diagnosed with HNSCC. Antihypertensive medication use at baseline was associated with reduced risk of CVD at 1- and 5-years post HNSCC diagnosis. Older age and diabetes at HNSCC diagnosis increased the risk of CVD at both time-points. Risk of CVD at 1- and 5-years varied by HNSCC treatment category; 1-year CVD risk was high in patients receiving HNSCC surgery, however, patients receiving radiation therapy had higher 5-year CVD risk compared to surgery patients. Compared to HPV-positive patients, HPV-negative patients were older and had a higher 5-year cumulative incidence of CVD.

Peri- and post-operative CVD complications in HNC patients receiving surgery have been reported in literature (16, 17, 24). Older age, extent of surgery, cancer-induced thrombosis, pre-existing comorbidities, previous history of coronary artery disease and heart failure are important predictors of adverse CVD events at 30- and 60-days post HNC surgery (24, 28). In our study, patients receiving HNSCC surgery had high 1-year risk of CVD. Even though immediate post-operative CVD risk was not our outcome of interest, the pattern we observed in cumulative incidence plots suggests association of extent of HNSCC surgery with post-operative CVD risk. Cumulative incidence of CVD was noticeably higher in patients receiving radical surgery during the first 90 days of follow-up; the difference became non-existent at 5-years post HNSCC diagnosis. Increased blood loss and hemodynamic fluctuations following radical surgery may have an influence on acute myocardial infarction. Death as competing risk might partially explain the lack of difference in CVD cumulative incidence at 5-years by surgery type, as patients receiving radical surgery were less likely to be alive by 5-years than other surgery groups (data not shown).

While 1-year CVD risk was lower in patients receiving no HNSCC treatment compared to surgery patients, it is important to note that a higher proportion of HNSCC patients in the "no HNSCC treatment" category had advanced stage at cancer diagnosis and might have died before they developed CVD. Patients receiving radiation therapy had higher 5-year risk of incident CVD than patients receiving surgery; however, no association of radiation therapy with short-term CVD risk was observed. This is not surprising, as previous studies have suggested long latent period between cancer radiation therapy and established atherosclerosis (12, 29). Even though dose-response relationship between HNC radiation and risk of ischemic stroke at 5-years post radiation therapy has been suggested (11), limited data availability restricted us from assessing incident CVD risk based on radiation dose. While a higher risk of myocardial infarction has been suggested in patients receiving chemotherapy (30), we observed no difference in CVD risk based on bolus and weekly administration of platinum-based chemotherapy in patients receiving chemotherapy only. The lack of difference could be due to small sample size in the chemotherapy only group. Five-year risk of CVD was not higher in patients who received chemoradiation compared to surgery patients. This is unexpected as chemoradiation is hypothesized to be associated with higher adverse cardiovascular events. However, in our study population, we observed statistically significant differences in demographics, traditional risk factors, and HNSCC-related factors between the different HNSCC treatment categories. Despite having an advanced TNM stage at HNSCC diagnosis, a higher proportion of patients who received chemoradiation were young, had oropharynx cancer, and had HPV-positive status than patients who received radiation only or surgery only. The combination of these factors could partly explain lower CVD risk in patients who received chemoradiation compared to radiation only patients. This finding also reiterates the lack of association between HNSCC stage at diagnosis and CVD risk.

Association of oncogenic HPV infection with increased risk of cardiovascular events has been suggested in women with vaginal HPV infection (31). Data on HPV and CVD and cerebrovascular event risk in HNC patients, however, are not conclusive. Addison et al. reported four-times higher risk of cerebrovascular events in HPV-positive patients compared to HPV-negative patients receiving radiation therapy (32); they also suggested that difference in cerebrovascular risk by HPV status became evident ∼2 years after radiation therapy and persisted throughout follow-up (32). On the contrary, Eytan et al. reported lower cumulative probability of congestive heart failure, myocardial infarction, and angina in HPV-positive patients at 5-years, with no difference in cumulative probability of stroke by HPV status (33). We also observed a higher 5-year cumulative incidence of CVD in HPV-negative patients than in HPV-positive patients. The cumulative incidence was consistently higher in HPV-negative patients for each HNSCC treatment category than in HPV-positive patients. Like previous studies (2, 34), HPV-positive patients in our study were diagnosed at a younger age and had better survival at 5-years. In sensitivity analysis, higher 5-year CVD risk persisted in HPV-negative patients, after adjusting for age; the association became statistically non-significant when we adjusted for HNSCC treatment. However, we did not adjust for changes in risk factors over time, as well as for overall comorbidity status; it is possible that residual confounding is there. Unlike Addison's study that assessed association of HPV with stroke and transient ischemic

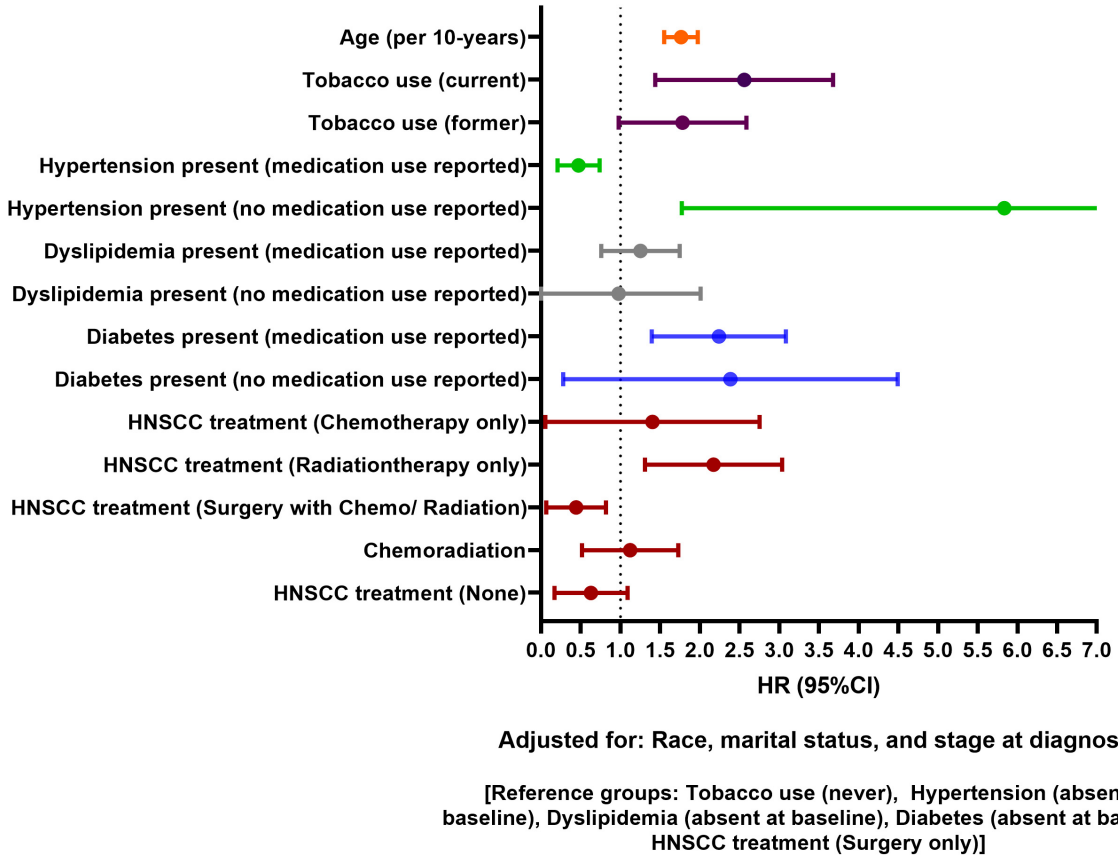

FIGURE 4
Forest plot showing adjusted association of head and neck squamous cell carcinoma (HNSCC)-related factors and traditional risk factors with 5-year cardiovascular disease (CVD) risk in HNSCC patients.

attack (32), our findings were driven by ischemic heart disease as the most common incident CVD outcome; we did not have enough ischemic stroke events to assess the association of HPV status with stroke separately.

Patients who used antihypertensive medications at baseline had significantly lower CVD risk at all time points. Even though association of hypertension and or antihypertensive medication use with incident CVD outcomes has not been reported widely in HNC literature (10), these associations have been reported in other cancer types (22, 35, 36). Strongman et al. reported increased risk of heart failure in non-Hodgkin's lymphoma patients who did not have hypertension at baseline. In patients with breast cancer, the evidence is somewhat conflicting. While some studies reported beta blockers to be more favorable in reducing chemotherapy induced cardiac events than other antihypertensive medication classes (35–37), others did not report superiority of either while comparing angiotensin converting enzyme inhibitors with beta blockers (38), and angiotensin II receptor blockers with beta blockers (39), Even though our cumulative incidence plot by hypertension status suggests protective effects of antihypertensive medication use, no statistically significant differences were observed in risk of incident CVD by antihypertensive medication types (data not shown). Future studies are needed to assess role of antihypertensive medications in reducing CVD risk in large, diverse HNSCC populations. Unlike antihypertensive medications, we did not observe any cardio-protective effects of lipid lowering medications or antidiabetic medications on incident CVD risk. Patients with diabetes at baseline had consistently higher CVD risk than patients without diabetes.

In all our models, age was a strong predictor of incident CVD. When stratified by age group, older age was associated with 1-year risk of incident CVD, but not with 5-year CVD risk in patients aged < 65 years. Age is not a modifiable risk factor, but the fact that 5-year risk of incident CVD did not increase with age in patients < 65 years has important clinical implications. Proactive screening and monitoring of modifiable risk factors in patients aged < 65 years can reduce the burden of CVD. Role of obesity in HNC patients is conflicting. While some studies report inverse association of BMI with HNC risk and survival (40, 41); others have identified obesity to be a risk factor for HNC (42). We did not observe any association between obesity and incident CVD in our study population, however, it would be too early to conclude lack of association based on BMI as the only indicator of adiposity. Patients who continue smoking post HNC therapy have a poorer prognosis (43). While current tobacco users had higher 5-year risk of CVD compared to never users, no association was observed between tobacco use and 1-year CVD risk. It is possible that tobacco use was under-reported in our study. It is also possible that altered tobacco habit following HNSCC diagnosis might have impacted CVD risk to some extent (44). However, more studies are needed to determine if the same is true for tobacco use in other HNSCC populations.

Our study had some limitations. Like any other cancer registries and EHR databases, information of HNSCC stage at diagnosis and

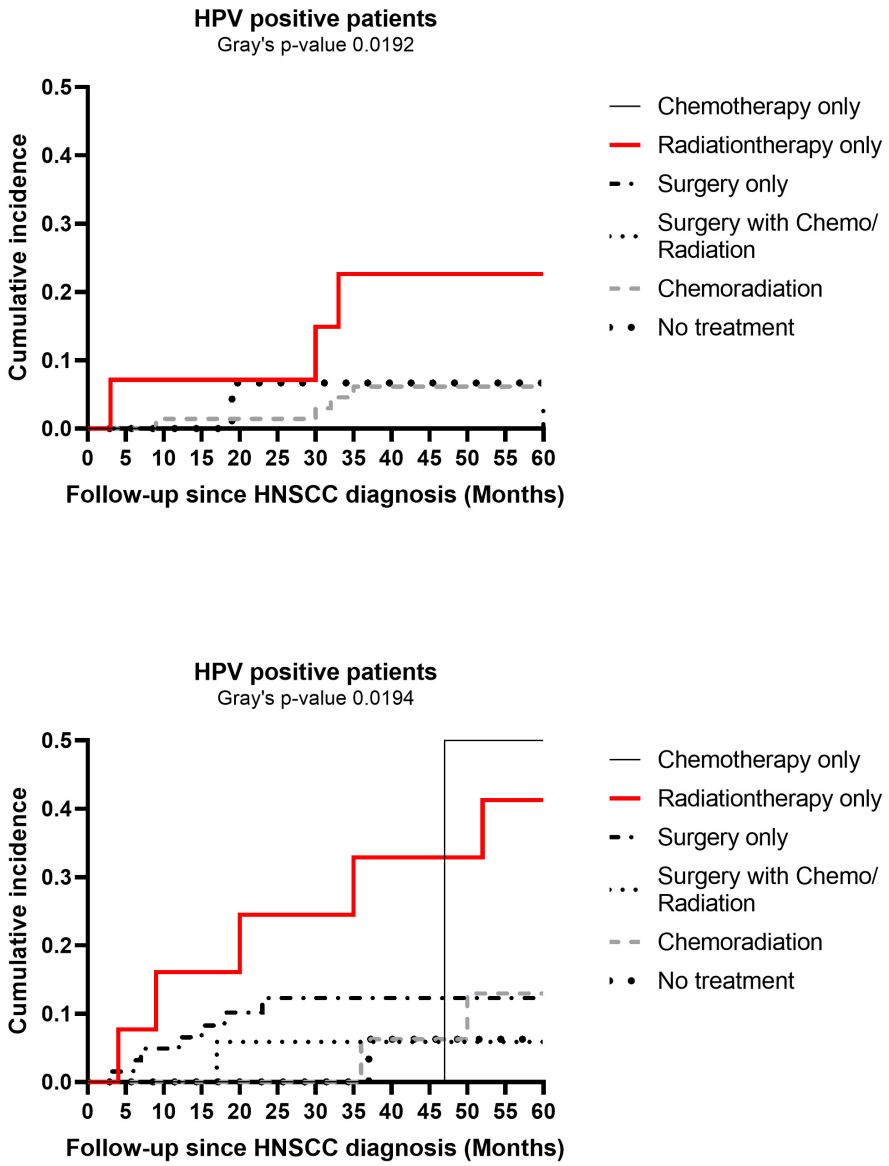

FIGURE 5
Cumulative incidence plots of cardiovascular disease (CVD) at 5-years post head and neck squamous cell carcinoma (HNSCC) diagnosis by human papillomavirus (HPV) status. Cumulative incidence plots of CVD at 5-years by cancer treatment categories are shown separately for HPV-positive and HPV-negative HNSCC patients.

treatment was incomplete for few patients. We did not have data available on radiation therapy dose, fractionation, or techniques; but these are limitations of using real-world clinical data that we could not address in our study. Under-reporting of CVD risk factors and CVD outcomes in the EHR is also possible, as not all cancer patients come to UAB for their primary care. We did not have information on amount and frequency of tobacco and alcohol use. However, differential bias is less likely as we included EHR data on consecutive HNSCC patients from all UAB clinics. Since ischemic heart disease was the most common incident CVD event in our study population; we did not have enough statistical power to assess risk of heart failure and ischemic stroke separately. Also, ischemic heart disease represents a broad spectrum of presentations ranging from asymptomatic stable coronary disease to acute myocardial infarction. Limited sample size restricted us from further delineating acute events.

Despite the noted limitations, our study provides insight in the complicated association of cancer-related factors and traditional risk factors with incident CVD risk in HNSCC patients. Confirmation of clinical data using medical charts improved validity of our findings. Our results highlight plausible association of antihypertensive medication use with risk of incident CVD in HNSCC patients and may help in identifying HNSCC patients who are at high risk of incident CVD during follow-up. Future research should focus on prophylactic use of antihypertensive, lipid-lowering, and antidiabetic medications, and role of HPV in CVD risk in HNSCC patients.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Data are not publicly available. The datasets

analyzed during the current study are available from the corresponding author on reasonable request. Requests to access these datasets should be directed to AM, amrita.x.mukherjee@kp.org.

Ethics statement

The studies involving human participants were reviewed and approved by the University of Alabama at Birmingham (UAB), Institutional Review Board (IRB), O'Neal Comprehensive Cancer Center Tumor Registry. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AM and SS contributed to the conception of research hypothesis, study design, and data acquisition. AM contributed to the data analysis, interpretation, and manuscript writing. SS, HW, and RG provided the feedback on analysis and interpretation of results. AM and AC contributed to the adjudication of clinical risk factors. CL, AC, LN, and CEL critically reviewed the manuscript and provided the clinical expertise in interpretation of results. All authors gave their final approval and are responsible for the content of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1024846/full#supplementary-material

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Incidence of adverse cardiovascular events associated with immune checkpoint inhibitors and risk factors for left ventricular dysfunction: A single-center prospective clinical study

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Background: The incidence of immune checkpoint inhibitors (ICI)-related adverse cardiovascular events (ACEs) may be underestimated, and there are few reports on the incidence and risk factors of ICI-induced left ventricular dysfunction (LVD).

Objectives: This study aimed to investigate the incidence of ACEs caused by ICI, in particular to analyze the incidence and risk factors of LV systolic and diastolic dysfunction.

Materials and methods: A prospective clinical study was performed on patients who received ICI in our hospital from November 2020 to October 2021. They received regular cardiovascular examinations, including echocardiography, ECG, cTnT, and NT-proBNP, etc. The incidence of various ACEs was counted, and the risk factors of LVD were analyzed.

Results: A total of 106 cancer patients treated with ICI were recruited. During the follow-up, 41 patients (38.68%) developed various ECG abnormalities, 39 patients (36.79%) developed LVDD, 9 patients (8.49%) developed CTRCD, and 2 patients (1.89%) developed new pericardial effusion. The patients with elevated cTnT, CK-MB, and NT-proBNP were 10 (9.43%), 8 (7.55%), and 8 (7.5%), respectively. Thirteen of the 52 patients with LVD had hypertension, while 4 of the 54 patients without LVD had hypertension (OR = 4.17, 95% CI: 1.26–13.78; P = 0.019). The baseline LVEF and LVFS of patients with LVD were 61.54 ± 4.15% and 33.78 ± 2.73%, while those of the control group were 64.16 ± 3.68% and 34.95 ± 2.84, respectively (P = 0.003 and P = 0.048). Compared with patients without LVD, patients with LVD had lower e' (6.99 ± 1.33 cm/s vs. 7.64 ± 1.39 cm/s, P = 0.029) and higher E to e' ratio (11.89 ± 3.15 cm/s vs. 10.43 ± 2.52, P = 0.024). Multiple regression analysis showed that a history of hypertension (HR = 26.52, 95% CI: 2.479–283.667, P = 0.007) and lower baseline e' (HR = 0.04, 95% CI: 0.003–0.709, P = 0.028) were risk factors for developing LVD.

Conclusion: Patients treated with ICI may develop multiple ACEs, including acute myocarditis, pericarditis, ECG abnormalities, and elevated cardiac biomarkers. ICI may lead to a high incidence of LVD, and echocardiography is helpful for early detection of LVD. Patients with hypertension or poor LV systolic or diastolic function at baseline were predictors of LVD after ICI treatment.

KEYWORDS

immune checkpoint inhibitor, cardiotoxicity, left ventricular dysfunction, myocarditis, myocardial fibrosis

Background

Immune checkpoints are a series of cellular receptors expressed on the cell surface that play a role in negative immune regulation. They play an important role in maintaining immune system balance and preventing autoimmunity (1). Currently, cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) are the most studied immune checkpoints. Immune checkpoint inhibitors (ICIs) are specific monoclonal antibodies against these immune checkpoints, which can activate the immune system to kill tumor cells (2). In the past 10 years, various ICIs have been gradually applied in clinical practice and have become a new progress in the field of tumor therapy (3, 4). However, activation of the immune system by ICI may lead to immune damage to one's own tissues or organs. In recent years, there have been numerous reports of immune-related adverse events (irAEs) in cancer patients treated with ICI, some of which were fatal (5, 6). Among them, although the incidence of adverse cardiovascular events (ACEs) caused by ICI is low, serious consequences and even death have occurred in some patients. In the past few years, reports of fulminant myocarditis or fatal heart failure caused by ICI have attracted the attention of the medical community (7–9).

However, ICI have only been used clinically for a few years and there is limited understanding of their cardiotoxicity. Current studies on ICI-related cardiotoxicity are mostly case reports, database-based statistical analyses, or retrospective studies, and the incidence of ACEs may be underestimated. On the other hand, most patients treated with ICI do not undergo regular echocardiography, resulting in limited data on left ventricular dysfunction (LVD), and the risk factors are poorly understood. LVD includes LV systolic and diastolic dysfunction. LV systolic dysfunction is one of the major cardiovascular complications associated with oncology drugs (10), known as cancer therapy-related cardiac dysfunction (CTRCD). LV diastolic dysfunction (LVDD) is associated with both cardiovascular and non-cardiovascular mortality (11), and cancer treatment may also contribute to LVDD (12). A study suggested that the development of LVDD in cancer patients may be significantly associated with the development of systolic dysfunction and all-cause mortality (13). However, studies on the incidence of LVDD caused by ICI are currently lacking.

This study is a prospective clinical study, and the purpose of our study is to regularly monitor the occurrence of cardiotoxicity in patients treated with ICI by electrocardiography (ECG), echocardiography, cardiac biomarkers, etc. In particular, echocardiography is used to detect LVD, including CTRCD and LVDD, and then we will count their incidence and screen for clinical predictors of LVD development through statistical analysis.

Materials and methods

Study population

This prospective study included all cancer patients who received ICI at the First Affiliated Hospital of Chongqing Medical University from November 1, 2020 to October 31, 2021. Members of our research team assessed the clinical status of these patients and interviewed patients who met the inclusion criteria. Patients were included in the study if they agreed to undergo periodic examinations, such as ECG, cardiac biomarkers, and echocardiography, as well as clinical follow-up if necessary.

Inclusion criteria

(1) The patient received at least 2 cycles of ICI treatment; (2) Patients agreed to undergo at least one ECG, cardiac biomarker, and echocardiogram before and after treatment; (3) Before receiving ICI, the patient's cardiac function was assessed as grade 3 or less by NYHA criteria. If the patient underwent echocardiography, the left ventricular ejection fraction (LVEF) should be greater than or equal to 50%.

Exclusion criteria

(1) Received known cardiovascular toxicity drugs, such as anthracyclines, HER-2 targeted drugs, etc., at the same time or within 3 months of ICI treatment; (2) Before receiving ICI, the patient's cardiac function was assessed as grade 4 according to NYHA criteria, or there was a history of myocardial infarction or acute heart failure within 3 months, or the LVEF by echocardiography was less than 50%; (3) Clinically diagnosed with acute viral myocarditis or infective endocarditis within 30 days; (4) Severe liver or renal insufficiency; (5) Severe pneumonia or respiratory failure; (6) A history of cardiomyopathy such as dilated cardiomyopathy, alcoholic cardiomyopathy, and myocardial amyloidosis; (7) The electrocardiogram showed atrial flutter or atrial fibrillation.

Basic information

Patients included in the study were asked to provide a detailed medical history and to undergo a physical examination after

admission. Basic information is recorded in detail, including the patient's clinical diagnosis: type and stage of cancer, and whether surgery was performed; demographic characteristics, including the patient's sex, age, height, weight, nicotine/tobacco use history, and alcohol intake; history of cardiovascular disease and risk factors; details of use of conventional chemotherapy drugs or ICI. ECG, chest computer tomography (CT), and cardiac biomarkers including cardiac troponin T(cTnT) and N-terminal pro brain natriuretic peptide (NT-proBNP) were performed on patients before and during treatment with ICI, and the results were recorded in detail.

Cardiac function assessed by echocardiography

Echocardiography was performed in accordance with the 2019 American Society of Echocardiography (ASE) guidelines for adult echocardiography (14). The examination items include the diameter of the heart chambers, the systolic and diastolic function of the LV. The evaluation indexes of LV systolic function were LVEF and left ventricular fraction shortening (LVFS), and LVEF was measured by biplane Simpson method.

The evaluation indexes of LV diastolic function were peak early diastolic mitral inflow velocity (E), peak early diastolic mitral annulus velocity (e') and the ratio of the two (E/e') (15). E was obtained from color flow imaging of the mitral valve obtained by pulsed-wave doppler imaging. e' (septal and LV lateral wall) was measured by tissue doppler imaging (TDI). E/e' is calculated by dividing the mitral valve E velocity by the mitral annular e' velocity.

Study endpoints

1) ICI-associated myocarditis: (1) Endomyocardial biopsy or autopsy with typical histological features of myocarditis; or (2) Guidelines-recommended scoring system for clinically suspected myocarditis, including clinical, biomarker, and imaging features (16).

2) New abnormal ECG, abnormal cardiac biomarkers, pericardial effusion. Among them, abnormal biomarkers were defined as cTnT $>$ 0.030 μg/L or NT-proBNP $>$ 300 ng/L.

3) CTRCD: LVEF decreased by $\geq$ 10% from baseline and absolute value $<$ 50% (17).

4) LVDD: Meet the following two. (1) E/e' $>$ 14. (2) At the level of the LV mitral annulus, e' $<$ 7 cm/s on the septal side or e' $<$ 10 cm/s on the LV lateral wall (15).

Statistical analysis

Continuous variables such as age, weight, etc., were described as mean ± standard deviation, and categorical variables such as gender, history of hypertension, etc., were described as percentages. According to pre-defined criteria, the number of patients with LVD (including CTRCD and LVDD) after receiving ICI was counted, and the percentage was calculated. Pericardial effusion, abnormal ECG and abnormal cardiac biomarkers were counted after ICI treatment, and results are presented as number of cases and percentages. The average value of LV cardiac function before and after ICI treatment in cancer patients was counted.

Statistical analysis was performed using SPSS 21.0 statistical software (IBM, Armonk, New York, USA). The K-S test was used to assess its normality. Continuous variables were compared using Student's *t*-test or Wilcoxon rank-sum test based on their normality. One-way ANOVA was used to compare the means of 3 groups or more. Univariate and multivariate regression were used to analyze risk factors for LVDD. All *P*-values are two-sided, with $P < 0.05$ considered statistically significant.

Ethical approval and informed consent

This study was conducted in strict accordance with the requirements of the Declaration of Helsinki. Our research also passed the ethics review by the Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (ethics number, 2018-10-2).

Results

Basic characteristics

Demographic characteristics

A total of 106 cancer patients treated with ICI were included in this study, and the mean follow-up time was 4.7 months. The average age was 60.08 ± 8.47 years (35–76 years), and the proportion of males was 85.8% (91/106). The mean body weight was 60.95 ± 9.48 kg, the mean BMI was 22.56 ± 2.93, and 17 patients had a BMI greater than 25. The mean systolic blood pressure (SBP) of the included patients was 124.01 ± 16.25 mmHg and diastolic blood pressure (DBP) was 76.94 ± 9.37 mmHg. According to the diagnostic criteria for elevated blood pressure (SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg), 26 patients had elevated SBP and 4 patients had elevated DBP. The average heart rate was 83.35 ± 10.22 beats/min, more than 100 beats/min in 5 people, and less than 60 beats/min in 1 person (**Table 1**).

Cancer types and treatment drugs

Of the 106 cancer patients treated with ICI, 62 (58.5%) were diagnosed with lung cancer, 31 (29.2%) with esophageal cancer, and 13 (12.3%) with other cancers. There were 4 (3.8%) patients in stage 1, 32 (30.2%) in stage 2, 47 (44.3%) in stage 3, 23 (21.7%) in stage 4, and 58 patients underwent surgery. The most commonly used ICI include carrelizumab, pembrolizumab, and tislelizumab (**Table 2**). In addition to ICI, most patients received conventional chemotherapy, the most common of which were docetaxel and albumin-paclitaxel (**Table 3**).

History of cardiovascular disease and its risk factors

Seventeen patients (16.0%) had a history of hypertension. There were 3 patients with coronary heart disease and 3 patients with diabetes (2.8% each). There were 56 cases (52.8%) with long-term smoking history and 34 cases (32.1%) with long-term drinking history (**Table 1**).

ICI-related adverse cardiovascular events

In this study, ECG, cardiac biomarkers, echocardiography, etc., were used to detect ICI-related ACEs. Among the 106 patients, one patient (0.94%) developed ICI-associated myocarditis and died during hospitalization. Forty-one patients (38.68%) had new-onset ECG abnormalities, 39 patients (36.79%) had LVDD, and 9 patients (8.49%) had CTRCD. Two patients (1.89%) developed new pericardial effusion. Some patients had elevated cardiac biomarkers, including 10 patients (9.43%) with elevated cTnT, 8 patients (7.55%)

TABLE 1 Baseline characteristics of patients and univariate regression analysis between studied parameters and left ventricle (LV) dysfunction.

	Total (*n* = 106)	Normal (*n* = 54)	LV dysfunction (*n* = 52)	Unadjusted OR (95% CI)	*P*-value
Demographic characteristics					
Sex (male)	91 (85.8)	46 (85.2)	45 (86.5)	1.12 (0.37–3.34)	0.842
Age (years)	60.08 ± 8.47	59.04 ± 9.41	61.17 ± 7.31	1.03 (0.98–1.08)	0.196
Wight (kg)	60.95 ± 9.48	60.94 ± 9.95	60.95 ± 8.97	1.00 (0.96–1.04)	0.997
BMI	22.56 ± 2.93	22.68 ± 2.98	22.44 ± 2.90	0.97 (0.85–1.11)	0.678
HR (bpm)	83.35 ± 10.22	84.28 ± 10.87	82.38 ± 9.51	0.98 (0.94–1.02)	0.343
SBP (mmHg)	124.01 ± 16.25	121.87 ± 14.76	126.23 ± 17.54	1.02 (0.99–1.04)	0.171
DBP (mmHg)	76.94 ± 9.37	76.11 ± 7.47	77.81 ± 11.01	1.02 (0.98–1.06)	0.352
Cancer type				0.80 (0.46–1.38)	0.414
Lung cancer	62 (58.5)	29 (53.7)	33 (63.4)	1.50 (0.69–3.26)	0.309
Esophageal cancer	31 (29.2)	18 (33.3)	13 (25.0)	0.67 (0.29–1.55)	0.347
Other cancer	13 (12.3)	7 (13.0)	6 (5.7)	2.62 (0.75–9.10)	0.130
Surgorn	59 (55.7)	31 (57.4)	28 (53.8)	0.87 (0.40–1.86)	0.712
Cancer stage				0.96 (0.60–1.55)	0.873
Stage 1	4 (3.8)	1 (1.9)	3 (5.8)	3.25 (0.33–32.2)	0.315
Stage 2	32 (30.2)	17 (31.5)	15 (28.8)	0.88 (0.39–2.03)	0.768
Stage 3	47 (44.3)	25 (46.3)	22 (42.3)	0.85 (0.40–1.83)	0.680
Stage 4	23 (21.7)	11 (20.4)	12 (23.1)	1.17 (0.47–2.96)	0.736
Cardiovascular disease and its risk factors					
Smoking	56 (52.8)	30 (55.6)	26 (50.0)	0.80 (0.37–1.72)	0.567
Drinking	34 (32.1)	20 (37.0)	14 (26.9)	0.63 (0.27–1.43)	0.266
Hypertension	17 (16.0)	4 (7.4)	13 (25.0)	4.17 (1.26–13.78)	0.019
Diabetes	3 (2.8)	2 (3.7)	1 (1.9)	0.51 (0.05–5.80)	0.587
CHD	3 (2.8)	3 (5.6)	0	–	–
Cardiac biomarker					
CK-MB	1.002 ± 0.294	1.045 ± 0.640	0.958 ± 0.640	0.80 (0.43–1.51)	0.494
cTnT (μg/L)	0.0083 ± 0.0041	0.0086 ± 0.0041	0.0081 ± 0.0040	0.00 (0.00–1430)	0.483
NT-proBNP (ng/L)	72.24 ± 63.91	82.93 ± 79.84	61.55 ± 40.75	0.99 (0.99–1.00)	0.148
Structure and function of left ventricle					
LVEDd (mm)	46.05 ± 3.75	46.19 ± 3.37	45.94 ± 4.09	0.98 (0.88–1.10)	0.751
IVS (mm)	10.140 ± 1.07	10.02 ± 1.080	10.24 ± 1.06	1.21 (0.82–1.79)	0.329
LVPW (mm)	9.76 ± 1.04	9.67 ± 1.04	9.84 ± 1.04	1.17 (0.79–1.74)	0.441
LA (mm)	29.98 ± 3.40	29.28 ± 3.05	30.58 ± 3.60	1.13 (0.99–1.28)	0.070
LVEF (%)	62.75 ± 4.13	64.16 ± 3.68	61.54 ± 4.15	0.85 (0.76–0.95)	0.003
LVFS (%)	34.32 ± 2.83	34.95 ± 2.84	33.78 ± 2.73	0.86 (0.74–1.00)	0.048
E (cm/s)	79.79 ± 18.93	77.93 ± 16.59	81.46 ± 20.84	1.01 (0.99–1.03)	0.382
e' (cm/s)	7.30 ± 1.39	7.64 ± 1.39	6.99 ± 1.33	0.69 (0.50–0.96)	0.029
E/e'	11.20 ± 2.94	10.43 ± 2.52	11.89 ± 3.15	1.22 (1.03–1.45)	0.024

LV, left ventricle; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; CK-MB, creatine kinase isoenzyme-MB; cTnT, cardiac troponin T; NT-proBNP, N-terminal pro brain natriuretic peptide; LVEDd, left ventricular internal dimension diastole; IVS, interventricular septal thickness diastolic; LVPW, left ventricular posterior wall; LA, left atrial diameter; LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening; E, peak early diastolic mitral inflow velocity; e', peak early diastolic mitral annulus velocity; E/e', the ratio of E to e'; OR, odd ratio; CI, confidence interval.

TABLE 2 The most commonly used immune checkpoint inhibitors (ICI) and their doses and frequencies.

Drug	Drug target	Approval agency	The usual dose and cycle of the drug		
Camrelizumab	PD-1	NMPA	200 mg	IV	Q3W
Tislelizumab	PD-1	NMPA	3 mg/kg	IV	Q3W
Pembrolizumab	PD-1	FDA, NMPA	2 mg/kg	IV	Q3W
Toripalimab	PD-1	NMPA	3 mg/kg	IV	Q3W
Durvalumab	PD-L1	FDA, NMPA	10 mg/kg	IV	Q3W
Navulumab	PD-1	FDA, NMPA	3 mg/kg	IV	Q3W
Sintilimab	PD-1	NMPA	200 mg	IV	Q3W

PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; FDA, food and drug administration; NMPA, national medical products administration.

TABLE 3 Traditional chemotherapeutic drugs and their commonly used methods.

Drug	The usual dose and cycle of the drug		
Docetaxel	75 mg/m^2	IV	Q3W
Albumin paclitaxel	260 mg/m^2	IV	Q3W
Nedaplatin	75 mg/m^2	IV	Q3W
Etoposide	150 mg (D1–D3)	IV	Q3W
Gemcitabine	1,250 mg/m^2	IV	Q3W
Paclitaxel	100 mg/m^2	IV	Q3W

with elevated creatine kinase isoenzyme-MB (CK-MB), and 8 patients with elevated NT-proBNP (7.55%) (Figure 1).

ICI-associated myocarditis

One patient developed ICI- associated myocarditis after receiving ICI. The patient is a 70-year-old man with right lung adenocarcinoma with bone metastases (Figure 2). Tumor stage was T2aN0M1cIVB. He had a history of hypertension (grade 3) for 6 years, and no history of diabetes or coronary heart disease. During the first hospitalization, cTnT, NT-proBNP, ECG, and echocardiogram were all normal. The first cycle was treated with 800 mg of pemetrexed and 130 mg of nedaplatin. Three weeks later, he was re-hospitalized for a second cycle of oncology treatment with pemetrexed 800 mg, nedaplatin 130 mg, and camrelizumab (a monoclonal antibody against PD-1) 200 mg. On day 20 after receiving camrelizumab, the patient developed shortness of breath. His self-measured heart rate was 34 beats per minute, and he had no chest pain, amaurosis, or syncope. He went to a nearby hospital for an ECG examination, which showed a third degree atrioventricular block. Laboratory tests showed CK-MB 31.5 ng/ml, myoglobin 1,103 ng/ml, cTnT 5.8 ng/ml, and NT-proBNP 1,280 ng/L. He was diagnosed with coronary heart disease and received related treatment, but his symptoms did not improve after 3 days.

On day 24 after receiving camrelizumab, he was admitted to the department of cardiovascular medicine of our hospital, and the ECG showed: (1) Sinus tachycardia; (2) Third-degree atrioventricular block with frequent accelerated idioventricular rhythm, ventricular escape; (3) Frequent multifocal premature ventricular contractions and short paroxysmal ventricular tachycardia; (4) Damaged ST-segment elevation in anterior wall and right ventricular leads. Echocardiography showed enlargement of right atrium and right ventricle; hypokinesis of right ventricular wall with decreased function; uncoordinated motion of LV wall and decreased LV function; moderate tricuspid regurgitation. Laboratory tests showed higher cardiac biomarkers than before. After discussion with the oncologist, the diagnosis of ICI-associated myocarditis was made. A temporary pacemaker was installed, and the ECG showed ventricular pacing rhythm. On the 26th day, intravenous infusion of methylprednisolone 1 g/d was given, but the patient gradually developed dyspnea, heart function got worse. The ECG on day 30 showed complete atrioventricular disjointness, junctional tachycardia, and anterior myocardial injury (Figure 3). The patient developed cardiac arrest in the early morning of the 31st day after receiving ICI, ECG monitoring showed pacing signal but no QRS complex and

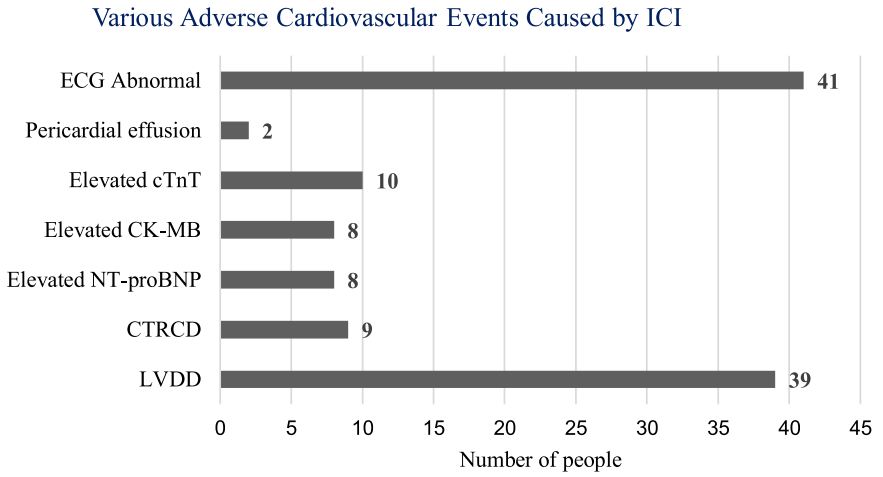

FIGURE 1
Number of adverse cardiovascular events caused by immune checkpoint inhibitors (ICI). ECG, electrocardiogram; cTnT, cardiac troponin T; CK-MB, creatine kinase isoenzyme-MB; NT-proBNP, N-terminal pro brain natriuretic peptide; CTRCD, cancer therapy-related cardiac dysfunction; LVDD, LV diastolic dysfunction.

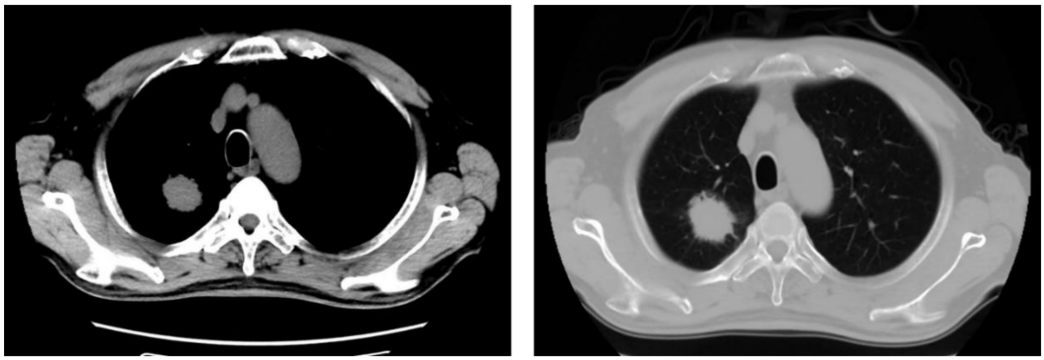

FIGURE 2
Chest computer tomography (CT) showed a space-occupying lesion in the right lung.

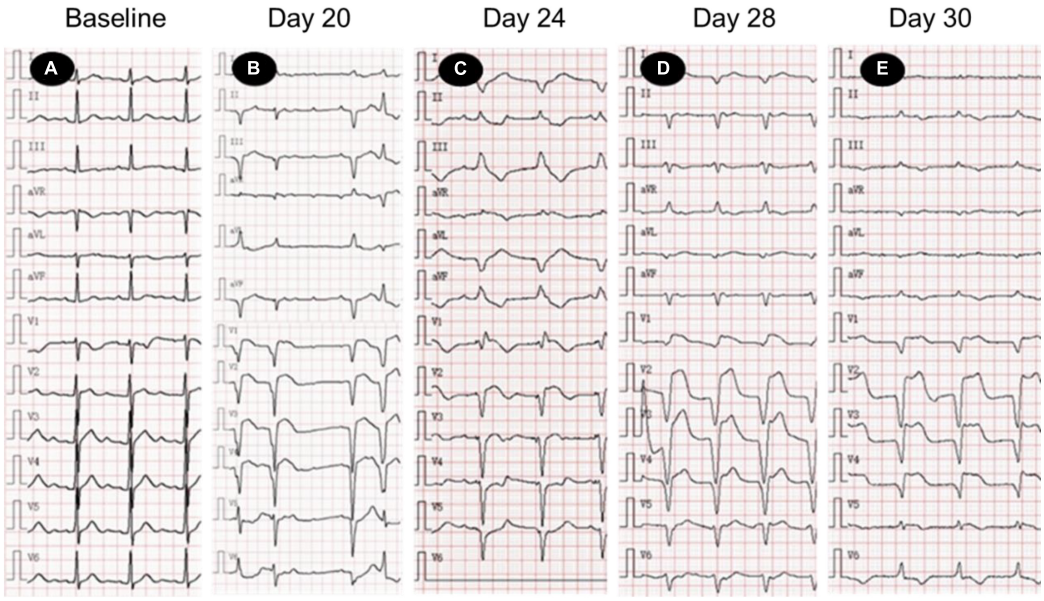

FIGURE 3
Electrocardiogram (ECG) changes in patients with acute myocarditis before and after immune checkpoint inhibitors (ICI) treatment. **(A)** Normal ECG; **(B)** sinus tachycardia, 3-degree atrioventricular block, frequent ventricular premature beats; **(C)** ventricular pacing rhythm (VVI, heart rate 70 times/min), ST segment elevation of anterior septum; **(D,E)** junctional tachycardia, ST segment elevation of anterior septum. ECG, electrocardiogram.

heartbeat, death still occurred after cardiopulmonary resuscitation (Figure 4).

Abnormal ECG

A total of 41 patients (38.68%) had various new-onset ECG abnormalities, which were the most frequent cardiovascular events caused by ICI. Including ST-T changes, sinus bradycardia, sinus tachycardia, atrial premature beats, ventricular premature beats, bundle branch block, and atrioventricular block.

Left ventricular dysfunction

The structure and function of the LV in patients undergoing ICI were examined by echocardiography. The results showed that the LV was enlarged in 2 cases (1.89%), and the left atrium (LA) was enlarged in 23 cases (21.70%). According to the diagnostic criteria, a total of 39 patients (36.79%) developed new-onset LVDD, and 9 patients (8.49%) developed new-onset CTRCD.

Statistical analysis showed that the mean LVEF and mean LVFS after ICI treatment decreased from baseline ($P < 0.001$), while mean LA diameter increased ($P < 0.001$). LV end-diastolic diameter was not significantly different from baseline after ICI treatment ($P = 0.473$) (Table 4, Figure 5). In addition, the mean E/e' increased compared to baseline ($P = 0.001$), and the mean e' was significantly lower than baseline ($P < 0.001$) (Table 5, Figure 5).

Time to adverse cardiovascular events

Electrocardiography (ECG) abnormalities and LVDD are the two most common cardiovascular system abnormalities caused by ICI, which began to appear 2–3 weeks after ICI treatment, and new cases continued to appear throughout the follow-up period, with an

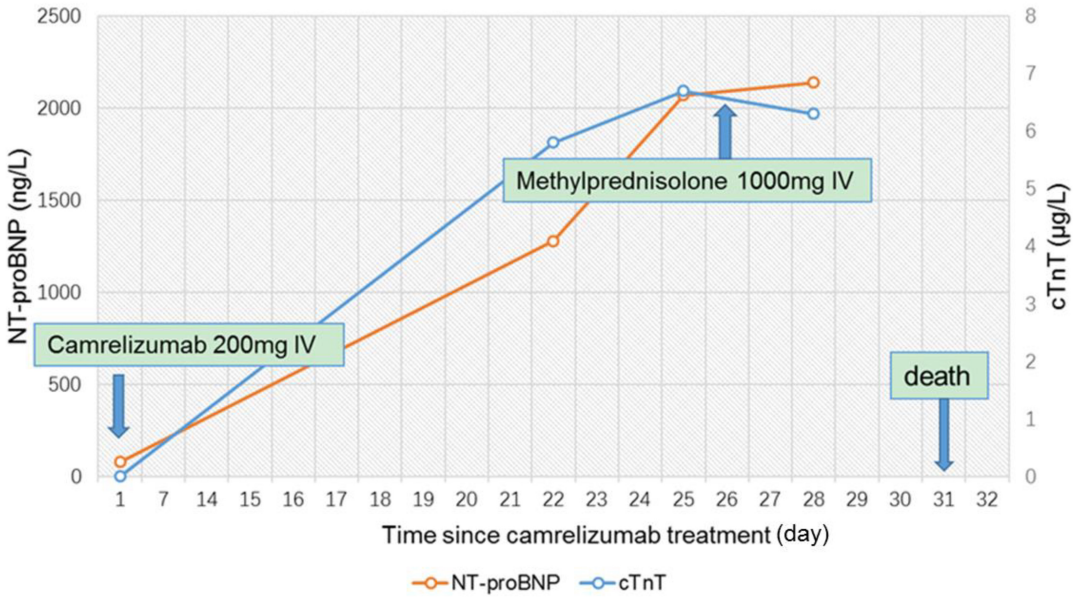

FIGURE 4
Changes of cardiac biomarkers in patients with acute myocarditis before and after immune checkpoint inhibitors (ICI) treatment. cTnT, cardiac troponin T; NT-proBNP, N-terminal pro brain natriuretic peptide.

average onset time of 89.3 and 49.5 days, respectively. The elevation of NT-proBNP occurred more frequently in the first 10 weeks, while CTRCD and the elevation of cTnT occurred continuously during the follow-up period after receiving ICI, with an average onset time of 102 and 75.4 days, respectively (Figure 6).

Risk factors of LVD caused by ICIs

Of the 106 patients treated with ICI, 52 developed LVD, including CTRCD or LVDD. Among them, before receiving ICI, the LVEF of all patients was above 50%, and 11 patients had LVDD. After ICI treatment, LV diastolic function returned to normal in 2 patients with LVDD, while 39 patients developed new-onset LVDD and 9 patients developed new-onset CTRCD (Figure 7). Risk factors for developing LVD were assessed using univariate regression analysis. Thirteen of the 52 patients with LVD had hypertension, while 4 of the 54 patients without LVD had hypertension. There was a significant difference between the two groups (OR = 4.17, 95% CI: 1.26–13.78; P = 0.019). Besides, the baseline LVEF and LVFS of patients with LVD were 61.54 ± 4.15% and 33.78 ± 2.73%, while those of the control group were 64.16 ± 3.68% and 34.95 ± 2.84, respectively. There was a statistically significant difference between the two groups (P = 0.003 and P = 0.048). Compared with patients without LVD, patients with LVD had lower e' (6.99 ± 1.33 cm/s vs. 7.64 ± 1.39 cm/s, P = 0.029) and higher E to e' ratio (11.89 ± 3.15 cm/s vs. 10.43 ± 2.52, P = 0.024). Baseline cardiac biomarkers, including CK-MB, cTnT, and NT-proBNP, were not significantly different between the two groups (Table 1).

Multivariate regression analysis showed that a history of hypertension (OR = 26.52, 95% CI: 2.479–283.667, P = 0.007) and lower baseline e' (OR = 0.04, 95% CI: 0.003–0.709, P = 0.028) were risk factors for developing LVD (Table 6).

TABLE 4 Mean LVEDd, LA, LVEF, and LVFS before and after immune checkpoint inhibitors (ICI) treatment.

Time (month)	N	LVEDd (cm)	LA (cm)	LVEF (%)	LVFS (%)
1	93	46.05 ± 3.75	29.98 ± 3.40	62.75 ± 4.13	34.32 ± 2.83
2	90	45.63 ± 3.94	31.47 ± 3.18*	59.30 ± 4.46*	33.07 ± 2.73*
3	58	45.78 ± 4.04	32.53 ± 3.05*	57.40 ± 4.29*	32.33 ± 2.73*
4	42	44.55 ± 3.98	31.71 ± 3.61*	57.95 ± 4.87*	31.81 ± 2.83*
5	32	45.66 ± 4.55	32.75 ± 3.37*	55.72 ± 4.10*	30.63 ± 2.39*
6	16	47.00 ± 5.39	32.44 ± 3.93*	55.93 ± 4.46*	30.34 ± 2.09*
7∼	15	45.40 ± 4.15	31.00 ± 3.96	57.53 ± 5.13*	31.47 ± 2.50*
Total	346	45.69 ± 4.06	31.42 ± 3.48*	59.18 ± 4.99*	32.71 ± 2.96*

*Compared with baseline, the difference was statistically significant (P < 0.05). LVEDd, left ventricular internal dimension diastole; IVS, interventricular septal thickness diastolic; LVPW, left ventricular posterior wall; LA, left atrial diameter; LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening.

Discussion

The incidence of various ACEs attributable to ICI may be underestimated, and it would be interesting to conduct studies to reveal their true incidence. We conducted this prospective clinical study to detect ICI-related cardiotoxicity. The main results are as follows: first, ICI can lead to various ACEs, such as acute myocarditis, various ECG abnormalities, LVD including CTRCD and LVDD, and

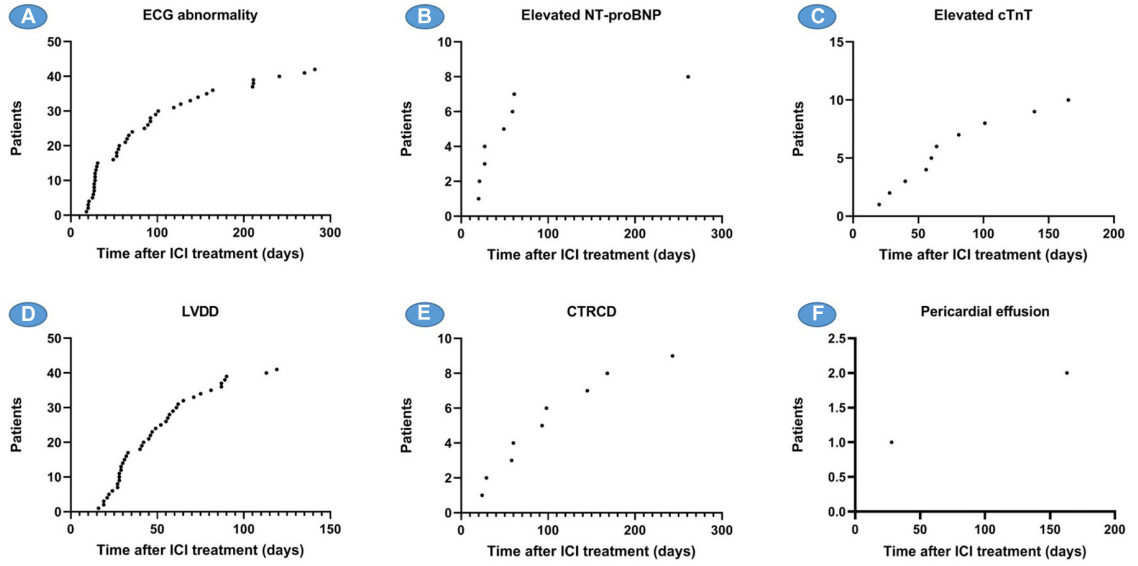

FIGURE 5
Time of onset of various ACEs since receiving ICI. **(A)** The number of patients with ECG abnormalities and the time of onset, **(B)** the number of patients with elevated NT-proBNP and the time of onset, **(C)** the number of patients with elevated cTnT and the time of onset, **(D)** the number of patients with LVDD and the time of onset, **(E)** the number of patients with CTRCD and the time of onset, and **(F)** the number of patients with pericardial effusion and the time of onset. ACEs, adverse cardiovascular events; NT-proBNP, N-terminal pro brain natriuretic peptide; cTnT, cardiac troponin T; LVDD, LV diastolic dysfunction; CTRCD, cancer therapy-related cardiac dysfunction.

pericardial effusion. Its incidence is higher than that reported in many previous articles. Second, echocardiography is a useful method to detect LV systolic and diastolic dysfunction caused by ICI, and a higher incidence of CTRCD and LVDD has been found. Third, hypertension and poor baseline LV systolic or diastolic function are predictors of LVD including CTRCD and LVDD. Last, combining echocardiography, ECG, cardiac biomarkers, chest CT, etc., can early detect cardiotoxicity caused by ICI, so that patients can receive timely diagnosis and treatment, thereby improving the prognosis.

Immune checkpoint inhibitors (ICI) can lead to acute myocarditis, with an incidence of 0.27 to 1.14% (18, 19), most of which occurs about 1 month after receiving ICI (20). One case of acute myocarditis occurred in the patients included in this study. The earliest clinical symptoms were dyspnea, and the ECG showed complete atrioventricular block. Abnormal findings on cardiac biomarkers and echocardiography further confirmed the diagnosis of myocarditis. Although the patient has been implanted with a pacemaker, ICI has led to myocardial injury, edema and heart failure and the patient may eventually die of heart failure and cardiac electromechanical separation. It is very important to closely observe whether there are cardiovascular symptoms such as dyspnea in patients receiving ICI. Once symptoms are present, early examination including ECG, cardiac biomarkers, echocardiography, or cardiac magnetic resonance (CMR) is helpful in diagnosing acute myocarditis. If possible, myocardial histopathology should be performed to confirm the diagnosis, otherwise, CMR is the first choice for non-invasive diagnosis of myocarditis (21).

TABLE 5 The average value of the indexes of left ventricle (LV) diastolic function before and after receiving immune checkpoint inhibitors (ICI).

Time (month)	*N*	E (cm)	e' (cm)	E/e'
1	89	79.81 ± 18.95	7.29 ± 1.39	11.21 ± 2.96
2	75	79.99 ± 18.69	6.11 ± 1.26*	13.50 ± 4.12*
3	42	78.36 ± 14.02	6.05 ± 1.28*	13.33 ± 3.04*
4	35	75.34 ± 17.17	6.11 ± 1.35*	12.71 ± 3.25*
5	22	74.50 ± 15.09	6.23 ± 1.60*	12.45 ± 3.08
6	9	75.47 ± 15.04	5.88 ± 1.24*	13.28 ± 3.51
7∼	8	69.98 ± 21.89	5.66 ± 2.51*	15.01 ± 7.87*
Total	280	78.24 ± 17.67	6.46 ± 1.49	12.60 ± 3.69

*Compared with baseline, the difference was statistically significant ($P < 0.05$). LV, left ventricle; E, peak early diastolic mitral inflow velocity; e', peak early diastolic mitral annulus velocity; E/e', the ratio of E to e'.

With the extensive clinical application of ICI, cases of ICI-related myocarditis have been reported continuously. Due to its high risk and high mortality, it has attracted more and more attention from oncologists and cardiologists (22, 23). However, the current understanding of cardiac dysfunction caused by ICI, especially chronic LV systolic and diastolic dysfunction, is still insufficient, and there are few reports. 2022 ESC Guidelines on cardio oncology mentioned that ICI can lead to asymptomatic or symptomatic CTRCD, which is one of the clinical manifestations of cardiovascular toxicity of ICI, indicating that cardiac dysfunction caused by ICI has begun to attract attention in the field of oncocardiology (24). The CTRCD caused by ICI is also called non-inflammatory left ventricular dysfunction. A retrospective study showed that the median time from the beginning of ICI treatment to presentation with myocarditis was 12 weeks, while the time to presentation with non-inflammatory left ventricular dysfunction was 26 weeks (25). This study found a higher incidence of LVD caused by ICI, including CTRCD and LVDD, which was only lower than ECG abnormalities. These results suggest that regular assessment of cardiac function during ICI therapy can aid in the early detection of LVD, which may help some patients receive timely treatment to improve outcomes.

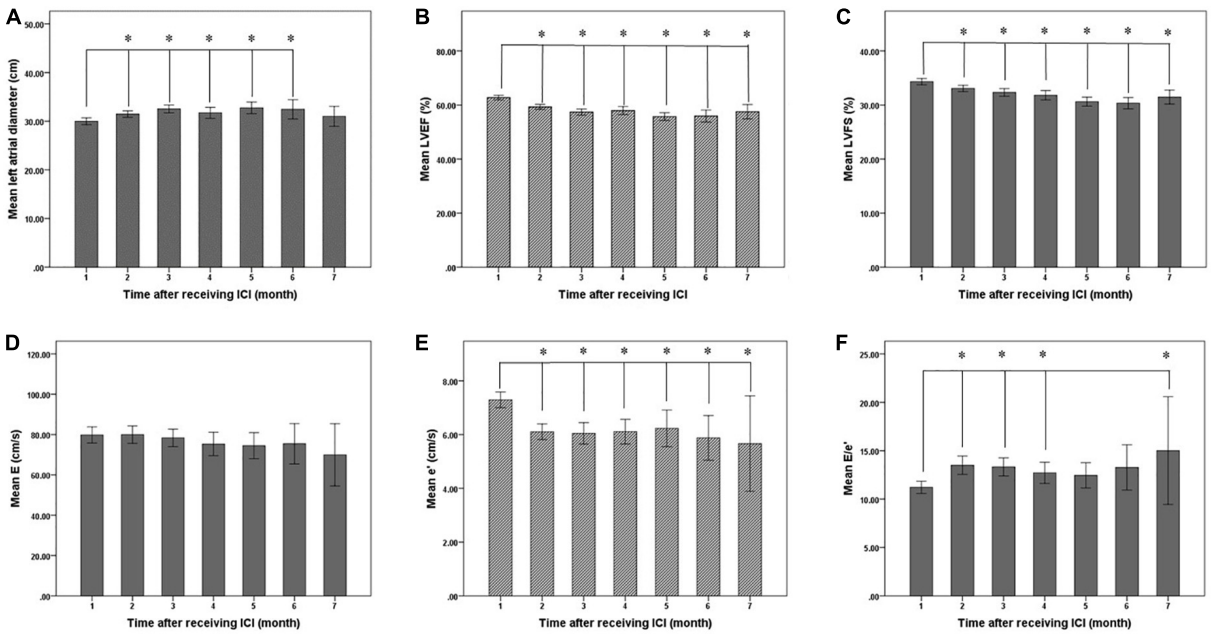

FIGURE 6
Changes of left ventricular systolic and diastolic function before (1 month) and after immune checkpoint inhibitors (ICI) treatment. **(A)** Mean left atrial diameter of patients before and after ICI treatment, **(B)** mean LVEF of patients before and after ICI treatment, **(C)** mean LVFS of patients before and after ICI treatment, **(D)** mean E of patients before and after ICI treatment, **(E)** mean e' of patients before and after ICI treatment, and **(F)** mean E/e' of patients before and after ICI treatment. LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening; E, peak early diastolic mitral inflow velocity; e', peak early diastolic mitral annulus velocity; E/e', the ratio of E to e'. *Compared with baseline, the difference was statistically significant ($P < 0.05$).

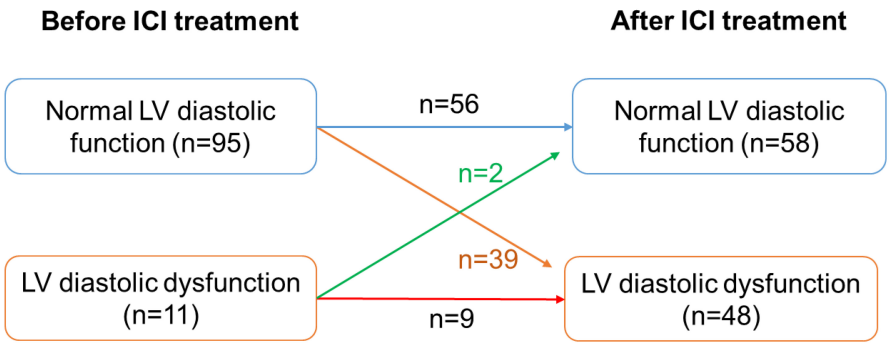

FIGURE 7
Number of patients with LV diastolic dysfunction before and after ICI treatment. LV, left ventricle.

Non-invasive cardiac function evaluation methods mainly include CMR and echocardiography. CMR is still the current "gold standard" for non-invasive evaluation of cardiac structure and function. Moreover, with the development in recent years, the ability of CMR to assess myocardial fibrosis (MF) has been confirmed by studies, and MF is closely related to the prognosis of cardiovascular disease (26). However, CMR is expensive, requires injection of contrast agent, takes a long time, and has contraindications for examination, making it difficult to be used as a routine clinical examination method.

Echocardiography is the most common method for non-invasive visualization of cardiac structure and assessment of cardiac function. It has the advantages of convenient operation, no contraindications, low price, non-invasive and non-radioactive. At present, echocardiography has been widely used in the evaluation of cardiac function before, during and after cancer therapy. However, research on ICI-induced LVD, especially LVDD, is still lacking. In this study, echocardiography was used to evaluate cardiac function in cancer patients treated with ICI. LV systolic dysfunction is one of the most common ACEs in cancer treatment and is defined as CTRCD. According to the latest recommendations from the British Society of Echocardiography (BSE) and the British Society of Cardio-Oncology (BCOS), a decline in LVEF of > 10 absolute percentage points to a value of < 50% is defined as CTRCD (17). According to this definition, 9 patients developed CTRCD after ICI treatment, an incidence of 8.49%. This incidence is higher than some database-based reports and may be related to the fact that most patients treated with ICI did not undergo

TABLE 6 Multivariate regression analysis with LVD.

Parameter	HR	95% CI	*P*-value
Hypertension	26.52	2.479–283.667	0.007
SBP (mmHg)	1.07	0.992–1.144	0.081
NT-proBNP (ng/L)	0.99	0.984–1.002	0.124
LA (mm)	1.08	0.804–1.458	0.602
LVEF (%)	0.80	0.629–1.008	0.058
LVFS (%)	0.59	0.324–1.075	0.085
e' (cm/s)	0.04	0.003 - 0.709	0.028
E/e'	0.609	0.232 – 1.621	0.324

LVD, left ventricular dysfunction; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; LA, left atrial diameter; LVEF, left ventricular ejection fraction; LVFS, left ventricular fraction shortening; e', peak early diastolic mitral annulus velocity; E/e', the ratio of E to e'; HR, hazard ratio; CI, confidence interval.

routine echocardiography, leading to an underestimation of the incidence of CTRCD.

Heart failure with preserved ejection fraction (HFpEF) has received increasing attention in recent years, its prevalence is high, accounting for 50% of all HF, and it is associated with significant morbidity and mortality (27, 28). Asymptomatic LVDD has been shown to be an independent predictor of late progression to HFpEF (29, 30), of which 13–28% may later develop HFpEF, so early diagnosis and intervention of LVDD may improve patient outcomes.

In this study, echocardiography was used to assess LV diastolic function. The results suggest that ICI can lead to a high incidence of LVDD. A total of 39 patients developed new-onset LVDD, and the incidence was 36.79%, which was significantly higher than that of CTRCD. It may be a more sensitive indicator for early detection of LVD and ICI-related cardiotoxicity. In addition, mean e' and E/e' were significantly higher than baseline after patients received ICI, suggesting that ICI resulted in a decrease in overall LV diastolic function. These results suggest that regular echocardiography can early detect LVD caused by ICI, including CTRCD and LVDD.

Myocardial fibrosis is one of the main pathological bases of arrhythmia and heart failure in many heart diseases. A meta-analysis showed that among patients with ICI associated myocarditis, CMR showed a prevalence of edema of 9 to 60% and a prevalence of late gadolinium enhancement (LGE) of 23 to 83% (31). This result suggested that ICI can lead to myocardial fibrosis, which may be the pathological basis of cardiac dysfunction in many patients.

Electrocardiography (ECG) can be used to detect cardiotoxicity associated with tumor therapy, which is convenient, fast and non-invasive. It can be used for early detection of arrhythmia and myocardial injury caused by tumor drugs (32). This study found that after ICI treatment, a total of 39 patients developed various new ECG abnormalities, including ST depression, T-wave inversions, sinus bradycardia, sinus tachycardia, premature atrial contractions, premature ventricular contractions, bundle branch block, and atrioventricular block. Its incidence is highest among ICI-related ACEs, suggesting that ECG abnormalities are sensitive markers for early assessment of ICI-related cardiotoxicity. Although ECG abnormalities are not specific and may occur in patients with subclinical myocardial injury and severe myocarditis, new ECG abnormalities may indicate the occurrence of cardiotoxicity. As previously described, this patient with ICI-associated myocarditis developed new ECG abnormalities, including atrioventricular block, ST-segment depression, and T-wave inversion. This shows that patients with abnormal ECG need to be concerned and followed up.

Immune myocarditis and heart failure are major causes of ICI-related death. Cardiac biomarkers are useful indicators of myocardial inflammation, injury and cardiac dysfunction (33). LVD induced by oncology drugs is a gradual development process, which first causes inflammatory damage of cardiomyocytes, and then gradually develops cardiac dysfunction (18). Studies have shown that elevated cardiac biomarkers such as BNP/NT-proBNP, cardiac troponin are associated with subsequent development of CTRCD or LVDD (34). Furthermore, in some patients, abnormal cardiac biomarkers appeared earlier than the time when LVEF was below normal (35). Therefore, regular cardiac biomarker testing can aid in the early detection of cardiotoxicity, such as myocarditis, heart failure, and asymptomatic subclinical cardiac injury. In this study, after ICI treatment, 10 patients developed cTnT elevation, 8 patients developed CK-MB elevation, and 8 patients developed NT-proBNP elevation, which should be followed closely.

We analyzed the risk factors for LVD in the enrolled patients after receiving ICI. Univariate regression analysis showed that hypertension was an independent risk factor for LVD. This is consistent with hypertension being one of the major risk factors for the development of LVDD (36). Furthermore, lower baseline systolic and diastolic function was associated with higher subsequent LVD incidence. Specifically, patients in the LVD group had lower baseline LVEF, LVFS, and e', and higher ratios of E to e', compared with controls. Multivariate regression analysis also showed that hypertensive patients had a higher incidence of LVD, and poorer systolic and diastolic function at baseline was associated with a higher subsequent incidence of LVD.

Study limitations

The current study has several limitations. First, it is a single-center prospective study. Second, the relatively small number of patients included in the study reduces the statistical power of our results. Especially when analyzing the risk factors for ICI leading to ACE, some possible risk factors may be missed. Third, in this study, patients underwent periodic echocardiography to assess their systolic and diastolic function. However, some patients developed cardiac displacement after extensive lobectomy, which resulted in unsuccessful measurement of global long-axis strain (GLS) of the LV. GLS may be a more sensitive measure of LV systolic function than LVEF. Last, because many patients treated with ICI have advanced cancer, follow-up time is inconsistent, and the long-term incidence of cardiotoxicity with ICI may be underestimated.

Conclusion

Immune checkpoint inhibitors (ICI) can lead to a variety of ACEs, including acute myocarditis, pericardial effusion, LVD, ECG abnormalities, and cardiac biomarker abnormalities. Its incidence is higher than some previous retrospective studies or database-based reports. The combined use of ECG, cardiac biomarkers, echocardiography, and CMR is helpful to early identify the cardiovascular toxicity of ICI. LVD, including CTRCD and LVDD, has a high incidence, and regular echocardiography is helpful for early detection of LVD. Patients with hypertension or poor LV systolic or diastolic function at baseline were predictors of LVD after ICI.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (ethics number, 2018-10-2). The patients/participants provided their written informed consent to participate in this study.

Author contributions

CZ conducted this clinical study, statistical analysis, and manuscript writing. SQ provided the direction and guidance throughout the preparation of this manuscript. ZZ conceived the comment and revised the manuscript. ZLC and LJS assisted in the collection of clinical data. YXZ reviewed and edited the manuscript before submission. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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QTc prolongation risk among patients receiving oral targeted antineoplastic medications: A real-world community-based oncology analysis

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Introduction: Thirty oral targeted antineoplastic agents are associated with prolongation of the QT interval. However, limited data exists regarding QTc prolongation and associated risk factors in the ambulatory oncology setting.

Methods: This retrospective study was completed to describe QTc prolongation incidence among patients receiving oral targeted tyrosine kinase inhibitors (TKI) and identify potential risk factors in the ambulatory community-based oncology clinic.

Results: Of the 341 patients identified as receiving oral TKI, 49 with a baseline and follow-up ECG were included. The incidence of QTc prolongation (QTc > 470 ms in males, QTc > 480 ms in females, or >20 ms increase in QTc from baseline) was 24%. Three patients developed significant QTc prolongation (QTc >500 ms or >60 ms increase in QTc from baseline). No patients discontinued therapy primarily due to QTc prolongation or experienced symptomatic torsades de pointes. Analysis of risk factors demonstrated that patients with QTc prolongation were more likely to receive concomitant therapy with a loop diuretic (41% vs 11%, respectively, p=0.029).

Discussion: The frequency of QTc prolongation may be higher in the real-world setting than that observed in clinical trials; however, continuation of therapy may be possible. Patients receiving concomitant loop diuretics should be monitored more closely for QTc prolongation and electrolyte abnormalities.

KEYWORDS

QTc prolongation, cardio-oncology, tyrosine kinase inhibitor, real-world analysis, risk factors

Introduction

Prolongation of the QT interval, a representation of ventricular repolarization, has long been associated with a potential increase in the risk of ventricular arrhythmia, specifically torsades de pointes (TdP). Over 250 drugs in clinical use have the potential to prolong the QT interval, 30 of which are oral antineoplastic targeted agents (1) that are being incorporated into the therapy of multiple malignancies. Retrospective analyses of these agents, predominantly tyrosine kinase inhibitors (TKIs), have demonstrated an incidence of QT corrected for heart rate (QTc) prolongation of 5.8% to 28%, depending on the definition of QTc prolongation used (2, 3). Significant QTc prolongation (QTc greater than 500 ms) was observed in 1.4% (2). The proposed mechanisms for TKI-induced QT prolongation include inhibition of the rapid component of the delayed rectifier potassium channel (IK_r) or phosphoinositide 3 kinase (PI3K) signaling pathway (4). Currently, there is a lack of data regarding the overall incidence of QTc prolongation specifically among those antineoplastic agents most closely associated with increases in the QT interval.

Utilizing known risk factors, risk stratification scores have been developed; however, these risk scores are specific to the inpatient, acute care setting (5–7). Ambulatory cancer patients are unique in that they are usually medically stable while having a potentially exaggerated risk above and beyond ambulatory patients without cancer. In this population, additional risks such as more frequent electrolyte abnormalities or dehydration due to anticancer therapy induced diarrhea and/or nausea/vomiting may be present. In an effort to describe TKI induced QTc prolongation in a real-world setting, we analyzed QTc intervals of patients treated with oral TKIs known to prolong the QTc interval at a community-based oncology clinic.

Methods

This was a retrospective analysis of adult patients over age 18 years initiated on an oral TKI known to prolong QTc between January 2017 and March 2021 at a large, community-based hospital, Franciscan Health, Indianapolis, Indiana. TKIs defined as having a known risk or possible risk for TdP by the Arizona Center for Education and Research on Therapeutics and available through their website (crediblemeds.org) were included in the analysis (Table 1). Known risk is defined as drugs that both prolong QT interval and are clearly associated with a known risk of TdP, while possible risk is defined as drugs that cause QT prolongation but lack evidence regarding a risk for TdP (1). Patients were excluded if they had a history of congenital long QT syndrome or atrial fibrillation, had an ICD or pacemaker, or did not have a baseline and follow-up electrocardiogram (ECG) documented and able to be queried in the electronic health record during therapy. The study was approved by the local Institutional Review Board.

Patients were reviewed from therapy initiation until discontinuation or for a total of six months if the drug was not discontinued before September 2021. The primary endpoint of the study was the incidence of QTc prolongation. Key secondary endpoints included the incidence of significant QTc prolongation, QTc prolongation resulting in therapy discontinuation, and the identification of potential risk factors for QTc prolongation. QTc prolongation was defined as a QTc greater than 470 ms in males, greater than 480 ms in females or greater than 20 ms increase in QTc from baseline. Significant QTc prolongation was defined as a QTc above 500 ms or a greater than 60 ms increase in QTc from baseline. QTc values at baseline and first follow-up were collected. QTc measurements were ECG machine derived and based upon the Bazett formula as reported

TABLE 1 Tyrosine kinase inhibitors classified as being associated with QTc prolongation by crediblemeds.org.

Drug	Risk	Drug	Risk
Bosutinib	PR	Lenvatinib	PR
Cabozantinib	PR	Midostaurin	PR
Certinib	PR	Mobocertinib	KR
Cobimetinib	PR	Nilotinib	PR
Crizotinib	PR	Osimertinib	PR
Dabrafenib	PR	Pazopanib	PR
Dasatinib	PR	Ribociclib	PR
Encorafenib	PR	Selpercatinib	PR
Entrectinib	PR	Sorafenib	PR
Gilteritinib	PR	Sunitinib	PR
Imatinib	PR	Vandetanib	KR
Ivosidenib	PR	Vemurafenib	PR
Lapatinib	PR		

KR, Known risk (defined as drugs that both prolong QT interval and are clearly associated with a known risk of TdP); PR, Probable risk (defined as drugs that cause QT prolongation but lack evidence regarding a risk for TdP).

in the electronic health record. Risk factors collected from the medical record were age, sex, use of loop diuretics, glomerular filtration rate, past medical history documented in the patient problem list (hypertension, diabetes, coronary artery disease, heart failure, myocardial infarction), and use of other drugs known to prolong QTc intervals.

The primary outcome was analyzed using descriptive statistics. Secondary outcomes were analyzed using the Mann-Whitney U test for continuous, non-parametric data, student t-test for continuous, parametric data, and the chi-squared test or Fisher's exact test, as appropriate for nominal data. P-values of < 0.05 were considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics 25 (IBM Corp, Armonk, Ny) software.

Results

Three hundred and forty-one patients receiving TKIs with a risk for QTc prolongation were identified and 49 patients met inclusion criteria. Reasons for exclusion were lack of baseline and follow-up ECG documented and able to be queried within the health record (n=215), therapy never initiated (n=20), history of atrial fibrillation (n=7), duplicate entry (n=4). In total, included patients received one of thirteen different TKIs (Table 2), the most common being dasatinib (n=9, 18%), pazopanib (n=7, 14%), and sunitinib (n=6, 12%). Fifty-five percent of the population were female and a majority had a cardiac comorbidity (Table 2). Four patients had a prolonged QTc interval at baseline. The median number of days between the baseline ECG and follow-up ECG was 38 days.

The primary endpoint, incidence of QTc prolongation (QTc > 470 ms in males, QTc > 480 ms in females, or >20 ms increase in QTc from baseline) occurred in twelve patients (24%). TKIs received by patients experiencing QTc prolongation can be found in Table 3. Of these, four patients (8%) had a QTc greater than the defined threshold (470 ms in males or 480 ms in females) and eleven (22%) had a greater than 20 ms increase in QTc from baseline (three patients experienced both a QTc above the threshold and greater than 20 ms increase from baseline). Significant QTc prolongation (QTc above 500 ms or greater than 60 ms increase in QTc from baseline) occurred in three patients (6%) of which one patient had a QTc greater than 500 ms and two patients had both a QTc above 500 ms and a greater than 60 ms increase from baseline. See Table 4 for details of individual patients experiencing significant QTc prolongation. Among those with significant QTc prolongation, two were receiving sunitinib and the third received sorafenib. One patient was receiving concomitant azithromycin. All patients had the TKI held upon discovery of the significantly prolonged QTc interval. At the time of significant QTc prolongation, the patient who was also receiving azithromycin was hypokalemic (2.6 meq/L) and had therapy resumed once normokalemia was restored and azithromycin therapy was completed. One patient experienced dehydration, acute kidney injury, and elevated transaminases at the time of significant QTc prolongation and had therapy resumed when the acute issues resolved. The last patient with significant QTc prolongation developed acute kidney injury and acute hepatic

TABLE 2 Baseline Characteristics.

Baseline Characteristic	N=49
Age (years), mean ± SD	64 ± 12
Female – n (%)	27 (55)
GFR ≤ 50, n (%)	7 (14)
Concomitant loop diuretic – n (%)	9 (18)
Hypertension – n (%)	32 (65)
Diabetes – n (%)	14 (29)
Coronary artery disease – n (%)	10 (20)
Heart failure – n (%)	7 (14)
History of myocardial infarction – n (%)	2 (4)
QT Interval (ms)– mean ± SD	395 ± 43
QTc Interval (ms) – mean ± SD	436 ± 29
QTc prolongation at baseline – n (%)	4 (8)
Tyrosine kinase inhibitor medication – n (%)	
Bosutinib	2 (4)
Dabrafenib	1 (2)
Dasatinib	9 (18)
Encorafenib	4 (8)
Lenvatinib	4 (8)
Midostaurin	1 (2)
Nilotinib	4 (8)
Osimertinib	6 (12)
Pazopanib	7 (14)
Ribociclib	2 (4)
Sorafenib	2 (4)
Sunitinib	6 (12)
Vemurafenib	1 (2)

GFR, glomerular filtration rate; n, number, SD, standard deviation.

TABLE 3 Kinase inhibitor medications utilized in patients experiencing QTc prolongation.

Drug	Number of Patients
Dabrafenib	1
Dasatinib	3
Encorafenib	1
Lenvatinib	2
Nilotinib	1
Pazopanib	1
Sunitinib	2

TABLE 4 Patient details for those developing significant QTc prolongation.

	78 year old male	59 year old female	75 year old male
Tyrosine kinase inhibitor	Sunitinib	Sunitinib	Sorafenib
Baseline QTc	468 ms	449 ms	453 ms
Follow up QTc	519 ms	521 ms	527 ms
Receiving Loop Diuretic	Yes – Torsemide 10 mg daily	No	Yes – Furosemide 60 mg daily
Past Medical History/ other risk factors	Hypertension, diabetes, coronary artery disease Developed acute kidney injury and acute hepatic failure	Hypokalemia (K 2.6 meq/L)	Diabetes Dehydration, acute kidney injury, and elevated transaminases
Concomitant QTc Prolonging Drugs		Receiving course of azithromycin	
Outcome	Therapy held and not restarted due to poor overall tolerability	Therapy held and resumed once normokalemia was restored and azithromycin therapy was completed	Therapy held and resumed when acute issues resolved

failure and the therapy was discontinued due to poor overall tolerability. No patients discontinued therapy primarily due to QTc prolongation or experienced symptomatic TdP.

Analysis of potential risk factors between those developing prolonged QTc and those without prolonged QTc intervals demonstrated that the two groups were similar overall, including in baseline demographics, relevant past medical history, baseline QTc interval, and potassium levels at baseline and first follow-up (Table 5). One significant difference observed between groups was the more frequent use of loop diuretics in the prolonged QTc interval group (42% *vs*. 11%, respectively, p=0.029). In the group without QTc prolongation all patients receiving loop diuretics also had a history of heart failure while among those with QTc prolongation, 2 of the 5 patients receiving a loop diuretic also had a history of heart failure. Loop diuretics received by those with QTc prolongation included torsemide in 3 patients (doses ranged from 10 mg to 40 mg daily) and furosemide in 2 patients (dosed at 40 mg and 60 mg daily). Among those without QTc prolongation, loop diuretics received included furosemide in all 4 patients (doses varied from 20 mg to 80 mg daily). Four patients (11%) without QTc prolongation were receiving one concomitant QTc prolonging medication at baseline compared to 1 patient (8%) who experienced QTc prolongation. Among the three patients experiencing significant QTc prolongation, two were receiving a loop diuretic, one had a history of hypertension, two had a history of diabetes, and one had a history of coronary artery disease.

Discussion

Despite almost a quarter of patients developing QTc prolongation while receiving TKIs with a known or possible risk for TdP, only 6% experienced significant QTc prolongation. The common terminology criteria for adverse effects (CTCAE) are often utilized to characterize adverse effects in oncology clinical trials and defines QTc prolongation as grade 1 if QTc 450-480 ms, grade 2 if QTc 481-500 ms, grade 3 if QTc greater than 500 ms or greater than 60 ms change from baseline, and grade 4 if a patient experiences TdP, polymorphic ventricular tachycardia, or signs/symptoms of a serious arrhythmia (8). In a retrospective study of 363 patients from four centers in the Netherlands and Italy who were receiving any TKI for solid tumors, there was a significant increase in CTCAE grade after starting a TKI, with 33 demonstrating an increase in grade (p=0.0003) (2). The majority (31) increased from grade 0 (less than 450 ms) to grade 1 or higher while only 2 increased from grade 1 to grade 2 or 3. The authors defined high-risk QTc as an interval above 470 ms, which was observed in 1.7% at baseline and 5.8% while on therapy and twenty patients transitioned from low risk to high risk. Only 1.4% developed a QTc greater than 500 ms. The median time to follow up ECG was 43 days. Variables identified that increase risk for progression to a higher CTCAE grade included age and hypokalemia. Variables associated with transitioning to the high-risk category included age and concomitant use of other QTc prolonging medications. Our study had more than twice the risk for developing a QTc interval greater than 500 ms and a slightly higher rate of QTc above 470 ms (5.8% *vs* 8% in our analysis). This may be due to the fact that we included only those TKI with the highest risk while the described study included any TKI, including some without a QTc prolongation risk such as erlotinib and gefitinib; however, the majority of the patients received those with a QTc prolongation risk (imatinib, lapatinib, pazopanib, sunitinib, sorafenib, and vemurafenib).

A more recent retrospective analysis of QTc prolongation risk among patients treated with TKI also looked at the incidence of QTc prolongation with all TKI, regardless of QTc prolongation risk (3). This analysis included 618 patients with 902 TKI administrations and defined QTc prolongation as a QTc interval of 450 ms or higher in men or 470 ms or higher in women. In total 29% experienced QTc prolongation, most commonly with nilotinib (39%) and dasatinib (41%). Risk factors for QTc prolongation included age, obesity, and history of hypertension, diabetes, hyperlipidemia, or congestive heart failure. QTc prolongation to an interval of 500 ms or greater or a 60 ms or higher increase from baseline occurred in 5% and 7% of TKI administrations,

TABLE 5 Analysis of risk factors for QTc prolongation.

Risk Factor Analysis	Non-Prolonged QTc N=37 n (%)	Prolonged QTc N=12 n (%)	p-value
Age, years, mean ± SD	64 ± 13	65 ± 10	0.760
Female, n (%)	20 (54)	7 (58)	0.796
Concomitant loop diuretic, n (%)	4 (11)	5 (42)	0.029
Number of concomitant QT prolonging medications at baseline, median (IQR)	0 (0)*	0 (0)^	0.807
GFR ≤ 50 ml/min[¥], n (%)	6 (16)	1 (8)	0.665
Hypertension, n (%)	24 (65)	8 (67)	0.233
Diabetes, n (%)	10 (27)	4 (33)	0.721
Coronary artery disease, n (%)	6 (16)	4 (33)	0.233
Heart failure, n (%)	5 (14)	2 (17)	1.0
History of myocardial infarction, n (%)	1 (3)	1 (8)	0.434
Baseline QTc (ms), mean ± SD	437 ± 31	432 ± 27	0.614
Baseline QTc prolongation, n (%)	4 (11)	0 (0)	0.560
Baseline potassium, meq/L, median (IQR)	4.0 (0.6)	4.1 (0.4)	0.100
Potassium at time of follow-up ECG	4.0 (0.6)	4.2 (1.1)	0.625

GFR, glomerular filtration rate; IQR, Interquartile range; n, number; SD, standard deviation.
*4 patients were receiving one concomitant QT prolonging medication at baseline; the remainder were not receiving any concomitant QT prolonging medications.
^1 patient was receiving one concomitant QT prolonging medication at baseline; the remainder were not receiving any concomitant QT prolonging medications.
[¥]GFR cut off utilized by Berger, et al. (7) was 50 ml/min, while Tisdale et al. (6) utilized a cut off of 30 ml/min. This analysis utilized the more conservative estimate of 50 ml/min.

respectively. Increase in QTc interval from baseline were statistically significant with dasatinib, imatinib, nilotinib, sunitinib, and pazopanib. Sixty-eight percent of patients with QTc prolongation had their therapy discontinued in response (21% were switched to a different TKI, 46% were switched to a different type of treatment such as chemotherapy, radiotherapy, or bone marrow transplant), 13.5% had doses reduced, and 8.1% had therapy temporarily withheld. Ventricular tachycarida, TdP, or sudden cardiac death occurred in 5.4% of those experiencing QTc prolongation. Though definitions utilized in this study were different from those utilized here, the incidences of QTc prolongation were similar to our study. Of note, concomitant QTc prolonging medication use was not analyzed in this study. Our clinic's standard of care is for every patient to undergo pharmacist review of their medication profile to minimize concomitant QTc prolonging medications, resulting in the majority (90%) in our study without any concomitant QTc prolonging medications.

In a meta-analysis of phase 2 and 3 trials with vascular endothelial growth factor receptor targeted TKIs, the relative risk for all CTCAE grades of QTc prolongation (QTc greater than 450 ms) was found to be 8.66 [95% confidence interval (CI): 4.92-15.2, $p < 0.001$] among the 6,548 patients from 18 trials (9). The majority of included trials (15 of 18 included trials) required QTc monitoring at baseline and periodically throughout the study (2 trials did not include QTc monitoring in the protocol and QTc monitoring practices was not addressed in 1 trial). The relative risk for high CTCAE grade QTc prolongation (QTc above 500 or serious arrhythmias) was 2.69 (95% CI: 1.33-5.44, p=0.006). All grade QTc prolongation was observed in 4.4% of the population, while high grade was observed in 0.83%. Agents included in this analysis were sunitinib, sorafenib, pazopanib, vandetanib, cabozanib, ponatninb, and regorafenib. When individual agents were analyzed, vandetanib and sunitinib demonstrated a significant increase in all grade QTc prolongation and pazopanib and axitinib use resulted in no increase in QTc prolongation. Interestingly, the relative risk for all grade QTc prolongation increased as the vandetanib dose increased (relative risk 10.6 at 300 mg *vs*. 4.83 at 100 mg). Trials with a longer treatment duration did not result in a higher risk of QTc prolongation. Despite a stricter definition of QTc prolongation, the rate of QTc prolongation in our study was higher than in this meta-analysis (24% *vs*. 4.4%, respectively) as was high grade QTc prolongation (1.4% *vs*. 0.83%). In our analysis, a total of 19 patients received vascular endothelial growth factor directed TKI, of which six (31.5%) developed QTc prolongation. These differences demonstrate the potential disparities witnessed between results obtained in controlled clinical trials and those observed in real-world clinic settings.

Real-world analyses, like this, are largely complementary to the data from randomized clinical trials in that they often include patients who may have been excluded from the clinical trials and are representative of the population treated in oncology clinics. As such, the increased rate of QTc prolongation in this analysis may be more typical of what is happening in clinic where patients likely have more risk factors, increased comorbidities, and decreased control over factors such as concomitant use of additional QTc prolonging medications. Likewise, real world analyses identify

opportunities for improvement in practice such as the lack of follow-up ECG in almost 2/3 of the patients identified for inclusion in this analysis and the delay in time to follow up ECG (38 days in this study and 43 days in the previously discussed retrospective study). According to a recent state-of-the-art review, a follow-up ECG should be considered 14 days after staring therapy in all patients receiving TKI with an increased risk for QTc prolongation (10).

Due to the risk for QTc prolongation associated with many oral TKI, multiple recommendations exist for the management of patients receiving these therapies (11–13). The International Cardio-Oncology Society consensus statement for defining cardiovascular toxicities of cancer therapies recommended action be taken if the QTc interval increased above 500 ms as the risk of TdP is low below this threshold, even if QTc increases more than 60 ms from baseline but QTc remains below 500 ms (11). The recommendations included a consideration for change in therapy when QTc exceeds 500 ms and to reassess QTc as changes in clinical status occur. Recently published European Society of Cardiology (ESC) guidelines on cardio-oncology, developed in association with the European Hematology Association, the European Society for Therapeutic Radiology and Oncology, and the International Cardio-Oncology Society provided comprehensive recommendations for the management of QTc prolongation associated with antineoplastic therapies (12). Evaluation of the ECG is recommended at baseline and once steady-state drug levels have been achieved in patients starting therapy known to cause QTc prolongation and routine ECG monitoring is recommended in patients at risk for QTc prolongation after dose increases, if electrolyte imbalances occur, or if concomitant QTc prolonging medications are added. Risk factors for QTc prolongation identified in these guidelines include concomitant QTc prolonging medications, bradyarrhythmia, electrolyte imbalance, renal or hepatic dysfunction with resultant inadequate antineoplastic dose adjustments, acute myocardial infarction, age greater than 65, prolonged baseline QTc, family history of sudden death, female sex, personal history of syncope or drug induced TdP, and pre-existing coronary artery disease, heart failure, or left ventricular hypertrophy.

Much of the data regarding patient specific risk factors are from the acute care setting where validated risk scores have been developed and implemented in practice (5–7). Though it is important to identify and address modifiable risk factors prior to starting drugs known to prolong QTc interval, the utility of such risk factors in determining the risk of a patient in the ambulatory setting may be limited as it is unclear if those factors identified in the acute care setting translate to the ambulatory setting (13). Likewise, routine QTc monitoring may not be prognostic in all patients as most with prolonged QTc intervals never experience TdP and many developing TdP have normal QT intervals prior to the event (4, 14). Unlike therapies for other diseases, many of the TKI for the treatment of malignancy lack alternatives and strict guidelines for QTc prolongation management may restrict the use of potentially life-prolonging medications (4). Our analysis of risk factors demonstrated that more patients developing QTc prolongation received concomitant loop diuretics. Two of the three risk scores developed for the acute care setting included loop diuretics in their scoring system (6, 7); however, this potential risk has not been demonstrated, to our knowledge, in the community-based outpatient setting among patients receiving TKI with a risk for QTc prolongation. Our data suggest that patients requiring use of a loop diuretic concomitantly with a QTc prolonging TKI may benefit from more close monitoring and correction of electrolyte abnormalities.

Strengths of our analysis include the real-world, community-based setting and the inclusion of patients receiving only those drugs with a risk for QTc prolongation. Additionally, individual risk factors and the use of concomitant QTc prolonging medications were assessed; however, these coadministrations occurred infrequently due to the proactive review and management by a pharmacist embedded within the oncology clinic. Our work is limited by the small number of patients in the analysis which reduces the power to make associations and the fact that not all previously identified risk factors were included. The small sample size was largely a result of a lack of follow-up ECG which have only more recently become the standard of care for patients receiving these medications. The fact that this was a retrospective and single center analysis is also a limitation; however, this does provide insight into the practice of monitoring and managing patients in the community setting. Additionally, as demonstrated by the number of patients without a follow-up ECG and therefore excluded from this analysis, there is a possibility of selection bias and an over estimation of the true incidence of QTc prolongation. Despite these limitations, when comparing the risk factors included, the groups were very similar apart from the more frequent utilization of loop diuretics in the group experiencing QTc prolongation.

Conclusion

This real-world analysis of TKIs known to prolong the QTc interval in a community-based oncology clinic demonstrated a potentially higher incidence of QTc prolongation compared to prior studies. However, despite nearly a quarter of patients with observed QTc prolongation, no patients discontinued therapy primarily because of QTc prolongation. It has been recently recommended that patients receiving QTc prolonging TKIs be screened at baseline and either once steady state has been reached or after 14 days of therapy. Due to the potential increase in risk among patients receiving concomitant loop diuretics, it may be prudent to monitor patients more closely for QTc prolongation and electrolyte abnormalities. Further study is warranted to investigate the potential association between QTc prolongation and the use of loop diuretics, as well as the impact of other potential risk factors for QTc prolongation in the ambulatory oncology setting.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by IRB00011381 - Franciscan Health IRB #1. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

These authors share first authorship: DR, MR. This author served in the senior authorship role: VR. All authors developed and approved of the retrospective study protocol. MR completed data collection. MR and DR completed data analysis. VR provided input into data analysis. DR created the first draft of the manuscript with input from VR and MR. VR provided critical input into manuscript revision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prediction of cardiovascular adverse events in newly diagnosed multiple myeloma: Development and validation of a risk score prognostic model

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Background: Multiple myeloma (MM) is the second most common hematological malignancy, and the treatments markedly elevate the survival rate of the patients in recent years. However, the prevalence of cardiovascular adverse events (CVAEs) in MM had been increasing recently. CVAEs in MM patients are an important problem that we should focus on. Clinical tools for prognostication and risk-stratification are needed.

Patients and methods: This is a retrospective study that included patients who were newly diagnosed with multiple myeloma (NDMM) in Shanghai Changzheng Hospital and Affiliated Jinhua Hospital, Zhejiang University School of Medicine from June 2018 to July 2020. A total of 253 patients from two medical centers were divided into training cohort and validation cohort randomly. Univariable analysis of the baseline factors was performed using CVAEs endpoints. Multivariable analysis identified three factors for a prognostic model that was validated in internal validation cohorts.

Results: Factors independently associated with CVAEs in NDMM were as follows: age>61 years old, high level of baseline office blood pressure, and left ventricular hypertrophy (LVH). Age contributed 2 points, and the other two factors contributed 1 point to a prognostic model. The model distinguished the patients into three groups: 3–4 points, high risk; 2 points, intermediate risk; 0–1 point, low risk. These groups had significant difference in CVAEs during follow-up days in both training cohort (p<0.0001) and validation cohort (p=0.0018). In addition, the model had good calibration. The C-indexes for the prediction of overall survival of CVAEs in the training and validation cohorts were 0.73 (95% CI, 0.67–0.79) and 0.66 (95% CI, 0.51–0.81), respectively. The areas under the receiver operating characteristic curve (AUROCs) of the 1-year CVAEs probability in the training and validation cohorts were 0.738 and 0.673, respectively. The AUROCs of the 2-year CVAE probability in the training and

validation cohorts were 0.722 and 0.742, respectively. The decision-curve analysis indicated that the prediction model provided greater net benefit than the default strategies of providing assessment or not providing assessment for all patients.

Conclusion: A prognostic risk prediction model for predicting CVAEs risk of NDMM patients was developed and internally validated. Patients at increased risk of CVAEs can be identified at treatment initiation and be more focused on cardiovascular protection in the treatment plan.

KEYWORDS

multiple myeloma, cardiovascular adverse events, prediction model, treatment plan, cardiovascular protection

Introduction

Multiple myeloma (MM) is a malignant disease with abnormal proliferation of clonal plasma cells, which leads to a series of target organ dysfunction and clinical manifestations (1). MM accounted for 1%–1.8% of all malignant tumors, and it is the second most common malignancy of the blood system (2). The global epidemic of MM still continues in recent years. The incidence of MM from 1990 to 2016 have increased by 126% globally (3). More than 155,688 people were diagnosed with MM worldwide in 2019 (4). A total of 100,000 people a year die of MM on average (5). In China, it was estimated that the incidence of MM increased significantly from 2006 to 2016 as well. In addition, the mortality was increased from 2006 to 2014 but remained stable from 2014 to 2016, which may be due to the maturity of hematopoietic stem cell transplantation (HSCT) and the application of new drugs such as proteasome inhibitors (PI) and immune modulators (IMiDs) (6). With the development of these "novel agents" in the past decade, the progression-free survival (PFS) and overall survival (OS) of MM patients have prolonged significantly. MM has gradually evolved into a kind of chronic relapsing disease (5). Therefore, it is important to have a good management on comorbidities and therapy-related toxicities to improve clinical outcomes and enhance the quality of life in these patients.

Cardiovascular adverse events (CVAEs) are common in MM. It includes increased risk of venous thromboembolic events (VTEs), arterial thromboembolic events (ATEs), hypertension, arrhythmia, ischemic heart disease, pulmonary hypertension, and heart failure (HF) (7). An observation study showed that the risk of any cardiac event, arrhythmia, HF, and cardiomyopathy was significantly higher for MM patients exposed to three or more types of therapy than for non-MM patients who were age and gender matched (8). Two large population-based study also demonstrated that the risk of vascular complications including VTE and ATE was significantly increased (9, 10). The reason of high incidence of CVAEs in MM can be broadly divided into two aspects. First of all, the median age of diagnosis in MM is 69 years, and 63% of MM patients were more than 65 years at the time of first diagnosis (5), which means a high baseline incidence of traditional cardiovascular risk factors in MM patients. It was estimated that approximately 66% of patients had cardiovascular disease at baseline (11). On the other hand, the risk of CVAEs was closely associated with the progression of MM. Chronic renal insufficiency and amyloidosis related to MM potentially lead to the high incidence of CVAEs (12, 13). As a consequence, it is important to assess the cardiovascular risk at baseline and control the cardiovascular complications in MM patients. Early recognition and making individual treatment strategies may improve outcomes in patients with MM.

Risk stratification can help identify different levels of risk patients upfront and enable informed therapeutic decision making. Although several risk factors have been associated with CVAEs in MM patients in previous studies (14), a validated clinical tool that could be used for risk adapted treatment approaches is lacking. Here, we explored the potential risk factors associated with CVAEs after chemotherapy for MM patients and reported a three-factor prognostic model that is intuitive and easy to use for predicting the CVAEs in MM patients.

Methods

Patients

We conducted a retrospective study on 253 consecutive patients with NDMM treated in Shanghai Changzheng Hospital of China and Affiliated Jinhua Hospital, Zhejiang University School of Medicine of China between June 2018 to June 2020. A total of 201 patients were from Shanghai Changzheng Hospital of China, and 52 patients were from the Affiliated Jinhua Hospital, Zhejiang University School of Medicine of China. The International Myeloma Working Group (IMWG) criteria was used to assess the diagnosis and treatment response. Patients with diseases such as Waldenström macroglobulinemia, lymphoma, plasma cell leukemia, systemic light chain amyloidosis (AL amyloidosis), and MM patients who previously had received chemotherapy were

excluded. The clinical information was collected retrospectively by reviewing the patients' medical records. Several baseline variables were selected in this study, including age, sex, body mass index (BMI), body surface area (BSA), Durie–Salmon (D-S) stage, International Staging System (ISS) stage, smoking and alcohol consumption history, history of hypertension, coronary heart disease, diabetes, and stroke, baseline office blood pressure, left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), first-line therapy regimens, C-reactive protein (CRP), hemoglobin, brain natriuretic peptide (BNP), albumin, uric acid, creatinine, glomerular filtration rate (GFR), β2 microglobulin (β2-MG), and high-risk cytogenetic abnormalities (high-risk CA) [high-risk CA includes t(4; 14), gain (1q), del (17p), t (14; 16), and t (14; 20)]. The primary outcome was CVAE. The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 was assessed for the occurrence of CVAEs. Overall survival (OS) of CVAEs was calculated from the beginning of first-line chemotherapy until the date of confirming CVAEs or the last date that the patient was known to be free of CVAEs. This study has been approved by the Ethics Committee of Shanghai Changzheng Hospital and followed the principles of the Declaration of Helsinki.

Statistical analysis

The cohort was divided into two groups randomly: a training cohort comprising 75% of the original group and a validation cohort consisting of the remaining 25%. The training cohort used to establish the Risk Score System. In the training cohort, the baseline clinical features mentioned above were assessed to identify predictors of CVAEs. The baseline continuous variables of normal distribution were represented by mean and standard deviation. Non-normal continuous variables were represented by median and quartile range (IQR); categorical variables were expressed as counts and percentages. Univariate analysis of potential risk factors for CVAEs was performed using the Cox proportional hazards regression model. Variables in the univariate analysis with $p< 0.10$ were chosen for multivariate Cox proportional hazard regression to identify the independent prognostic factors. Based on the results of the multivariate Cox regression analyses, the Risk Score System to predict the risk of CVAEs for NDMM patients was formulated.

We validated the prognostic performance of the model by identifying and calibrating measurements in the training, validation, and entire cohort. Concordance index (C-index) was used to assess the predictive power of the model. The calibration of the prediction model was performed by a visual calibration plot comparing the predicted and actual probability of CVAEs. The outcome discrimination is most often assessed by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. The closer the AUC value is to 1, the better discrimination capacity the prediction model has. We also adopted bootstrapping methods (1,000 bootstrap resamples) for internal validation to quantify the extent of model overfitting and optimism.

Additionally, we have printed decision curve analysis (DCA) curves to assess the clinical utility of this prediction model. All data were analyzed using R software (version 4.0.3, R Foundation), and $p <0.05$ was considered statistically significant.

Results

Rate of CVAEs: All types of CVAEs

During a median follow-up of 12.5 months, 74 patients (29.2%) experienced CVAEs in the entire cohort; 41 patients (17.0%) experienced Grade 3 or greater CVAEs (CTCAE≥3). The subtypes of CVAEs occurring during treatments are listed in Table 1. Heart failure (35.1%), arrhythmias (33.8%), and hypertension (18.9%) were the most commonly represented CVAEs. Premature beats (23.0%) are the major type of arrhythmias. In addition, heart failure (53.7%) is also the most common type in Grade≥3 CVAEs.

Clinical characteristics of the training and validation cohorts

The baseline clinical characteristics of the training and validation cohorts are presented in Table 2. A total of 253

TABLE 1 Lists of all types of CVAE.

CVAEs		Patients n=74	CVAEs	
			Grade 1–2 (n=33)	Grade≥3 (n=41)
Heart failure		26(35.1)	4(12.1)	22(53.7)
Arrhythmia	Premature beats	17(23.0)	11(33.3)	6(14.6)
	Atrial fibrillation	5(0.07)	2(6.1)	3(7.3)
	PSVT	3(0.04)	0	3(7.3)
Hypertension		14(18.9)	10(30.3)	4(9.8)
ACS		3(0.04)	0	3(7.3)
Pulmonary hypertension		2(0.03)	2(6.1)	0
Pericardial effusion		4(0.05)	4(12.1)	0

CVAEs, cardiovascular adverse events; ACS, acute coronary syndrome; PSVT, paroxysmal supraventricular tachycardia.

patients were included in our study. The median age was 63.0 years [interquartile range (IQR), 56.0–68.0 years]. There were 151 men (59.7%) and 102 (40.3%) women. Everyone was treated with proteasome inhibitors (PI), and 124 patients (46.2%) accepted the treatment of immunomodulator drugs (IMiDs), including lenalidomide and thalidomide. A total of 34 patients (13.4%) accepted treatment of anthracycline, including doxorubicin and doxorubicin hydrochloride liposome. A total of 253 patients from two medical centers were divided into training cohort and validation cohort randomly. The randomization was performed through a computerized random numbers procedure by R software and conducted independently of the study investigators. The training cohort comprised 190 patients (75% of the original group), and the validation cohort consisted of 63 patients (25% of the original group). There were no significant differences between the two groups of patients in age, sex, MM type, D-S stage, ISS stage, high-risk CA rate, smoking and alcohol consumption history, history of hypertension, coronary heart disease, diabetes mellitus, and stroke, baseline CRP, hemoglobin, BNP, creatine, albumin, uric acid, β2-MG, GFR, baseline high level of office blood pressure rate, LVEF, LVMI, first-line therapy regimens, and combined CV-related drugs.

The risk factors of CVAEs

Patients in the study cohort were followed up for a median of 12.5 months. CVAE occurred in 74 patients (29.2%). To screen the better variables related to CVAEs, we had transformed continuous variables into categorical variables by drawing 1- and 2-year survival ROC curves and the cutoff value in the training cohort. We had transformed the continuous variables that have clinical significance and the area under the curve (AUC) >0.5 (Supplementary Figure). Finally, age was divided into two groups by 61 years old, β2-MG was divided into two groups by 3.71 mg/L, and uric acid was divided into two groups by 439 mmol/L. Univariate and multivariate analyses were performed on baseline indicators for the training set (Table 3). In the univariate analysis, age group, history of smoking, history of atrial fibrillation, baseline high level of office blood pressure (defined as blood pressure≥140/90mmHg), LVEF, left ventricular hypertrophy (LVH) (defined as >125 g/m^2 in men and >120 g/m^2 in women), β2MG group were significantly associated with CVAEs. Multivariate analyses were performed using the significant risk factors determined in the univariate analysis, and age group, baseline high level of office blood pressure, and LVH were revealed as significant independent factors for CVAEs. Grade 3 or greater CVAEs (CTCAE≥3) received more attention in clinical situation; univariate and multivariate analyses were also performed on baseline indicators for the entire cohort (Table 4). In the univariate analysis, history of smoking, diagnosis of ISS stage above stage III, baseline high level of office blood pressure (defined as blood pressure≥140/90mmHg), LVH (defined as >125 g/m^2 in men and >120g/m^2 in women), β2MG group, and GFR were significantly associated with Grade 3 or greater CVAEs. Multivariate analyses were performed using the significant risk factors determined in the univariate analysis; history of smoking and LVH were revealed as significant independent factors for Grade 3 or greater CVAEs.

Construction and validation of the risk score system

Based on these results, age >61 years old, baseline high level of office blood pressure, and LVH were identified as risk factors of CVAEs. Regression coefficients for each co-variate were rounded to the nearest integer to derive weights to develop the risk score prognostic model (Supplementary Table). Age >61 years old contributed 2 points, and the other two factors contributed 1 point to a prognostic model. We developed a risk score system to predict the occurrence of CVAE in 1 and 2 years. On the basis of the separation of CVAEs occurrence in the training set by the cumulative number of risk factors (Figure 1), we distinguished three prognostic risk groups: 3–4 points, high risk; 2 points, intermediate risk; and 0–1 point, low risk. In both training and validation cohort, the intermediate- and high-risk groups had significantly inferior OS of CVAEs when compared with the low-risk group (Table 5). In the training cohort, the intermediate- and high-risk groups had significantly increased risk in CVAEs when compared with the low-risk group (p<0.0001). In the validation cohort, the intermediate- and high-risk groups had significantly increased risk in CVAEs when compared with the low-risk group as well (p=0.0018). When combining all cohorts, the 1-year CVAEs risk for low-, intermediate-, and high-risk groups were 6.4%, 22.3%, and 42.0%, and the 2-year CVAEs risk were 8.3%, 31.9%, and 56.0%, respectively (p<0.001).

To adjust optimism, bootstrapping approach was used for internal validation. The discrimination power of the risk score system was evaluated by the C-index values and ROC curves. The C-indexes for the prediction of OS of CVAEs in the training cohorts were 0.73 (95% CI, 0.67–0.79), and the calibration plots showed good agreement between the predicted OS of CVAEs and the observed OS of CVAEs rate (Figures 2A–D). The C-indexes for the prediction of OS of CVAEs in the validation and entire cohorts were 0.66 (95% CI, 0.51–0.81) and 0.71 (95% CI, 0.65–0.77), respectively. The calibration plots also showed good agreement between predictions and observations in both validation cohort (Figures 2B–E) and entire cohort (Figures 2C–F). The areas under ROC curves (AUROCs) of the 1-year CVAEs probability in the training and validation cohorts were 0.738 and 0.673, respectively. The AUROCs of the 2-year CVAEs probability in the training and validation cohorts were 0.722 and 0.742, respectively (Figure 3).

Clinical value of the risk score system

The decision-curve analysis (DCA) is a better approach than AUROC in evaluating prognostic strategies, and it had been widely used in recent years (15). The 1- and 2-year DCA curves for the risk score system in training, validation, and entire cohorts are presented in Figure 4. The DCA curves indicated that the prediction model provided greater net benefit than the default strategies of providing or not providing assessment for all patients.

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TABLE 2 The baseline characteristics of the train and validation cohorts.

Factors	Subgroup	Overall (n=253)	Train cohort(n=190)	Validation cohort(n=63)	*p*-value
Age,years,median(IQR)		63.0 [56.0, 68.0]	63.0 [57.0, 68.0]	62.0 [55.0, 67.0]	0.25
Sex, n (%)	Female	102 (40.3)	79 (41.6)	23 (36.5)	0.57
	Male	151 (59.7)	111 (58.4)	40 (63.5)	
Type, n (%)	Non-secretory	12 (4.7)	11 (5.8)	1 (1.6)	0.16
	Light-chain	44 (17.4)	28 (14.7)	16 (25.4)	
	IgA	60 (23.7)	44 (23.2)	16 (25.4)	
	IgD	13 (5.1)	10 (5.3)	3 (4.8)	
	IgE	1 (0.4)	1 (0.5)	0 (0.0)	
	IgG	120 (47.4)	95 (50.0)	25 (39.7)	
	IgM	3 (1.2)	1 (0.5)	2 (3.2)	
D-S, n (%)	I	10(4.0)	9(4.7)	1(1.6)	0.18
	II	28(11.1)	18(9.5)	10(15.9)	
	III	215(85.0)	163(85.8)	52(82.5)	
ISS, n (%)	I	53 (20.9)	40 (21.1)	13 (20.6)	0.95
	II	96 (37.9)	73 (38.4)	23 (36.5)	
	III	104 (41.1)	77 (40.5)	27 (42.9)	
High-risk CA, n (%)	No	151 (59.7)	117 (61.6)	34 (54.0)	0.36
	Yes	102 (40.3)	73 (38.4)	29 (46.0)	
Smoke, n (%)	No	172 (68.0)	130 (68.4)	42 (66.7)	0.92
	Yes	81 (32.0)	60 (31.6)	21 (33.3)	
Alcohol consumption, n (%)	No	210 (83.0)	156 (82.1)	54 (85.7)	0.64
	Yes	43 (17.0)	34 (17.9)	9 (14.3)	
BSA, m^2, median (IQR)		1.7 [1.6, 1.8]	1.7 [1.6, 1.8]	1.7 [1.6, 1.8]	0.59
Hypertension, n (%)	No	156 (61.7)	114 (60.0)	42 (66.7)	0.43
	Yes	97 (38.3)	76 (40.0)	21 (33.3)	
Coronary heart disease, n (%)	No	226 (89.3)	170 (89.5)	56 (88.9)	1
	Yes	27 (10.7)	20 (10.5)	7 (11.1)	
Atrial fibrillation, n (%)	No	247 (97.6)	186 (97.9)	61 (96.8)	1
	Yes	6 (2.4)	4 (2.1)	2 (3.2)	
Heart failure	No	251 (99.2)	189 (99.5)	62 (98.4)	1
	Yes	2 (0.8)	1 (0.5)	1 (1.6)	
Diabetes mellitus, n (%)	No	232 (91.7)	175 (92.1)	57 (90.5)	0.89
	Yes	21 (8.3)	15 (7.9)	6 (9.5)	
Stroke, n (%)	No	228 (90.1)	172 (90.5)	56 (88.9)	0.89
	Yes	25 (9.9)	18 (9.5)	7 (11.1)	
CRP, mg/L, median (IQR)		3.1 [1.0, 7.1]	3.0 [1.0, 6.3]	4.0 [1.2, 8.9]	0.16
Hb, g/L, median (IQR)		98.0 [80.0, 118.0]	98.0 [76.5, 119.0]	103.0 [84.5, 113.5]	0.44
BNP, pg/ml, median (IQR)		134.0 [54.7, 554.0]	145.0 [56.2, 545.5]	120.0 [42.8, 589.5]	0.57
Cr, μmol/L, median (IQR)		75.0 [62.0, 103.0]	75.0 [61.2, 102.5]	76.0 [63.0, 109.0]	0.33

(Continued)

TABLE 2 Continued

Factors	Subgroup	Overall (n=253)	Train cohort(n=190)	Validation cohort(n=63)	*p*-value
Alb, g/L, median (IQR)		34.6 (7.0)	34.6 (6.9)	34.6 (7.4)	0.95
Uric acid, μmol/L, median (IQR)		377.0 [306.0, 474.0]	375.0 [306.0, 471.5]	401.0 [313.5, 486.5]	0.37
β2-MG, mg/L, median (IQR)		4.3 [3.0, 7.0]	4.1 [3.0, 7.5]	4.6 [2.9, 6.7]	0.7
GFR, ml/min, median (IQR)		69.5 [49.7, 97.8]	68.9 [49.7, 99.3]	70.5 [49.1, 93.7]	0.53
Baseline HBP, n (%)	No	197 (77.9)	147 (77.4)	50 (79.4)	0.88
	Yes	56 (22.1)	43 (22.6)	13 (20.6)	
LVEF, %, median (IQR)		65.0 [62.0, 68.0]	65.0 [62.0, 68.0]	65.0 [62.0, 67.0]	0.42
LVMI, g/m^2, median (IQR)		96.6 [82.1, 110.8]	96.6 [82.1, 111.1]	98.9 [82.7, 108.8]	0.88
First therapy regimens contains					
iMiDs, n (%)	No	129 (51.0)	99 (52.1)	30 (47.6)	0.64
	Yes	124 (49.0)	91 (47.9)	33 (52.4)	
Anthracycline, n (%)	No	219 (86.6)	167 (87.9)	52 (82.5)	0.39
	Yes	34 (13.4)	23 (12.1)	11 (17.5)	
Combined CV-related drugs					
Aspirin	No	222 (87.7)	165 (86.8)	57 (90.5)	0.59
	Yes	31 (12.3)	25 (13.2)	6 (9.5)	
ACEI/ARB	No	216 (85.4)	157 (82.6)	59 (93.7)	0.05
	Yes	37 (14.6)	33 (17.4)	4 (6.3)	
Beta-blockers	No	234 (92.5)	177 (93.2)	57 (90.5)	0.67
	Yes	19 (7.5)	13 (6.8)	6 (9.5)	
CCB	No	202 (79.8)	149 (78.4)	53 (84.1)	0.43
	Yes	51 (20.2)	41 (21.6)	10 (15.9)	
Statin	No	227 (89.7)	170 (89.5)	57 (90.5)	1
	Yes	26 (10.3)	20 (10.5)	6 (9.5)	
Diuretics	No	242 (95.7)	182 (95.8)	60 (95.2)	1
	Yes	11 (4.3)	8 (4.2)	3 (4.8)	

D-S, Durie–Salmon staging system; ISS, International Staging System; high-risk CA, high-risk cytogenetic abnormalities; CRP, C-reactive protein; Hb, hemoglobin; Cr, creatine; β2-MG, β2-microglobulin; IMiDs, immunomodulatory drugs; CCB, calcium channel blockers; CV, cardiovascular.

TABLE 3 Univariate and multivariate Cox analyses for OS of CVAEs in patients with NDMM in training cohort.

Variable	Univariate	*p*	Multivariate	*p*
	HR (95% CI for HR)		HR	
Age group	6.967 (2.993-16.220)	<0.001	4.935(2.063-11.804)	<0.001*
Smoke	1.967 (1.166-3.318)	0.011	1.632(0.940-2.834)	0.115
Atrial fibrillation	4.601 (1.656-12.780)	0.003	2.150(0.716-6.460)	0.073
Baseline HBP	3.072 (1.818-5.190)	<0.001	1.795(1.031-3.125)	0.018*
LVEF	0.944 (0.892-0.999)	0.049	0.961(0.905-1.019)	0.176
LVH	2.598 (1.373-4.917)	0.003	2.208(1.110-4.391)	0.022*
β2MG group	1.969 (1.093-3.547)	0.024	1.093(0.567-2.110)	0.889
Diuretic	2.963 (1.267-6.928)	0.0122	1.746(0.696-4.381)	0.235

Baseline HBP, baseline high level of office blood pressure; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; β2-MG, β2-microglobulin. *P<0.05.

TABLE 4 Univariate and multivariate Cox analyses for OS of Grade 3–5 CVAEs in patients with NDMM in entire cohort.

Variable	Univariate	*p*	Multivariate	*p*
	HR (95% CI for HR)		HR	
Smoke	2.799 (1.498-5.232)	0.001*	2.3256 (1.2033-4.495)	0.012*
DM	2.138 (0.894-5.110)	0.088	1.0267(0.3645-2.892)	0.960
Stroke	2.210 (0.964-5.066)	0.061	1.6827 (0.6534-4.333)	0.281
ISS above III	2.085 (1.118-3.890)	0.021*	1.0138(0.4228-0.4228)	0.976
Baseline HBP	2.272 (1.164-4.434)	0.016*	1.8977(0.9525-3.781)	0.069
LVH	3.410 (1.703-6.827)	<0.001*	2.8347(1.3313-6.036)	0.007*
β2MG group	2.497 (1.222-5.101)	0.012*	1.3768(0.5368-3.532)	0.506
GFR	0.989 (0.980-0.998)	0.015*	1.0029(0.9864-1.008)	0.601

DM, diabetes mellitus; ISS above III, ISS stage above III; Baseline HBP, baseline high level of office blood pressure; LVH, left ventricular hypertrophy; β2-MG, β2-microglobulin; GFR, glomerular filtration rate. *$P<0.05$.

Discussion

We developed a prognostic scoring system highly predictive of the risk of CVAEs in MM patients. Age >61 years old, high level of baseline office blood pressure, and LVH were independently associated with the occurrence of CVAEs. In addition, LVH was also independently associated with the occurrence of severe CVAEs (CTCAE≥3). The three-factor scoring system stratified the risk of CVAEs in our cohort into three groups: high-, intermediate-, and low-risk groups. The occurrence of CVAEs showed significant difference among the three groups of patients during a mean follow-up of 12.5 months. The C-indexes of this scoring system for predicting the occurrence of CVAEs were 0.73 (95% CI, 0.67–0.79) in the training set, 0.66 (95% CI, 0.51–0.81) in the validation set, and 0.71 (95% CI, 0.65–0.77) in entire cohort. The C-indexes and ROC curves demonstrated that this scoring system showed excellent individually predictive effects in predicting the occurrence of CVAEs of patients with NDMM in the training, validation, or entire cohort.

There are several advantages in this prognostic model. First of all, the three-factor model is practical and easy to implement in general practice because it is built on parameters that are the most common

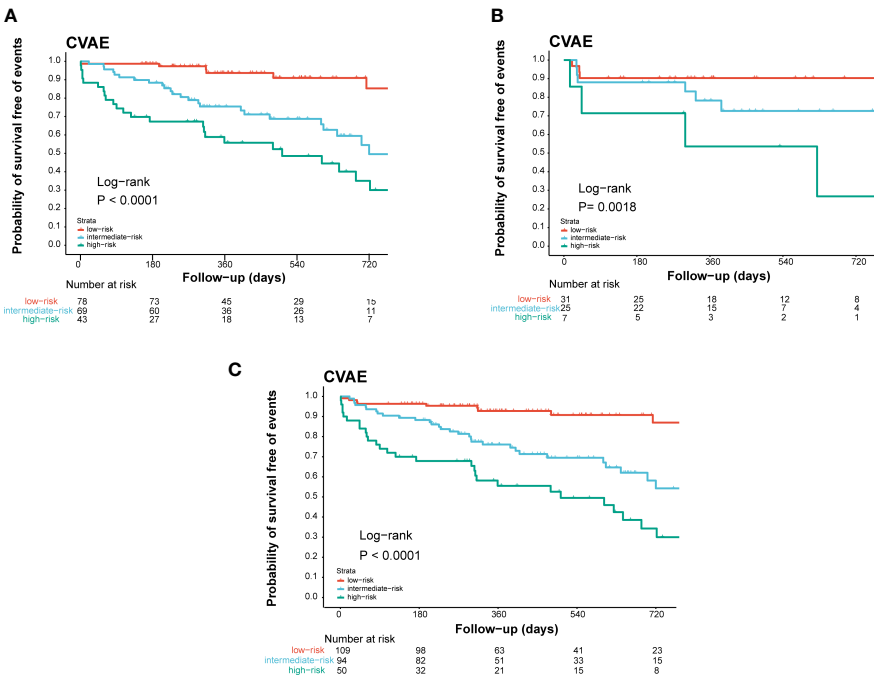

FIGURE 1
Validation of the prognostic index of CVAEs occurrence in NDMM patients. Kaplan–Meier estimates of CVAE-free survival in **(A)** the training cohort, **(B)** the internal validation cohort, and **(C)** the combined cohort validation cohort. High, high-risk group; Int, intermediate-risk group; Low, low-risk group.

TABLE 5 Survival of the clinical risk groups stratified by the three-factor model.

Risk Group	Three-Factor Score	No. Patients	HR[a](95%CI)	*p*
Training cohort		190		
Low	0-1	78	1	–
Int	2	69	4.965 [2.034, 12.123]	<0.01
High	3-4	43	10.822 [4.474, 26.175]	<0.01
Validation cohort		63		
Low	0-1	31	1	–
Int	2	25	3.018 [0.776, 11.734]	0.11
High	3-4	7	9.624 [2.271, 40.790]	<0.01

HR, hazard ratio; a, Comparison of the low-risk group with other risk groups within the same cohort.

indications in clinical testing. Second, MM is a group of very heterogeneous disorders, and a variety of treatment plans were used in MM patients in real-world situation. The patients in the study cohort were based on real treatment plan of MM and were followed up to determine the occurrence of CVAEs. The prognostic model constructed by this kind of data may reflect the real condition on the occurrence of CVAEs in MM. Third, several cardiovascular risk assessment protocols have been proposed in cancer patients undergoing cardio-toxic treatment in previous studies (16–18). However, few of them could apply to MM patients. In recent years, a prospective study that investigated the relationship between Carfilzomib (CFZ) therapy in MM and CVAEs has established a risk score for CVAEs in MM patients (19). However, this risk score system is inapplicable in predicting the occurrence of CVAEs in MM, which have a range of different treatment plans. To our knowledge, it is the first prognostic model applied to predict the occurrence of CVAEs for MM in real treatment regimens.

In our prognostic model, age >61 years old, high level of baseline office blood pressure, and LVH were revealed as significant independent factors for CVAEs. Age contributed 2 points, and the other two factors contributed 1 point to a prognostic model. In contrast, several classic clinical factors, such as the history of cardiovascular disease, BNP, creatinine, and GFR, did not have consistent or independent prognostic value. Several factors have related to this result. First, only two independent medical centers were incorporated in our study, and a limited number of subjects were included. These traditional factors were not enough to make a difference during our follow-up time. Second, the NDMM patients who have the history of cardiovascular disease might have received more attention on cardiovascular protection and have less cardiovascular toxicity regimens in the beginning of the therapy. Lastly, age, LVH, and baseline office blood pressure were also closely related to cardiac dysfunction. Until now, age is the best predictor of cardiovascular disease (CVDs) (20, 21). The risk of cardiovascular disease increases with age (22). LVH was one of echocardiographic characteristics of the left ventricle that has been studied in recent years. Most LVH are associated with chronic stress, volume overload, and ischemic disease from a population standpoint (23). The ability of LVM to predict CVD outcomes has been demonstrated in earlier studies. After adjusting the other baseline characteristics, baseline LVM was considered to have a significant predictive ability in the incidence of CVD, CVD-related death, and all-cause mortality in the Framingham Heart Study (24). Recent studies showed a continuous relationship between LVM and

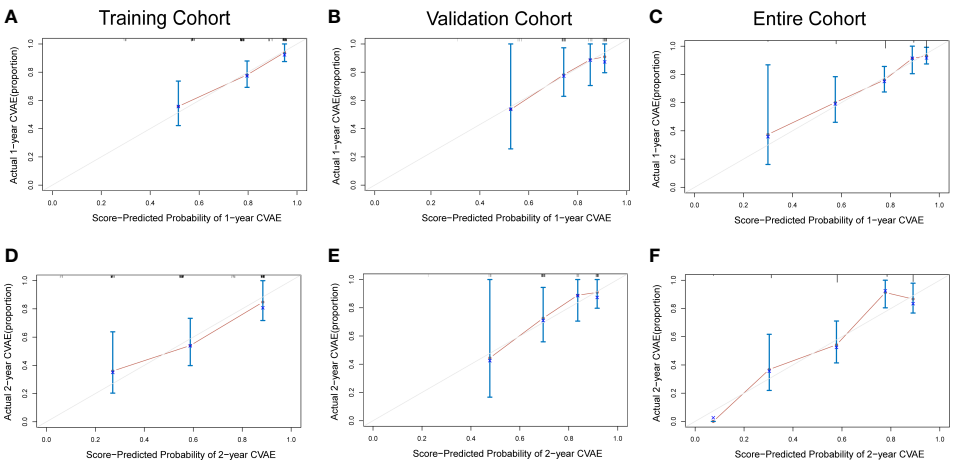

FIGURE 2
Calibration curves for predicting 1- and 2-year CVAE-free survival in the **(A, D)** training cohort, **(B, E)** validation cohort, and **(C, F)** entire cohort.

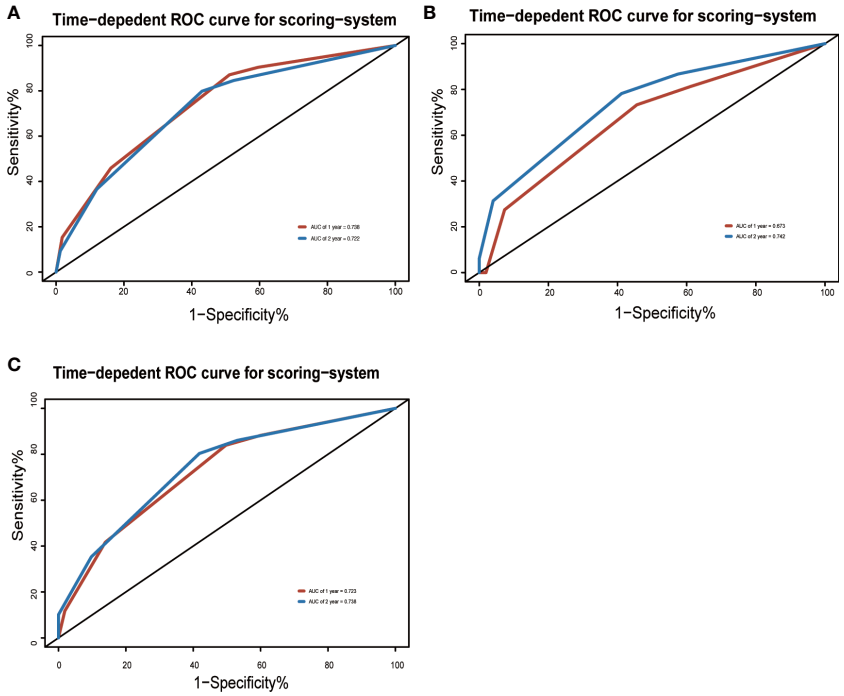

FIGURE 3
Area under the ROC curves of the three-factor risk score system in the **(A)** training cohort, **(B)** validation cohort, and **(C)** entire cohort.

CVD events as well. It was reported that every 39 g/m^2 increase in LVM was associated with a 40% increase in cardiovascular disease risk (25). This continuous relationship has also been validated in a prospective study (26). It is needed to study further about the relationship between LVH and CVAEs after MM treatment. Abnormal baseline office blood pressure was considered as undiagnosed, untreated, or uncontrolled hypertension. Hypertension is the leading risk factor for CVD (27). High blood pressure that was undiagnosed or inadequately controlled with medication accounts for a significant portion (28). It means that we should pay attention to blood pressure monitoring in the treatment of NDMM. The underlying mechanisms between abnormal baseline office blood pressure and CVAEs might be blood vessel damage and stiffening. A study showed that Carfilzomib could increase coronary perfusion pressure, resting vasoconstricting tone, and the spasmogenic effect of different

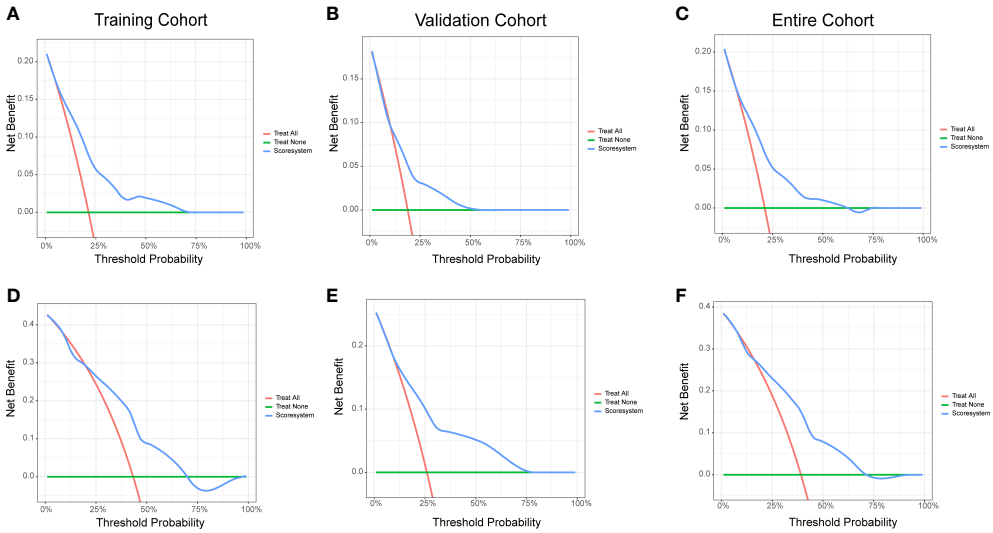

FIGURE 4
Decision curve analysis of the risk score system for the CVAE-free survival prediction of NDMM patients. **(A)** One-year survival in the training cohort. **(B)** One-year survival in the validation cohort. **(C)** One-year survival in the entire cohort. **(D)** Two-year survival in the training cohort. **(E)** Two-year survival in the validation cohort. **(F)** Two-year survival in the entire cohort.

agents (29). Further studies are warranted to verify and expand on the relationship between blood pressure and MM treatment.

However, our study still has some limitations that undermine its generalizability. First, it is a retrospective study, and data bias exists. Second, our risk score system was developed and validated using data from two medical centers, and the lack of external validation may limit its wide application. Third, a relatively small number of patients were enrolled in our study, and the median follow-up time was only 12.5 months. The longer-term CVAEs cannot be accurately assessed. Fourth, although there were no significant differences in baseline treatment regimens, there were still differences in treatment regimens among patients. Some drugs have presented cardiovascular toxicity definitely in previous studies such as Doxorubicin (DOX) (30, 31). However, this study did not show a clear association between DOX and CVAEs. The reason may be that the number of DOX patients was not enough to reflect the statistical difference, and DOX may not develop CVAEs with statistical difference during our follow-up period. Thus, the results in our study need further prospective studies and external validation by other research centers to ensure its clinical applicability.

Conclusion

In conclusion, we developed a prognostic risk prediction model for predicting CVAE risk of NDMM patients. The internal validation showed good performance in predicting 1- and 2-year CVAEs. Patients at increased risk of CVAEs can be identified at treatment initiation and be more focused on cardiovascular protection in treatment plan.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SY, J-YZ, B-ZY, H-XH and RL designed the research and drafted the manuscript. T-JZ and Z-LX presided over the enrollment and exclusion of patients and followed up the patients and collected the data. Z-LX checked the data. SY and J-YZ statistically analyzed the data. RL supervised the conduct of the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1043869/full#supplementary-material

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Long-term and real-life incidence of cancer therapy-related cardiovascular toxicity in patients with breast cancer: a Swedish cohort study

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Background: The administration of anticancer drugs in females with comorbidity increases the risk for cancer therapy-related cardiovascular toxicity (CTR-CVT), which in turn contributes to cardiovascular disease (CVD). Furthermore, a pathophysiological connection between cancer and cardiovascular disease may exist.

Objective: To assess the long-term risks and predictors of CTR-CVT, including clinical hypertension (HT), coronary artery disease (CAD), heart failure (HF), atrial fibrillation (AF), as well as all-cause mortality in women diagnosed with early breast cancer (BC) and eligible for adjuvant chemotherapy in Sweden.

Methods: Data were extracted from Swedish registers and medical records on 433 women, 18-60 years of age, diagnosed 1998-2002 with lymph node-positive BC, and considered for adjuvant chemotherapy. CTR-CVT was defined as HT, CAD, HF, or AF after the diagnosis of BC. Follow-up was from the date of BC diagnosis until November 30, 2021, or death. Prevalence of CTR-CVT and all-cause mortality were calculated. Hazard ratios (HR) were determined for factors associated with CTR-CVT.

Results: The median age was 50 (interquartile range (IQR) 32) years. 910 CTR-CVT events were diagnosed in 311 women with a median of 19.3 (IQR 15,3) years follow-up. The proportions of CTR-CVT events were: HT 281 (64%); CAD 198 (46%); HF 206 (47%); and AF 225 (51%). The cumulative incidence of CTR-CVT was 71.8%, and 50% of all 433 patients developed CTR-CVT within 11.7 years of BC diagnosis (standard deviation (SD) 0.57, 95% confidence interval (CI) 10.6-12.9). Age was a risk factor for CTR-CVT. Anthracycline increased the risk for HF (p=0,001; HR 2,0; 95%CI 1,4-2,8), CAD (p= 0,002; HR 1,7; 95% CI 1,2-2,4), and AF (p=0,013; HR 1,5; 95% CI 1,0-2,0). At the end of the 24-year study period, 227 of the 433 women were alive, and the total cumulative mortality was 47,6%.

Conclusion: The prevalence of CTR-CVT and all-cause mortality is high after BC diagnosis and treatment, particularly in older patients and those receiving anthracyclines. These findings and the onset of CTR-CVT support cardio-oncology guidelines recommending initial risk stratification and cardiovascular monitoring during treatment, followed by long-term annual screening for cardiovascular risk factors and CTR-CVT among BC survivors.

KEYWORDS

antineoplastic agents, anthracyclines, breast neoplasms, cardiovascular diseases, heart failure, hypertension, coronary artery disease, atrial fibrillation

Introduction

Cardio-oncology comprises all forms of cardiovascular care to oncology patients before, during, and after cancer treatment. Current European Society of Cardiology guidelines on cardio-oncology recommend evaluation of cardiovascular risk factors, cardiovascular monitoring during treatment and one year, followed by long-term follow-up after breast cancer (BC) treatment (1, 2). BC is the most common form of cancer in females (3). In Sweden, the annual new case average between 2008 and 2021 was 8,600 (4). Early detection, surgery, refinement of older treatments, and the introduction of new therapies have resulted in improved outcomes (5–8). Anthracycline-based adjuvant chemotherapy such as 5-fluorouracil, doxorubicin or epirubicin, and cyclophosphamide (FAC or FEC) have been shown to reduce the relative risk of 10-year BC mortality by 20% when given in a higher cumulative dose compared to the non-anthracycline-based regimens containing including cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) (6). However, at an early stage, it was discovered that anthracyclines could cause irreversible cancer therapy-related cardiovascular toxicity (CTR-CVT) (9, 10).

The individual patient data meta-analyses of randomized trials found an increase in cardiovascular (CV) mortality for anthracycline-based regimens when compared to CMF regiments (relative risk (RR) 1.50, standard error (SE) 0.38) or no chemotherapy (RR 1.61, SE=0.31). However, CV mortality did not outweigh the reduction in BC mortality (6). Other factors that increase the risk for CTR-CVT are targeted therapies with or without chemotherapy and radiotherapy (RT) that involves the heart, particularly the myocardium and coronary arteries (3, 9, 11). The administration of anticancer drugs in women with existing cardiovascular risk factors or cardiovascular disease (CVD) increases the risk for CTR-CVT. This is further increased by higher age and comorbidities such as diabetes, renal dysfunction, pulmonary disease, and endocrinopathies (1, 2). Furthermore, several common pathophysiological mechanisms linking CVD to cancer exist, including inflammation, neuro-hormonal activation, oxidative stress, and a dysfunctional immune system (12–14). Patients with CVD and cancer contracting SARS–CoV-2 are among the highest risk groups for poor outcomes (15). The prevalence of CTR-CVT varies, and it can be induced during cancer treatment or later on (16, 17).

The aim of this study was thus to assess the long-term risk for CTR-CVT as well as all-cause mortality amongst women in Sweden diagnosed with BC and eligible for adjuvant chemotherapy between January 1998 and December 2002. The various demographic and clinical factors associated with CTR-CVT were also explored.

Materials and methods

Study population

Women in the Southeast Healthcare Region of Sweden (1 million inhabitants) below 60 with early lymph node-positive BC diagnosed between January 1998 and December 2002 were identified *via* the Southeast Regional Quality Registry for Breast Cancer in Sweden. The study population was chosen to capture women that fulfilled the criteria to be considered for adjuvant chemotherapy. According to regional treatment guidelines 1998-2002, only women younger than 60 with one or more lymph node metastases were eligible for adjuvant chemotherapy.

Women with primary metastatic disease, adjuvant HER2-targeted therapies, and women with known CVD and unknown cancer treatment were excluded. The cohort consisted of women with early BC treated with surgery who also received adjuvant oncological treatment. Three study groups were formed: 1) Anthracycline-containing chemotherapy (anthracycline); 2) Non-anthracycline-containing chemotherapy (other Chemo); 3) No chemotherapy (no Chemo) given. Follow-up was up to 24 years after BC surgery. By law, patients registered in national quality registries in Sweden do not need to provide written informed consent for their data to be included in healthcare research. They are notified that their data stored in registries may be removed if so wished. This study was approved by the Regional Ethics Committee (Dnr: 2012/172-31).

Breast cancer treatment between 1998-2002

The recommended chemotherapeutic regiments that most women received were 9 cycles of anthracycline-containing chemotherapy, FEC

(5-fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, cyclophosphamide 600mg/m^2) or 9 cycles non-anthracycline-containing chemotherapy, CMF (cyclophosphamide 600 mg/m^2, 5-fluorouracil 600 mg/m^2 and methotrexate 40 mg/m^2) both administered intravenously at 3-week intervals. Epirubicin, an anthracycline, was administered as a short infusion over 15-20 minutes.

RT to the breast was mandatory after breast-conserving surgery and sometimes to the chest wall after mastectomy. Patients with lymph node-positive disease received loco-regional RT (45-50 Gray) with the treatment goal of < 10% mean heart dose.

Adjuvant antiestrogen therapy, such as tamoxifen or aromatase inhibitors, was administered after chemotherapy and/or RT to women with an estrogen receptor-positive tumor or unknown hormone receptor status, depending on their menopausal status. Premenopausal women received 5 years of tamoxifen, a selective estrogen receptor modulator (SERM) that binds to estrogen receptors, preventing estrogen binding. Postmenopausal women received 5 years of tamoxifen or aromatase inhibitors, blocking estrogen production. In some cases, they received 2 years of tamoxifen followed by 3 years of aromatase inhibitors (switch treatment).

Data sources

This was a retrospective registry-based cohort study where information on participants was crossmatched with various registers and medical records. Data were obtained from the Southeast Regional Quality Registry for Breast Cancer, which included data for patients from the Southeast Healthcare Region diagnosed with BC from January 1998 through December 2002. Data on the date of BC diagnosis and surgery, age at the time of BC diagnosis, laterality (right or left), tumor staging, nodal status, tumor biology (Elston Ellis grade, estrogen/progesterone status), and adjuvant treatment (chemotherapy, endocrine therapy, and RT) were retrieved from the Southeast Regional Quality Registry for Breast Cancer. Data on the type and accumulated dose of adjuvant chemotherapy, location of and total dose (Gy) of RT, and type of endocrine treatment (aromatase inhibitors or tamoxifen), baseline risk factors at the time of BC diagnosis such as obesity (BMI), diabetes mellitus, and smoking were collected from medical records. The Swedish National Board of Health and Welfare maintains the National Patient Registry (NPR) and the Swedish Cause of Death Registry (COD). The NPR collects data on inpatient (hospital) healthcare episodes and outpatient specialist care (18). The NPR and medical records were also used to retrieve data on CVD. For each patient, we recorded and categorized menopausal status, smoking habits, obesity, laterality, staging, tumor biology of the BC, and type of adjuvant oncological treatment (e.g., RT, chemotherapy, hormonal therapy, unspecified treatment, no treatment, or missing treatment data). Data on the time and cause of death were collected from the COD and medical records.

The International Classification of Diseases 10 (ICD 10) was used to retrieve data on CVD and mortality. Data from these registers and medical records were crossmatched for each patient using the unique national identification number assigned to every Swedish resident at birth or when granted permanent residency.

Covariates

Patients were divided into 3 different age categories (≤ 40, 41-50, and 51-60 years). We also recorded and categorized menopausal status, smoking habits, obesity, laterality, staging, and tumor biology of BC, and type of oncological adjuvant treatment such as radiotherapy, chemotherapy, hormone therapy, unspecified treatment, no treatment, or missing treatment data). Left-sided BC was used as a surrogate for patients where the heart was subjected to RT.

The TNM classification system was used for tumor staging (19), but if T, N, or M data were unavailable, the tumor stage was designated missing.

Outcome measures

The primary outcome measure used for the study was the CTR-CVT event from the time of BC surgery until the end of follow-up or death.

For this study, a CTR-CVT event was defined as hypertension (HT), coronary artery disease (CAD), heart failure (HF), or atrial fibrillation (AF) after BC diagnosis. The ICD 10 codes covered were: I 10-15 (hypertensive disease); I 20-25 (ischemic heart disease); I 50 (heart failure); and I48 (atrial fibrillation). Women with >1 CTR-CVT were included in each event category.

All-cause mortality was defined as the time (in years) between BC diagnosis and the end of follow-up (November 30, 2021) or death. Hence, for the whole cohort, data were collected over a period of at least twenty-four years.

Statistical analysis

Patient characteristics and baseline data were summarised with descriptive statistics for the entire cohort according to the treatment group and reported as number, percentage, median and interquartile range (IQR). Cumulative incidences were reported in median and standard deviation (SD) with a 95% confidence interval (CI).

Univariable Cox proportional hazards regression was used to identify factors significantly associated with risk for CTR-CVT or all-cause mortality. A multivariate Cox analysis adjusted for, laterality, Elston Ellis Grade, estrogen receptor status, obesity, smoking, endocrine treatment, and diabetes mellitus was performed and reported for the different treatment groups and age groups regarding HT, CAD, HF, and AF. Factors with a p-value < 0.10 were initially included in a multivariable Cox regression model and reduced by backward elimination. A p-value < 0.05 indicated statistical significance and retained in the model, and hazard ratios (HR) and 95% CI were estimated. All-cause mortality was defined as the time from BC surgery to the date of death. The follow-up period was from January 1, 1998, to November 30, 2021, or death. The cumulative morbidity and mortality are illustrated by Kaplan-Meier curves and analyzed with Log Rank, Breslow, and

Tarone-Ware tests. Data were analyzed and presented as descriptive and comparative statistics using IBM SPSS version 28 (Armonk, New York, USA).

Results

524 women below 60 were diagnosed with lymph node-positive early BC between January 1, 1998, and December 31, 2002, in the Southeast Healthcare Region, Sweden. Of these, 91 were excluded: 22 (4.0%) had primary metastatic disease; 5 (1.0%) received adjuvant HER2-targeted therapy within a clinical trial; 17 (3.0%) had current CVD; and 47 (9.0%) had unknown oncological treatment since the medical records (at that time, paper archives) could not be retrieved, leaving a total of 433 women that comprised the study population. Of these, 228 (53.0%) received anthracycline, 78 (18.0%) other Chemo, and 127 (29.0%) no Chemo (Figure 1).

For the total period of the study, the median follow-up was 19.3 (IQR 15.3) years: 21.2 years (IQR 2.4) for survivors and 5.8 years (IQR 8.4) for the deceased. The demographic and clinical baseline characteristics at BC diagnosis in the three treatment groups are listed in Table 1.

Cancer therapy-related cardiovascular toxicity (CTR-CVT)

A total of 910 events, including HT, CAD, HF, and AF, were diagnosed in 311 women. The cumulative incidence for CTR-CVT was 71.8%, and 50.0% of the patients developed CTR-CVT within 11.7 years (SD 0.57; 95% CI 10.6-12.9) (Figure 2).

The distribution of events was: anthracycline group 501 CTR-CVT events (55.1%); other Chemo group 185 events (20.3%); and the no Chemo group 224 events (24.6%) (Table 1). During the 24-year follow-up period, 120 (27.0%) women had no CTR-CVT, 86 women (20.0%) had one event category, 33 women (7.0%) had two categories, 18 (4.0%) had three categories, and 176 women (41.0%) suffered all four event categories (HT, CAD, HF, and AF). Cumulative incidence shows that 50.0% of all 433 patients developed HT within a median of 12.8 years (SD 0.7; 95% CI 11.3-14.2), CAD within 23 years (SD n/a), HF within 22.9 years (SD n/a), and AF within 20 years (SD n/a) (Figure 3).

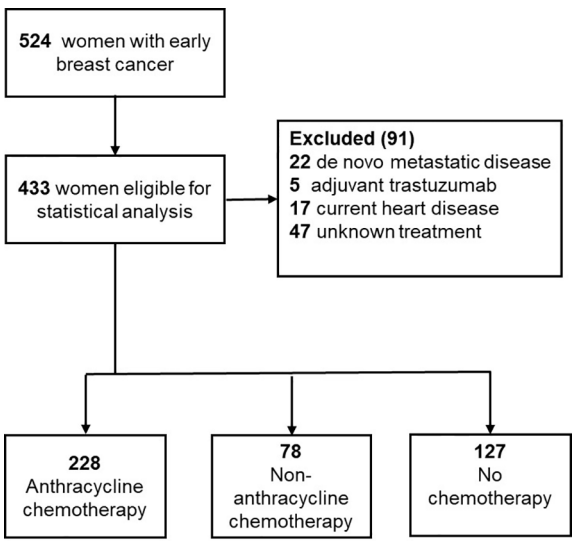

FIGURE 1
Flowchart of the data.

Anthracycline treatment was associated with 51.0% of HTs, 57.0% of CADs, 60.0% of HFs, and 54.0% of AFs (Figure 4A). The hazards ratio showed an increased risk for HF (p=0.001; HR 2.0; 95% CI 1.4-2.8), and CAD (p= 0.002; HR 1.7; 95% CI 1.2-2.4) and AF (p=0.013; HR 1.5; 95% CI 1.0-2.0), but for HT the HR was not significant (p=0.127; HR 1.2; 95% CI 0.96-1.6). The other Chemo group showed lower proportions of associated events: HT 21.0%; CAD 21.0%; HF 18.0%; and AF 21.0% (Figure 4A). HRs were not significant (data not shown). Distribution of 910 CTR-CVT events in those ≤ 40 years of age 130 (14%), in those 41-50 years 289 (32%), and those 51-60 years 494 (54%) (Figure 4B).

Cumulative incidence of four CTR-CVT events by treatment group are shown in Figure 5A. The highest cumulative incidence was detected in the youngest age group during the first 5-10 years (p=0.018): After that, the difference between age groups continued throughout the rest of the 24-year follow-up (p=0.030) (Figure 5B).

Time to first CTR-CVT event

The median time to the first CTR-CVT event after BC diagnosis was 7.6 years (SD 0.69; 95% CI 6.3-8.9). The youngest age group had its first CTR-CVT after a median of 4.1 years (SD 1.0; 95% CI 2.1-6.0), the 41-50 year group after 7.8 years (SD 1.2; 95% CI 5.4-10.1), and the oldest group (51–60) after 8.1 years (SD 0.8; 95% CI 6.2-8.9). The overall median time to the first CTR-CVT event was for HT 7.6 years (SD 0.7; 95% CI 6.1-9.0), CAD 5.2 years (SD 0.4; 95% CI 4.3-63.0), HF 5.3 years (SD 0.5; 95% CI 4.5-6.1) and for AF 5.3 years (SD 0.4; 95% CI 4.5-6.0) (Figure 6).

Hypertension

Hypertension was the most prevalent event (64%), with significant differences in cumulative incidence between the three age groups (p=0.007) (Figure 7). In the youngest group (≤ 40), the risk for HT was higher the first eight years of observation (p=0.04) but decreased with time compared to elderly groups. The cumulative incidence of HT among the older groups did not significantly differ until after ten years. Then it became significantly higher in the oldest age group (p=0.03), where 74% had HT (Figure 7). The cumulative incidence of HT differed significantly between the anthracycline and the other Chemo group compared with the no Chemo group (p= 0.02) (Figure 8). Still, when adjusted in the multivariate analysis, there was no significantly increased risk (HR) in the anthracycline or the other Chemo group. Elston Ellis Grades II and III (histological grading of BC) were associated with significantly higher risk for HT: Grade II (p=0.047; HR 1.4; 95% CI 1.0-2.1) and Grade III (p=0.03; HR 1.7; 95% CI 1.2-2.5) compared with Grade I.

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TABLE 1 Demographic and clinical characteristics of 433 patients[a] with lymph node-positive early breast cancer (BC) at diagnosis in the Southeast Healthcare Region, Sweden, January 1, 1998, to December 31, 2002.

Population per study group	Anthracycline[b] 228 (53%)	Other Chemo[c] 78 (18%)	No Chemo[d] 127 (29%)
Median age, years (IQR)	48 (11)	52 (10)	52 (10)
Age group, years			
≤ **40** (n=61) numbers (%) Median age, years	 50 (21%) 37.5	 5 (6%) 37.0	 6 (5%) 37.5
41-50 (n=163) numbers (%) Median age, years	 90 (40%) 47.0	 24 (31%) 46,5	 49 (39%) 47,0
51-60 (n=209) numbers (%) Median age, years	 88 (39%) 55.2	 49 (63%) 56.0	 72 (57%) 57.0
Menopausal status			
Premenopausal	94 (41.6%)	19 (24.4%)	30 (23.8%)
Peri-menopausal	13 (5.8%)	4 (5.1%)	4 (3.2%)
Postmenopausal	79 (35.0%)	43 (55.1%)	63 (50.0%)
Not given	40 (17.7%)	12 (15.4%)	29 (23%)
Smoking status			
Smoker	18 (7.9%)	9 (11.5%)	3 (2.4%)
Non-smoker	90 (39.5%)	26 (33.3%)	55 (43.3%)
Ex-smoker (cessation > 6 months)	8 (3.5%)	2 (2.6%)	3 (2.4%)
Not given	112 (49.1%)	41 (52.6%)	66 (52.0%)
Obesity (BMI>30 kg/m^2)			
Yes	16 (7.0%)	5 (6.4%)	5 (3.9%)
No	193 (84.6%)	68 (87.2%)	102 (80.3%)
Not given	19 (8.3%)	5 (6.4%)	20 (15.7%)
Laterality of BC			
Left	111 (48.7%)	40 (51.3%)	64 (50.4%)
Right	117 (51.3%)	38 (48.7%)	63 (49.6%)
Type of surgery			
Mastectomy	142 (62.3%)	50 (64.1%)	62 (48.8%)
Conservative	85 (37.3%)	28 (35.9%)	65 (51.2%)
Not given	1 (0.4%)	0	0
Type of axillary surgery			
Sentinel node	0	0	1 (0.8%)
Axilla evacuation	227 (99.6%)	77 (98.7%)	126 (99.2%)
Not given	1 (0.4%)	1 (1.3%)	0
Stage			
II	103 (45.2%)	54 (69.2%)	116 (91.3%)
III	125 (54.8%)	22 (28.2%)	10 (7.9%)
Not given	0	2 (2.6%)	1 (0.8%)

(Continued)

TABLE 1 Continued

Population per study group	Anthracycline[b] 228 (53%)	Other Chemo[c] 78 (18%)	No Chemo[d] 127 (29%)
Elston Ellis grade			
Grade 1	8 (3.5%)	6 (7.7%)	27 (21.4%)
Grade 2	72 (31.6%)	25 (32.1%)	52 (41.3%)
Grade 3	120 (52.6%)	27 (34.6%)	21 (16.7%)
Not given	28 (12.3%)	20 (25.6%)	26 (20.6%)
Estrogen receptor status			
Positive	131 (57.5%)	52 (66.7%)	109 (85.8%)
Negative	89 (39.0%)	25 (32.1%)	17 (13.4%)
Uncertain	5 (2.2%)	1 (1.3%)	0
Not given	3 (1.3%)	0	1 (0.8%)
Progesterone receptor status			
Positive	130 (57.0%)	46 (59.0%)	103 (81.1%)
Negative	93 (40.8%)	31 (39.7%)	22 (17.3%)
Uncertain	2 (0.9%)	0	0
Not given	3 (1.3%)	1 (1.3%)	2 (1.6%)
Radiotherapy			
None	5 (2.2%)	1 (1.3%)	7 (5.5%)
Breast/chest wall	3 (1.3%)	1 (1.3%)	5 (3.9%)
Breast/chest wall, regional lymph nodes	139 (61.0%)	60 (76.9%)	83 (65.4%)
Breast/chest wall, regional lymph nodes, parasternal lymph nodes	76 (33.3%)	16 (20.5%)	14 (11.0%)
Axillary lymph nodes only	3 (1.3%)	0	14 (11.0%)
Not given	2 (0.9%)	0	4 (3.1%)
Hormonal treatment			
None	79 (34.6%)	22 (28.2%)	15 (11.8%)
Tamoxifen	129 (56.6%)	52 (66.7%)	101 (79.5%)
Aromatase inhibitor	11 (4.8%)	2 (2.6%)	6 (4.7%)
Switch[e]	9 (3.9%)	2 (2.6%)	2 (1.6%)
Zoladex	0	0	1 (0.8%)
Not given	0	0	2 (1.6%)

Data are presented as numbers (percentages) if not otherwise indicated.
BC, breast cancer; IQR, interquartile range; BMI, body mass index; Elston Ellis Grade, grading for breast cancer I-III.
[a]Patients included those who were between 18 years and 60 years old at the time of the diagnosis of eBC, had one or more lymph node metastases, fulfilled the criteria to be considered for adjuvant chemotherapy according to regional guidelines between 1998 and 2002, and did not have any cardiovascular disease prior to eBC diagnosis.
[b]Anthracycline-containing chemotherapy (anthracycline).
[c]Non-anthracycline-containing chemotherapy (other Chemo).
[d]No chemotherapy given (no Chemo).
[e]Switch: 2 years' tamoxifen followed by 3 years' aromatase inhibitors.

Coronary artery disease

CAD was seen in 198 (46%) women with no significant difference in cumulative incidence between age groups: for the youngest during the first years (p= 0.054) and for the oldest during the follow-up time (p= 0.059) and at the end of follow-up (p=0.062) (Figure 7). The risk for CAD was significantly higher in the other Chemo group (p=0.02. HR 1.8. 95% CI 1.1-2.7) and the anthracycline group (p=0.02. HR 1.7. 95% CI 1.2-2.4) compared to the no Chemo group (Figure 8). Elston Ellis Grade III was associated with a significantly higher risk for CAD (p=0.001; HR 2.3; 95% CI 1.4-3.7) compared with Grade I.

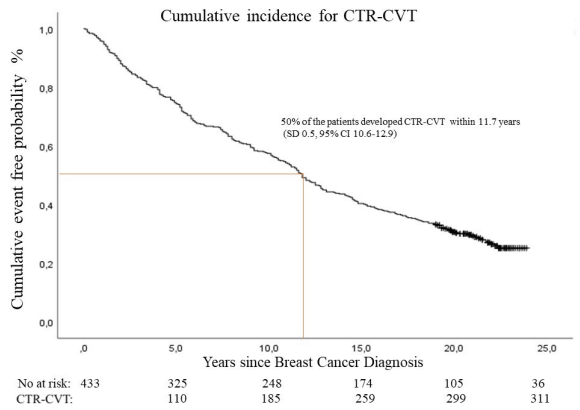

FIGURE 2
Cumulative incidence of cancer therapy-related cardiovascular toxicity (CTR-CVT) after breast cancer by years since diagnosis. 910 cancer therapy-related cardiovascular disease events in 311 patients with lymph node-positive early breast cancer at diagnosis in the Southeast Healthcare Region, Sweden, January 1, 1998, to December 31, 2002.

Heart failure

HF occurred in 206 (47%) women, where similarly increased cumulative incidences were seen in both anthracycline and other Chemo groups (p=0.001) compared to no Chemo and age (p= 0.17) (Figure 8). The HR for HF significantly increased with anthracycline treatment (p=0.025; HR 1.5; 95% CI 1.0-2.2). Elston Ellis Grade III was associated with a significantly higher risk for HF (p=0.008; HR 2.1; 95% CI 1.3-3.4) compared with Grade I.

Atrial fibrillation

AF occurred in 225 (51%) of the 443 women, with similar higher cumulative incidences in both the anthracycline and other Chemo groups (p=0.03) compared to no Chemo (Figure 8). Cumulative incidence was increased in the younger age group (p=0.02) (Figure 7). The HR for AF was higher in patients in the other Chemo group (p=0.02; HR 1.6; 95% CI 1.0-2.3) and the anthracycline group (p=0.02; HR 1.4; 95% CI 1.0-1.9) compared to no Chemo. Elston Ellis Grade III was associated with a significantly higher risk for AF (p=0.001; HR 1.9; 95% CI 1.3-2.9) compared with Grade I.

In all treatment and age groups, obesity significantly increased the risk for all CTR-CVT categories (p=0.001; HR 2.6; 95% CI 1.6-4.1), but the total number of obese patients (BMI>30 kg/m^2) in this study was low (n=26).

None of the laterality, estrogen receptor status, smoking, endocrine treatment, and diabetes mellitus was significantly associated with a higher incidence of CTR-CVT (data not shown).

All-cause mortality two decades after surgery

At the end of the 24-year study period, 227 of the 433 women were alive, and the total cumulative mortality was 47.6%. Mortality rates in the three age groups were 55.7% among those ≤ 40-years-of-age, 39.9% in patients aged 41-50 years, and 51.2% in patients 51-60 years old. The younger (≤ 40 years) and older (51-61 years) groups had significantly higher mortality rates during the observational

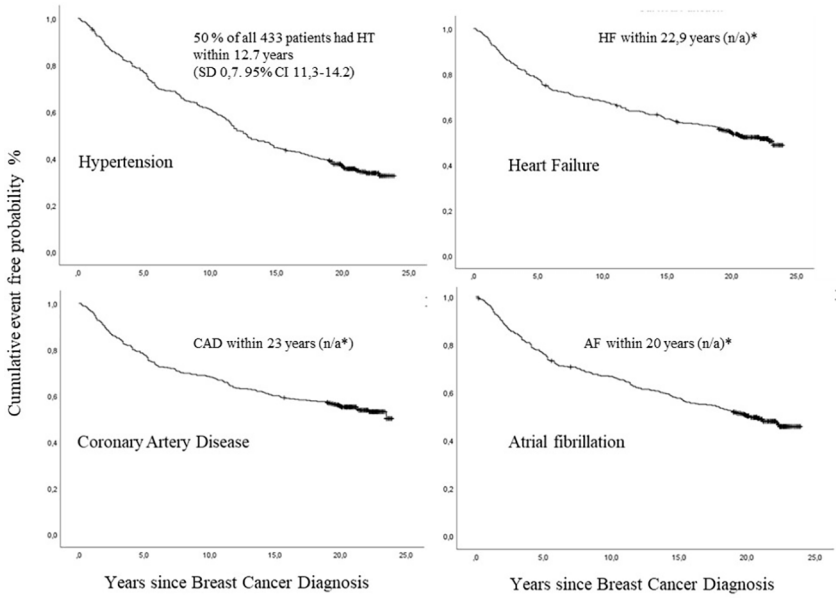

FIGURE 3
Cumulative incidence of hypertension (HT), coronary artery disease (CAD), heart failure (HF) and atrial fibrillation (AF) after breast cancer (BC) diagnosis by number of years since diagnosis, among 433 patients with lymph node-positive early breast cancer, with death as a competing risk, in the Southeast Healthcare Region, Sweden, January 1, 1998, to December 31, 2002.

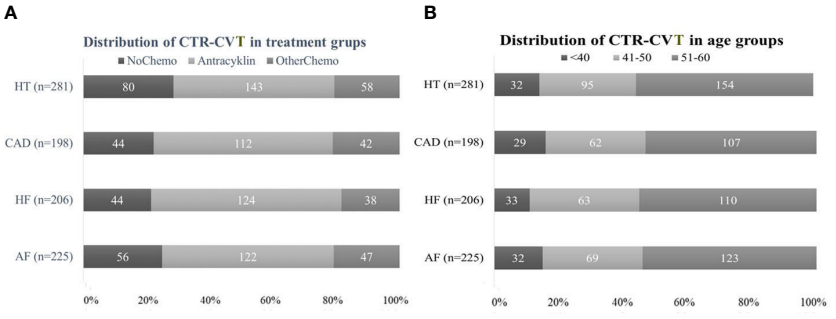

FIGURE 4
Distribution of 910 cancer therapy-related cardiovascular toxicity (CTR-CVT) events including hypertension (HT), coronary artery disease (CAD), heart failure (HF), and atrial fibrillation (AF) in 31 patients with lymph node-positive early breast cancer (BC) at diagnosis in the Southeast Healthcare Region, Sweden, January 1, 1998, to December 31, 2002. **(A)** (Left panel): Distribution of four CTR-CVT events by treatment group. Distribution of 910 CTR-CVT events in the anthracycline group 501 (55%), the other Chemo group 185 (20%), and the no Chemo 224 (25%). **(B)** (Right panel): Distribution of CTR-CVT by age group. Distribution of 910 CTR-CVT events in those ≤ 40-years-of-age 130 (14%), in those 41-50 years 289 (32%), and those 51-60 years 494 (54%).

period than the group aged 41-50 years p=0.009 and p=0.037, respectively) (Figure 9).

For the whole study period, the mortality risk was significantly higher in both chemotherapy groups compared to no Chemo. During the first five years of the study period, mortality was significantly higher in the anthracycline group (p=0.001; HR 3.3; 95% CI 1.6-6.8) and other Chemo group (p=0.007; HR 3.11; 95% CI 1.4-7.0) compared to no Chemo. During the almost 24-year study period, the overall mortality risk was significantly higher in both chemotherapy groups: anthracycline (p=0.001; HR 1.8; 95% CI 1.3-2.6) and other Chemo (p=0.01; HR 1.75; 95% CI 1.2-2.7) (Figure 9).

Discussion

To our knowledge, this population-based Swedish cohort study is one of the largest published studies describing the prevalence of long-term chemotherapy-related cardiovascular toxicity in patients with early-stage breast cancer. It assesses whether patient- and disease-related factors, including age at the time of BC diagnosis and type of adjuvant chemotherapy, are associated with the development of CTR-CVT.

Up to 24 years after diagnosis of BC (median 19.3 years), the total cumulative incidence of all CTR-CVT events was 71.8%. Higher age at BC diagnosis, higher histological grading of BC, and adjuvant anthracycline treatment were all associated with the development of CTR-CVT after BC diagnosis. The incidence of CVD was higher compared to a population-based study comparing two Swedish cities (135 000 inhabitants each) in the same catchment area as the present study, where the mean cumulative incidence of CVD among women aged 45 to 64 years was 12%. The incidence of CAD, HF, and HT for the same populations were 4.1%, 0.95%, and 7.02%, respectively (20).

The majority of women developed all four CTR-CVT categories (HT, CAD, HF, and AF) during the study period, and HT was the most prevalent diagnosis regardless of the treatment group. The

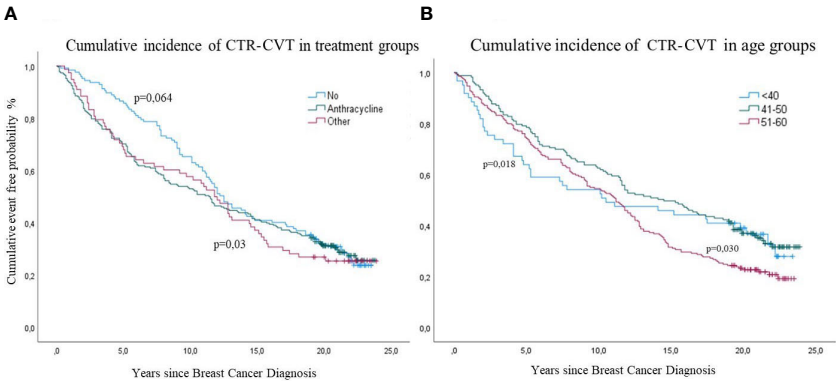

FIGURE 5
Cumulative incidence of cancer therapy-related cardiovascular toxicity (CTR-CVT) after breast cancer (BC) by years since diagnosis, with death as a competing risk, in 433 patients with lymph node-positive early breast cancer at diagnosis in the Southeast Healthcare Region, Sweden, January 1, 1998, to December 31, 2002. **(A)** (Left panel): Cumulative incidence of four CTR-CVT events by treatment group, analyzed with Log Rank (p=0,03) for all, and Breslow (p=0,06) for the no Chemo group. **(B)** (Right panel): Cumulative incidence of CTR-CVT by age group, analyzed with Log Rank (p=0,018) for all age groups and Tarone-Ware (p=0,030) for the latest years.

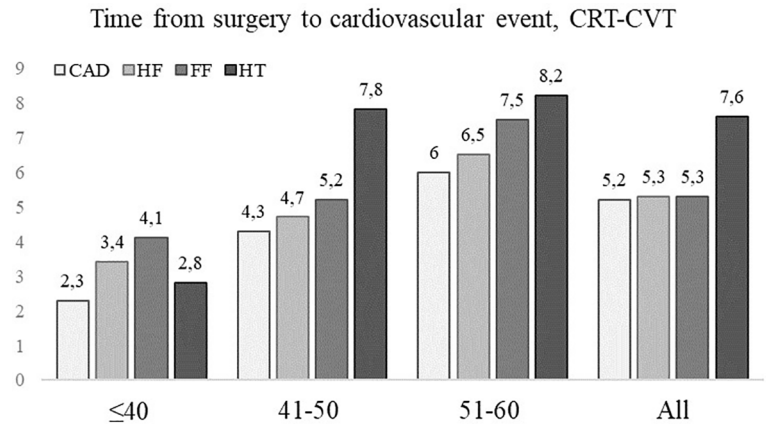

FIGURE 6
The median times to cancer therapy-related cardiovascular toxicity (CTR-CVT); hypertension (HT), coronary artery disease (CAD), heart failure (HF), and atrial fibrillation (AF) by age group after breast cancer (BC) by years since diagnosis in 433 patients with lymph node-positive early breast cancer (BC) at diagnosis in the Southeast Healthcare Region, Sweden, January 1, 1998, to December 31, 2002. Age groups: ≤ 40-years-of-age, 41-50 years, and 51-60 years.

median time to CTR-CVT after BC diagnosis was 5.8 years, CAD was the earliest to develop (within 5.2 years), and HT was the latest (within 7.6 years).

The risk for CTR-CVT is twice as high in survivors of several solid cancers and lymphoma compared with the general population (21–23). The long-term real-life data in this study reveal an even higher cumulative incidence after BC, with a cumulative CTR-CVT incidence of 71.8%. The increased risk for CTR-CVT may have been due to the over-representation of postmenopausal women in the no Chemo group with already asymptomatic atherosclerotic changes or increased risk for cardiovascular disease due to shared pathophysiological mechanisms with cancer (12, 13, 16, 21). The similar incidences of CTR-CVT between age groups among women who did not receive chemotherapy compared to those receiving anthracycline might result from more prolonged survival in the no Chemo group considering the risk of CTR-CVT increases with time and age (24). However, in our study, patients with previous CVD were excluded. Further, the women in the no Chemo group were older. Thus, the risk of CVD should have been higher, and survival

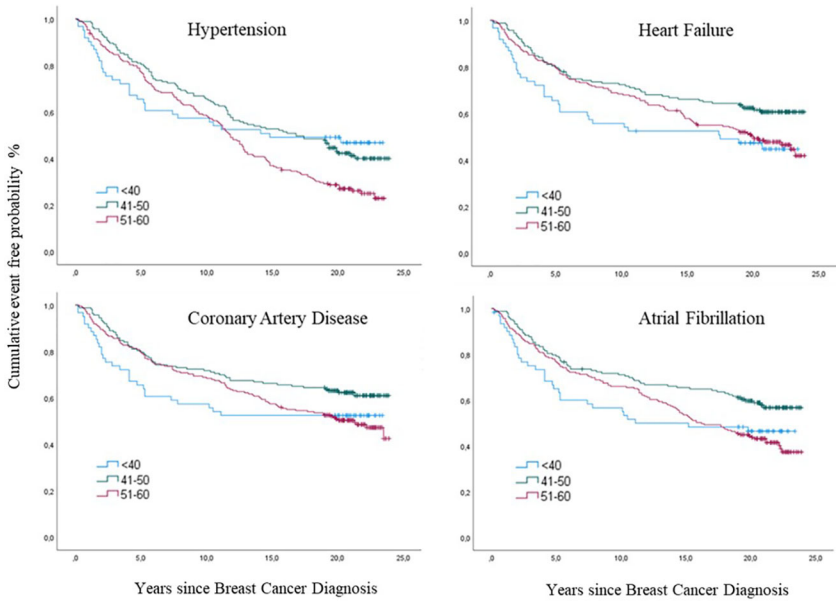

FIGURE 7
Cumulative incidences of cancer therapy-related cardiovascular toxicity (CTR-CVT); hypertension (HT), coronary artery disease (CAD), heart failure (HF) and atrial fibrillation (AF) by age group at diagnosis of breast cancer (BC) by years since diagnosis, with death as a competing Risk, in 433 patients with lymph node-positive early breast cancer at diagnosis in the Southeast Healthcare Region, Sweden, January 1, 1998, to December 31, 2002. The three age groups were ≤ 40-years-of-age, 41-50 years, and 51-60 years.

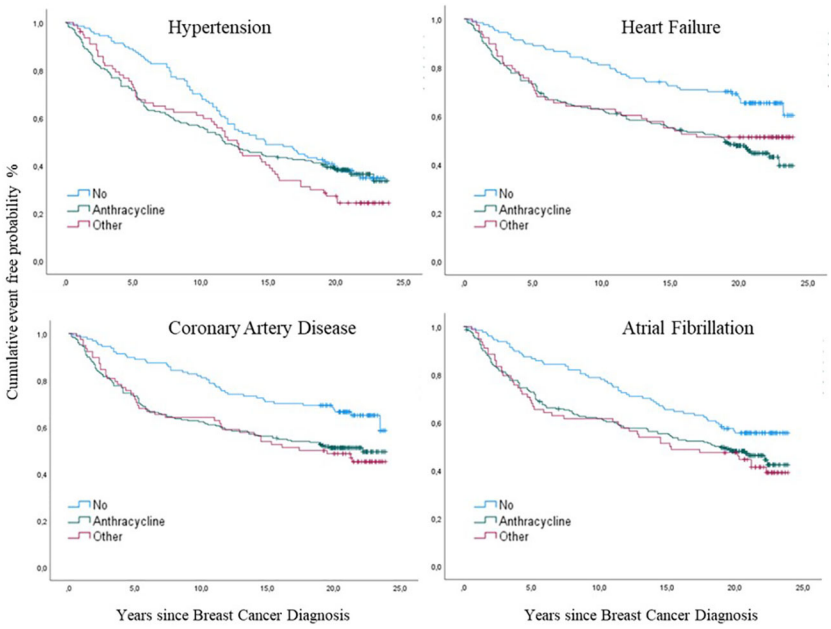

FIGURE 8
Cumulative incidences of cancer therapy-related cardiovascular toxicity (CTR-CVT); hypertension (HT), coronary artery disease (CAD), heart failure (HF) and atrial fibrillation (AF) by treatment group after breast cancer (BC) by years since diagnosis, with death as a competing risk in 433 patients with lymph node-positive early breast cancer at diagnosis in the Southeast Healthcare Region, Sweden, January 1, 1998, to December 31, 2002. Treatment groups were the anthracycline, the other Chemo, and the no Chemo groups.

should have been shorter in the no Chemo group compared to other groups.

Women with aggressive BC were more likely to receive chemotherapy due to the higher risk of BC relapse and death than women with less aggressive BC who did not receive chemotherapy, which impacts the risk of CTR-CVT. However, this study included women who received relatively low doses of anthracyclines (the vast majority received epirubicin 60 mg/m^2). This lower exposure level could explain why the risk of developing CTR-CVT was lower than expected since a dose-response relationship is believed to exist between CTR-CVT and the cumulative dose of anthracycline (25). A randomized trial between 1990 and 1998 in Sweden and Denmark, comparing the efficacy of FEC against CMF, the same chemotherapy regimens as those in our cohort, showed that the risk of CTR-CVT was similar in the two groups, as suggested by the results of this study (26).

Radiation therapy used in BC treatment increases the risk of developing

CVT, since the heart is considered radiosensitive. This risk is amplified by anthracycline therapy (21). However, radiation therapy techniques have improved since the end of the last century and the beginning of 2000, and there has been less risk

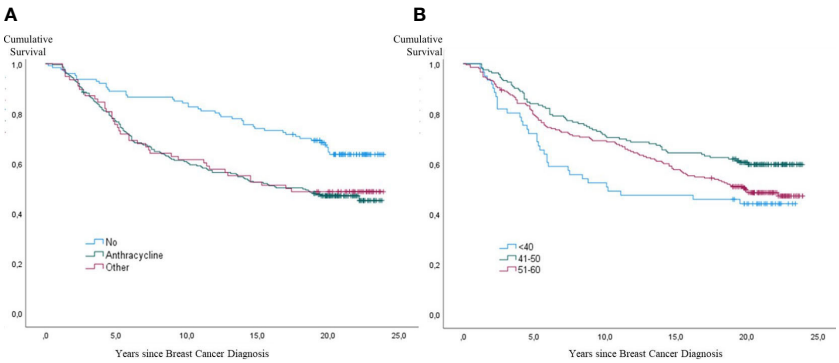

FIGURE 9
Kaplan-Meier curves showing all-cause mortality in 433 patients with lymph node-positive early breast cancer (BC) at diagnosis in the Southeast Healthcare Region, Sweden, January 1, 1998, to December 31, 2002. **(A)** (Left panel): Cumulative incidence of all-cause mortality by treatment group: Anthracycline Group, other Chemo group, and no Chemo group. **(B)** (Right panel): Cumulative incidence of all-cause mortality by age group: ≤ 40-years-of-age, 41-50 years, and 51-60 years ($p < 0.001$).

for cardiac damage (27). This could explain our results of no significant increased risk for CTR-CVT among those who received left-sided RT compared to light-sided RT.

The younger age group (≤40) developed all four CTR-CVT events, and death occurred sooner, partly due to more aggressive tumors and anthracycline-containing chemotherapy as adjuvant treatment. When considering the numbers in each age group, the youngest group had similar proportions to the four CTR-CVT categories.

For all age and treatment groups, obesity was significantly associated with a higher incidence av CTR-CVT (p=0.001), but the number of patients with obesity was low.

The incidence of HT was 64% and significantly increased in the anthracycline and other Chemo groups during the first years (p=0.045). This may be due to the potential estrogen-like agonist activity and protective effect of adjuvant tamoxifen in the no Chemo group that may have delayed the development of HT (28, 29). This is consistent with our findings showing that after approximately five years, corresponding to the time of completion of tamoxifen treatment, the no Chemo group showed a similar HT incidence as the other groups. Compared with figures from the Framingham Study showing that more than 50% of 55-year-old and 66% of 65-year-old women had developed HT (30), the long-term incidence of HT in the present study could be due to age and not CTR-CVT during this long-term follow-up.

The cumulative incidence of HF of 47% was high compared to figures from the Framingham study, where cumulative incidence varied from a few percent for 50-year-old women to 10% for women aged 85 (31). Even compared to a Swedish population study showing 0.95% for women aged 45-64 years (20). Since age, treatment with an anthracycline (risk factor for HF (p=0.046)) and high Elston Ellis Grade (risk factor for HF (p=0.008)) were all found to increase the risk for HF. this comes as no surprise.

The cumulative incidence of CAD was 46% in the present study. This is higher than in 1-1.4% incidence of myocardial infarction in women 65-85 years without cancer in a report by the Swedish Public Health Department and in a regional population study showing a 4.1% incidence of CAD in women aged 45-64 years (20). Cancer has been associated with CAD development and an increased risk for recurrent myocardial infarction and major bleeding in patients with myocardial infarction (13, 32, 33). Treatment with aromatase inhibitors can induce hyperlipidemia and HT, thereby increasing the risk for CAD (34) and the impact of these risk factors on plaque progression. This is of great importance in younger patients (35).

AF had a cumulative incidence of 51%, which is high compared to the general population, with 2.7% among women aged 60-69 years and 8.1% in those 70-79 years. 5-Fluorouracil has potent CVT mediated by vascular endothelial injury and vasospasm. Our study's high incidence of AF was most likely induced by vasospasm mediated by 5-FU (36). The cumulative incidence of CAD and AF was higher in the other Chemo group patients than those who received anthracyclines. This can be due to the other chemo group's more prolonged survival due to better cancer prognosis than the other two groups.

Cancer has an influence on both inflammation, and the progression of CVD, in that cell proliferation is mainly driven by inflammatory molecules (37, 38). Indeed, inflammation is suggested to cause tumor initiation progression, angiogenesis, and metastasis (39). Inflammation is also paramount in the pathogenesis of atherosclerosis and CAD; inflammation and age contribute to CVD (40). Biomarkers of inflammation seem to provide prognostic information concerning cardiovascular outcomes in patients with AF (41, 42). It is possible that aggressive tumor biology, reflected in higher Elston Ellis Grading, also had an impact on inflammation and, thus, a significant impact on all CTR-CVT categories.

Of the 433 women in the study, 227 were alive after 24 years, giving a cumulative all-cause mortality of 47.6%. The younger (≤ 40 years) and the older (51-61 years) groups had significantly higher mortality during the study period compared to the 41-50 year-old group (p=0.009 and 0.037 respectively), with the highest mortality in the youngest group (p=0.001). Despite aggressive treatment, the overall mortality risk was significantly increased in both chemotherapy groups compared to the no Chemo group.

Strengths and limitations

The study has strong internal validity because of the use of data from high-quality patient registries with low dropout rates. Furthermore, this study was on a well-defined population reflecting real-life situations, *i.e.*, the inclusion of subjects that would probably not have been included in a clinical trial, and used registries with good national coverage. The study also followed individuals over time and assessed the incidence of CTR-CVT events and their development time. These strengths suggest that our findings can be generalized to patients diagnosed with early BC living in countries with comparable breast cancer and cardiology care.

The study has several limitations, including that observational studies can only assess associations, not causal relationships. First, we did not have data regarding the socioeconomic status of the women. Thus, several factors potentially influencing the development of CTR-CVT were absent from our analyses. Future studies examining these factors would provide us with a complete understanding of whether they impact the development of CTR-CVT in patients with BC. Second, the doses and regimens used during the study period were not modern. Third, CV risk factors and CVD medication and interventions, which could protect from CTR-CVT and increase survival, were not registered, analyzed, or discussed in this study.

In summary, women under the age of 60 diagnosed with aggressive BC 1998-2002 in the Southeast Healthcare Region of Sweden had a significantly higher risk for CTR-CVT and all-cause mortality. The high incidence and the time to onset of CTR-CVT amplifies the guidelines' recommendation of annual long-term screening for cardiovascular risk factors and CTR-CVT among BC survivors (1).

Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available because of Swedish laws and regulations, but they are available from the corresponding author upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Declaration of Helsinki and Regional Ethics Review Board at Linköping University (Dnr: 2012/172-31). Permission was obtained to access and use the national registries and review the medical records. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

EH and LH contributed to the study's conception and design. AP, LH, PM, and PK performed material preparation, data collection, and analysis. LH wrote the first draft of the manuscript, and all authors commented on subsequent versions. All authors contributed to the article and approved the submitted version.

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Conflict of interest

EH receives research funding from Roche and Pierre Fabre, all paid to Karolinska University Hospital. LH received payments from Astellas for traveling, accommodation and lecture fees at educational professional meetings. PK reports a fee for a lecture from Vifor and a personal fee for a lecture from AstraZeneca, all paid to Region Jönköping.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1095251/full#supplementary-material

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Does cardiac imaging surveillance strategy influence outcomes in patients with early breast cancer?

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Background: Many patients with breast cancer receive therapies with the potential to cause cardiotoxicity. Echocardiography and multiple-gated acquisition (MUGA) scans are the most used modalities to assess cardiac function during treatment in high-risk patients; however, the optimal imaging strategy and the impact on outcome are unknown.

Methods: Consecutive patients with stage 0-3 breast cancer undergoing pre-treatment echocardiography or MUGA were identified from a tertiary care cancer center from 2010-2019. Demographics, medical history, imaging data and clinical events were collected from hospital charts and administrative databases. The primary outcome is a composite of all-cause death or heart failure event. Clinical and imaging predictors of outcome were evaluated on univariable and multivariable analyses.

Results: 1028 patients underwent pre-treatment MUGA and 1032 underwent echocardiography. The groups were well matched for most clinical characteristics except patients undergoing MUGA were younger, had more stage 3 breast cancer and more HER2 over-expressing and triple negative cases. Routine follow-up cardiac imaging scan was obtained in 39.3% of patients with MUGA and 38.0% with echocardiography. During a median follow-up of 2448 (1489, 3160) days, there were 194 deaths, including 7 cardiovascular deaths, and 28 heart failure events with no difference in events between the MUGA and echocardiography groups. There were no imaging predictors of the primary composite outcome or cardiac events. Patients without follow-up imaging had similar adjusted risk for the composite outcome compared to those with imaging follow-up, hazard ratio 0.8 (95% confidence interval 0.5,1.3), p=0.457.

Conclusion: The selection of pretreatment echocardiography or MUGA did not influence the risk of death or heart failure in patients with early breast cancer.

Many patients did not have any follow-up cardiac imaging and did not suffer worse outcomes. Cardiovascular deaths and heart failure event rates were low and the value of long-term cardiac imaging surveillance should be further evaluated.

KEYWORDS

cardiac imaging, breast cancer, cardiotoxicity, surveillance, survival

Introduction

Cardiotoxicity is a recognized complication arising from anticancer therapy and may lead to cardiac and cancer morbidity and premature death (1). Cancer treatment regimens containing anthracyclines and/or human epidermal growth factor-2 (HER2) targeted therapies have significant cardiotoxic potential, therefore, patients with breast cancer are particularly vulnerable to adverse cardiac outcomes (2). Anthracyclines can cause direct myocardial damage in dose-dependent fashion and may result in cardiac dysfunction, irreversible cardiomyopathy, and heart failure (1). Trastuzumab, a monoclonal antibody directed against HER2 receptors, has been associated with a two-fold risk of worsening cardiac function and a five-to-seven-fold risk of overt heart failure (3, 4). Monitoring of left ventricular ejection fraction (LVEF) is recommended for the first 12 months in all patients receiving HER2-targeted therapy and/or anthracyclines with a cumulative dose of 250 mg/m^2 of doxorubicin or equivalent (5). Furthermore, long-term (5+ years) imaging surveillance of cardiac function is recommended for cancer survivors at high-risk for heart failure (4). Cancer treatment related cardiac dysfunction may be prevented and treated with beta blockers and/or renin-angiotensin inhibitors (5–7).

Echocardiography (echo) and multiple-gated acquisition (MUGA) radionuclide ventriculography scans are commonly used modalities to assess cardiac function in patients at high-risk for cancer therapy related cardiotoxicity. Current European Society of Cardiology guidelines recommend echo before MUGA as the first-line modality to assess cardiac function due to a superior safety profile and a more comprehensive cardiac assessment (5). However, in many centers, MUGA is more available and accessible than echo. Previous studies found that MUGA is more sensitive for detecting changes in LVEF than echo (8–10). However, the main disadvantage of MUGA is radiation exposure (~5 to 10 mSv per scan) which is significant in patients undergoing long-term surveillance with repeated exams (1). Furthermore, it has been suggested that patients with cancer are more likely to receive beta-blocker therapy and be referred to a cardiologist for reduced cardiac function detected on echo compared to MUGA (11).

Therefore, we sought to determine if the cardiac imaging modality (echo or MUGA) used for cardiotoxicity surveillance in patients with early breast cancer influences short and long-term cardiovascular outcomes. Furthermore, we sought to understand the pattern of use and duration of cardiac imaging monitoring in these patients.

Methods

Patient characteristics

Consecutive adult patients with stage 0-3 breast cancer were identified from a prospective cardio-oncology echocardiography registry at a tertiary cardiac hospital (Mazankowski Alberta Heart Institute, Edmonton, Alberta, Canada) from January 1, 2010, to December 31, 2019. Similar patients undergoing pre-treatment MUGA during the same timeframe were also identified from an affiliated tertiary cancer center (Cross Cancer Institute, Edmonton, Alberta, Canada).

Individual patient charts and electronic health records were reviewed to determine baseline characteristics including prior medical history, cancer type and staging, cancer treatments, cardiac imaging surveillance, and clinical outcomes. Patients with Eastern Cooperative Oncology Group performance status 3 or 4 were excluded. Breast cancer staging was determined according to the TNM classification proposed by the American Joint Committee on Cancer (12). The European Society of Cardiology (ESC) 2022 Heart Failure Association–International Cardio-Oncology Society (HFA-ICOS) risk classification was used to assess the baseline cardiovascular toxicity risk (5). However, previous chemotherapy data and baseline serum biomarkers were unavailable for most patients and were therefore not included in the risk calculation.

The treating medical oncology team ordered cardiac imaging prior to initiating cancer therapy and the modality, echo or MUGA, was usually selected according to availability. As MUGA was scheduled and performed at the cancer center, patients requiring rapid access to cardiac imaging (e.g. stage 3 or neoadjuvant) more commonly underwent this exam. Echocardiograms were acquired at the cardio-oncology clinic using an ultrasonographic system (EPIQ 7C, Philips Medical Systems, N.A., Bothell, USA) equipped with a X5-1 transducer. All patients received echocardiographic contrast (Definity, Lantheus Medical Imaging, North Billerica, USA) bolus regardless of non-contrast image quality in order to minimize variability of LVEF measurements. LVEF was measured from the contrast recordings using the biplane Simpson's method on commercially available software (13). MUGA scans were

performed with technetium 99 m-labeled red blood cells with an activity of approximately 11 to 13 MBq/kg. Images were acquired with a dual-head gamma camera (Siemens Healthineers, Erlangen, Germany and Philips Medical Systems, N.A., Bothell, USA). Scintigrams were smoothed off-line using standard algorithms, and background correction was performed. LVEF was calculated from left ventricular time-activity curves according to the current recommendations (14). For this analysis, patients were assigned either to a MUGA, or echo cohort based on the imaging modality used at baseline. Patients with both imaging modalities at baseline were assigned to the imaging group with the date closest to their cancer diagnosis. Follow-up imaging surveillance strategies were recorded and classified as all echo, all MUGA or mixed modality (both MUGA and echo were performed). Only cardiac imaging performed within 15 months from the baseline scan was included to reflect the standard duration of follow-up at our cancer center. Left ventricular ejection fraction was recorded for each cardiac imaging encounter.

Outcomes

The primary outcome is a composite of all-cause death and/or new or worsening heart failure diagnosis, and secondary outcomes are (i) cardiovasular death or heart failure event, and (ii) new or worsening heart failure. Events were collected from Jan 11, 2010, to December 31, 2020.

Clinical outcomes data were obtained from medical charts and an independent review of health administrative databases (Alberta Strategy for Patient Oriented Research Support Unit). Information obtained included (i) all admissions to acute care facilities; (ii) all ambulatory encounters, including emergency department visits and (iii) vital statistics including the date and cause of death. Diagnoses were classified using the International Classification of Diseases, Canadian Enhancement; ICD-10. Heart failure events included any new heart failure or cardiomyopathy related encounters during the follow-up period.

Cancer therapy–related cardiac dysfunction (CTRCD) was defined as a reduction in LVEF of ≥10% to a value <50% (5, 15). Cardiac biomarkers and left ventricular strain measurements were not available for many patients and were therefore not used for determining CTRCD events.

Statistical analysis

The Shapiro-Wilk normality test was used to test the normal distribution of continuous variables and continuous variables were expressed as mean ± standard deviation or median (25^{th}, 75^{th} percentile), as appropriate. Categorical variables were expressed as frequency and percentage. Chi-square testing or Fisher's exact test was used to compare categorical variables between two groups undergoing echo or MUGA at baseline. Two sample t-test or Mann-Whitney U test was used to compare continuous variables among two groups of patients, as appropriate. Univariable Cox proportional regression of outcome was performed in all clinical (cancer-related and cardiovascular disease-related) and imaging metrics at baseline and stepwise forward selection of parameters with p-value<0.2 was used to identify the best predictors of outcome. In the multivariable Cox proportional hazard analysis, all non-collinear 1-year parameters of interest with univariable p-value<0.2 were independently tested for their association with adverse outcomes after adjustment for baseline risk. The Kaplan-Meier method was used to plot time to clinical events for significant parameters from multivariable analysis. A p value less than 0.05 was considered significant for all tests. Statistical analyses were performed using STATA version 17.0 software (StataCorp LP, College Station, Texas).

Ethics review

This study complies with the Declaration of Helsinki and was approved by the University of Alberta Research Ethics Board (HREBA.CC-16-0511). Informed patient consent was not required due to the minimal risk to the patients involved.

Results

Patient characteristics

During the study period, we identified 1028 patients with early-stage breast cancer undergoing pre-treatment MUGA and 1032 patients undergoing pre-treatment echo who fulfilled study entry criteria. Significant baseline differences included older age and prior cancer diagnosis in the echo group and more advanced cancer stage, more aggressive cancer receptor types and more anthracycline and trastuzumab use in the MUGA group (Table 1). Patients were well balanced for their baseline cardiovascular risk factors and cardiovascular medications except for more angiotensin-converting enzyme inhibitor use in the MUGA group, and more angiotensin receptor blocker use in the echo group. Baseline HFA-ICOS cardiovascular toxicity risk was similar between cohorts, with 54.1% of MUGA patients and 57.3% of echo patients classified as low risk (Table 1).

Imaging findings

Baseline LVEF was slightly lower in the MUGA group compared to echo, median LVEF 64% vs. 65%, p = 0.0064 (Table 2). At least one follow-up cardiac imaging scan was obtained in 39.3% of patients undergoing pre-treatment MUGA and in 38% with pre-treatment echo within 15 months from the baseline scan. No follow-up imaging was found in 90.4% of patients receiving anthracycline-based treatment compared to 5.1% of patients receiving trastuzumab. Patients who had a baseline MUGA were more likely to be scanned with another imaging modality and had more cardiac imaging tests compared to patients with echo (Table 2). The incidence of CTRCD was similar in both groups, 12.2% for MUGA and 12.1% for echo

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TABLE 1 Baseline Characteristics.

Variable		MUGA cohort (n=1,028)	Echo cohort (n=1,032)	p-value
Age		53 (47, 61)	55 (48, 62)	0.0071
Female		1019 (99.1%)	1025 (99.3%)	0.610
Body mass index (kg/m^2)		28.2 (24.0, 32.7)	27.8 (24.2, 32.3)	0.59
Medical History				
Diabetes		90 (8.8%)	98 (9.5%)	0.564
Hypertension		257 (25.0%)	266 (25.8%)	0.696
Dyslipidemia		122 (11.9%)	126 (12.2%)	0.818
Coronary artery disease		10 (1.0%)	20 (1.9%)	0.067
Prior heart failure		7 (0.7%)	10 (1.0%)	0.628
Chronic kidney disease		14 (1.4%)	10 (1.0%)	0.41
Chronic obstructive pulmonary disease		35 (3.4%)	32 (3.1%)	0.694
Previous cancer		60 (5.8%)	98 (9.5%)	0.002
Smoking	Never smoker	549 (53.4%)	588 (56.9%)	
	Current smoker	184 (17.9%)	151 (14.6%)	0.101
	Ex-smoker	295 (28.7%)	294 (28.5%)	
Antiplatelet		52 (5.1%)	73 (7.1%)	0.056
Anticoagulant		7 (0.7%)	13 (1.3%)	0.261
Beta blocker		57 (5.5%)	47 (4.6%)	0.302
ACE-inhibitor		117 (11.4%)	85 (8.2%)	0.016
Angiotensin receptor blocker		80 (7.8%)	118 (11.4%)	0.005
Aldosterone antagonist		1 (0.1%)	4 (0.4%)	0.374
Statin		107 (10.4%)	128 (12.4%)	0.157
Calcium channel blocker		51 (5.0%)	63 (6.1%)	0.259
Diuretic		91 (8.9%)	88 (8.5%)	0.788
Breast Cancer Characteristics				
Stage	0	5 (0.5%)	7 (0.7%)	
	I	126 (12.3%)	144 (13.9%)	
	II	576 (56.0%)	635 (61.5%)	
	III	321 (31.2%)	247 (23.9%)	0.001
Receptor Status	Hormone positive, HER2 negative	512 (49.8%)	591 (57.2%)	
	HER2 positive	404 (39.3%)	357 (34.6%)	
	Triple negative	112 (10.9%)	85 (8.2%)	0.002
Cancer Therapy				
Chemotherapy (any)		958 (93.2%)	902 (87.4%)	<0.001
Anthracycline		538 (52.3%)	510 (49.4%)	
Trastuzumab		346 (33.7%)	315 (30.5%)	
Anthracycline and trastuzumab		35 (3.4%)	11 (1.1%)	
Other		39 (3.8%)	66 (6.4%)	<0.001

(Continued)

TABLE 1 Continued

Variable		MUGA cohort (n=1,028)	Echo cohort (n=1,032)	p-value
Anthracycline dose (mg/m^2)		312 ± 79	301 ± 57	0.0124
Completed trastuzumab 17 cycles*		357 (93.7%)	298 (91.4%)	0.2612
Hormone therapy		703 (68.4%)	778 (75.3%)	<0.001
Radiation (any)		833 (81.0%)	853 (82.6%)	0.364
Left chest irradiation		415 (40.4%)	418 (40.5%)	0.54
Breast cancer surgery		1017 (98.9%)	1024 (99.1%)	0.645
Left segmentectomy/mastectomy		487 (47.4%)	476 (46.1%)	
Right segmentectomy/mastectomy		457 (44.5%)	489 (47.4%)	
Bilateral mastectomy		61 (5.9%)	47 (4.6%)	0.227
HFA-ICOS risk	Low	556 (54.1%)	592 (57.3%)	
	Moderate	397 (38.6%)	361 (35.0%)	
	High or Very high	75 (7.3%)	80 (7.8%)	0.213

*only patients on trastuzumab included.
All results are expressed as median (25th, 75th percentile) or frequency (percentage) except anthracycline dose which is expressed as mean ± standard deviation. MUGA, multi-gated acquisition; ACE, angiotensin converting enzyme; HER2, human epidermal growth factor receptor-2; HFA-ICOS, European Society of Cardiology Heart Failure Association - International Cardio-Oncology Society

(Table 2). For patients with high or very high HFA-ICOS risk, CTRCD occurred in 36% compared to 10.8% and 9.8% for moderate and low risk patients respectively, odds ratio 2.2 (95% confidence interval (1.9, 2.7), p < 0.001.

Outcomes

During a median follow-up of 2448 (1489, 3160) days, there were 194 deaths and 28 heart failure events with no difference in events between the MUGA and echo cohorts. The cause of death was cancer related in 171 (88%) cases and cardiovascular related in 7 (3.6%). The 7 cardiovascular related deaths included 4 from coronary artery disease, 1 from arrhythmia, 1 from stroke and 1 from complications of diabetes mellitus. For the 12 patients with late heart failure events after 24 months, 3 were low HFA-ICOS risk at baseline, 5 were moderate risk, 1 was high risk and 3 were very high risk. The timing of cardiac events was also not significantly different between the MUGA and echo groups (Table 3).

Multivariable analysis identified prior heart failure, chronic kidney disease, chronic obstructive pulmonary disease, aldosterone antagonist therapy, stage 3 breast cancer, triple negative receptor status and absence of cardiac imaging surveillance as predictive of the primary outcome (Table 4). The selection of MUGA or echo at baseline was not predictive of clinical events (Tables 4–6, Figure 1). Baseline LVEF and the type of cardiac imaging were not predictive of outcomes (Tables 4–6). Lack of imaging follow-up was not predictive of adverse outcomes, even

TABLE 2 Cardiac Imaging Findings.

Variable		MUGA cohort (n=1,028)	Echo cohort (n=1,032)	p-value
Baseline LVEF, %		64 (60, 69)	65 (61, 69)	0.0064
Patients with follow-up imaging within 15 months		404 (39.3%)	392 (38%)	0.556
Median number of baseline and follow-up scans*		6 (5, 6)	6 (5, 6)	0.234
Number of follow-up imaging scans*		1737	1535	0.024
Follow-up imaging modality	Same modality	325 (31.6%)	360 (34.9%)	0.123
	Mixed modality	79 (7.7%)	32 (3.1%)	<0.001
	None	624 (60.7%)	640 (62.0%)	0.556
Cancer therapy related cardiac dysfunction*		125 (12.2%)	125 (12.1%)	0.974
Lowest LVEF, %, at follow-up		58 (54, 61)	58 (55, 62)	0.0427

*Only in patients with follow-up imaging in first 15 months.
All results are expressed as median (25th, 75th percentile) or frequency (percentage). MUGA, multi-gated acquisition; LVEF, left ventricular ejection fraction.

TABLE 3 Clinical Events.

All-Cause Death or Heart Failure		MUGA cohort (n=1,028)	Echo cohort (n=1,032)	p-value
Duration of follow up (days)		2534 (1487, 3288)	2401 (1529, 3004)	0.0013
Total events*		118 (11.5%)	94 (9.1%)	0.077
Number of events	0-12 months	8 (0.8%)	12 (1.2%)	0.373
	13-24 months	22 (2.1%)	19 (1.8%)	0.627
	24+ months	88 (8.6%)	63 (6.1%)	0.033
Cardiovascular Death or Heart Failure		**MUGA cohort (n=1,028)**	**Echo cohort (n=1,032)**	**p-value**
Duration of follow up (days)		2534 (1487, 3288)	2401 (1528, 3004)	0.0012
Total events		16 (1.6%)	16 (1.6%)	0.991
Number of events	0-12 months	4 (0.4%)	6 (0.6%)	0.753
	13-24 months	5 (0.5%)	5 (0.5%)	1.00
	24+ months	7 (0.7%)	5 (0.5%)	0.579
New Heart Failure		**MUGA cohort (n=1,028)**	**Echo cohort (n=1,032)**	**p-value**
Duration of follow up (days)		2695 (1724, 3372)	2510 (1710, 3123)	<0.001
Total events		15 (1.5%)	13 (1.3%)	0.696
Number of events	0-12 months	3 (0.3%)	5 (0.5%)	0.726
	13-24 months	5 (0.5%)	3 (0.3%)	0.506
	24+ months	7 (0.7%)	5 (0.5%)	0.579

*Only first event was considered.
All results are expressed as median (25^{th}, 75^{th} percentile) or frequency (percentage). MUGA, multi-gated acquisition.

TABLE 4 Prediction of All-Cause Death or Heart Failure Event- 2060 subjects (212 events).

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.01 (1.00, 1.02)	0.131		
Body mass index	1.00 (0.98, 1.02)	0.748		
Medical History				
Diabetes	1.4 (0.9, 2.1)	0.143		
Hypertension	1.3 (0.9, 1.7)	0.136		
Dyslipidemia	1.1 (0.7, 1.6)	0.731		
Coronary artery disease	2.1 (0.9, 4.8)	0.071		
Prior heart failure	4.2 (1.9, 9.5)	0.001		
Chronic kidney disease	3.0 (1.3, 6.7)	0.008	2.6 (1.1, 5.9)	0.024
Chronic obstructive pulmonary disease	2.1 (1.2, 3.7)	0.006	1.9 (1.1, 3.3)	0.019
Smoking	1.0 (0.9, 1.2)	0.958		
Beta blocker	1.2 (0.7, 2.1)	0.497		
ACE-inhibitor	1.0 (0.6, 1.6)	0.999		
Angiotensin receptor blocker	1.4 (1.0, 2.2)	0.078		

(Continued)

TABLE 4 Continued

		Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Aldosterone antagonist		6.6 (2.1, 20.5)	0.001	6.3 (1.9, 20.1)	0.002
Statin		1.0 (0.7, 1.6)	0.853		
Breast Cancer Characteristics					
Cancer stage	0 or 1	Reference			
	2	1.4 (0.8, 2.4)	0.25	1.3 (0.7, 2.3)	0.415
	3	3.9 (2.2, 6.8)	<0.001	3.7 (2.1, 6.6)	<0.001
Receptor status	Hormone positive, HER2 negative	Reference			
	HER2 positive	0.8 (0.6, 1.2)	0.294	1.6 (0.8, 3.1)	0.154
	Triple negative	2.8 (2.0, 3.9)	<0.001	3.0 (2.1, 4.2)	<0.001
Cancer Therapy					
Use of anthracycline therapy		1.17 (0.89, 1.54)	0.251		
Anthracycline dose		1.00 (1.00, 1.00)	0.704		
Number of trastuzumab cycles		0.97 (0.95, 0.99)	0.003	1.0 (0.9, 1.0)	0.064
Left chest irradiation		0.96 (0.71, 1.31)	0.799		
Cardiac Imaging					
Baseline imaging (Echo vs. MUGA)		0.8 (0.6, 1.1)	0.159		
Baseline LVEF, per 1% increase		1.0 (1.0, 1.0)	0.429		
Occurrence of CTRCD		1.2 (0.8, 1.8)	0.264		
Follow-up cardiac imaging	All MUGA	Reference			
	All Echo	0.9 (0.5, 1.4)	0.517		
	Mixed modality	1.4 (0.9, 2.3)	0.136		
	None	0.9 (0.6, 1.3)	0.532		
HFA-ICOS risk	Low	Reference			
	Moderate	1.2 (0.9, 1.6)	0.319	1.0 (0.8, 1.4)	0.961
	High or Very high	2.1 (1.4, 3.3)	<0.001	2.2 (1.4, 3.4)	<0.001

All results are expressed as hazard ratio (95% confidence intervals) or frequency (percentage).
For the composite outcome, the above parameters with univariable P<0.2 underwent stepwise forward selection. The final model includes chronic kidney disease, chronic obstructive pulmonary disease, aldosterone antagonist, cancer stage 3, triple negative receptor status and "high or very high" HFA-ICOS risk. Other parameters are no longer significant in the multivariable model.
HR, hazard ratio; CI, confidence intervals; MUGA, multi-gated acquisition; ACE, angiotensin converting enzyme; HER2, human epidermal growth factor receptor-2; CTRCD, cancer therapy related cardiac dysfunction; HFA-ICOS, European Society of Cardiology Heart Failure Association - International Cardio-Oncology Society.

after excluding patients receiving non-anthracycline, non-trastuzumab treatments (Supplemental Tables 1-3) and after excluding low HFA-ICOS risk patients (Supplemental Tables 4-6). In the overall cohort, risk of cardiac death or heart failure was similar in the 1264 patients without follow-up imaging compared to the 796 patients with follow-up imaging, hazard ratio 0.9 (95% confidence interval 0.5,1.9), p=0.813 (Figure 2). However, the HFA-ICOS risk was predictive cardiac death or heart failure on multivariable and adjusted survival analyses (Table 5 and Figure 3).

Discussion

In this large, real-world cohort study of patients with early-stage breast cancer, we found that the pretreatment cardiac imaging modality (MUGA or echo) was not associated with all-cause death or new heart failure during extended follow-up. Over 60% of patients had no follow-up cardiac imaging after the baseline scan and lack of imaging surveillance was not associated with adverse cardiac outcomes. HFA-ICOS risk was consistently associated with death, cardiac death and heart failure on multivariable analysis.

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TABLE 5 Prediction of Cardiovascular Death or Heart Failure Event- 2060 subjects (32 events).

		Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age		1.05 (1.02, 1.10)	0.006		
Body mass index		1.06 (1.01, 1.10)	0.009		
Medical History					
Diabetes		4.0 (1.8, 8.6)	<0.001		
Hypertension		2.1 (1.0, 4.2)	0.044		
Dyslipidemia		2.9 (1.3, 6.2)	0.007		
Coronary artery disease		10.4 (3.7, 29.8)	<0.001		
Prior heart failure		19.7 (6.9, 56.2)	<0.001	3.5 (1.1, 11.0)	0.036
Chronic kidney disease		3.1 (0.4, 23.0)	0.261		
Chronic obstructive pulmonary disease		3.1 (0.9, 10.2)	0.061		
Smoking		1.2 (0.8, 1.8)	0.283		
Beta blocker		5.2 (2.2, 12.0)	<0.001		
ACE-inhibitor		2.6 (1.1, 5.9)	0.027		
Angiotensin receptor blocker		1.8 (0.7, 4.7)	0.223		
Aldosterone antagonist		0.0 (0.0, 0.0)	1.000		
Statin		2.6 (1.2, 5.8)	0.018		
Breast Cancer Characteristics					
Cancer stage	0 or 1	Reference			
	2	0.7 (0.2, 1.9)	0.455		
	3	1.2 (0.4, 3.4)	0.749		
Receptor status	Hormone positive, HER2 negative	Reference			
	HER2 positive	0.8 (0.4, 1.8)	0.61		
	Triple negative	1.3 (0.4, 3.8)	0.635		
Cancer Therapy					
Use of anthracycline therapy		0.97 (0.48, 1.94)	0.931		
Anthracycline dose		1.00 (1.00, 1.00)	0.436		
Number of trastuzumab cycles		0.97 (0.93, 1.02)	0.26		
Left chest irradiation		1.12 (0.48, 2.64)	0.795		
Cardiac Imaging					
Baseline imaging (Echo vs. MUGA)		1.0 (0.5, 2.1)	0.92		
Baseline LVEF, per 1% increase		1.1 (1.0, 1.1)	0.025		
Occurrence of CTRCD		3.4 (1.6, 7.2)	0.001		
Follow-up cardiac imaging	All MUGA	Reference			
	All Echo	10.5 (1.4, 79.5)	0.023		
	Mixed modality	17.2 (2.3, 130.6)	0.006		
	None	0.5 (0.0, 5.8)	0.602		

(Continued)

TABLE 5 Continued

		Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
HFA-ICOS risk	Low	Reference			
	Moderate	2.4 (0.9, 6.2)	0.069	2.4 (0.9, 6.2)	0.069
	High or Very high	16.3 (6.6, 40.4)	<0.001	13.0 (4.9, 34.2)	<0.001

All results are expressed as hazard ratio (95% confidence intervals) or frequency (percentage).
For this secondary outcome, parameters with univariable P<0.2 underwent stepwise forward selection. The final model includes prior heart failure and "high or very high" HFA-ICOS risk. Other parameters are no longer significant in the multivariable model.
HR, hazard ratio; CI, confidence intervals; MUGA, multi-gated acquisition; ACE, angiotensin converting enzyme; HER2, human epidermal growth factor receptor-2; CTRCD, cancer therapy related cardiac dysfunction; HFA-ICOS, European Society of Cardiology Heart Failure Association - International Cardio-Oncology Society.

TABLE 6 Prediction of Heart Failure Event- 2060 subjects (28 events).

		Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age		1.06 (1.02, 1.10)	0.006		
Body mass index		1.06 (1.01, 1.10)	0.011		
Medical History					
Diabetes		4.8 (2.2, 10.6)	<0.001		
Hypertension		2.3 (1.1, 4.8)	0.033		
Dyslipidemia		3.0 (1.3, 6.7)	0.009		
Coronary artery disease		8.6 (2.6, 28.5)	<0.001		
Prior heart failure		15.4 (4.6, 51.0)	<0.001		
Chronic kidney disease		3.4 (0.5, 25.3)	0.226		
Chronic obstructive pulmonary disease		3.5 (1.1, 11.7)	0.039		
Smoking		1.3 (0.8, 1.9)	0.26		
Beta blocker		5.1 (2.1, 12.6)	<0.001	2.4 (0.9, 6.1)	0.07
ACE-inhibitor		2.5 (1.0, 6.2)	0.045		
Angiotensin receptor blocker		1.6 (0.6, 4.6)	0.378		
Aldosterone antagonist		– (–, –)	–		
Statin		2.6 (1.1, 6.2)	0.026		
Breast Cancer Characteristics					
Cancer stage	0 or 1	Reference			
	2	0.5 (0.2, 1.4)	0.185		
	3	1.1 (0.4, 3.1)	0.85		
Receptor status	Hormone positive, HER2 negative	Reference			
	HER2 positive	0.7 (0.3, 1.7)	0.499		
	Triple negative	1.4 (0.5, 4.1)	0.566		
Cancer Therapy					
Use of anthracycline therapy		1.0 (0.5, 2.1)	0.948		
Anthracycline dose		1.0 (1.0, 1.0)	0.412		
Number of trastuzumab cycles		0.98 (0.94, 1.03)	0.532		

(Continued)

TABLE 6 Continued

		Univariable analysis		Multivariable analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Left chest irradiation		1.0 (0.4, 2.6)	0.972		
Cardiac Imaging					
Baseline imaging (Echo vs. MUGA)		0.9 (0.4, 1.9)	0.787		
Baseline LVEF, per 1% increase		1.04 (0.98, 1.10)	0.222		
Occurrence of CTRCD		3.6 (1.6, 7.9)	0.002		
Follow-up Cardiac Imaging	All MUGA	Reference			
	All Echo	1.3 (0.4, 4.7)	0.657		
	Mixed modality	1.4 (0.3, 7.7)	0.694		
	None	1.0 (0.3, 3.0)	0.983		
HFA-ICOS risk	Low	Reference			
	Moderate	3.4 (1.2, 9.7)	0.025	3.2 (1.1, 9.2)	0.032
	High or Very high	19.4 (6.8, 55.0)	<0.001	16.0 (5.5, 47.1)	<0.001

All results are expressed as hazard ratio (95% confidence intervals) or frequency (percentage).
For this secondary outcome, the above parameters with univariable P<0.2 underwent stepwise forward selection. The final model includes moderate or "high or very high" HFA-ICOS risk. Other parameters are no longer significant in the multivariable model.
HR, hazard ratio; CI, confidence intervals; MUGA, multi-gated acquisition; ACE, angiotensin converting enzyme; HER2, human epidermal growth factor receptor-2; CTRCD, cancer therapy related cardiac dysfunction; HFA-ICOS, European Society of Cardiology Heart Failure Association - International Cardio-Oncology Society.

Follow-up imaging and clinical outcomes

ESC cardio-oncology guidelines recommend that asymptomatic patients receiving trastuzumab have follow-up cardiac imaging every 3 months for the first 12 months and repeat testing at 24 months (5). Similarly, patients receiving anthracycline-based chemotherapy should have follow-up cardiac imaging at 12 months and higher risk individuals should undergo 4 intervening scans during and after treatment (5). Additionally, asymptomatic patients at high or very high HFA-ICOS risk are recommended to have follow-up imaging at years 1, 3 and 5 and possibly every 5 years thereafter (5). In this real-world study of patients with early breast cancer receiving cardiotoxic therapy, no follow-up imaging was seen in 61.4%, including 90.4% of patients treated with anthracyclines. Patients with no cardiac imaging follow-up had similar outcomes compared to patients with echo and/or MUGA surveillance, although, heart failure event rates were low. Our findings build on existing knowledge regarding the utility of surveillance cardiac imaging in patients with breast cancer (16, 17). While cardiology involvement in the care of breast cancer patients can lead to adherence to guideline recommended cardiac surveillance during cancer treatment (18), the impact of cardiac monitoring on hard endpoints is unclear. For example, Yu et al. found a lack of association between adherence to routine echocardiogram monitoring and clinical heart failure, suggesting that routine LVEF assessments may be insufficient to decrease the risk of heart failure (17).

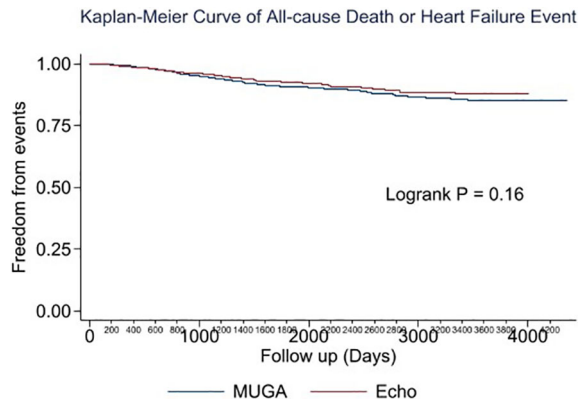

FIGURE 1
Plot of unadjusted Kaplan-Meier event-free survival for patients with breast cancer assigned to pretreatment multiple-gated acquisition (MUGA) scan (Blue) or echocardiography (Red). The composite event included all-cause death or new heart failure.

In our cohort, we found that patients undergoing echo were more likely to have same modality compared to MUGA (Table 2). Although current guidelines recommend using the same imaging method given observed differences in LVEF measurements between different modalities (1, 8, 19), our study did not find that the type of follow-up imaging (same modality or mixed modality) to be a significant predictor of clinical outcomes.

Comparison with other real-world studies of cardiotoxicity

Among patients with follow-up imaging, 12.2% in the MUGA group and 12.1% in the echo group developed CTRCD. Furthermore, cardiac death or heart failure occurred in only 32

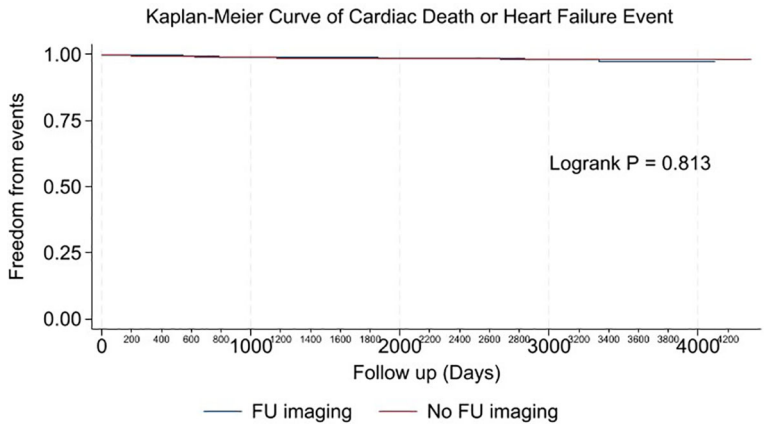

FIGURE 2
Plot of unadjusted Kaplan-Meier event-free survival curve for cardiac death or new heart failure in patients with imaging follow-up (Blue), and no imaging follow-up (Red).

patients (1.6%) during a median follow-up of 6.7 years. The incidence of CTRCD in our cohort is similar to that found in other studies. In the CARDIOTOX registry, which included 865 patients receiving high-risk cancer treatment regimens (84.5% anthracyclines), López-Sendón et al. found the overall incidence of CTRCD was 37.5% (20). However, the majority of the CTRCD were mild (31.6%), defined as asymptomatic patients with LVEF ≥50% with elevated biomarkers or at least one additional abnormal echo parameter, whereas 5.9% of patients had LVEF <50% (20). In another study of 373 patients with breast cancer followed for a mean of 2.4 ± 1 years, there were no cases of LV dysfunction in the anthracycline cohort (0/202), and 16/171 (9%) in the anti-HER2 therapy group (21). In a study by Battisti et al. which included patients with early breast cancer treated with trastuzumab, 5.91% of the patients experienced a LVEF decline ≥ 10% to below 50% but only 5% developed symptomatic heart failure (4.5% with New York Heart Association class II and 0.5% with class III-IV) (22).

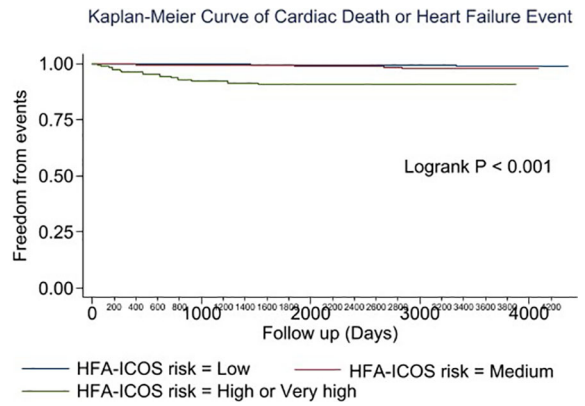

FIGURE 3
Plot of the adjusted survival curve for cardiac death or new heart failure in patients with breast cancer assigned to low (Blue), moderate (Red), high or very high (Green) European Society of Cardiology Heart Failure Association-International Cardio-Oncology Society risk.

Utility of HFA-ICOS baseline risk stratification

ESC guidelines recommend using HFA-ICOS risk to guide strategies preventing cancer therapy associated cardiotoxicity (5). In our study, patients with high or very high HFA-ICOS risk (7.5% of the overall cohort) were at increased risk for CTRCD as well as cardiac death or heart failure compared to patients with moderate or low risk. This finding is consistent with recent studies that examined the utility of HFA-ICOS proforma in predicting LV dysfunction and heart failure events in patients with breast cancer (21). In a smaller breast cancer cohort, Tini et al. found a similar distribution of HFA-ICOS baseline risk and that patients with increased risk receiving anti-HER2 therapy experienced a greater incidence of LV dysfunction (21). While HFA-ICOS risk predicts cardiac events in patients with breast cancer receiving anthracycline and/or anti-HER2 therapies, future studies should evaluate whether imaging surveillance in higher risk individuals mitigates this risk.

Limitations

This was a single-center, retrospective study of the relationship between cardiac imaging and clinical outcomes. This design introduces the potential for bias and these results should therefore be confirmed in multicenter, prospective studies. Nevertheless, this is one of the largest studies of cardiotoxicity with a long period of follow-up (median 6.7 years). Heart failure event rates were relatively low compared to other studies of cardiotoxicity in patients with breast cancer. However, it is unlikely that heart failure events were missed given that data was extracted multiple sources including manual chart review and provincial health administrative databases. Referrals to cardiology and the initiation of cardiac medications were not systematically collected in our study and we are therefore not able to determine the potential impact of cardiac imaging on these outcomes. Cardiac biomarkers and left ventricular strain measurements were unavailable for most patients. Therefore, CTRCD was defined using

only the LVEF criteria. The role of echo strain to guide management is unclear (23, 24).

Conclusion

In this contemporary study of patients with early breast cancer undergoing cardiotoxic cancer therapy, the selection of baseline cardiac imaging (MUGA or echo) did not influence the risk of death or heart failure. Many patients did not have any follow-up cardiac imaging and did not suffer worse outcomes. Cardiac death and heart failure event rates were low and the value of long-term cardiac imaging surveillance should be further evaluated.

Data availability statement

The datasets presented in this article are not readily available because we would require approval from our health research ethics board and possibly a legal agreement to share this data with individuals from outside institutions. Requests to access the datasets should be directed to dpaterson@ottawaheart.ca.

Ethics statement

The studies involving human participants were reviewed and approved by University of Alberta Health Research Ethics Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Study conception: KW, SP, JRM, KK, HB, EP, DIP. Data acquisition: KW, SP, MY, WB, AS, HB, DIP. Data analysis: KW, SP, LX, DIP. Manuscript writing and critical review: All. All authors contributed to the article and approved the submitted version.

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Conflict of interest

DIP reports funding from Pfizer and AstraZeneca. HB receives funding from Lantheus and Bracco and is on the advisory board for Lantheus.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1168651/full#supplementary-material

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