RE-BALANCING THE BALANCE: ANOTHER STORY OF CARDIO-ONCOLOGY

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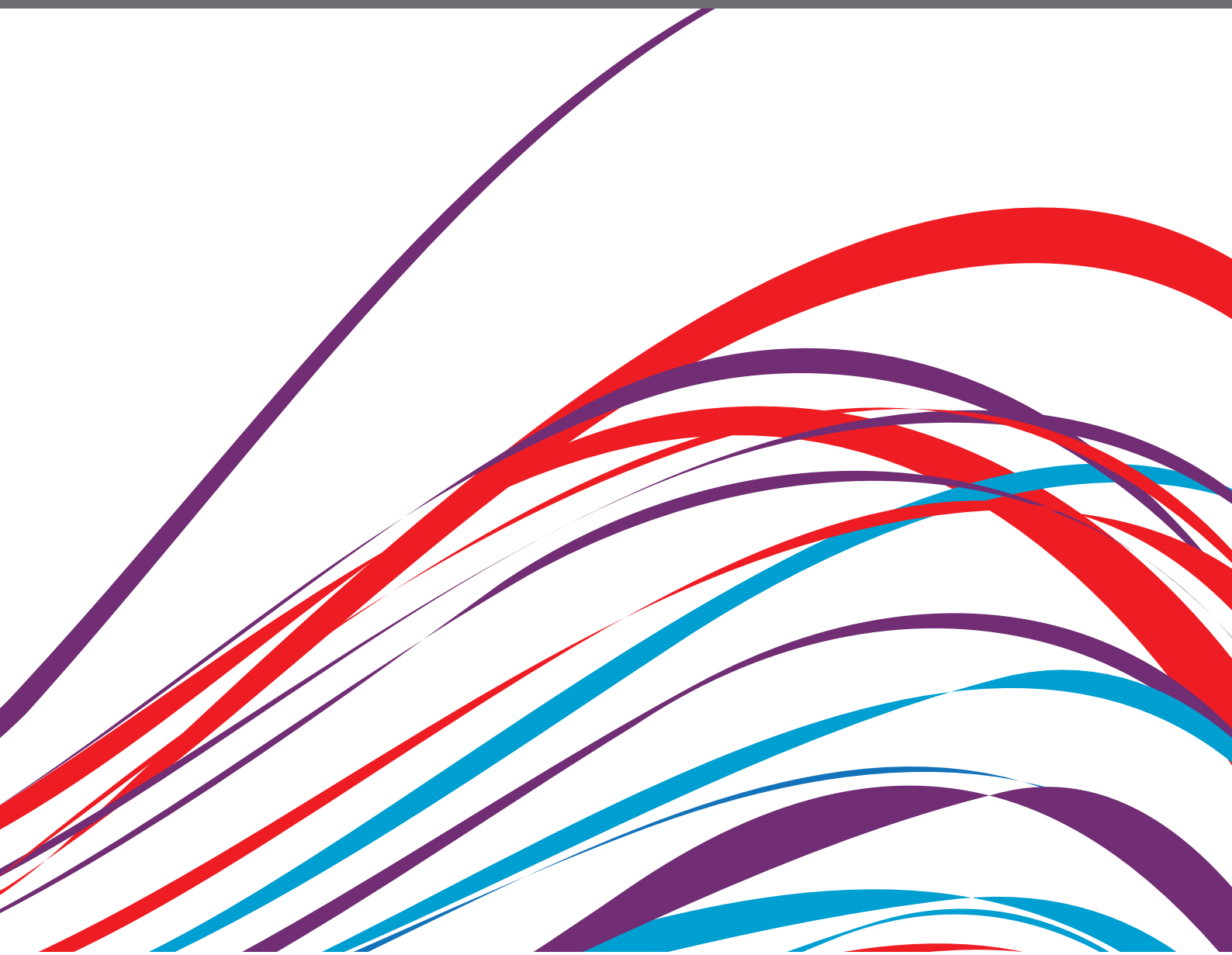

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RE-BALANCING THE BALANCE: ANOTHER STORY OF CARDIO-ONCOLOGY

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BRIEF RESEARCH REPORT
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Vascular Inflammation and Cardiovascular Burden in Metastatic Breast Cancer Female Patients Receiving Hormonal Treatment and CDK 4/6 Inhibitors or Everolimus

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Background: Chemotherapy regimens for breast cancer treatment can promote vascular dysfunction and lead to high cardiovascular risk.

Purpose: To investigate the cardiovascular burden and vascular inflammation in metastatic breast cancer patients receiving CDK 4/6 inhibitors or everolimus in addition to standard hormonal treatment.

Methods: 22 consecutive female patients with metastatic breast cancer were enrolled. Relative wall thickness (RWT) and left ventricle mass (LVM) measurements by transthoracic echocardiography were obtained followed by 24-h ambulatory blood pressure monitoring, and ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography imaging. Uptake of the radiotracer in the aortic wall was estimated as tissue-to-background ratio (TBR). Each patient was assessed for the aforementioned parameters before the initiation and after 6 months of treatment.

Results: At follow up, patients assigned to CDK 4/6 treatment demonstrated increased 24-h systolic blood pressure (SBP) ($p = 0.004$), daytime SBP ($p = 0.004$) and night time SBP ($p = 0.012$) (Group effect). The 24-h mean arterial pressure measurements were also higher in CDK 4/6 population, in comparison to everolimus that displayed firm values (Group effect- $p = 0.035$, Interaction effect-$p = 0.023$). Additionally, 24 h diastolic blood pressure recordings in CDK 4/6 therapy were higher opposed to everolimus that remained consistent (Interaction effect- $p = 0.010$). In CDK 4/6 group, TBR aorta also

increased significantly, whereas TBR values in everolimus remained stable (Interaction effect-$p = 0.049$). Both therapeutic regimens displayed statistically significant damaging effect to RWT and LVM.

Conclusion: CDK 4/6 inhibitors and hormonal treatment can lead to increased vascular inflammation, and higher blood pressure compared to the combination of everolimus and hormonal treatment. Moreover, both treatment strategies promoted left ventricle remodeling.

Keywords: vascular inflammation, remodeling and dysfunction, breast cancer, blood pressure, CDK 4/6 inhibitor, cardiovascular toxicity from anticancer drugs

INTRODUCTION

Breast cancer has been established as the commonest diagnosed type of cancer in women and a prominent cause of mortality among cancer patients, globally (1, 2). Until early 2020, more than 3.5 million women had a recorded history of breast cancer in the U.S. while almost 300,000 new cases were estimated to be newly diagnosed during the following months (3). Nearly 60% of female patients with breast cancer aged under 50 are hormone receptor (HR)- positive and human epidermal growth factor receptor 2(HER)-negative (4), while the contemporary standard of care treatment in pre- and post-menopausal patients comprises endocrine therapy with the addition of everolimus or cyclin dependent kinases (CDK) 4 and 6 inhibitors (5–7).

Even though hormonal treatment has been studied extensively through the past decades, the crucial role of CDK4/6 pathway inhibition in moderating breast cancer cells propagation and the progress of the disease began to arise in 2015 (8). Many randomized multicentered studies since (PALOMA1-2, MONARCH 3, MONALEESA 2-7) have proven the efficacy and the clinical improvement stemming from this type of targeted treatment (1, 8, 9). Today 3 types of CDK 4/6 inhibitors (palpociclib, ribociclib, abemaciclib) have been approved by the European Medical Association and the Food Drug Administration (FDA) while known adverse effects of this therapy include neutropenia, liver dysfunction, diarrhea (abemaciclib), QTc prolongation (ribociclib), and venous thromboembolism (1, 8–11).

Everolimus is an inhibitor of the mammalian target of rapamycin (mTOR) and specifically of the mTorc1 complex. The mTOR axis is essential in cell multiplication, differentiation, and angiogenesis in breast cancer. Its widespread use in clinical practice emerged after BOLERO 2-3 clinical trials established its efficacy in combination with an aromatase inhibitor in postmenopausal metastatic breast cancer patients (12, 13). Common side effects of treatment are myelosuppresion, non-infectious pneumonitis, hyperglycemia, hyperlipidemia, and hypertension (12, 14).

Both types of therapy might also impair cardiovascular health by means of endothelial injury and vascular dysfunction/inflammation (1, 10, 12, 14–19). Considering the significant overlap between immune and inflammatory response in cancer patients, positron emission tomography (PET)/computed tomography (CT) can be a valuable tool for assessing the post- treatment status of the vasculature, because of its high sensitivity for inflammation detection (20–22). Abnormal values of novel and traditional inflammatory markers such as hsCRP, IL-6, TNF-a, galectin-3, myeloperoxidase (MPO), ST-2, growth differentiation factor (GDF)-15, and microRNAs have been described to be detected in cancer patients with drug induced cardiotoxicity; however it still remains unclear in many cases, whether the inflammatory activation pathway is the result of an ongoing malignancy or a direct result of cardiotoxicity after treatment schemes (23). Moreover, specific widely used biomarkers associated with vascular inflammation in patients receiving CDK 4/6 treatments have not been currently identified and the inflammatory clinical response, with regards to inflammatory assays, is yet to be determined (24). The aim of the current study was therefore, to investigate and compare the cardiovascular and inflammatory impact of CDK 4/6 or everolimus alongside with hormonal treatment in female patients with metastatic HR-positive HER2-negative metastatic breast cancer.

METHODS

This single center prospective observational study included 22 consecutive female patients with metastatic breast cancer that expressed estrogen and/or progesterone receptor and were HER2-negative in a 12 month period. The study protocol was approved by the Alexandra General Hospital review board and ethics committee and each patient provided written consent before the enrollment. Patients with active infection, chronic autoimmune disease, and history of chemotherapy for the metastatic disease and/or adjuvant chemotherapy during the past 3 years were excluded (Total number of patients assessed for eligibility $n = 31$, patients meeting exclusion criteria $n = 9$). All subjects received hormonal treatment and of those, 10 received everolimus and 12 received therapy with CDK 4/6 inhibitors (palpociclib, ribociclib). All patients were free of major cardiovascular events for the past 6 months. Evaluation of left ventricle remodeling, 24 h arterial blood pressure and the inflammation of the aortic wall were performed at baseline and before the initiation of treatment and 6 months after ongoing therapy for both groups. Patients demonstrating increased arterial blood pressure values at baseline measurements were treated according to

2017 ESC/ESH guidelines on arterial hypertension. Hypertensive patients already under treatment before the initiation of chemotherapy continued their standard medication throughout the study protocol.

Complete transthoracic echocardiography (TTE) study was performed using a GE Vivid E9 ultrasound system. The estimation of left ventricle geometry and mass was conducted by 2 experienced operators after careful examination of the acquired images. Relative wall thickness (RWT) was calculated by using the formula: RWT = 2*posterior wall diameter (PWd)/left ventricle end diastolic diameter (LVEDD) while left ventricle mass (LVM) was evaluated using Cube's formula as LVM = $0.8\{1.04[([LVEDD + IVSd + PWd]^3 - LVEDD^3)]\} + 0.6g$ (IVSd = interventricular septum diameter).

Twenty four hour arterial blood pressure monitoring (24ABPM) was conducted during a usual working day and each patient was advised to act and work normally. Spacelabs 90217 ambulatory blood pressure monitoring (Spacelabs Inc, Redmond, Wash) system was used with a previously described standard protocol (25).

FDG PET/Ct Imaging

All participants underwent FDG-PET/CT imaging after fasting for at least 12 h prior to the study. None of the patients had blood glucose levels >180 mg dL-1 before injection. FDG was injected intravenously (5MBq/Kg) and scanning was performed at 120 min post injection for vascular tracer uptake assessment. Patients were encouraged to void before imaging and images of the thorax and abdomen were obtained by a hybrid PET/CT scanner (Biograph 6; Siemens, Forchheim). A low dose computed tomography (CT) scan in supine position was obtained, with patients' arms placed above their heads when possible. No CT IV contrast was administered. CT images were acquired with 30 mA, 130 KV, axial slice thickness of 5 mm and table feed rotation of 27 mm per tube rotation. CT radiation exposure was estimated in the region of 5 mSV. PET scanning followed immediately over the same pre-defined body region and the images were reconstructed with a standard Iterative Ordered-Subset Expectation Maximization (OSEM) algorithm using 4 Iterations and 8 subsets. FDG-PET radiation exposure was in the region of 7 mSV for an injected activity of 10 mCi (370 MBq).

Aortic FDG Uptake Assessment

Aortic FDG uptake was assessed by using previously described validated and reproducible methodology without knowledge of patients' data or laboratory values (26). In brief, regions of interest (ROI) around the aortic wall were manually drawn along the entire aorta in consecutive axial slices at intervals of 5 mm. Metabolic activity within each arterial ROI was measured by maximum standardized uptake value (SUVmax). In the next step, 6 consecutive circular ROIs of 3 mm diameter, were drawn within the superior vena cava and an average venous SUVmean value was calculated. The arterial target-to-background ratio (TBR) was then derived by dividing the mean aortic SUVmax to the average value of venous SUVmean. Finally, aortic TBR was calculated as the sum of TBRs of ascending and descending aorta, aortic arch, suprarenal, and infrarenal abdominal aorta divided by 5.

Statistical Analysis

Data are expressed as mean ± 1 standard deviation (S.D.) for continuous variables and as percentages for categorical data. The Kolmogorov-Smirnov test was used in order to assess the normality of distributions. Comparisons of baseline variables between groups of treatment were performed utilizing Student's unpaired *t*-test and the non-parametric Mann-Whitney U test as appropriate. Comparisons of continuous paired variables (pre-treatment, post-treatment) were performed utilizing paired *t*-test and Wilcoxon Signed Ranks test as appropriate. To test for changes within and differences between treatment groups after 6 months of treatment, repeated measurement analysis of variance (RMANOVA) was performed with the changes in parameters of ambulatory BP monitoring, echocardiography and PET-scan as dependent variables, and time, treatment group and baseline measurements as fixed parameters. The statistical tests were two-tailed and performed at the 5% level of significance. All statistical analysis was performed using SPSS (Version 20.0, SPSS Inc., Chicago, IL).

TABLE 1 | Baseline characteristics.

	Everolimus (*n* = 10)	**CDK 4/6 (*n* = 12)**	***p***
Age (years)	62.8 ± 13.6	62.1 ± 17.2	0.925
Hypertension (*n*)	4	5	0.801
ACEi/ARB	2	3	0.594
CCB	1	2	0.571
b-blocker	3	1	0.223
diuretic	2	2	0.632
Diabetes (*n*)	1 (IDDM)	1 (NIDDM)	0.943
Dyslipidemia (*n*)	3	1	0.223
Statin use (*n*)	2	1	0.429
Smoking (*n*)	4 (active)	1 (active)	0.097
Previous cancer treatment (*n*)	6	10	0.221
Previous radiotherapy (*n*)	2	3	0.594
24-h SBP (mmHg)	120.6 ± 10.9	130.0 ± 11.2	0.067
24-h DBP (mmHg)	73.9 ± 9.9	73.3 ± 8.3	0.895
24-h MBP (mmHg)	90.3 ± 9.0	93.3 ± 7.3	0.424
Daytime SBP (mmHg)	122.7 ± 11.4	132.4 ± 11.4	0.068
Daytime DBP (mmHg)	75.4 ± 10.6	74.9 ± 8.8	0.910
Daytime MBP (mmHg)	92.3 ± 9.5	95.8 ± 7.0	0.444
Nighttime SBP (mmHg)	113.4 ± 13.5	122.2 ± 14.0	0.160
Nighttime DBP (mmHg)	67.6 ± 10.6	68.3 ± 9.4	0.880
Nighttime MBP (mmHg)	83.3 ± 10.7	87.8 ± 10.8	0.347
TBR aorta	1.87 ± 0.25	1.92 ± 0.32	0.632
EF (%)	54 (8)	55 (5)	0.251
RWT	0.37 ± 0.06	0.39 ± 0.06	0.470
LVM (g)	124.6 ± 36.3	116.9 ± 22.4	0.572

ACEi, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CCB, calcium channel blocker; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; TBR, tissue-to-background ratio; EF, ejection fraction; RWT, relative wall thickness; LVM, left ventricular mass.

RESULTS

In a cohort of 22 consecutive female patients with metastatic breast cancer, 10 received hormonal therapy with everolimus, and 12 received hormonal therapy with CDK 4/6 inhibitors. Baseline characteristics did not differ significantly between two groups, including blood pressure, body mass index (BMI), and TBR (**Table 1**). Intra-correlation coefficients (ICCs) with 95% confidence intervals were calculated to test the intraobserver variability (2-way random effects model with absolute agreement), and also to assess interobserver agreement (2-way mixed effects model with absolute agreement) (27) for TBR assessment. The average measure intra-class correlation coefficient (ICC) was 0.996 with a 95% confidence interval from 0.990 to 0.998, $p < 0.001$. The interrater agreement was strong with a 95% confidence interval from 0.884 to 0.992, $p < 0.001$. Concordance correlation coefficients (CCCs) with 95% confidence intervals were calculated to test the intraobserver variability (2-way random effects model with absolute agreement), and also to assess interobserver agreement (2-way mixed effects model with absolute agreement) for TTE measurements regarding LVM and RWT assessment. The average measure intra-class correlation coefficient (CCC) was 0.998 with a 95% confidence interval from 0.996 to 0.999, $p < 0.001$.

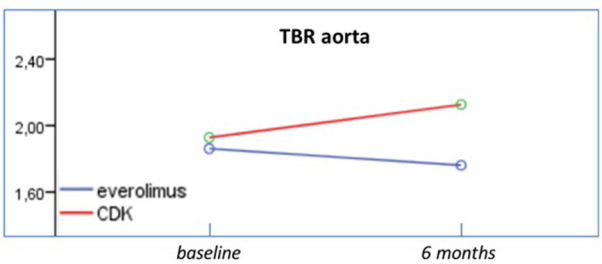

FIGURE 1 | Effects of everolimus and CDK 4/6 on TBR. TBR measurements increased significantly in CDK 4/6 group whereas TBR values in everolimus remained stable at follow up.

At follow up, patients assigned to CDK 4/6 treatment demonstrated increased measurements of 24-h SBP ($p = 0.004$), daytime SBP ($p = 0.004$), and night time SBP ($p = 0.012$) (Group effect). The 24-h MAP measurements were also higher in CDK 4/6 population, in comparison to everolimus that displayed firm values (Group effect: $p = 0.035$, Interaction effect: $p = 0.023$). Additionally, 24-h DBP recordings in CDK 4/6 therapy were higher opposed to everolimus that remained consistent (Interaction effect: $p = 0.010$). Profile plots from ambulatory BP monitoring are presented in **Figure 2**. Regarding FDG uptake in the aorta, TBR measurements increased significantly in CDK 4/6 group whereas TBR values in everolimus remained stable at follow up as presented in **Figure 1** (Interaction effect: $p = 0.049$). Results of repeated measurement analysis of variance are presented in **Table 2**.

Both therapeutic regimens displayed statistically significant damaging effect with regards to the following echocardiographic variables: RWT and LVM (**Figure 2**). On the contrary, ejection fraction did not significantly change in both groups (from 54 to 50% for Everolimus, $p = 0.109$, and from 55 to 55% for CDK 4/6 group $p = 1.000$).

DISCUSSION

CDK 4/6 treatment strategy promoted vascular inflammation by means of increased TBR values, higher blood pressure values as recorded by 24 h ABPM and induced left ventricle remodeling. CDK4/6 inhibitors function as ATP competitive inhibitors, while they intervene in the phosphorylation and inactivation of retinoblastoma, a key tumor suppressor fundamental in cell cycle and the inactivation of FOXM-1. Thus, moderation of breast cancer cells proliferation occurs, without directly causing their

TABLE 2 | Results of repeated measurement analysis of variance for ambulatory blood pressure monitoring and 18-FDG uptake.

	Everolimus		CDK 4/6		*p*	
	Baseline	6 Months	Baseline	6 Months	Group effect	Interaction effect
AMBULATORY BLOOD PRESSURE MONITORING						
24-h SBP	120.6 ± 10.9	119.8 ± 15.9	130.0 ± 11.2	137.9 ± 7.6	0.004	0.139
24-h DBP	73.9 ± 9.9	121.4 ± 15.7	73.3 ± 8.3	141.2 ± 9.7	0.004	0.092
24-h MBP	90.3 ± 9.0	111.2 ± 16.5	93.3 ± 7.3	128.3 ± 9.1	0.012	0.261
Daytime SBP	122.7 ± 11.4	70.7 ± 10.5	132.4 ± 11.4	81.5 ± 8.5	0.161	0.011
Daytime DBP	75.4 ± 10.6	72.2 ± 10.9	74.9 ± 8.8	83.0 ± 10.1	0.185	0.024
Daytime MBP	92.3 ± 9.5	64.3 ± 9.9	95.8 ± 7.0	73.0 ± 8.3	0.215	0.063
Nighttime SBP	113.4 ± 13.5	88.9 ± 12.9	122.2 ± 14.0	102.2 ± 8.0	0.036	0.023
Nighttime DBP	67.6 ± 10.6	90.5 ± 13.5	68.3 ± 9.4	104.0 ± 9.7	0.042	0.035
Nighttime MBP	83.3 ± 10.7	81.9 ± 12.7	87.8 ± 10.8	93.4 ± 7.4	0.054	0.166
18-FDG PET						
TBR	1.86 ± 0.28	1.76 ± 0.16	1.92 ± 0.32	2.13 ± 0.36	0.089	0.049

DBP, diastolic blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure mmHg; TBR, tissue-to-background ratio.

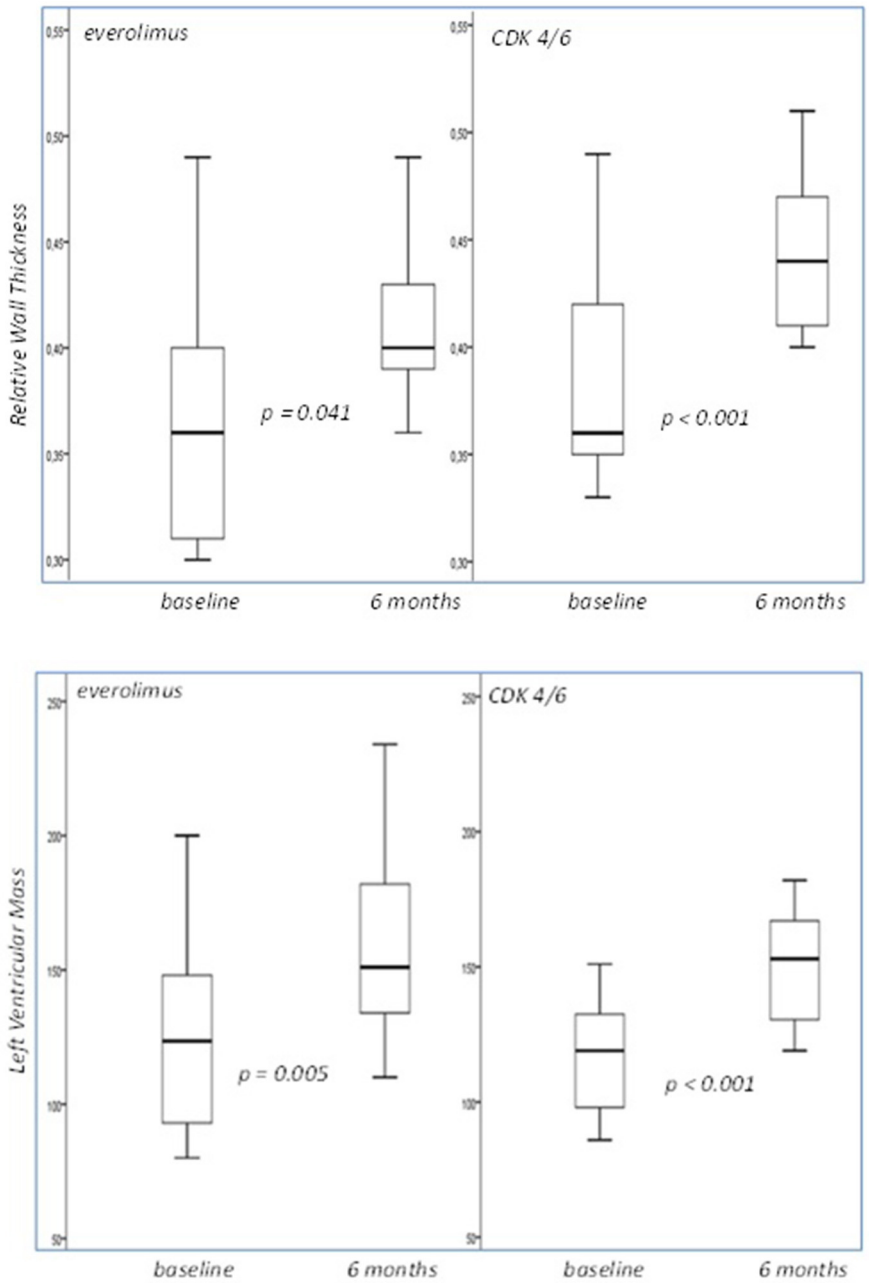

FIGURE 2 | Box plots of the relative wall thickness and left ventricular mass cross-tabulated by different treatment regimens. Both displayed statistically significant damaging effect. LVM was measured in grams.

apoptosis, and enhance their capacity to present antigen and stimulate cytotoxic T cells (1, 9, 15).

CDK inhibition has been found to trigger interferon production and indirectly moderate cytotoxic T cells activation against tumor cells proliferation (15). CDKs are widely expressed in breast cancer cells and play a crucial role in the initiation of an inflammatory cascade comprising IL-8, IL-6, VEGF-A, and others (28). However, specific blockade of certain kinases (4 and 6) in the context of metastatic breast cancer might lead to compensatory upregulation or do not alter at all the function of other members of CDK family such as 7 and 9, kinases that have been proven to regulate neutrophil apoptosis and promote inflammatory response (17). Additionally, novel findings of new interstitial lung disease, pneumonitis, and inflammation in

patients receiving CDK 4/6 inhibitors support the notion that the inflammatory pathway is not blocked adequately with regards to this group of patients and moreover can exacerbate inflammatory response (16). The above cumulative reports led recently the FDA to issue an official safety announcement warning about the complete class of CDKI (29).

Hypertensive response as a result of an inflammatory process has been described extensively (18, 19, 30). Chronic inflammatory activation has been implicated to the dysregulation of angiotensin II axis, sodium retention, and increased sympathetic outflow. The stimulation of angiotensin-aldosterone pathway and catecholamines promote reactive oxygen species (ROS) production in vasculature thus enhancing chemokine and adhesion molecules fabrication. Moreover, activated T cells interact with macrophages and leukocytes resulting in the activation of other inflammatory assays, such as IL-6, TGF-β, and the production of IL-17 and other cytokines by direct T cells. The above changes promote further ROS production, sodium retention and vasoconstriction (30–33).

The increased RWT and LVM values recorded in the group of CDK4/6 inhibitors can be interpreted as a result of ventricle remodeling and in the context of an inflammatory induced hypertensive state. Many studies have proposed the role of cytokines such as TNF-a, IL-1, and IL-6 in alterations of left ventricle geometry and progressive diastolic and systolic functional impairment (34–36). Concurrently, increased ventricular wall stress as a result of a raised systemic afterload (in cases such as hypertension) has been found to promote further release of inflammatory cytokines in systemic circulation leading to further remodeling and geometry alterations that might lead to severe diastolic and systolic dysfunction (cytokines pleiotropic effect-positive feedback mechanism) (36, 37).

The group that received Everolimus did not demonstrate significant alterations at follow up in TBR and 24 h ABPM recordings. Everolimus interacts exclusively with the mTORC1 compound (direct inhibition) and promotes phosporylation of P70 ribosomal S6 protein kinase. Furthermore, it blocks HIF-1 expression and moderates angiogenesis with an impact on VEGF and smooth muscle and endothelial cells propagation. As an anticancer agent it does not promote direct cardiotoxicity; its impact on vasculature stems from hyperglycemia, hyperlipidemia and hypertension that it might induce (12–14).

In the present study however, RWT and LVM were increased at 6 months follow up. Despite the fact that established hypertension was not apparent in this group, the above findings support the theory of concentric remodeling of the left ventricle in the context of possible microvascular dysfunction induced by Everolimus treatment (14) and an ongoing chronic inflammatory process(metastatic breast cancer) promoted by the cytokine pathway (34–36).

Study Limitations

The present study exhibits the results of a single center observational report including a relatively limited number of patients. Secondly the study protocol did not include the measurement of inflammatory markers.

CONCLUSION

The findings of the present study suggest that both treatment strategies might impair cardiovascular function. Specifically, CDK 4/6 inhibitors and hormonal treatment promotes vascular inflammation, hypertensive response, and alters left ventricle geometry. On the contrary, Everolimus and hormonal treatment does not have such a compounding impact on cardiovascular burden, by means of TBR and 24 h ABPM measurements, although left ventricle concentric remodeling was noted in TTE at 6 months of follow up.

To our knowledge, this is the first study to assess the cardiovascular impact of contemporary anti-neoplasmatic treatment in metastatic female breast cancer patients with HR-positive HER2-negative phenotype, using a combination of different techniques including PET-CT imaging. Taking into consideration the above findings, the authors have the notion that close monitoring with TTE and ABPM at baseline and during treatment would be a reasonable approach in this subgroup of breast cancer patients. Moreover, long term consequences of increased vascular inflammation might be accessed further with the implementation of peripheral vascular imaging and/or aortic and peripheral arteries functional alterations, assessed by well-established methods such as IMT (intima media thickness), ABI (ankle branchial index), and/or PWV (pulse wave velocity), respectively, especially in cases with emerging signs and symptoms of cardiovascular dysregulation. Both cardiologists and oncologists, ought to be alert and in close collaboration for the prompt detection of cardiovascular toxicity when treating breast cancer patients receiving either CDK 4/6 inhibitors or Everolimus.

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 Alexandra General Hospital Review board and Ethics committee, Athens, Greece. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.638895/full#supplementary-material

Supplementary Figure 1 | Indicative comparative images of ^{18}FDG PET/CT scanning between the two groups.

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BRIEF RESEARCH REPORT
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Early Detection of Checkpoint Inhibitor-Associated Myocarditis Using ^{68}Ga-FAPI PET/CT

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Objective: Checkpoint inhibitors (ICIs) have gained importance in recent years regarding the treatment of a variety of oncologic diseases. The possibilities of diagnosing cardiac adverse autoimmune effects of ICIs are still limited. We aimed to implement FAPI PET/CT imaging in detecting ICI-associated myocarditis.

Methods: In a retrospective study, FAPI PET/CT scans of 26 patients who received ICIs from 01/2017 to 10/2019 were analyzed. We compared tracer enrichment in the heart of patients without any signs of a cardiac disease ($n = 23$) to three patients with suspected ICI-associated myocarditis. To exclude any significant coronary heart disease, cardiac catherization was performed. All three patients' myocardial biopsies were examined for inflammatory cells.

Results: Three patients showed clinical manifestations of an ICI syndrome including myocarditis with elevated levels of hsTnT (175 pg/ml, 1,771 pg/ml, 157 pg/ml). Further cardiological assessments revealed ECG abnormalities, lymphocyte infiltration of the myocardium in the biopsies or wall motion abnormalities in echocardiography. These patients' FAPI PET/CTs showed cardiac enrichment of the marker which was less distinct or absent in patients receiving ICIs without any signs of immunological adverse effects or cardiac impairment ($n = 23$) [Median SUV myocarditis patients: 1.79 (IQR: 1.65, 1.85), median SUV non-myocarditis patients: 1.15 (IQR: 0.955, 1.52)].

Conclusions: Apart from the successful implementation of ICIs in oncological treatments, ICI-associated myocarditis is still a challenging adverse effect. FAPI PET/CT may be used in order to identify affected patients at an early stage. Moreover, when integrated into cancer stage diagnostics, it contributes to cardiac risk stratification besides biomarker, ECG and echocardiography.

Keywords: checkpoint- inhibitors, cardio-oncology, myocarditis, positron emission tomography, cardiotoxcity

KEY POINTS

- **Question:** Is FAPI PET/CT able to diagnose ICI-associated myocarditis?
- **Pertinent findings:** In a cohort study, FAPI PET/CT was applied in 26 cancer patients receiving ICIs. Three patients with evidence of ICI-myocarditis showed elevated SUVs in the myocardium above the median compared to 23 patients without any evidence of myocarditis.
- **Implications for patient care:** FAPI PET/CT might fill the diagnostic gap to diagnose ICI-associated myocarditis.

INTRODUCTION

Based on their groundbreaking effects on cancer, immune checkpoint inhibitors (ICIs) are currently investigated in more than 2,500 clinical studies for almost all types of cancer. Despite the antitumor effects, adverse immune related responses can lead to serious adverse events (1). Among the variety of organ manifestations, ICI-associated myocarditis has shown a high fatality rate of up to 50% (2). Due to the fact that the reported incidence is very low (around 1.4%) and that the phenotype of this novel syndrome is highly variable, a definitive diagnosis is still challenging. Cardiac MRI, ECG and cardiac biomarkers often show an inconsistent pattern. Therefore, myocardial biopsy with the detection of CD3/CD8+ cells is currently considered as the gold standard (3, 4).

Fibroblast activation protein (FAP) is a protease with endopeptidase activity, cleaving at specific postproline bonds (5). It is involved in various biological processes [e.g., wound healing (6), tissue remodeling (7), or tumor growth (8)]. In cardiomyopathies, in particular, FAP belongs to the most upregulated proteins (9).

The discovery of a fibroblast activation protein inhibitor (FAPI) (10) allowed the development of an imaging technique with the use of a radiotracer to image FAP density (11). ^{68}Ga-FAPI PET/CT is currently in clinical use to detect malignancies (11–13). In rats, FAPI PET/CT revealed enrichment in the myocardium after experimental induction of myocardial infarction (MI) (14).

To date, a sensitive, non-invasive method for the detection of ICI-associated myocarditis is still missing. The study was designed to determine whether ^{68}Ga-FAPI PET/CT imaging can be used in order to detect ICI-associated myocarditis.

MATERIALS AND METHODS

Patients

From 2017 to 2019, 26 patients were treated with PD-1, PD-L1, or CTLA-4 inhibitors at University Hospital Heidelberg because of their malignant disease and received ^{68}Ga-FAPI PET/CT scans to asses their cancer stage.

Patients who are treated with ICIs are observed within a close surveillance protocol at the oncology departments. Creatine kinase is assessed on a regular basis. If there are increased levels or clinical signs and symptoms for acute coronary syndrome or heart failure, cardiac biomarkers are evaluated. According to these observations, a detailed cardiological assessment, including catherization with myocardial biopsy, echocardiography and cardiac MRI, is initiated. Clinically, there have been no signs of heart failure or acute coronary syndrome in the non-myocarditis patients as well as no relevant elevations of creatine kinase.

Further, cardiac assessments including cardiac MRI and cardiac catherization were performed in the myocarditis patients. These patients received ^{68}Ga-FAPI PET/CT after the suspect of ICI-associated myocarditis was raised. The pathological results have not been accessible at that timepoint.

The study protocol was approved by the ethics committee of the Medical Faculty of University Heidelberg (S-286/2017, S016/2018).

^{68}Ga-FAPI PET/CT

FAPI PET/CT scans were performed using 122–336 mBq of Gallium 68 (^{68}Ga)-labeled fibroblast activation protein inhibitor (FAPI) which was administered intravenously 60 min before examination. The PET/CT scans were performed with a Biograph mCT Flow™ PET/CT-Scanner (Siemens Medical Solutions) using the following parameters: slice thickness of 5 mm, increment of 3–4 mm, soft-tissue reconstruction kernel, care dose. Immediately after CT scanning, a whole-body PET was acquired in 3D (matrix 200 × 200) in FlowMotion™ with 0.7 cm/min. The emission data was corrected for random, scatter and decay. Reconstruction was conducted with an ordered subset expectation maximization (OSEM) algorithm with two iterations/21 subsets and Gauss-filtered to a transaxial resolution of 5 mm at full-width half-maximum (FWHM). Attenuation correction was performed using the low-dose non-enhanced CT data. The quantitative assessment of standardized uptake values (SUV) was done using a region of interest technique.

Cardiac MRI

Standard CMR was performed supine in a 1.5-T Ingenia (1.5-T) or 3-T Ingenia CX (3-T) whole body scanner (Philips Healthcare, Best, The Netherlands), with a commercial cardiac phased array receiver coil. Following localizing scans, cine long axis 2-, 3-, and 4-chamber views as well as short axis (SAX) cine images covering the whole LV from the anulus of the atrioventricular valves to the apex (8 mm slice thickness, no gap between each slice) were obtained using a breath-hold, segmented-k-space balanced steady-state free precession sequence (bSSFP) employing retrospective ECG or pulse oximetric gating with 35 phases per cardiac cycles for cardiac morphology.

Data Accession and Analysis

Patient specific data, including ECG and biomarker, was extracted from the electronic medical reports. For ^{68}Ga-FAPI PET/CT analysis, 17 segments of the left ventricle were measured based on the anatomic structure regardless of focal signal enrichment. Graphs were built in R version 3.4.4 with inhouse scripting using the shape and RColorBrewer packages. SUVs have been specified as median values and interquartile range.

For histological sections, myocardial biopsies were stained with Hematoxlin and eosin, anti-CD3 and anti-CD8.

RESULTS

Clinical Cases of ICI-Associated Myocarditis

Three patients receiving immune checkpoint inhibitors were admitted with suspected autoimmune myocarditis (**Table 1**).

- A 62-year-old male patient received two doses of Pembrolizumab (200 mg, q3w) to treat melanoma until he was admitted to our cardio-oncology unit due to elevations of hs-troponinT (hsTnT) (39 pg/ml) and NT-proBNP (2,900 ng/l). Symptoms of heart failure or acute coronary syndrome were absent.
- A 70-year-old male patient was treated with Durvalumab (1,500 mg, q4w), a PD-L1 inhibitor monotherapy due to a hepatocellular carcinoma. After two doses, he complained of pronounced shortness of breath, classified as NYHA III-IV. The worsening of the respiratory deficiency required long-term mechanical ventilation, most likely due to an emerging myasthenia-like syndrome. Aside from the myocarditis therapy, the patient was successfully treated with pyridostigmine to improve the weaning of the ventilation.
- A 74-year-old female patient, diagnosed with metastatic adenocarcinoma of the uterus was treated with Pembrolizumab (200 mg, q3w), a PD-1 inhibitor. 9 months after the initiation of therapy, the patient showed elevated levels of hsTnT (46 pg/ml) and increased NT-proBNP (723 ng/l). Clinically, she suffered from dyspnea (NYHA II-III) but denied typical chest pain.

All patients fulfilled the criteria for definite ICI-associated myocarditis which have recently been suggested (4). Myocardial biopsy revealed CD3/CD8+ cells for patient #1 and patient #2. Exemplary images are shown in **Figure 1D**. In Patient #3, myocardial biopsy revealed <14 CD3/CD8+ cells/mm^2. However, wall motion abnormalities in the echocardiography, elevated cardiac biomarker (hsTnT, NT-proBNP) and ST depressions in the ECG were found. In addition, the patient developed an autoimmune syndrome, including a general myositis with elevation of creatine kinase.

All patients were treated with steroids, followed by tapering over several weeks. Holter ECG did not reveal higher grade arrhythmias, but the initial ECG showed T-wave inversions or ST depressions in all three patients (**Figure 2**). Echocardiography showed a preserved to slightly reduced LVEF in all patients. Cardiac MRI confirmed the preserved systolic ejection fraction (**Supplementary Videos 1**, **2**) and an angiography was able to exclude significant ischemia in the area of FAPI enrichment (**Supplementary Videos 3–5**). Patient #2 received a coronary intervention of the right coronary artery. We did not observe late gadolineum enhancement nor tracer accumulation in the FAPI PET/CT in the inferior segments, but CD3/CD8+ cells in the myocardial biopsy. Patient #1 showed globally elevated T1-mapping, in patient #2 we found late gadolineum enhancement at the basal segments. The two patients did not show any signs of cardiac edema as evaluated by T2-mapping. In patient #3 no MRI was performed.

Cardiac Imaging With the Use of the ^{68}Ga-FAPI Tracer

Given that the results of the biopsies were not available immediately, we decided to perform a PET/CT with ^{68}Gallium FAPI which enables the identification of activated fibroblasts. In addition to an uptake in the neoplastic tissues, the examination revealed an accumulation of the tracer either diffusely distributed in the left ventricle (patient #1), rather localized at the septal area (patient #2) or in the apical posterior wall of the left ventricle (patient #3) (**Figures 1A,C**).

We did not find comparable cardiac enrichments of the tracer in the control patients who received ICIs but who were not suspected of ICI-associated myocarditis. Even though some patients in our control group (patients #5, #6, #8, and #23) have shown slightly elevated SUVs in the heart, they have not shown obvious signs of either acute coronary syndrome, heart failure or myocarditis ($n = 23$, **Figure 1B**, **Supplementary Figure 1**). Regarding the clinical data of the patients, we found two patients with diabetes, five patients with atrial fibrillation and three patients with coronary heart disease in our non-myocarditis group. Three patients' history included chest radiation (**Supplementary Table 1**). Two patients in the control group with slightly elevated SUVs in the heart were diagnosed with coronary heart disease and one patient was subjected to chest radiation.

The median SUV in the myocarditis patients was 1.79 (IQR: 1.65, 1.85), whereas the median SUV in non-myocarditis patients was found to be 1.15 (IQR: 0.955, 1.52).

Thus, FAPI PET/CT allowed the identification of locally defined myocardial remodeling due to ICI-associated cardiac inflammation. Upon steroid treatment, cardiac troponin levels normalized in all three cases and the symptoms of dyspnea disappeared.

DISCUSSION

The Challenge of the Early Diagnosis of ICI-Associated Myocarditis

Current cardiac imaging techniques fail to detect early stages of ICI-associated myocarditis, especially in the absence of functional impairments. Myocardial biopsies, currently considered as gold standard, do not allow an immediate conclusion. Biopsies further appear to be false-negative in some cases based on local differences in leukocyte infiltrations as seen in biopsies of patient #3 (3). This notion is supported by the diffuse pattern of ^{68}Ga-FAPI enrichment, which was seen in this patient. Considering the increasing demand of ICIs and bearing the potentially life-threatening consequences of their use in mind, novel strategies for the diagnosis of ICI-associated myocarditis are needed.

The Use of ^{68}Ga-FAPI PET/CT in Cancer Staging and Cardiac Applications

Fibroblast activating protein (FAP) is known to be significantly upregulated in tissue remodeling, indicating tumor activity or fibrosis following the activation of fibroblasts (11, 12, 15). In

TABLE 1 | ICI-patient characteristics.

Demog	Medical History			ICI regimen; number of doses received	Time to onset myocarditis; concurrent irAE	Myocarditis presentation	Immuno-modulators and other support (treatment sequence)	Outcome
	Cancer	Cardiovascular	Auto-immune					
62y, M, 96 kg	Malignant melanoma, St.p. excision, Adjuvant chemotherapy with Pembrolizumab	- atrial fibrillation - St.p. mechanical aortic valve replacement	- bronchial asthma	Pembrolizumab (200 mg/3 weeks); two doses	27 days; myositis	Asymptomatic clinical course, hsTnT- and NTproBNP-elevation, coughing	250 mg prednisolone for 3 days with subsequent tapering	- No oncological sign of relapse - Persistent increased hsTnT and NT-proBNP levels - Normalization of initially significantly increased creatine kinase
70y, M, 120 kg	Hepatocellular carcinoma, Monotherapy Durvalumab	- CHD, PCI of RCA - Pulmary artery embolism - atrial fibrillation	none	Durvalumab (1,500 mg/ 4 weeks), two doses	39 days; myasthenia-like syndrome	Dyspnea (NYHA III- IV), fatique	500 mg prednisolone for 3 days with subsequent tapering, pyridostigmine	- Longterm mechanical ventilation, tracheostomy - rehabilitation after weaning - at least 4 months survival - Oncological reevaluation pending
74y, F, 62 kg	Adenocarcinoma of the uterus, metastasized peritoneal, vaginal, LN; St.p. hysterectomy prior to chemotherapy with Carboplatin and Paclitaxel 2018, Letrozol and Palbociclib 2018-01/2019, Pembrolizumab since 01/2019	- CHD without major lesions	none	Pembrolizumab (200 mg/ 3 weeks), 11 doses	271 days	Dyspnea (NYHA II), hsTnT- and NT-proBNP-elevation	100 mg prednisolone for 3 days with subsequent tapering	- Partial response peritoneal and LN - Declining hsTnT, stable dyspnea (NYHA II) - Alive at 3 months after the initial suspect of myocarditis

Patient overview table, CHD, coronary heart disease; F, female; kg, kilogram; M, male; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association classification; hsTnT, high sensitive Troponin T; PCI, percutaneous coronary intervention; RCA, right coronary artery; St.p., status post; y, years.

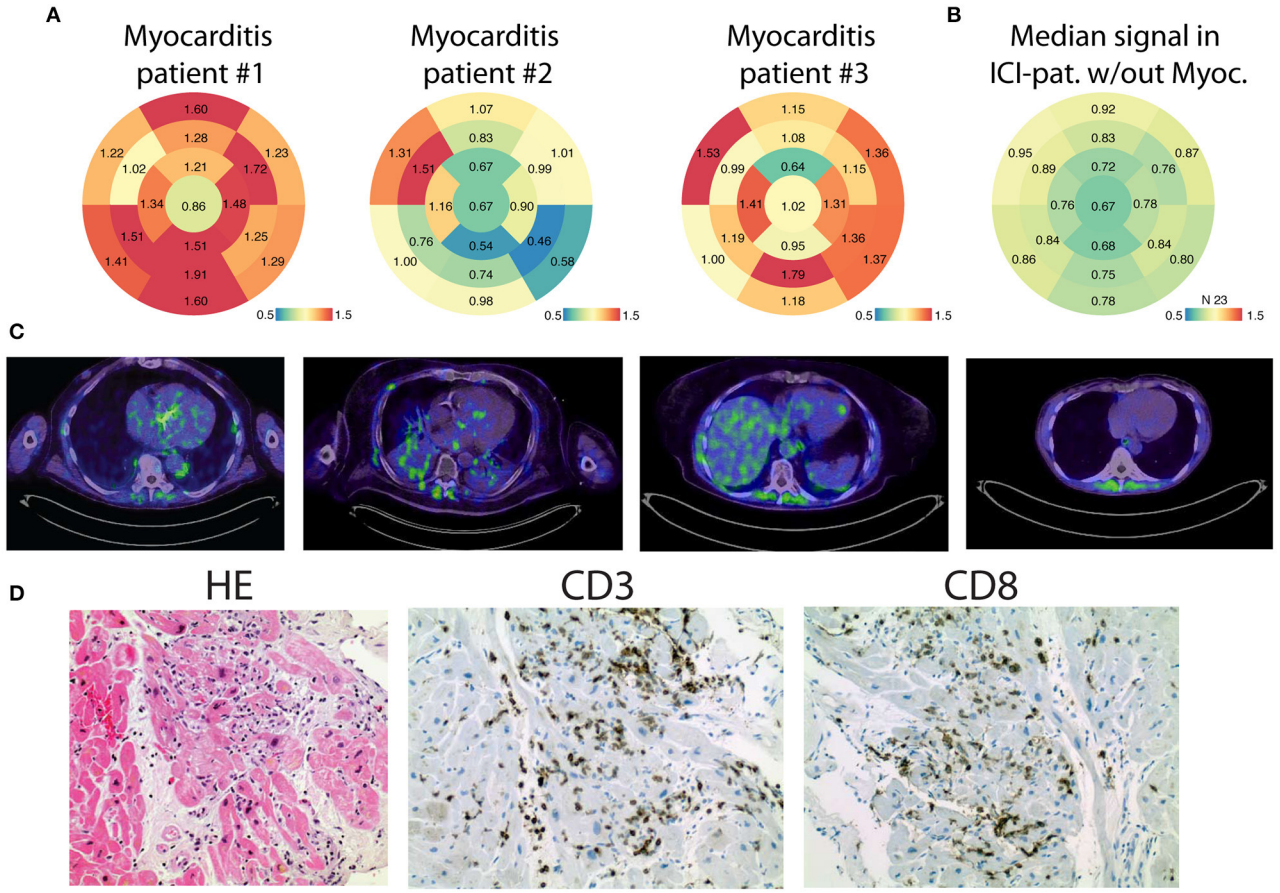

FIGURE 1 | FAPI PET/CT illustrates ICI-associated myocarditis. **(A)** Bulls Eye Illustration of standardized uptake values (SUVs) showing their distribution in the myocardium of the left ventricle in 17 defined areas. The enrichment is shown for ICI-associated myocarditis patients #1–#3. **(B)** In comparison, the median signal of patients which have received immune checkpoint inhibitors ($n = 23$) without signs of myocarditis is summarized. **(C)** Exemplary images of ^{68}Ga-FAPI PET/CT showing tracer uptake in the myocarditis patients' left ventricle and one example for the diagnostic findings in a non-myocarditis patient (right). **(D)** Exemplary histological sections of the left ventricle (HE: Hematoxylin staining, CD3- and CD8-immunostaining), confirming autoimmune myocarditis.

terms of oncological staging, ^{68}Ga-FAPI PET/CT showed a definite enrichment of the tracer in highly prevalent cancers and was beneficial for tumor characterization and discovering metastasis (16). It was able to show characterizations superior to FDG-PET analysis (13). A further application of ^{68}Ga-FAPI PET/CT could be radioligand therapies of the neoplastic tissue as recently supposed (15).

Cardiac fibroblasts, as well as tumor fibroblasts, reliably express FAP during remodeling due to injury or disease [e.g., in dilated and hypertrophic cardiomyopathy or after myocardial infarction (14)]. Preclinical data indicates that selectively targeting FAP may serve as a therapeutical approach to inhibit cardiac fibrosis and to restore heart function after administration of Angiotensin II and Phenylephrine (9).

Here, we show the first use of ^{68}Ga-FAPI PET/CT in the detection of myocardial alterations caused by ICI-associated myocarditis. Apart from myocardial infarction and coronary heart disease, there was no study yet to investigate its use in cardiac diseases. Derived from the pathomechanism, myocarditis in general and fibrosis in terms of cardiomyopathy might be detectable by FAPI PET/CT, as they are based on inflammation and tissue remodeling. Recently, it was shown that diabetes is associated with elevated tracer enrichment in FAPI PET/CT in the heart (17). This was associated with an enrichment of tracer accumulation within all segments of the left ventricle, whereas patients with ICI-associated myocarditis revealed a localized enrichment. Prior diagnosed coronary heart disease and chest radiation might be the reason why we observed tracer enrichment in some patients of our non-ICI-myocarditis group (patients #5, #6, #8, and #23).

The distribution of fibrosis, measured via late gadolineum enhancement in cardiac MRI, was shown to be diffusely distributed in the left ventricle in hypertrophic cardiomyopathy and focal in ischemic cardiomyopathy (18). Myocarditis of any cause, either autoimmune or virus-associated, is described to be a localized disease (19). In cardiac MRI, elevated T2-mapping or late gadolineum enhancement was found in <50% of patients with ICI-associated myocarditis (20). This may be the reason why

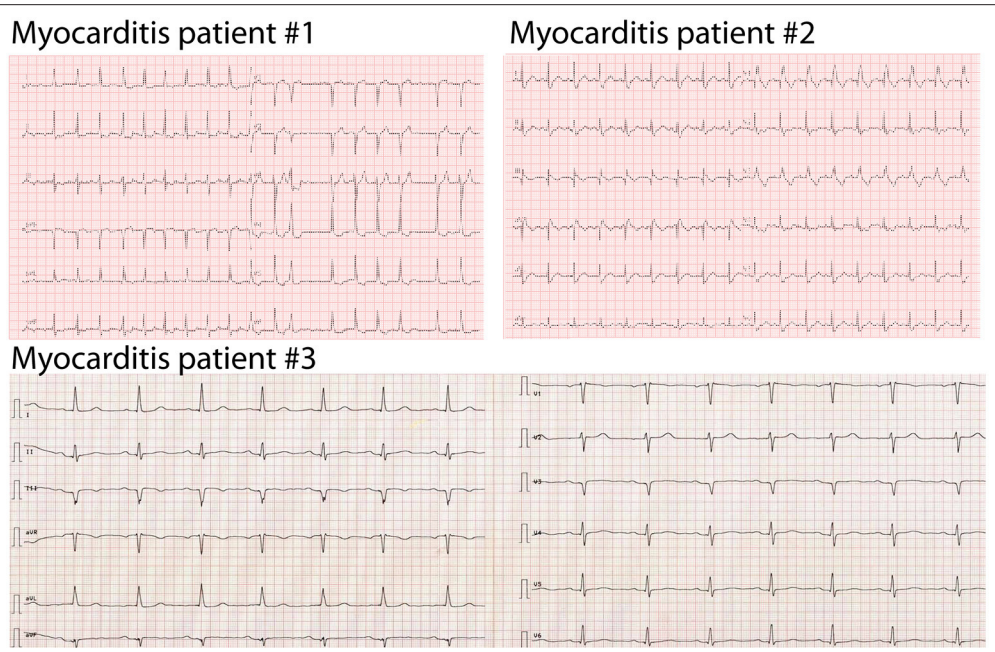

FIGURE 2 | Initial presentation of ICI-associated myocarditis patients. Initial ECG at presentation in the hospital when ICI-associated myocarditis was diagnosed. Patient #1: 25 mm/s, patient #2: 25 mm/s, patient #2, patient #3: 50 mm/s.

we were not able to correlate the MRI results with enrichment in FAPI PET/CT. Summarizing the limited clinical data that is published on ICI-associated myocarditis, the disease is supposed to show locally defined lymphocyte infiltrations as well (21).

Thus, we can link the locally defined tracer enrichment seen in the present FAPI images to the current knowledge of ICI-associated myocarditis. Further studies need to evaluate if FAPI-guided biopsies can reveal higher rates of positive CD3/CD8 immunostaining.

Since the onset of ICI-associated myocarditis is hard to define and the disease has a supposed transient character, mild intensities of the enrichment in the present study may be explained by the timing of the scan. However, in every patient with evidence of myocarditis, we see median SUVs above the median of our control group and in 2/3 patients immunostaining was able to detect relevant lymphocyte infiltration. The strength of this approach is a potential interdisciplinary evaluation of cancer staging and detection of myocarditis as an adverse effect at the same time. As recently shown in glioblastoma, FAPI enrichments are tissue-specific and do not have a strong correlation with blood flow and perfusion (22).

CONCLUSION

Novel approaches for sensitive, non-invasive diagnostics are needed because myocardial biopsies require cardiac catheterization and results are not immediately available. In addition, in many cases they appear to be false-negative. We propose that ^{68}Ga-FAPI PET/CT could be a non-invasive, unbiased method for the diagnosis of ICI-associated myocarditis.

Further studies need to address the predictive value and best time-window to diagnose ICI-associated myocarditis via FAPI PET/CT.

LIMITATIONS

Some limitations of this work need to be acknowledged. Due to the rare manifestation of ICI-associated myocarditis, we could only enroll a relatively small number of patients with evidence of ICI-associated myocarditis.

In our control group, containing patients receiving ICIs without any evidence of myocarditis or further cardiac pathologies, we were not able to perform a detailed cardiac assessment containing cardiac catherization and cardiac MRI as shown for the three cases of ICI-associated myocarditis. Anamnestically, there were no hints for the occurrence of a cardiac disease in those patients. FAPI PET/CT was done at one time point. Thus, we bear in mind the possibility of changes in the tracer enrichment during the time course of ICI therapy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Medical Faculty of

University Heidelberg. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DF and LHL conceived and designed the study and wrote the manuscript. DF, MH, EH, HK, UH, FL, and LHL analyzed and interpreted the data. DF, LL, MH, UH, FL, and LHL drafted the manuscript and revised it critically. All authors have read and approved the manuscript.

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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.2021.614997/full#supplementary-material

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Conflict of Interest: LHL has served on the advisory board for Daiichi Sankyio, Senaca and Servier, and received speakers' honoraria from Novartis and MSD. DF, MH, UH, HK and LHL have filed a patent for the use of FAPI imaging for the detection of pathological cardiac remodeling.

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.

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ORIGINAL RESEARCH
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QT Prolongation in Cancer Patients

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Background: QT prolongation and torsades de pointes pose a major concern for cardiologists and oncologists. Although cancer patients are suspected to have prolonged QT intervals, this has not been investigated in a large population. The purpose of this study was to analyze the QT interval distribution in a cancer population and compare it to a non-cancer population in the same institution.

Methods: The study was a retrospective review of 82,410 ECGs performed in cancer patients (51.8% women and 48.2% men) and 775 ECGs performed in normal stem cell donors (47.9% women and 52.1% men) from January 2009 to December 2013 at the University of Texas MD Anderson Cancer Center. Pharmacy prescription data was also collected and analyzed during the same time period. Correction of the QT interval for the heart rate was performed using the Bazett and Fridericia formulas.

Results: After QT correction for heart rate by the Fridericia formula (QTcF), the mean and 99% percentile QTc for cancer patients were 414 and 473 ms, respectively. These were significantly longer than the normal stem cell donors, 407 and 458 ms, $p < 0.001$, respectively. Among the cancer patients, the QTc was longer in the inpatient setting when compared to both outpatient and emergency center areas. The most commonly prescribed QT prolonging medications identified were ondansetron and methadone.

Conclusion: Our study demonstrates significantly longer QTc intervals in cancer patients, especially in the inpatient setting. Frequently prescribed QT prolonging medications such as antiemetics and analgesics may have a causative role in QT prolongation seen in our cancer hospital.

Keywords: QT prolongation, cardiooncology, ECG, torsades de pointes, cardiac monitoring in clinical trials

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INTRODUCTION

Prolongation of the QT interval is a well-recognized risk factor for potentially life-threatening ventricular arrhythmias and sudden cardiac death (1). With the development of novel anticancer therapies, many new biologic, immunologic, and targeted agents have been shown to alter cardiac repolarization and prolong the QT interval. A classic example is arsenic trioxide, which is an effective agent used to treat acute promyelocytic leukemia—an otherwise fatal disease. In one study of such treatment, severe QT prolongation (greater than 500 ms) was noted in 40% of patients receiving arsenic (2). Commonly used tyrosine kinase inhibitors such as vorinostat, dasatinib, lapatinib, and nilotinib have also been associated with QT prolongation (3–6).

QT prolongation is an important consideration in drug development and regulation. In light of the potentially fatal outcome of severe QT prolongation in investigational agents, the US Food and Drug Administration recommends periodic QT monitoring (7). Postmarketing data have identified drug-induced QT prolongation as the most common indication for withdrawal of medications from the market (8). In addition to safety regulation, the increasing costs of preclinical drug development (9) has limited the viability of otherwise promising investigational agents. Some pharmaceutical companies allocate 22% of total initial phase 1 clinical costs to QT monitoring and with advancement to phase 2, those costs may increase 6-fold (9).

Population studies have been used to identify the normal ranges of QT intervals. Unfortunately, there has been a paucity of data in oncologic patients, and only a few studies have investigated the QT intervals and cardiac event distributions in these populations (10, 11). These studies are limited by small patient populations, but seem to suggest a different range of QTc in cancer patients. In one such study (11), 15% of cancer patients required premature discontinuation or exclusion from potential curative cancer therapy when QTc exclusion guidelines were applied because the QTc cutoffs were derived from healthy populations. Often, cancer patients who enroll in investigational drug studies have previously been treated with multiple cancer therapeutics and are receiving several concurrent medications including anti-emetics, which are known to prolong the QTc interval. This further limits the determination of an investigational drug's effect on cardiac repolarization. Additional confusion arises regarding the clinical significance of QTc prolongation in the cancer patient population. Currently, there is limited data on the incidence of QTc-associated serious cardiac events in cancer patients. Available data in the non-cancer population has yielded a wide range of incidence rates from as low as 2.5 serious events per million years (12) in some large observational studies to as high as 12.5% incidence with the initiation of certain anti-arrhythmic agents (13, 14).

The primary objective of our study was to describe the QT intervals in cancer patients and compare them with those of healthy stem cell donors.

METHODS

The study and methodology were reviewed and approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center.

Study Population

For our primary objective, we collected the first performed electrocardiogram (ECG) for oncologic patients older than 18 years who were treated at The University of Texas MD Anderson Cancer Center from January 2009 to December 2013 in the emergency department, outpatient, and inpatient settings. By protocol, we excluded pediatric patients to limit the exposure of age-related QT interval differences. Additional exclusion criteria were any ECG findings that would limit accurate measurement of the QT interval, including the presence of a significant intraventricular conduction delay or a paced rhythm. We also collected the first available ECGs from healthy stem cell donors in the same time interval to serve as a comparison control. The QT intervals were measured using an automated computerized ECG analysis algorithm and then confirmed manually by an interpreting cardiologist.

Standard 12-lead ECGs were obtained at 25 mm/s and 0.1 mV/mm on strips of lined paper. Digital ECG measurements and calculations were made using the hospital Cardiac Science ECG system. The QT interval was defined as the first reflection of the QRS complex to the return of the T wave to the isoelectric line, excluding the U wave. The computer analysis selected the longest QT interval from the lead that had a clear QRS complex and T wave. All ECG measurements were evaluated and manually confirmed by a cardiologist. The QT interval was corrected for heart rate variation using both the Bazett ($QTcB = QT/\sqrt{RR}$) and Fridericia ($QTcF = QT/\sqrt[3]{RR}$) formulas.

Medication prescription data was also collected during the same time interval. Both inpatient and outpatient pharmacy queries were performed and the most frequently prescribed medications were obtained for review.

Statistical Analysis

Mean values with standard deviations (SDs) were given for continuous data. Frequency statistics were provided for categorical data. Differences in continuous variables and categorical variables between two groups were assessed by two-sample *T*-tests and Chi-Squared tests, respectively. ANOVA tests with Bonferroni correction were used to compare continuous variables between multiple groups. Statistical significance was set at a two-tailed probability level < 0.05 for all analyses. A Bland and Altman plot was performed to compare differences in QTcB and QTcF against the mean of QTcB and QTcF among cancer patients at different heart rate ranges. Statistical analyses were performed using STATA 14.2 software (StataCorp, College Station, TX) and R 3.3.1.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

We identified 221,332 ECGs performed in cancer patients and stem cell donors from January 2009 to December 2013. After exclusion criteria were applied, 82,410 first reported ECGs performed in cancer patients were selected and 775 ECGs performed in healthy stem cell donors remained for analysis. The baseline demographics of these two groups are shown in **Table 1**.

The mean QTcB and QTcF values were significantly higher for the cancer patient population than for the donor control population (427 vs. 413 ms, $p < 0.001$; 414 vs. 407 ms, $p < 0.001$, **Table 1**), respectively. The 99th percentile for QTcB and QTcF for the cancer patients were also significantly higher than the donor control population (491 vs. 468 ms, $p < 0.001$; 473 vs. 458 ms, $p < 0.001$). In addition, there were a greater number of patients with QTcB and QTcF values greater than or equal to 450 ms in the cancer patients. The percentage of cancer patients with QTcB $\geq$ 450 ms was 15.7 vs. 6.1% in the control patients.

TABLE 1 | Characteristics of cancer patients and healthy stem cell donors.

Characteristic	Cancer patients (n = 82,410)	Healthy stem cell donors (n = 775)	P-value
Age, mean (SD), y	59.1 (13.5)	47.1 (14.3)	<0.001
Men, %	48.2	52.1	0.03
Number of ECGs performed	82,410	775	
HR, mean (SD), bpm	74.1 (17.0)	66.1 (11.7)	<0.001
QRS duration, mean (SD), ms	89.2 (10.3)	90.7 (9.58)	<0.001
Bazett QTc, ms			
Mean (SD)	427 (23.9)	413 (23.4)	<0.001
99th percentile	491	468	<0.001
QTc ≥ 450	12,933 (15.7%)	47 (6.1%)	<0.001
QTc > 500	163 (0.2%)	0 (0%)	0.412
Fridericia QTc, ms			
Mean (SD)	414 (22.1)	407 (19.9)	<0.001
99th percentile	473	458	<0.001
QTc ≥ 450	4,513 (5.5%)	22 (2.8%)	0.001
QTc > 500	53 (0.06%)	0 (0%)	1.00

HR, heart rate.

This was also reflected by QTcF although to a lesser degree, 5.5 vs. 2.8%, respectively.

The mean QTcB from ECGs performed in the inpatient setting were higher than those from ECGs obtained from outpatient clinics and the emergency department (430 vs. 426 ms, $p < 0.001$; 430 vs. 423 ms, $p < 0.001$, **Table 2**). The same analyses were performed on QTcF among the cancer patient population showing similar results.

The distribution of QTc values by the Bazett and Fridericia formulas are shown in **Figure 1**, and comparisons between these formulas at different heart rates are shown in **Table 2**. The distribution of QTc intervals was a typical bell-shaped curve distribution. The difference of the QTcB and QTcF was compared against different heart rate ranges in a Bland and Altman plot which demonstrated higher values of QTcB compared to QTcF at heart rates > 100 bpm (**Figure 2**).

The pharmacy prescription data was collected and segregated between inpatient and outpatient pharmacies as shown in **Table 3**.

DISCUSSION

Our results demonstrate that cancer patients have significantly prolonged QTc intervals compared with individuals without cancer. The differences noted in historical healthy controls were consistent with our internal matched stem cell donor controls.

Epidemiologic surveys of healthy individuals (15–18) have established that QTcB is abnormally prolonged when it exceeds 450 ms in men and 460 ms in women. These same studies suggest a normal mean (SD) QTcB of 390 (20) ms. With these criteria, it is estimated that less than 1% of healthy individuals have abnormal QTc prolongation at baseline.

Similar epidemiologic data is scarce in the cancer patient population, but such data is of importance in guiding clinical management as well as the design and inclusion strategies for oncology clinical trials. Varterasian et al. described the QTc distribution in 128 patients with various malignancies being evaluated for inclusion in a clinical trial. The researchers found at baseline a mean (SD) QTc of 417 (27) ms, suggesting that ∼15% of cancer patients would be excluded from clinical trials based on the presence of a borderline prolonged QTc (10). Sarapa et al. reported similar findings in a survey of 160 patients (11). The ICH E14 guidelines recommend excluding from early-phase clinical trials patients with a baseline QTc greater than 450 ms, especially those with concomitant risk factors for arrhythmias (7, 19). However, these QTc cutoffs have not been rigorously evaluated in the cancer patient population and have little clinical data to support their endorsement.

Our study is the largest epidemiologic study to date attempting to define the QTc spectrum in a cancer patient population. The mean (SD) QTcF was 414 (22.1) ms related to the largest peak of the Gaussian distribution curve. This finding suggests that the QTc distribution spectrum in the cancer patient population has a significant rightward shift compared with both historical non-cancer patient reports and our non-cancer stem cell donor control population. Approximately 5.5% of the cancer patients had a QTcF greater than 450 ms compared to only 2.8% in the stem cell donors. Although the 99th percentile for QTcB in published historical healthy controls of 450 ms was smaller than that of our stem cell donor control population (468 ms), there was a greater difference when compared with the 99th percentile of our cancer patient population (491 ms). This significant shift in the cancer patient population's baseline QTc can likely be explained by several contributing factors, including polypharmacy with concomitant QTc-prolonging medications, higher incidence of electrolyte abnormalities, advanced age, and associated cardiovascular disease. In addition, our analysis demonstrated that the Fridericia correction had less variability at higher heart

TABLE 2 | ECG characteristics of cancer patients.

Group	Bazett QTc, ms				Fridericia QTc, ms			
	99th percentile	*p*-value*	Mean (SD)	*p*-value**	99th percentile	*p*-value*	Mean (SD)	*p*-value**
All patients		0.608		<0.001		0.548		<0.001
Women	491		430 (22.7)		472		416 (21.8)	
Men	491		423 (24.6)		473		411 (22.2)	
Heart rate		<0.001		<0.001		<0.001		<0.001
60-80 bpm	487		426 (21.8)		475		416 (20.9)	
81-100 bpm	495		437 (21.3)		462		410 (20.1)	
Age								
(1) ≤30 y	488	(1)–(2) ($p = 1.00$)	422 (25.7)	(1)–(2) ($p < 0.001$)	459	(1)–(2) ($p = 0.003$)	404 (22.6)	(1)–(2) ($p < 0.001$)
(2) 31–60 y	489	(1)–(3) ($p = 0.147$)	426 (23.5)	(1)–(3) ($p < 0.001$)	468	(1)–(3) ($p < 0.001$)	412 (21.2)	(1)–(3) ($p < 0.001$)
(3) >60 y	493	(2)–(3) ($p < 0.001$)	428 (24.0)	(2)–(3) ($p < 0.001$)	476	(2)–(3) ($p < 0.001$)	416 (22.5)	(2)–(3) ($p < 0.001$)
Clinic setting								
(1) Outpatient	488	(1)–(2) ($p < 0.001$)	426 (23.5)	(1)–(2) ($p < 0.001$)	472	(1)–(2) ($p = 0.004$)	414 (21.6)	(1)–(2) ($p < 0.001$)
(2) Inpatient	497	(1)–(3) ($p = 0.017$)	430 (25.7)	(1)–(3) ($p < 0.001$)	476	(1)–(3) ($p = 0.009$)	412 (24.5)	(1)–(3) ($p = 0.230$)
(3) Emergency department	484	(2)–(3) ($p < 0.001$)	423 (22.6)	(2)–(3) ($p < 0.001$)	467	(2)–(3) ($p < 0.001$)	413 (20.6)	(2)–(3) ($p < 0.001$)

*Permutation test comparing 99th percentiles; pairwise permutation test with Bonferroni adjustment.

**T-test comparing means; pairwise t-test with Bonferroni adjustment.

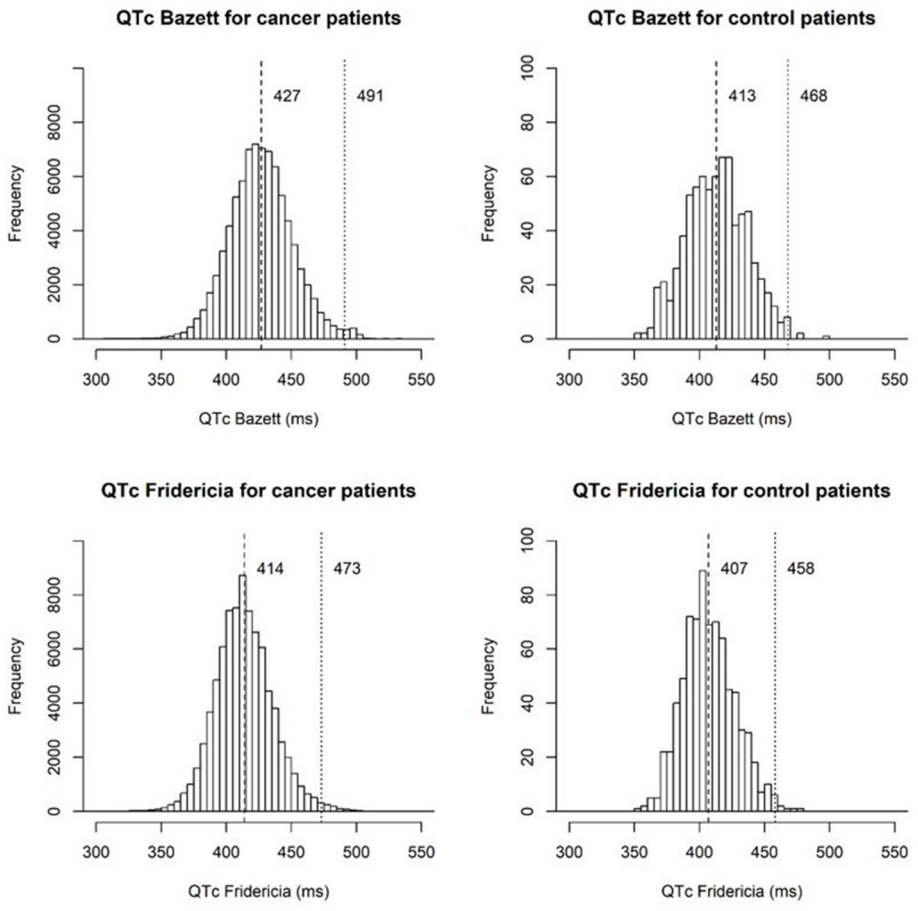

FIGURE 1 | Histograms of QTc intervals by the Bazett and Fridericia formulas for cancer patients and stem cell donor controls marking the mean and 99th percentile QT values.

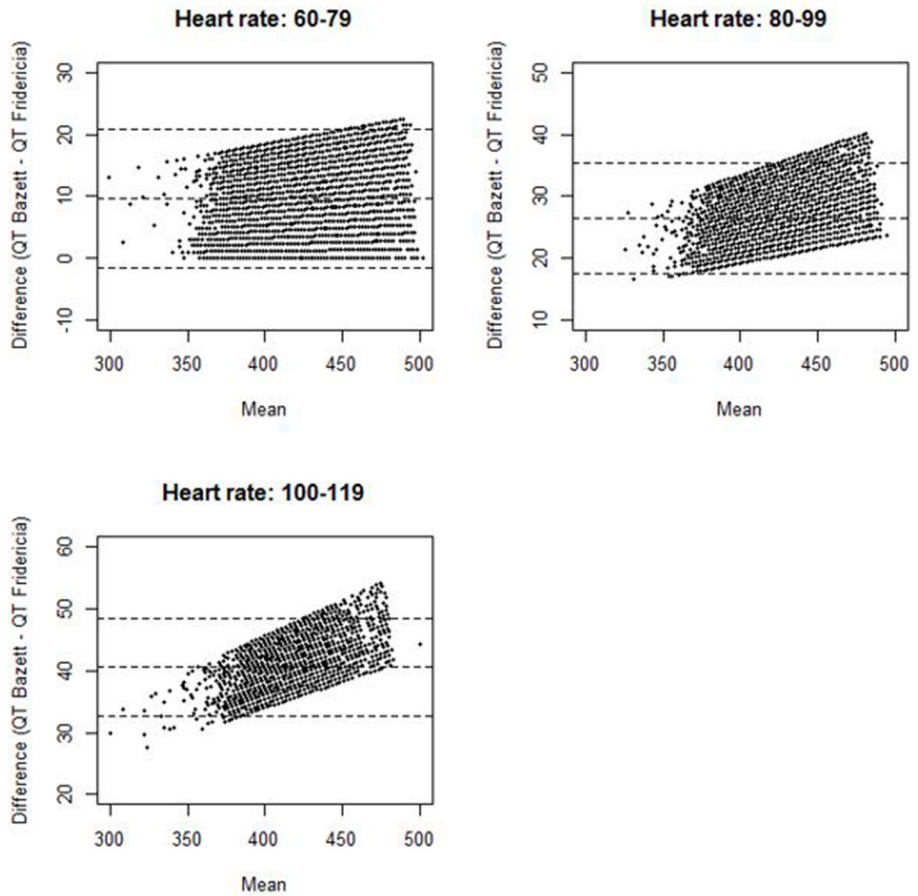

FIGURE 2 | Bland and Altman plot for difference of QT Bazett and QT Fridericia against mean of QT Bazett and QT Fridericia among cancer patients stratified by heart rate (the dotted lines represent the upper limit of agreement, mean difference, and lower limit of agreement).

rates, and confirmed the utility of QTcF correction over QTcB in our patient population.

Although we were unable to collect individual medication data on all of the included patients, we were able to collect pharmacy prescription throughout the institution in both inpatient and outpatient pharmacies as shown in **Table 3**. The second most commonly administered inpatient medication was ondansetron which is known to cause QT prolongation. Three other commonly prescribed inpatient medications (diphenhydramine, pantoprazole, and piperacillin/tazobactam) also had conditional or possible risk of QT prolongation. Among the commonly prescribed outpatient prescriptions, two medications had known QT prolongation (methadone and ondansetron) and two had conditional or possible QT prolongation risks (metoclopramide and tramadol). The common use of these medications may be related to the differences of QT prolongation seen in the inpatient and outpatient ECGs.

Our findings raise several important concerns and questions in the observation of cancer patients' risk of arrhythmic events. Compared with both historical controls and our own cancer-free stem cell donors, QT intervals in our cancer patients were significantly elevated with noticeably higher QTc in the inpatient setting. The translation of longer QTc in cancer patients into clinical events needs further investigation. Also, the exact mechanism of this high incidence of QT prolongation is probably multifactorial and not well-understood. Although our pharmacy prescription data suggests this could be partly related to several QT prolonging medications, additional analysis of risk factors, including electrolyte imbalance, structural heart disease, and pre-existing ischemic heart disease will be needed to elucidate risk factors. Alternatives strategies to pain management and emesis control should be considered to lower the risk of prolonged QTc, as the use of methadone and ondasetron was quite prevalent.

The limitations to our study include its retrospective data collection and possible referral bias. Although QT intervals can be influenced by age, gender, certain medications, electrolyte imbalances, and structural heart disease, the purpose of this study was not to account for all individual confounding variables, but to rather describe the QT interval distribution in a generalized cancer population. Also, the differences in QTc

TABLE 3 | Medications prescribed from 1/1/2009 to 12/31/2013.

Inpatient Medications		Outpatient Pharmacy Prescriptions	
Medication	**Doses**	**Medication**	**Doses**
Magnesium Sulfate	278,544,448	Acetaminophen/Hydrocodone	10,443,662
Ondansetron HCl	245,888,164	Xyloxylin	6,662,270
Dextrose	208,604,526	Sucralfate	3,979,366
Diphenhydramine	155,038,997	Hydromorphone	3,491,924
Acetaminophen	107,456,448	Oxycodone	3,445,530
Hydromorphone	94,697,820	Morphine	2,625,967
Dexamethasone Sodium Phosphate	84,320,780	Gabapentin	2,178,045
Heparin Sodium (Porcine)	81,200,126	Lactulose	1,958,813
Morphine	63,157,890	Methadone	1,821,234
Enoxaparin	31,922,397	Heparin Sodium (Porcine)	1,802,220
Acetaminophen/Hydrocodone	20,463,002	Metoclopramide	1,786,597
Pantoprazole Sodium	16,501,050	Docusate Sodium	1,744,570
Metoprolol Tartrate	12,775,562	Nystatin	1,557,765
Vancomycin HCl	10,002,811	Sennosides-Docusate Sodium	1,522,647
Piperacillin/Tazobactam	8,204,540	Sennosides	1,452,763
Cefepime HCL	7,090,713	Ondansetron HCl	1,407,213
Sodium Bicarbonate-Sodium Chloride	2,512,896	Magnesium Oxide	1,370,704
Sennosides-Docusate Sodium	2,235,408	Dexamethasone	1,282,392
Valacyclovir HCL	1,847,692	Tramadol HCl	1,256,464

Green, No known risk of QT prolongation.
Yellow, Conditional/Possible risk of QT prolongation.
Red, Known risk of QT prolongation.

were not compared to clinical endpoints such as ventricular arrhythmias and sudden cardiac death which would be an area of future research.

CONCLUSION

Our study shows that QTc prolongation is more common in the cancer patient population, particularly in the inpatient setting than in previously reported healthy historical models. Drug prescription patterns for pain and emesis control might be associated with these findings. The association of serious arrhythmic events related to QT prolongation needs to be investigated in cancer patients. Further study in the application of QT intervals and setting appropriate thresholds in the routine monitoring of cancer patients is needed to better risk stratify the potential harm of newer cancer therapies.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Radiation-Induced Vascular Disease—A State-of-the-Art Review

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Since the 1990s, there has been a steady increase in the number of cancer survivors to an estimated 17 million in 2019 in the US alone. Radiation therapy today is applied to a variety of malignancies and over 50% of cancer patients. The effects of ionizing radiation on cardiac structure and function, so-called radiation-induced heart disease (RIHD), have been extensively studied. We review the available published data on the mechanisms and manifestations of RIHD, with a focus on vascular disease, as well as proposed strategies for its prevention, screening, diagnosis, and management.

Keywords: radiation therapy, cardio-oncology, coronary artery disease, cancer, peripheral arterial disease

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INTRODUCTION

Since the 1990s, there has been a steady decline in cancer-related mortality, and consequently an increase in the number of cancer survivors to ∼17 million in 2019 in the United States alone (1). Cardiovascular complications from cancer therapy weigh heavily in terms of both morbidity and mortality (2). Among those, radiation-induced cardiovascular disease is one of the most important.

The cardiovascular effects of ionizing radiation were initially observed in atomic bomb survivors and later in patients with therapeutic radiation treatment for medical purposes (3, 4). Radiation therapy (RT) was initially applied to patients with breast cancer and Hodgkin's lymphoma, while today its use has expanded to a variety of malignancies and over 50% of cancer patients (5). The effects of ionizing radiation on cardiac structure and function, so-called radiation-induced heart disease (RIHD), have been extensively studied (6). We review the available published data on the mechanisms and manifestations of RIHD, with a focus on radiation-induced vascular disease (RIVD), as well as proposed strategies for its prevention, screening, diagnosis, and management.

PATHOGENIC MECHANISMS

Ionizing radiation affects not only cancerous, but also non-cancerous cells, especially those that are rapidly proliferating, such as endothelial and bone marrow cells, along with the local parenchymal cells within the radiated territory. Cell cycle arrest, senescence, and apoptosis are induced as a consequence of DNA damage (7) (**Figure 1**). In high doses, ionizing radiation can result in depletion of parenchymal and vascular endothelial cells, with both macro- and microvascular effects (8).

Oxidative stress due to radiolysis of water molecules into reactive oxygen species promotes endothelial dysfunction and inflammatory changes to the radiation field. Accordingly, radiation induces release of thromboxane and von Willebrand factor and decreased production of prostacyclin, thrombomodulin, and ADPase (9). Von Willebrand factor increases the platelet adhesion to endothelial cells, which may predispose to arterial thrombosis (10). Moreover, degeneration of the vascular smooth muscle, aggregation of foamy histiocytes and adventitial fibrosis have been observed. This is believed to be the precursor of lipid-laden foam cells and the beginning of atherosclerosis formation under the influence of pro-inflammatory cytokine release, such as interleukin(IL)-1, IL-6, tumor necrosis factor (TNF)-α, transforming growth factor-β (TGF-β). Among those, TGF-β is one of the most pleiotropic cytokines, affecting many cellular processes including epithelial cell growth, mesenchymal cell proliferation, and extracellular matrix synthesis (11). Ionizing radiation, even in low doses, induces TGF-β activation, affecting fibroblasts which are transformed into matrix-producing myofibroblasts and leading to fibrosis, a common feature observed in radiation induced heart disease. In individuals with non-small cell lung cancer, when plasma TGF- β1 levels are less than the pretreatment value and <7.5 ng/mL, the chance of radiation induced complications is decreased with higher radiation dose (>73.6 Gy) compared to those in whom the levels are high (12).

Human pathology studies have described increased intima-media thickness of irradiated arteries, similar to atherosclerotic vascular disease, although medial thinning and adventitial fibrosis were more prominent after irradiation (9, 13) (**Figure 2**). Intimal lesions following radiation exposure consist primarily of fibrous tissue, while a minority of lesions containing lipid or calcium deposits in addition to fibrosis (15–17). An early finding post-radiation is increased vascular permeability. This is mediated in part by histamine as well as accumulating endothelial cell death. Fibrinogen and von Willebrand factor leak outside the vessels as a result of the increased permeability (18, 19). Fibrinogen is converted to fibrin and evolves into fibrous tissue over time. This permeability is also the likely cause of lipid accumulation and accelerated atherosclerosis in hypercholesterolemic animals (9). In large arteries, damage to the vasa vasorum may contribute to radiation-induced vasculopathy (20). Rarely, arterial ruptures of the aorta, carotid, femoral, or pulmonary arteries have been reported early after massive radiation, although most have argued that it was related to surgery; however, rare case reports describe smooth muscle absence and fraying of elastic fibers (14, 21). In astronauts, spaceflight-associated neuro-ocular syndrome is hypothesized to be caused by radiation-induced angiosclerosis, given the increased radiation exposure during long-duration space flight and on the International Space Station (22).

In addition to intimal fibrosis, the media is often replaced by fibrous tissue, and the adventitia becomes fibrotic. Fibrosis evolves over time and involves all three layers of the vessel wall. Experimental models indicate that cholesterol plaques and thrombosis form within a period of days after radiation exposure (23). Radiation in arteries of hypercholesterolemic animals results in accelerated atherosclerosis (24). The composition, however, is different; the lesions in the aortic roots of irradiated animals are macrophage rich and lipid filled, whereas lesions in non-irradiated ones are collagenous with only minimal macrophage infiltration (25). The plaque burden does not appear to be different with or without radiation.

Pakala et al. recognized a vulnerable plaque phenotype after localized irradiation (26). Another experimental animal study identified increased number of lesions with macrophage-rich cores, low collagen content, and intraplaque hemorrhage in irradiated arteries (13). Intraplaque hemorrhage is known to induce atherosclerosis progression and plaque instability or rupture in human atherosclerotic lesions (27). The effects of one single high radiation dose in the absence of other factors may differ considerably from what is seen in patients who receive multiple cumulative dose fractions. Also, the response to the same radiation dose in different vascular beds may vary for reasons that remain unclear today.

In the coronary circulation the typical pattern associated with radiation-induced coronary artery disease (RICAD) is ostial stenosis with a significantly higher incidence of severe left main disease, followed by ostial right coronary artery and left anterior descending artery stenoses (17). The location and severity directly correlate with the direction and dose of radiation beam (28–30) (**Figure 3**). Extensive mantle radiation such as for Hodgkin's lymphoma, breast cancer, and esophageal cancer is more likely to cause ostial and multivessel stenoses (23, 28). Conversely, radiation (usually tangential and focal) for breast cancer is more likely to cause focal disease in the mid to distal LAD distribution for left sided breast lesions, whereas involvement of proximal RCA is more common after radiation for right breast lesions) (31, 32).

In the peripheral circulation, vascular toxicity is located in the areas of targeted radiation. The mechanisms of developing PAD relate to vascular damage from ionizing radiation as outlined above. PAD can occur acutely as peri-arterial inflammation, or a chronic process of progressive atherosclerosis and peri-arterial fibrosis (33, 34).

Radiation-associated valvular disease has also been observed in up to ∼80% of patients who received chest irradiation, most frequently symptomatic aortic stenosis (35, 36). Surgical aortic valve replacement (SAVR) appears to be associated with worse outcomes in patients who underwent chest irradiation compared to transcatheter aortic valve replacement (TAVR) (37, 38). Bioprosthetic valves, which are increasingly used over mechanical valves (39), are vulnerable to structural valve degeneration (40). The durability of transcatheter bioprostheses appears to be low and similar to surgical bioprostheses, although data are currently limited to at most 10-year follow-up (41). It is currently unclear how these observations relate specifically to patients who underwent chest irradiation, however, several reports suggest that accelerated structural valve degeneration may occur (42, 43). It is unclear whether this effect is due to direct valvular damage (i.e., fibrosis and calcification, as is the case with the native valve), or due to other hematological causes that may also predispose to coronary plaque formation or increased risk of restenosis post-coronary intervention. This hypothesis is further strengthened by the observation that chemotherapy,

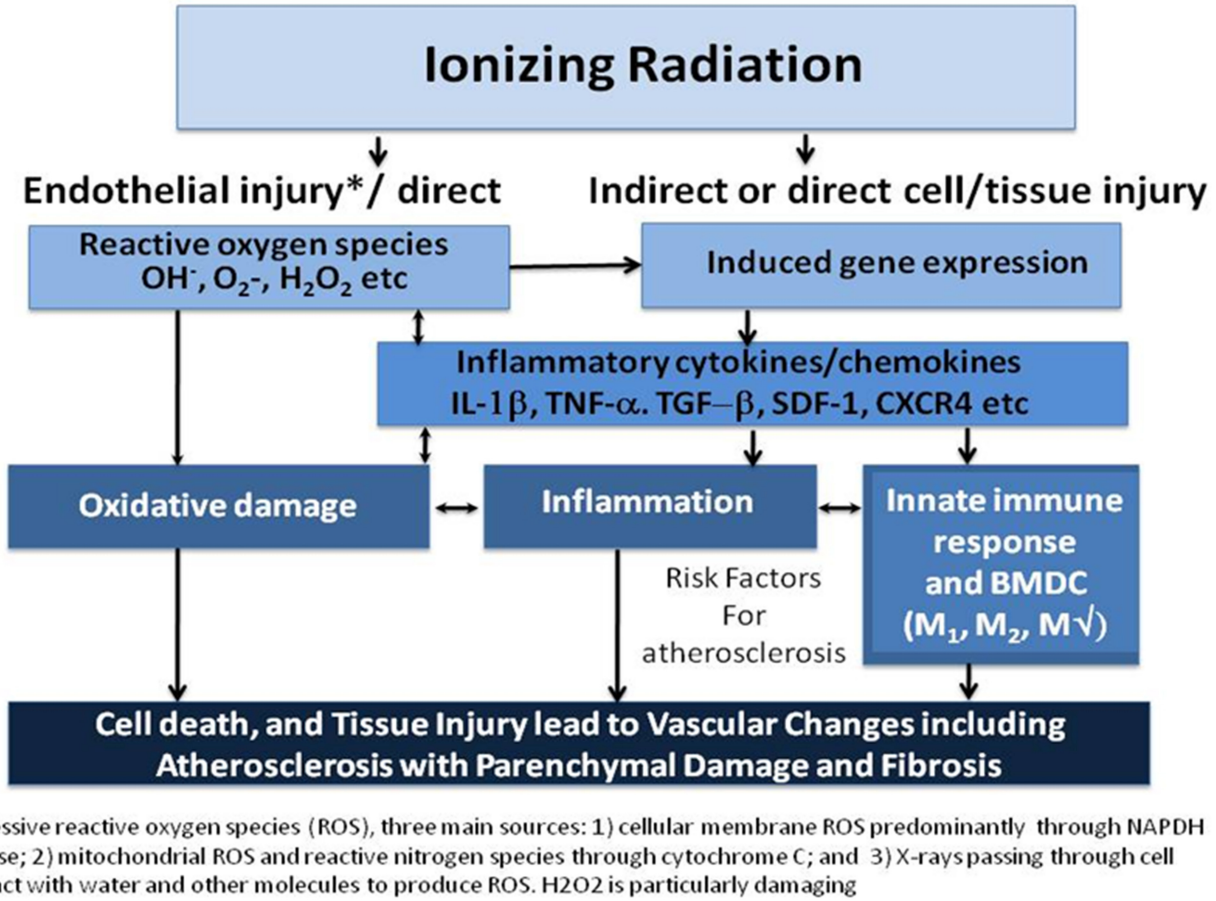

FIGURE 1 | Ionizing radiation causes cell death, both parenchymal and vascular, by multiple mechanisms. Historically, the direct cytotoxicity of radiation was the first identified pathway leading to tissue injury. More recently, another pathway involving inflammation has been identified. A third pathway has been studied in the last few years that implicates the innate immune response including bone marrow-derived cells (BMDC) and both M1, and M2 macrophage (MΦ) in resultant tissue damage. Arrows represent influence of one mechanism on another and suggest potential targets for interfering with the process. Cell death and tissue injury result in accelerated atherosclerosis over 1 to 2 decades that may also result in parenchymal injury to the myocardium and the valves resulting in fibrosis [Modified from (8)].

not only radiation therapy, may predispose to accelerated structural valve degeneration, highlighting the need for further research (43).

PREVENTION

Radiation therapy planning aims to minimize the volume of the heart irradiated as well as the radiation dose to the heart. Multiple strategies should be undertaken, including intensity modulated radiation therapy, breath-holding, image guided radiation therapy, and 4-dimensional imaging (44–46). While contemporary approach in radiation oncology has dramatically changed since the initial landmark studies, the impact of such an approach on minimizing cardiovascular risk has not been systematically studied and likely requires long term follow up.

In animal studies, the use of atorvastatin before radiation prevented vascular damage and promoted healing of radioactive injury wound (47, 48). In *in-vitro* studies, pravastatin demonstrated anti-inflammatory and anti-thrombotic effects on irradiated endothelial cells by inhibiting the overproduction of monocyte chemoattractant protein-1, IL-6, and IL-8, and by enhancing the expression of intercellular adhesion molecule-1 (49). Moreover, pravastatin down-regulated the radiation-induced activation of the transcription factor activator protein-1 but not of nuclear factor-kappa-B. In human, pravastatin limits the radiation-induced vascular dysfunction in the skin by decreasing interactions between leukocytes and endothelium and limiting the radiation-induced downregulation of eNOS (50). Finally, an inhibition by pravastatin of increased adhesion of leukocytes and platelets to irradiated endothelial cells was observed. Thus, statins may be considered in therapeutic strategies for the management of patients treated with radiation therapy. However, there are currently no randomized clinical trials that definitively measure the impact of statins on outcomes in RIVD. More robust evidence is required to assess the potential clinical benefit of statins in this setting.

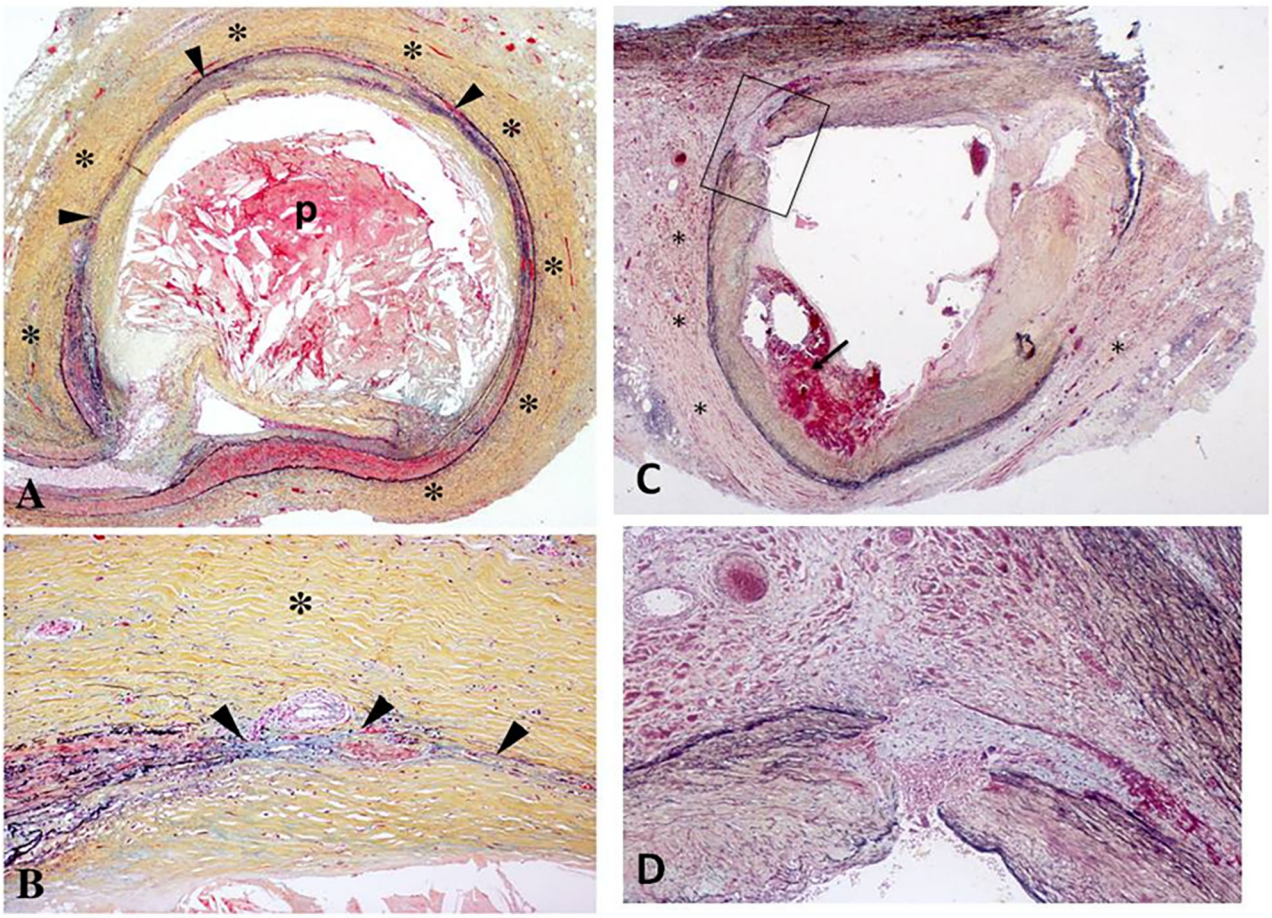

FIGURE 2 | (A,B) Histologic section of the left circumflex coronary artery from a 67-year-old patient who received radiation therapy for carcinoma of the lung 7 years prior to sudden death. Low power view **(A)** demonstrates severe adventitial fibrosis (*) and focally extensive destruction of the media (arrowheads) with intimal plaque (p) causing 75% luminal narrowing. The plaque consists mostly of necrotic core that is rich in cholesterol clefts. Note a markedly thickened adventitia (*) at high power **(B)** with medial destruction (arrowheads) [Reproduced with permission from (9)]. **(C,D)** Right coronary artery from a 62-year old man with mediastinal radiation therapy for Hodgkin's disease 25 years antemortem. At autopsy, there was 70% lumen area narrowing **(C)** with intraplaque hemorrhage (arrow), marked adventitial fibrosis (*), and focal destruction of the arterial media (arrowheads). The boxed in area in **(A)** is shown at higher magnification in **(B)**; note medial disruption (arrowheads) and replacement by smooth muscle cells in a collagenous matrix [Reproduced with permission from (14)].

SCREENING AND SURVEILLANCE OF RICAD

The most common causes of radiation to mediastinum include treatment for HL and breast cancer. Because of this, a disease of relatively young individuals with very favorable long-term prognosis, CAD, can become a real issue. Up to 3- to 4-fold increase in the risk of myocardial infarction due to coronary artery disease (CAD) has been observed, especially in HL survivors who had mediastinal irradiation or in combination with chemotherapy (51, 52). There is no consensus on the optimal timing at which screening should commence. Some have suggested that screening should be undertaken after 5 years of radiation therapy in patients older than 45 years and between 5 and 10 years for those younger than 45 years. A recent review of non-invasive screening modalities for CAD in HL survivors reported significantly limited diagnostic performance of exercise testing, with a sensitivity of 59% for significant CAD stenosis. Moreover, 25% of those patients subsequently developed symptomatic CAD within a follow-up duration of 6.5 years (53, 54).

Multi-slice CT coronary angiography (CTA) seems an attractive screening modality in this patient subgroup. Recently, high diagnostic accuracy of screening with computed tomographic coronary angiography (CTA) has been shown in asymptomatic patients at intermediate or high risk for CAD (55). Kupeli screened 119 childhood HL survivors of whom only 50% had received mediastinal radiotherapy (median dose 27.5 Gy) after a relatively short median follow-up period of 10 years. Abnormalities on CTA were found in 16%. In a recent

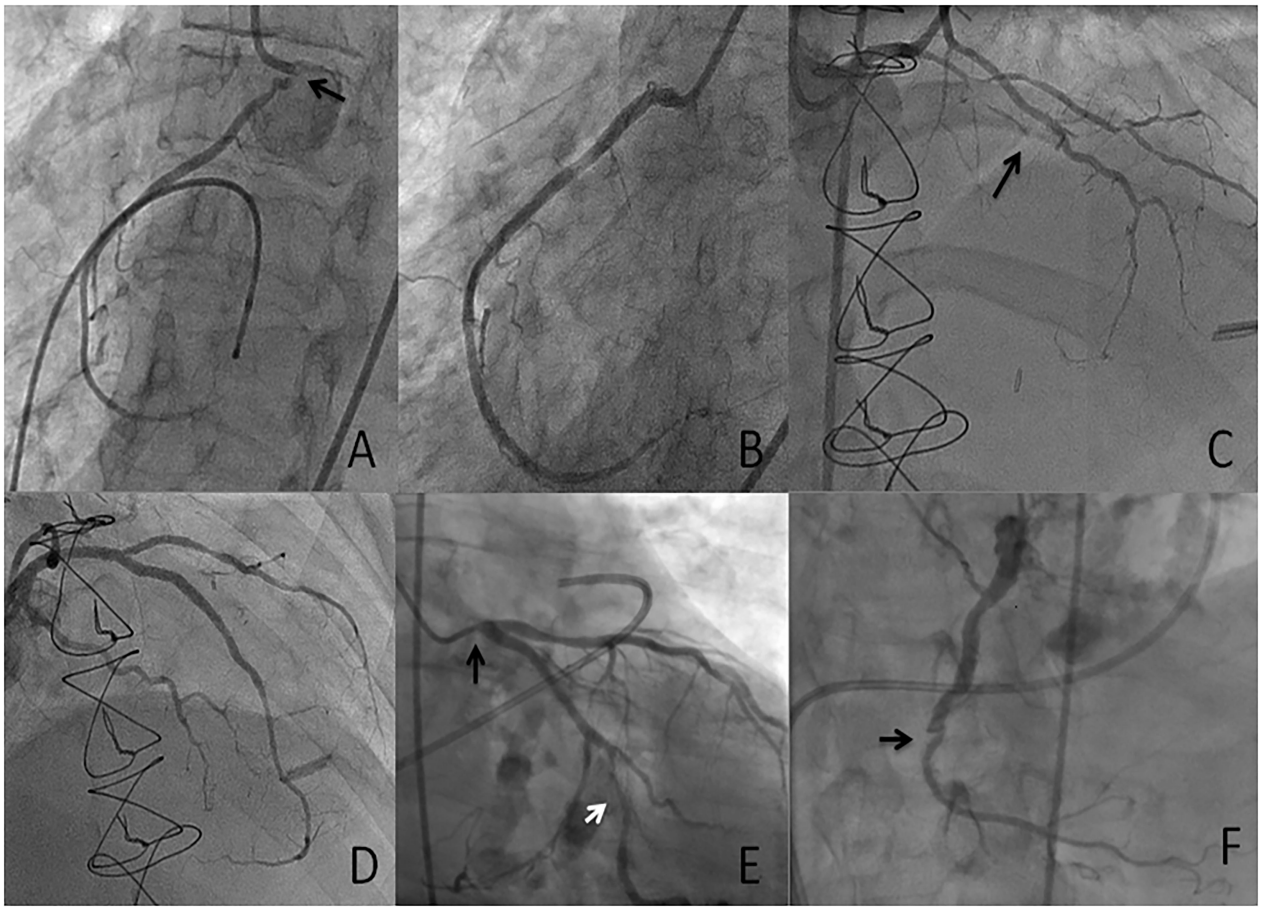

FIGURE 3 | Case presentation 1 **(A,B)** 53-year-old with unstable angina who received mantle radiation 45 years ago for Hodgkin's lymphoma. Severe ostial RCA (arrow) stenosis **(A)** successfully treated with PCI **(B)**. Case presentation 2 **(C,D)** 33-year-old with class III angina who received radiation 7 years ago for thymic carcinoma. Severe diffuse LAD disease (arrow) successfully treated with PCI. Case presentation 3 **(E,F)** 75-year-old with severe symptomatic aortic stenosis who received extensive mantle radiation for esophageal cancer 15 years ago. Diffuse obstructive atherosclerosis involving the ostial left main (**E**, black arrow), the obtuse marginal (OM) branch (**E**, white arrow) and chronic totally occluded right coronary artery \(RCA) (**F**, arrow). The patient was managed with transcatheter aortic valve replacement (TAVR) and PCI of the left main and the OM.

phase II trial of asymptomatic HL survivors, the diagnostic accuracy of CTA was evaluated in 48 patients (time since HL diagnosis 21 years). The prevalence of significant CAD (>50% luminal narrowing) on CTA was 20% ($N = 9$). Importantly, stress EKG exhibited very disappointing performance. The two patients with severe left main artery stenosis on CTA and coronary angiography showed no signs of ischemia during the ECG exercise test (56).

Given the limitations of traditional risk prediction tools and non-invasive modalities, asymptomatic nature of underlying CAD and high risk of subsequent events, patients with prior chest radiation at risk for RICAD must undergo aggressive screening for the presence of underlying CAD. CTA appears to be a very promising test, however, larger studies are needed to confirm the utility of CTA in this population (57) (**Figure 4**).

SCREENING AND SURVEILLANCE OF RIPAD

The timeline as to when to begin screening asymptomatic patients with a history of neck radiotherapy for carotid/subclavian artery disease appears to be dependent on several factors: (1) the type of malignancy (i.e., HL, head and neck malignancies); (2) the age of the patient at the time of treatment; and (3) other cardiovascular risk factors. Although older HL patients who underwent neck radiotherapy appeared to be of higher risk of stroke within a shorter period of time from treatment (around 5 years), patients who were treated at a younger age tended to manifest more subclavian or carotid stenosis after at least a decade of treatment. Retrospective studies of patients who underwent radiation therapy for head and neck malignancies consistently show a significant increase

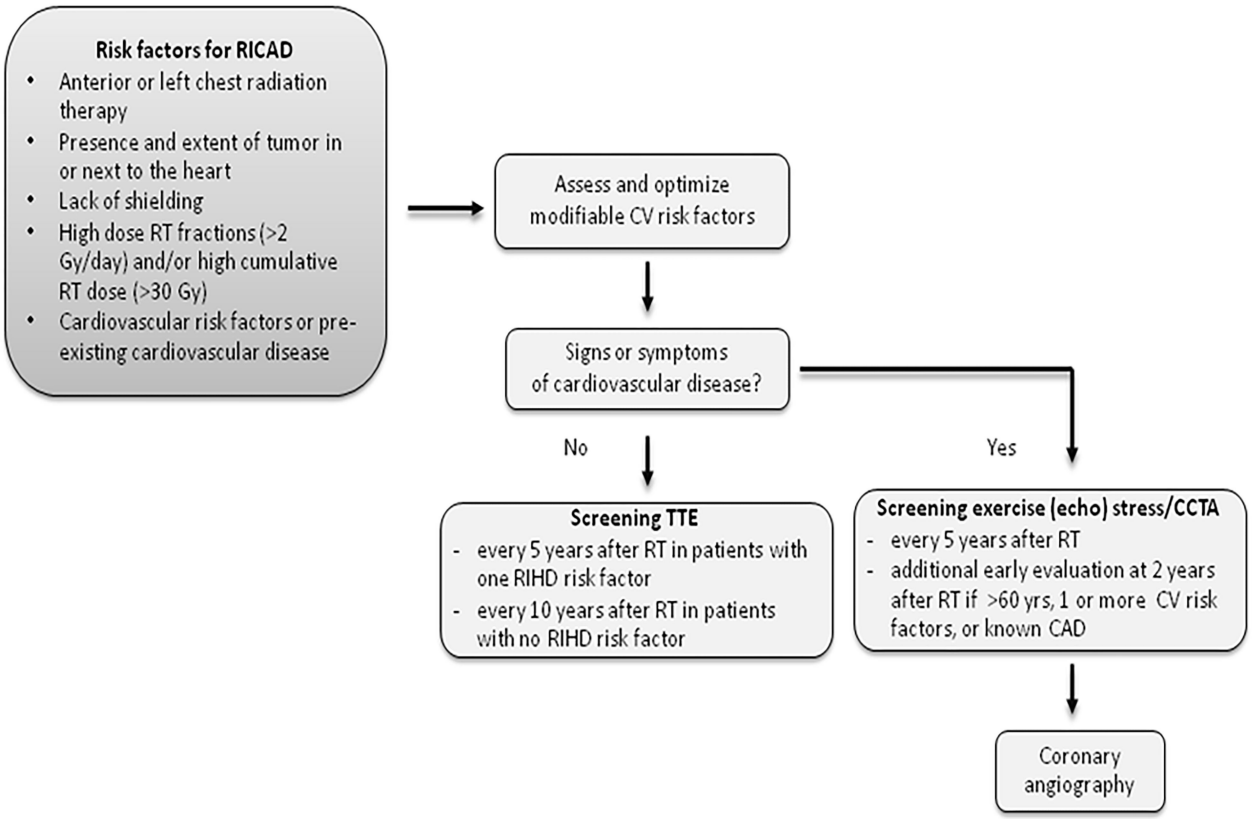

FIGURE 4 | Recommended screening for patients with RICAD. RICAD, radiation-induced coronary artery disease; RT, radiation therapy; CCTA, coronary computed tomography angiography; TTE, transthoracic echocardiogram.

in the risk of cerebrovascular events at 10 years, implying the need for more aggressive, earlier screening in asymptomatic survivors. Suggestions for screening include initial carotid duplex ultrasonography 5 years after radiation treatment, followed by annual ultrasonography, and then tailored to the patient's burden of disease (58–60).

The American Society of Echocardiography, in their 2013 Expert Consensus Statement for patients who have undergone radiation therapy, also mentions carotid artery disease as a long-term sequela of neck irradiation but does not provide recommendations on interval surveillance, other than carotid ultrasound screening in the setting of neurologic symptoms (61). Groarke et al. also suggests screening upon discovering the presence of a carotid bruit or neurologic symptoms and suggests annual surveillance if carotid disease is found that does not warrant intervention; however, data regarding optimal surveillance intervals are lacking (54).

For survivors of childhood/young adult cancer, the Children's Oncology Group Long-term Follow-Up Guidelines recommend that cancer survivors who received >/=40 Gy to the neck region undergo annual neurologic examination and assessment for diminished carotid pulses and/or carotid bruits, with diagnostic imaging of the carotid arteries as recommended. It was also advised to consider a baseline carotid duplex ultrasonography 10 years after radiotherapy. For survivors who received >/=18 Gy of cranial irradiation, an annual neurologic examination is recommended, with brain MRI with diffusion-weighted imaging and MR angiography (62).

For survivors of head and neck tumors, the American Society of Neuroimaging advises screening for carotid artery disease in patients who have received unilateral or bilateral RT at 10 years after treatment. This recommendation was based on studies from patients who received doses >45 Gy, but they acknowledged that no clear relationship has been seen with dose and duration of radiation treatment to validate specific radiation dose information to determine appropriate dose cutoffs for screening. The interval between repeat imaging was unknown, and screening for preexisting carotid artery stenosis prior to radiation treatment was not recommended (63).

More aggressive screening measures are warranted overall in the setting of radiation exposure in the abdomen and lower extremities although the timeline and progression to clinically significant symptoms are less defined. Regardless, patients who experience claudication with a history of abdominal radiation exposure should undergo arterial duplex ultrasound screening and subsequent further imaging (i.e., CTA, MRA) if needed,

while the indication to intervene should also be accordance with established guidelines.

CLINICAL MANIFESTATIONS

Coronary Artery Disease

The latency period between RT and CAD depends on the radiation dose and volume. For doses above 30–35 Gray, RIHD may occur within a year or two of exposure, with the risk increasing with higher radiotherapy dose, younger age at the time of RT, and the presence of traditional atherosclerotic risk factors (51, 52, 64–67). At lower doses, the typical latency period is much longer and is often more than a decade. Survivors of breast cancer and HL are at a greater risk of RICAD as they have a relatively longer cancer specific survival.

In the largest study to date, 2168 breast cancer survivors undergoing radiation therapy were studied in Denmark (64). Patients with major adverse coronary events (myocardial infarction, coronary revascularization and death from ischemic heart disease) were compared to controls. The mean radiation dose to the heart was 4.9 Gy (6.6 Gy for left breast and 2.9 Gy for right breast). There was an exponential relationship between mean radiation dose and major adverse cardiovascular events (MACE). MACE increased by 7.4% for each increase of 1 Gy radiation to the heart with no apparent threshold below which there was no risk. History of previous CAD (relative risk [RR] 6.7), CAD risk factors (RR 1.96), diabetes, smoking and other vascular disease were independently associated with MACE risk. The radiation-related increase in the risk of major coronary events began within the first 5 years after exposure (44% MACE events occurred in the first 10 years of cancer diagnosis, 33% between 10–19 years and 23% 20 years or more) (64).

Similarly, early increases in the risk of myocardial infarction have been reported in studies of patients with HL who received RT, with the risk persisting 25 years and longer. Since HL happens at younger ages and the cumulative radiation dose is higher, the RR of CAD and MACE is proportionately higher compared to older patients (51, 52, 65, 66). The highest risk has been reported in patients aged <25 years at the time of RT, among which the 30-year cumulative rates for any cardiovascular disorder or myocardial infarction are 34.5 and 12.9%, respectively (52). In one large study of 2,232 survivors of disease (mean age 29 years at treatment) the risk of death from heart disease after a mean follow-up of 9.5 years was 3.9% (66). Of the 88 cardiac deaths, 55 were due to myocardial infarction. The average age at death from infarction was 49 years, with 22 deaths in patients <45 years of age. Another large, retrospective single-center study of 415 consecutive patients treated with mantle radiation therapy for HL between 1962 and 1998 found an actuarial incidence of CAD (defined as a history of documented myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, or more than 75% diameter stenosis on coronary angiography or autopsy) to be 3% at 5 years, 6% at 10 years, and 10% at 20 years. The RR for cardiac death was highest for patients who received a total radiation dose to the chest of >30 Gy and were <20 years of age at the time of their treatment (67). Finally, a Dutch retrospective cohort study of 2,524 Hodgkin's lymphoma patients, with a median age of 27.3 years at the time of diagnosis, showed a significant 40-year cumulative incidence of cardiovascular disease of 50% in patients who had undergone chemotherapy and/or radiotherapy. The presence of mediastinal radiotherapy increased the risks of coronary heart disease (HR 2.7, 95% CI 2.0–3.7), valvular heart disease (HR 6.6, 95% CI 4.0–10.8), and heart failure (HR 2.7, 95%, CI 1.6–4.8) (68).

Patients with RICAD are often younger than those with typical atherosclerotic CAD. In a study evaluating the long-term outcomes of Hodgkin's lymphoma patients by Hancock and colleagues, 69% of patients who suffered a fatal MI because of radiation-induced CAD had no prior symptoms of angina, heart failure or known CAD (69). In older patients, the clinical presentation is similar to atherosclerotic CAD presentation, most often with stable angina (70), acute coronary syndromes or heart failure. Additionally, given the wide spectrum of cardiovascular manifestations from radiation to the heart including pericardial disease (effusion/constriction), valvular heart disease, cardiomyopathies and conduction abnormalities, presence of these should prompt evaluation for suspected RICAD. The location of RT may impact the phenotype of CAD. Tagami et al. demonstrated on a CTA-based study that RT-treated left breast cancer patients were at significantly higher risk of CAD compared to a matched group of right breast cancer patients (28).

The evaluation for suspected CAD in this group of patients should follow the American College of Cardiology guidelines, although atypical symptoms and premature disease should alert the physician to conduct more frequent testing (71). Importantly, as a large proportion of CAD in those patients includes ostial left main and multivessel disease, stress perfusion imaging may result in false negative results on account of balanced ischemia (72). Because of the known limitations of traditional non-invasive functional stress testing, coronary angiography should be considered if there is high clinical suspicion for symptoms, and/or functionally significant disease due to RICAD.

Radiation-Induced Peripheral Arterial Disease

Peripheral arterial disease (PAD) remains a concern for patients who receive extra-cardiac treatments, although their sequelae and complications are less reported than those of CAD.

Stroke and Carotid Artery Disease After Head and Neck Radiation

In patients with head and neck tumors (laryngeal carcinoma, pleomorphic adenoma, and parotid carcinoma), Dorrestejin et al. demonstrated an increased risk (RR 5.6) for ischemic stroke in 367 patients under the age of 60 (median age of 49.3 at the time of treatment) who received RT (dose range 50–66 Gy) as part of their treatment (73). All subtypes of head and neck malignancies were associated with a risk in ischemic stroke, and the RR of stroke also increased with concurrent risk factors such as diabetes and hypertension. In Dorrestejin's study, the 10-year relative risk for a CVA event was 10.1 (95% CI 4.4–20.0), and the 15-year cumulative risk 12.0% (95% CI 6.5–21.4%). Radiation for head and neck tumors often utilizes a higher dose than that for HL, with a mean of 60.6 Gy in one study, and may be as

high as 70–80 Gy (59, 74). Dorrestejin et al.'s patient population had received a range of doses from 50 to 66 Gy, while another study with a dose range of 40–50 Gy did not find a statistically significant increase in stroke (75, 76). Haynes et al. did not find a dose effect for ischemic stroke in patients with history of head and neck irradiation, however follow-up was only 2 years (much shorter than the observed time to symptoms after radiation), and the dose range (59.4–76.8 Gy) was likely too narrow to detect a statistical effect. Seventy-one patients with nasopharyngeal carcinoma (mean age of 53.6 years) with a history of RT (mean dose of 56.4 Gy) were compared with a control group which showed an increased prevalence of 79% for carotid artery stenosis as diagnosed by duplex carotid ultrasound compared to 21% in the control group who had similar cardiovascular risk factors. Time to diagnosis from treatment ranged from 4 to 20 years (77).

An analysis of 6,862 patients greater than the age of 65 from the Surveillance, Epidemiology and End Results (SEER)-Medicare cohort who were diagnosed with non-metastatic head and neck cancer between 1992 and 2002 found a higher 10-year incidence of cerebrovascular events in patients treated with RT alone vs. those treated with surgery and RT, and those treated with surgery alone (34% vs. 25% vs. 26%, $p < 0.001$). No difference was found for surgery plus RT vs. surgery alone, and patients with RT had no increased cardiac risk compared to other treatment groups (78).

Data regarding the contribution of RT toward stroke risk in patients undergoing RT for pituitary adenomas is conflicting, although it overall appears to be higher compared to age-matched controls, regardless of the use of adjuvant RT. In a total of 462 patients with pituitary adenomas undergoing surgery with or without RT (median age of 46 years in the RT cohort), a higher incidence of stroke was seen compared with the general population after a median time of 9 years of follow-up. However, there was no association of increased risk of stroke with postoperative radiotherapy (median of 45 Gy). Major stroke risk factors included preexisting coronary and/or peripheral vascular disease and hypertension (79). However, different findings were seen in another study of 806 patients (mean age of 48.3 years with mean follow up time of 10.0 years) with the RT arm ($n = 456$) receiving a mean dose of 46.2 Gy. A higher incidence of cerebrovascular events was seen in men who underwent RT compared to those who did not (hazard ratio 2.99, 95% CI 1.31–6.79); no significant difference was seen in women who underwent RT. There was also no association of RT with mortality (80).

In adult survivors of childhood/young adult cancers, an analysis of the Childhood Cancer Survivor Study (CCSS), a cohort of long-term childhood cancer survivors diagnosed between 1970 and 1986, revealed an overall 10-fold higher relative risk for stroke in the cohort subjects compared to their siblings as controls. Within the CCSS, 27.4% reported history of brain radiation and up to 21.8% history of chest irradiation. Conditions with elevated long-term stroke risks were acute lymphoblastic leukemia (ALL), brain tumors, and Hodgkin's lymphoma (81). Mean cranial radiation doses of >/= 30 Gy were associated with an increased stroke risk in both leukemia and brain tumor survivors in a dose-dependent fashion (82). Within the CCSS, Hodgkin's disease patients who suffered a cerebrovascular event received a median mantle radiation dose of 40 Gy (82).

In patients who have received cranial radiation for disease states such as brain tumors, HL, and/or leukemia, the incidence of vascular related sequelae is not well-defined. For primary brain tumors located in the suprasellar region, high doses of RT (>/= 45 Gy) may be needed for effective treatment doses. However, a variety of cerebrovascular sequelae have been described, such as narrowing of the internal carotid arteries to form a moyamoya-like state, leading collateral blood vessel formation to supply flow to hypoperfused areas of the brain. Vascular malformations can also develop, including venous based cavernous malformations, aneurysms, and telangiectasias. Intracranial aneurysms are rare complications from radiotherapy but can be life-threatening. Small vessel vasculopathy can also develop, that can lead to calcification of the basal ganglia, leading to symptoms such as complicated migraine-like symptoms that can also present with stroke-like findings; this finding is referred to as Stroke-Like Migraine after Radiation Therapy (SMART) syndrome (83, 84).

For glottis tumors requiring neck radiotherapy, an analysis of 1,413 patients who were >66 years of age showed a high 10-year risk of cerebrovascular disease of up to 56.5% vs. 48.7% who received surgery alone without radiation, which was not statistically significant between the two groups but showed an overall high rate of cerebrovascular events likely due to preexisting comorbidities (85). The elapsed time interval after radiation is the strongest predictor of cerebrovascular events (86).

Supraclavicular and Mediastinal Radiation

For patients with a history of supraclavicular and mediastinal radiation, several malignancies have been associated with a higher risk of cerebrovascular events and carotid artery disease, particularly lymphoma and head and neck malignancies. A retrospective analysis of 415 patients with a history of mantle field radiation for HL showed a 7.4% prevalence of carotid and/or subclavian artery disease after a median follow-up time of 17 years. For those who suffered a TIA or stroke, the median age when undergoing radiotherapy was 51 years and the median time from therapy to event was 5.6 years (67). On the contrary, the median age of patients with isolated subclavian or carotid artery stenosis was 20 years at the time of therapy and the median time from therapy to event was 21 years. The median cumulative low-cervical radiation dose for patients who developed subclavian stenosis and carotid artery disease was 44 and 38 Gy, respectively (67). Another retrospective study of 2,201 survivors of HL treated with mantle field radiation therapy before the age of 51 years showed at a median follow up of 17.5 years an incidence ratio of stroke of 2.2 (95% CI 1.7–2.8) and 3.1 for TIA (95% CI 2.2–4.2). Radiation to the neck and mediastinum was an independent risk factor for ischemic cerebrovascular disease (HR 2.5, 95% CI 1.1–5.6) 30 years after treatment in addition to hypertension, diabetes and hypercholesteremia while obesity and smoking were not (87).

A retrospective analysis of radiation induced carotid artery disease from mostly laryngeal/nasopharyngeal cancer and lymphoma survivors showed a higher incidence of plaque that was ulcerative, mobile, and vulnerable by MRI and ultrasound

imaging compared to control subjects who did not receive radiation. There was also a higher cerebrovascular event rate in patients who underwent carotid artery stenting (CAS) vs. carotid endarterectomy (CEA) (88). Another prospective cohort studied 42 patients (mean age 53 years) with a history of head and neck cancer survivors who underwent radiotherapy (mean dose to common carotid and internal carotid arteries of 57 and 61 Gy, respectively) and underwent carotid MRA imaging at a mean follow up of 6.8 years. Significantly more vessel wall thickening (>/=2 mm) was seen in irradiated vs. non-irradiated carotid arterial segments (58% vs 27% in common carotid arteries, 24% vs. 6% of internal carotid arteries, $p < 0.05$) with no difference in signal intensities of the vessel walls (89). An overall meta-analysis of case-control studies and randomized clinical trials on neck-directed radiation-induced disease of the extracranial carotid arteries demonstrated a statistically significant difference in overall stenosis rate in patients who received radiotherapy than controls, with a pooled risk ratio of 4.38 (95% CI 2.98–6.45, $p < 0.00001$) and severe stenosis with a pooled risk ratio of 7.51 (95% CI 2.78–20.32, $p < 0.0001$) (90).

Symptomatic axillary artery stenosis requiring percutaneous intervention and manifesting more than 10 years after radiation therapy for breast cancer has also been reported (91).

Abdominal and Pelvic Radiation

RIPAD has been reported in patients who received abdominal radiation for lymphoma (92, 93), abdominal sarcomas (94), as well as for genitourinary malignancies (95). Clinical presentations have ranged from acute thrombotic occlusion to chronic claudication. Radiation induced renovascular hypertension has been reported in HL (92, 93), and severe iliac peripheral vascular disease has been documented in patients who received RT for cervical cancer with preoperative external radiotherapy ranging from 40 to 45 Gys (not including vaginal brachytherapy) presenting anywhere from 1 to 47 years after exposure (95).

Radiation-Induced Venous and Lymphatic Disease

There are few data on radiation-induced venous and lymphatic disease, mostly limited to case reports. Radiation-associated venous endothelial injury predisposing to thrombosis has been hypothesized, with few case reports describing upper extremity deep venous thrombosis years after chest irradiation (96–98). However, a causal relationship is difficult to demonstrate, as cancer patients and survivors are already at increased risk of vascular thrombosis due to the pro-thrombotic state of malignancy, independently of radiation therapy. Venous stenosis imposing endovascular stenting, as well as fibrosis without thrombosis, have also rarely been described (99–101).

Lymphedema is a well-described complication of radiation therapy. However, there are few data on the mechanisms and long-term clinical implications of this complication. Histologic studies suggest that radiation induces a loss of capillary lymphatics and a dose-dependent increase in lymphatic endothelial cells apoptosis, leading to delayed fibrosis (102, 103). Damage to the pulmonary lymphatic vasculature has been described even after a single dose of radiation, which may lead to delayed lung repair (103).

TREATMENT CONSIDERATIONS FOR RICAD

Medical treatment for RICAD should follow the same secondary prevention strategies that are recommended for traditional atherosclerotic CAD per ACC/AHA guidelines, including aspirin 81 mg per day (in the absence of contraindications), lifestyle interventions and pharmacotherapies to achieve target LDL, blood pressure and blood sugar goals (104). While there is significant paucity of data on the role of preventive therapies in patients with RICAD, it only seems intuitive to aggressively institute preventive measures in patients at risk for RICAD. Long term, prospective trials are needed in looking at the primary prevention impact of aforementioned pharmacologic strategies of patients exposed to radiotherapy. For symptomatic patients and asymptomatic patients with high risk anatomy (and or large ischemic burden) revascularization should be undertaken.

Role of Percutaneous Coronary Intervention

The role of percutaneous coronary intervention (PCI) with drug eluting stents (DES) may be a viable and potentially durable revascularization strategy for flow limiting RICAD (105–107). However, there have been few studies reporting outcomes (108–111).

In one of the earlier studies, 15 lymphoma patients with RICAD undergoing bare metal stent (BMS) implantation were compared to 7 lymphoma patients without previous radiation and over 12,000 controls undergoing BMS implantation (108). On follow up angiography at 6 months, the authors noted a very high rate of angiographic in-stent restenosis (>50% diameter stenosis) in the RICAD arm compared to others (85.6% vs. 17% vs. 25%). Two thirds (66%) of patients in the RICAD arm underwent repeat PCI compared to 14% and 16% in the other two groups, respectively. Importantly, there were no adverse events in the RICAD group within the first 30 days. At 1 year, there was no mortality reported in the RICAD group vs. 4.4% in the control arm. This study demonstrated a very high incidence of angiographic restenosis with the use of BMS in RICAD patients (108). It is unclear how many of these were physiologically significant and clinically relevant as there was only one myocardial infarction at 1 year in the RICAD group. DES may be the preferred modality in such patients, although clinical data are lacking.

In another case control study comparing 41 patients with RICAD (68% breast cancer treated) with 82 control patients showed an excess of all cause (39% vs. 12%) and cardiac mortality (12% vs. 3.7%) in RICAD patients compared to controls at a mean follow up of 5+/−2 years after stenting (80% BMS). There was no difference in acute myocardial infarction (4.9% vs. 3.7%) during the follow up period (109).

The effect of more recent radiation before stenting, or radiation after stenting is unknown. Liang et al. (110) studied

115 patients treated with EBRT (external beam radiation therapy) for a median of 3.6 years after stenting (group A) and 45 patients treated with EBRT a median 2.2 years before stenting (group B), demonstrating that long-term mean target lesion revascularization rates in group A (3.2 vs. 6.6%; $p = 0.31$) and group B (9.2 vs. 9.7%; $p = 0.79$) were similar to rates in corresponding control patients (group A: 1,390 control patients; group B: 439 control patients). The authors concluded that thoracic EBRT is not associated with increased stent failure rates when used a few years before or after PCI, and a history of PCI should not preclude the use of curative thoracic EBRT in cancer patients or vice versa. Sixty percent of patients in group B had DES. Given the median duration of 2.2 years after EBRT, it remains unclear, if this was indeed RICAD. Nevertheless, these results do provide some reassurance that radiation therapy in itself does not increase the risk of stent failure (although data are not available for early radiation after stenting) and PCI could be considered as a viable revascularization option.

Endovascular treatment for radiation-induced venous stenosis has also been reported, although data are limited to case reports (101).

Role of Surgical Revascularization

Cardiac surgery in the previously radiated thorax is associated with higher rates of post-operative complications, as well as short- and long-term mortality (32, 112, 113). Major contributing factors include extensive scar tissue and adhesions around the heart, lungs and pericardium from previous radiation that make isolation and harvesting of grafts difficult, fragility and disease of LIMA, presence of concomitant valvular lesions, pericardial constriction (often requiring concomitant corrective surgeries at the time of CABG), left ventricular dysfunction and poor pulmonary reserve (114–121). Importantly, surgeons have historically shied away from using LIMA grafts, although the evidence for such practice is conflicting (119, 120). Furthermore, the discrepancy in the use of LIMA as well as surgical outcomes are variable depending on the extent of previous thoracic radiation (mortality (in hospital and at 4 years) 2.4%/20% in tangential/limited radiation (breast cancer) vs. 13%/43% in extensively radiated patients (HL/thymoma) (122). Studies reporting favorable outcomes with use of LIMA predominantly enrolled patients with previous breast surgery (limited tangential radiation) (121). If surgical revascularization is considered for multivessel RICAD, then angiography of the LIMA and/or RIMA should be done in mediastinal radiation patients to ensure patency of these vessels as potential graft conduits.

A recent study from the Cleveland Clinic, evaluated 173 patients with radiation heart disease (75% women; age, 63 ± 14 years) undergoing cardiac surgery (largest cohort to date) and 305 comparison patients (74% women; age, 63 ± 14 years) (123). In the RT group, the vast majority had prior breast cancer (53%) and HL (27%), and the mean time from radiation was 18 ± 12 years. Only one third of patients in either group had isolated single-valve or coronary bypass procedure (only 15% patients underwent isolated CABG); the rest were combination procedures (CABG with valve replacements/repair). During a mean follow-up of 7.6 ± 3 years, a significantly higher proportion of patients in the radiation group died compared to controls (55% vs. 28%; log-rank $P < 0.001$). Furthermore, even in patients undergoing isolated CABG mortality was significantly higher compared to controls (46% vs. 28%). On multivariable Cox proportional hazard analysis, the presence of radiation heart disease (hazard ratio, 2.47; 95% confidence interval, 1.82–3.36), increasing EuroSCORE (hazard ratio, 1.22; 95% confidence interval, 1.16–1.29), and lack of β-blockers (hazard ratio, 0.66; 95% confidence interval, 0.47–0.93) were associated with increased mortality (all $p < 0.01$). Based on these findings, the authors recommended alternate approaches to RICAD including percutaneous coronary and or valvular approaches.

CLINICAL DECISION MAKING

Generally, patients with RICAD should undergo PCI per ACC/AHA guidelines and appropriateness criteria. Given the proximal location of RICAD lesions and the high risk of stent failure with BMS, DES are preferred. For patients with complex RICAD, a multidisciplinary approach involving the "heart team" and oncologist is important for optimal clinical decision making. Depending on local surgical and interventional expertise, surgical risk patients may be amenable to percutaneous or even hybrid approaches. Totally percutaneous approaches for valvular heart disease and CAD may be appropriate. Isolated LM disease has comparable or even superior outcomes than CABG. Current guidelines provide a Class IIa (Level of Evidence B) recommendation for PCI of left main ostial or shaft disease when it exists in isolation or in combination with 1-vessel disease. Our team has recently published an expert consensus statement regarding special consideration of cardio-oncology patients in the cardiac catheterization laboratory (124).

Treatment Considerations for RIPAD

In the era of percutaneous approaches with distal embolization protection showing favorable outcomes compared to surgical intervention for significant carotid artery disease with regards to MACE (CREST, SAPPHIRE, Gurm-SAPPHIRE), multiple case series have shown favorable outcomes in percutaneous carotid artery stenting for radiation induced carotid artery stenosis (125–128). However, these studies were small and localized to specific institutions, where the level of competency may vary. Carotid stenting in several case series have shown low rates of stroke—Al-Mubarak et al. reported that 1 in 14 patients had a stroke post-stenting (129) and Ting et al. reported 1 stroke out of 16 patients that later led to death (126). A meta-analysis comparing carotid artery stenting and carotid endarterectomy (CEA) for radiation induced carotid artery disease showed similar pooled rates of perioperative cerebrovascular events (3.9% for stenting vs. 3.5% for endarterectomy), although late outcomes favored CEA. There was a higher risk for cranial nerve injury after CEA but higher rate of restenosis after carotid artery stenting (130). The major limitation of this review was the lack of randomized studies, as well as variation in patient selection and small sample sizes. A recent study comparing CAS in patients with radiation therapy-associated carotid stenosis showed similar composite 30-day stroke, myocardial infarction, and mortality (XRT: 2.6% vs.

non-XRT: 3.9%; P = NS.) and 50% restenosis rates (XRT: 9.4% vs. non-XRT: 8.6%; P = NS) compared to CAS performed in patients with no radiation therapy (131). While a randomized trial comparing the two strategies is warranted, ultimately the individual institutional experience must be put into account when determining the most optimal interventional strategy for radiation induced carotid artery disease, and should overall be in accordance with ACC/AHA/SCAI guidelines.

For RIPAD, because of the concern of concurrent accelerated fibrosis and associated elastic recoil has led to the idea that stenting as opposed to percutaneous angioplasty alone is more effective, particularly for iliofemoral disease from RT (94, 132). Percutaneous transluminal angioplasty with or without stent placement was performed with success in radiation induced renal artery stenosis (92, 93). Lower extremity bypass has also been employed showing efficacy in small case series and case reports (94, 95). However, data is overall extremely limited due to the overall lack of peripheral vascular disease related cases in the literature, and this may represent underreporting.

Medical management for patients with significant risk factors (as with cardiovascular disease) should be on aggressive antiplatelet and statin therapy as well as antihypertensive therapy as needed. It is essential for each institution to weigh the risks and benefits when determining surgical vs. percutaneous approaches in a multidisciplinary fashion amongst interventional cardiologists, interventional radiologists, and vascular surgeons. In the absence of randomized controlled trials, recommendations regarding surgical vs. percutaneous management of RIPAD should be individualized based on the "vascular team" consensus.

CONCLUSION

As the population of cancer survivors is increasing with more effective cancer therapies, RIHD emerged as an important component of radiation cardiotoxicity. RICAD and RIPAD should be screened, diagnosed, and promptly managed to assure better quality of life and improved survival rates. Collaboration between cardiologists and hematologists/oncologists is of prime importance. Most data on RIVD is derived from case series and single-center studies vulnerable to selection bias, from institutions with different strategies and levels of experience in addressing RIVD. The decision of endovascular vs. surgical management of RIPAD should be individualized based on patient factors, as well as institutional experience. Further research via focused randomized controlled trials is needed to determine the optimal prevention, screening, and management methods.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
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Machine Learning-Augmented Propensity Score Analysis of Percutaneous Coronary Intervention in Over 30 Million Cancer and Non-cancer Patients

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Background: It is unknown to what extent the clinical benefits of PCI outweigh the risks and costs in patients with vs. without cancer and within each cancer type. We performed the first known nationally representative propensity score analysis of PCI mortality and cost among all eligible adult inpatients by cancer and its types.

Methods: This multicenter case-control study used machine learning–augmented propensity score–adjusted multivariable regression to assess the above outcomes and disparities using the 2016 nationally representative National Inpatient Sample.

Results: Of the 30,195,722 hospitalized patients, 15.43% had a malignancy, 3.84% underwent an inpatient PCI (of whom 11.07% had cancer and 0.07% had metastases), and 2.19% died inpatient. In fully adjusted analyses, PCI vs. medical management significantly reduced mortality for patients overall (among all adult inpatients regardless of cancer status) and specifically for cancer patients (OR 0.82, 95% CI 0.75–0.89; $p < 0.001$), mainly driven by active vs. prior malignancy, head and neck and hematological malignancies. PCI also significantly reduced cancer patients' total hospitalization costs (beta USD$ −8,668.94, 95% CI −9,553.59 to −7,784.28; $p < 0.001$) independent of length of stay. There were no significant income or disparities among PCI subjects.

Conclusions: Our study suggests among all eligible adult inpatients, PCI does not increase mortality or cost for cancer patients, while there may be particular benefit by cancer type. The presence or history of cancer should not preclude these patients from indicated cardiovascular care.

Keywords: PCI - percutaneous coronary intervention, cancer, cardio-oncology, onco-cardiology, disparites, machine laerning

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HIGHLIGHTS

This is a nationally representative multicenter comprehensive analysis of inpatient mortality and total costs of PCI in all eligible hospitalized patients with and without cancer (including sub-group analysis by CAD, cancer by primary organ site, active vs. prior cancer, and ACS). Our analysis is the first in this population to suggest a significant and independent inpatient mortality and cost benefit for PCI vs. medical management particularly for cancer patients (shown both with propensity score adjusting for the likelihood of undergoing PCI among all inpatients and within CAD patients alone), while suggesting there may be a unique cancer and coronary artery disease interaction that is seen in our analysis with certain cancer types having more pronounced mortality benefit compared to others. This study suggests that PCI is safe for cancer patients regardless of their primary malignancy type, active or prior malignancy status, and ACS status.

INTRODUCTION

Cardiovascular diseases and cancer are the most prevalent chronic diseases and are the leading causes of morbidity and mortality in the world; specifically, one in six deaths and an estimated total of 9.6 million deaths in 2018 were attributable to cancer (1–3). Cardiovascular diseases and several cancer types share similar modifiable risk factors: high body mass index, low fruit and vegetable intake, lack of physical activity, and tobacco and alcohol use (4–7). Cancer itself is a pro-inflammatory and hypercoagulable state that increases the risk of cardiovascular events (4, 8–14). Certain primary malignancies are more likely than others to be associated with CAD, either due to shared risk factors or because their required treatments are associated with accelerated atherosclerosis (4, 5, 15–17). Aside from the clinical impact, the economic impact of cancer also is increasing with the United States' annual direct medical costs (i.e., the total of all healthcare expenditures) for cancer totaled over $80 billion (7, 18).

Further cancer patients with comorbid CAD are less likely to be treated with percutaneous coronary intervention (PCI) compared with the general population (9, 19) as they present with higher risk of complications from PCI and increased frailty (20–24). This risk is more pronounced in specific primary malignancies (i.e., lung cancer) and with the presence of metastases (20). With improved patient survival from novel cancer treatments, as well as the parallel increase in the safety of interventional procedures, the use of PCI in patients with comorbid cancer has recently been revisited (9, 20, 21, 25–32). This recent Nationwide Inpatient Sample offers an opportunity to evaluate the impact of current (with and without metastatic disease) or historical cancer diagnosis on clinical and economical outcomes (cost and length of stay). We sought therefore to conduct the first nationally representative analysis of PCI vs. no PCI among all CAD inpatients with and without cancer and among all available cancer types for mortality and cost using machine learning-augmented propensity score analysis including with racial and income disparity analysis.

METHODS

Study Design

We sought to conduct the first nationally representative analysis of PCI vs. no PCI among all CAD inpatients with and without cancer and among all available cancer types for mortality and cost using machine learning-augmented propensity score analysis including with racial and income disparity analysis This study is thus a multi-center analysis of inpatient mortality (primary endpoint) and total costs (secondary endpoint) among all eligible hospitalized adults; it assessed the association among the endpoints and PCI (yes/no) for acute coronary syndrome (ACS, including unstable angina/including non-ST segment elevation myocardial infarction [UA/NSTEMI] and STEMI) and PCI and cancer (yes/no overall, including overall and comparatively by primary organ site). To reduce confounding bias in this non-randomized studies, the above endpoints were assessed in the above sub-group stratified analyses to facilitate result interpretation. The 2016 NIS dataset was selected for this study because it is the latest and best reflects current clinical trends in PCI use. Study inclusion criteria were all NIS hospitalizations for adults 18 years or older during 2016. This study used de-identified data and was conducted according to the ethical principles in the Declaration of Helsinki.

Subjects undergoing PCI were identified by the ICD-10 procedure codes of 00.66 (percutaneous transluminal coronary angioplasty), 36.06 [insertion of non-drug-eluting coronary artery stent(s)], or 36.07 [insertion of drug-eluting coronary artery stent(s)]. HCUP tools such as the Clinical Classification Software, which had been used prior to the NIS 2016 dataset for such purposes as classifying cancer (e.g., by primary type, current vs. historical), were not used in this study because they were found by HCUP as a beta version to be unreliable when applied to the 2016 dataset's ICD-10 data.

Data Source

The data source for this study was the 2016 NIS for hospital discharges. The NIS is largest all-payer inpatient dataset in the nation, sponsored by the US Department of Health and Human Services' Agency for Healthcare Research and Quality and maintained within the Healthcare Cost and Utilization Project (HCUP). The NIS began in 2004 with data collection from select hospitals and expanded in 2012 to encompass discharge data from all HCUP participating hospitals. In 2016, the NIS data coding adopted the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). The NIS currently accounts for ∼1 in 5 discharges from all community hospitals in the United States. To reduce sampling bias, the sampling strategy has been modified in the most recent data to produce results more generalizable to all inpatient discharges in the country and so the associated sampling weights were applied to this analysis.

Statistical Analysis

Descriptive statistics for demographics (i.e., age, sex, race, insurance) and comorbidities were performed for the full sample. Comorbidities were selected for analysis (and identified in

the dataset by their ICD-10 scores) on the basis of their clinical and/or statistical significance for similar studies in the existing literature. The comorbidities included in this study were diabetes, hypertension, peripheral vascular disease, hyperlipidemia, smoking, obesity, poor diet, stroke, congestive heart failure, cardiac arrest, myocardial infarction, cardiogenic shock, valvular disease, anemia, chronic obstructive pulmonary disease, coagulopathy, chronic kidney disease, and malignancy (overall and by primary malignancy type).

Bivariable analysis was then conducted separately according to the following: (a) inpatient mortality (yes/no); (b) PCI (yes/no) among the overall sample, stratified by metastases (yes/no) and in subgroup analyses among patients with malignancy; (c) PCI vessel number (multi- vs. single-vessel); (d) malignancy (yes/no) in subgroup analyses among patients who died with UA/NSTEMI and separately among those with STEMI; (e) length of stay by primary malignancy type; (f) total cost by primary malignancy type. For continuous variables, independent sample *t*-tests were performed to compare means and Wilcoxon rank sum tests were performed for medians. For categorical variables, Pearson chi square tests or Fisher exact tests were performed to compare proportions.

Variables found to be statistically significant in the bivariable analysis were then included in forward and backward stepwise regression to augment decision-making on which variables should be included in the final multivariable regression models. This regression analysis was conducted to assess the following outcomes: (a) inpatient mortality (by logistic) and, (b) total hospital costs (by linear, adjusting with the additional variable of length of stay). The regression models separately assessed these outcomes according to the following major predictors: (a) historical or active malignancy (yes/no), and primary malignancy type (brain and nervous system, head or neck, thyroid, breast, lung, esophagus, stomach, pancreas, liver or bile system, rectum or anus, colon, peritoneum, bone or connective tissue system, hematological malignancies [including Hodgkin lymphoma, Non-Hodgkin lymphoma, leukemia, and multiple myeloma], skin, uterus, cervix, ovarian, prostate, testes, bladder, and renal). Sub-group analysis without propensity score adjustment was conducted separately according to history of CAD (additionally with stratified analysis by ACS and active or prior malignancy), active malignancy, prior malignancy, presenting diagnosis of ACS, UA/NSTEMI, and STEMI. These models featured the interaction between PCI and malignancy, while adjusting for age, race, income, metastases, and mortality risk by DRG (other variables were excluded based upon the below machine learning analysis and diagnostic testing to produce the most clinically and statistically justifiable models).

Next, machine learning–backed propensity score–adjusted multivariable regression was conducted for mortality and controlled for age, race, income, presence of metastases, and mortality risk by diagnosis-related group in addition to the likelihood of undergoing PCI and the NIS weights accounting for the cluster sample data structure. The propensity score was then created for the likelihood of undergoing PCI (the treatment), balance was confirmed among blocks, and then the propensity score was included in the final regression models as an adjusted variable. This causal inference approach (propensity score adjustment) was selected because it is a widely accepted methodology to reduce but not eliminate selection bias and the effect of confounding variables. Such competing causal inference approaches as fixed, random, and mixed effects were not appropriate (though these have the added advantage of reducing unobserved variable bias) because the dataset lacked adequate repeated hospitalizations from the same subjects. Propensity score adjustment was used rather than covariate adjustment without the propensity score to enable a more complicated propensity score model (i.e., able to test interactions and higher order terms to produce the most robust estimated probability of treatment assignment) without risking over-parameterizing while still permitting diagnostic analysis of the final models to be done to confirm superior performance to simple covariate adjustment without the propensity score. Finally, propensity score adjustment rather than competing propensity score techniques was used because of its superior performance in the appropriate context (confirmed by current statistical theory and adequate diagnostic quantitative testing of the final models in cardiovascular studies) (33, 34).

The utility of this above hybrid analytic approach, which integrates the traditional statistical method of frequentist-based multivariable regression (supported by propensity score-based causal inference analysis) and supervised learning-based machine learning has been previously demonstrated, as causal inference results which are more familiar to medical science audiences can be confirmed and replicated automatically through machine learning (and thus may accelerate real-time findings on larger high-dimensional datasets as they already increasingly do for other economic sectors outside of medicine), while producing more rapid and accurate results compared to traditional statistics (35–40).

To modify the final models until optimal performance was achieved, performance was first assessed relative to results from backward propagation neural network machine learning to ensure comparability by root mean squared error and accuracy. Regression model performance was additionally assessed with correlation matrix, area under the curve, Hosmer-Lemeshow goodness-of-fit test, Akaike and Schwarz Bayesian information criterion, variance inflation factor, and tolerance, multicollinearity, and specification error. An academic physician-data scientist and biostatistician confirmed that the final regression models were sufficiently supported by the existing literature and clinical and statistical theory. Fully adjusted regression results were reported with 95% confidence intervals (CIs) with statistical significance set at a 2-tailed $p < 0.05$. Statistical analysis was performed with STATA 14.2 (STATA Corp, College Station, Texas, USA), and machine learning analysis was performed with Java 9 (Oracle, Redwood Chores, California, USA).

RESULTS

Overall Sample Descriptive and Bivariable Analyses

Among the 30,195,722 hospitalized patients meeting study criteria, the mean (SD) age was 57.51 (20.33) years; 17,558,812

TABLE 1 | Descriptive statistics by common primary malignancies and bivariable analysis by cancer ($N = 30,195,722$).

Variables	Sample	Cancer*		Breast*	Lung*	Colon*	Prostate*	Hematological*	Skin*
	***N* = 30,195,722**	**No (*n* = 25,535,129)**	**Yes (*n* = 4,660,593)**	***n* = 751,105**	***n* = 566,434**	***n* = 442,755**	***n* = 637,100**	***n* = 660,260**	***n* = 500,445**
Demographics, no. (%)									
Age, mean (SD)	57.51 (20.33)	55.46 (0.01)	68.70 (0.01)	70.33 (13.76)	69.77 (10.84)	71.59 (13.62)	75.28 (0.03)	65.97 (0.4)	73.43 (12.60)
Female	17,558,812 (58.15)	15,203,616 (59.54)	2,353,133 (50.49)	743,068 (98.93)	279,875 (49.41)	218,987 (49.46)	0 (0.00)	294,212 (44.56)	217,143 (43.39)
Race									
All groups									
White	20,469,680 (67.79)	16,909,362 (66.22)	3,560,693 (76.40)	571,290 (76.06)	449,012 (79.27)	332,863 (75.18)	478,207 (75.06)	490,045 (74.22)	475,273 (94.97)
Black	4,568,613 (15.13)	16,909,362 (15.80)	535,968 (11.50)	97,118 (12.93)	66,726 (11.78)	55,344 (12.50)	96,521 (15.15)	75,864 (11.49)	4,704 (0.94)
Hispanic	3,273,216 (10.84)	2,949,307 (11.55)	322,047 (6.91)	46,644 (6.21)	24,413 (4.31)	31,878 (7.20)	36,824 (5.78)	54,736 (8.29)	11,010 (2.20)
Asian	812,265 (2.69)	704,770 (2.76)	108,592 (2.33)	16,524 (2.20)	12,971 (2.29)	10715 (2.42)	10,002 (1.57)	16,176 (2.45)	1,702 (0.34)
Native American	187,213 (0.62)	168,532 (0.66)	17,244 (0.37)	2,554 (0.34)	1,926 (0.34)	1,727 (0.39)	1,529 (0.24)	2,311 (0.35)	751 (0.15)
Other	884,735 (2.93)	768,607 (3.01)	115,583 (2.48)	16,975 (2.26)	11,329 (2.00)	10,183 (2.30)	14016 (2.20)	21,194 (3.21)	7,006 (1.40)
Insurance									
All groups									
Commercial	8,343,078 (27.63)	7,292,833 (28.56)	1,051,430 (22.56)	161,112 (21.45)	101,958 (18.00)	84,743 (19.14)	103,465 (16.24)	170,149 (25.77)	92,532 (18.49)
Medicare	14,167,833 (46.92)	11,123,102 (43.56)	3,043,367 (65.30)	518,788 (69.07)	392,142 (69.23)	312,231 (70.52)	497639 (78.11)	403,353 (61.09)	379,187 (75.77)
Medicaid	5,622,443 (18.62)	5,232,148 (20.49)	392,888 (8.43)	52,577 (7.00)	50,186 (8.86)	30,727 (6.94)	17,329 (2.72)	60,216 (9.12)	15,764 (3.15)
VA	887,754 (2.94)	789,035 (3.09)	102,067 (2.19)	11,342 (1.51)	14,161 (2.50)	8,545 (1.93)	13,889 (2.18)	15,252 (2.31)	8,808 (1.76)
None	1,171,594 (3.88)	1,100,564 (4.31)	70,375 (1.51)	7,286 (0.97)	7,873 (1.39)	6,508 (1.47)	4,715 (0.74)	11,356 (1.72)	4,154 (0.83)
Medical history									
Diabetes	5,703,972 (18.89)	4,739,320 (18.56)	964,277 (20.69)	153,826 (20.48)	106,603 (18.82)	100,505 (22.70)	144,494 (22.68)	126,968 (19.23)	98,137 (19.61)
Hypertension	16,405,336 (54.33)	13,347,212 (52.27)	3,055,951 (65.57)	506,846 (67.48)	369,768 (65.28)	302,933 (68.42)	478,781 (75.15)	394,703 (59.78)	364,024 (72.74)
PVD	1,105,163 (3.66)	947,353 (3.71)	218,582 (4.69)	26,814 (3.57)	40,160 (7.09)	21,252 (4.80)	38,417 (6.03)	24,033 (3.64)	30,677 (6.13)
HLD	9508632.8578 (31.49)	7,673,306 (30.05)	1,834,875 (39.37)	302,620 (40.29)	227,140 (40.10)	172,896 (39.05)	320,334 (50.28)	224,026 (33.93)	253,575 (50.67)
Smoking	673,365 (2.23)	620,504 (2.43)	51,267 (1.10)	5,483 (0.73)	10,252 (1.81)	4,073 (0.92)	5,798 (0.91)	5,810 (0.88)	3,853 (0.77)
Obesity	4,399,517 (14.57)	3,878,786 (15.19)	520,588 (11.17)	98,921 (13.17)	41,973 (7.41)	48,216 (10.89)	58,868 (9.24)	62,989 (9.54)	60,254 (12.04)
Poor diet	27,176 (0.09)	56,177 (0.22)	6,059 (0.13)	1,052 (0.14)	623 (0.11)	531 (0.12)	956 (0.15)	858 (0.13)	751 (0.15)
CVA/TIA	1,295,396 (4.29)	1,090,350 (4.27)	195,745 (4.42)	35,602 (4.74)	26,226 (4.63)	17,267 (3.90)	36,315 (5.70)	23,571 (3.57)	32,929 (6.58)
CHF	1,669,823 (5.53)	1,371,236 (5.37)	298,278 (6.40)	49,798 (6.63)	38,744 (6.84)	30,417 (6.87)	49,120 (7.71)	46,812 (7.09)	37,684 (7.53)
HFrEF	766,971 (2.54)	633,271 (2.48)	132,827 (2.85)	18,102 (2.41)	17,050 (3.01)	13,548 (3.06)	25,611 (4.02)	21,591 (3.27)	16,365 (3.27)
Cardiac arrest	238,546 (0.79)	201,728 (0.79)	37,285 (0.80)	4,732 (0.63)	6,401 (1.13)	3,365 (0.76)	5,033 (0.79)	6,140 (0.93)	3,153 (0.63)

(Continued)

TABLE 1 | Continued

Variables	Sample	Cancer*		Breast*	Lung*	Colon*	Prostate*	Hematological*	Skin*
	N = 30,195,722	No (*n* = 25,535,129)	Yes (*n* = 4,660,593)	*n* = 751,105	*n* = 566,434	*n* = 442,755	*n* = 637,100	*n* = 660,260	*n* = 500,445
Myocardial infarction	1,008,537 (3.34)	893,730 (3.50)	135,157 (2.90)	20,881 (2.78)	16,710 (2.95)	12,973 (2.93)	26,503 (4.16)	17,629 (2.67)	18,116 (3.62)
STEMI	226,468 (0.75)	204,281 (0.80)	22,837 (0.49)	3,455 (0.46)	2,832 (0.50)	2,125 (0.48)	4,778 (0.75)	2,839 (0.43)	2,903 (0.58)
UA/NSTEMI	806,226 (2.67)	692,002 (2.71)	112,786 (2.42)	17,501 (2.33)	13,934 (2.46)	10,892 (2.46)	21,789 (3.42)	14,922 (2.26)	15,214 (3.04)
Cardiogenic shock	135,881 (0.45)	120,015 (0.47)	16,778 (0.36)	2,479 (0.33)	2,266 (0.40)	1,461 (0.33)	2,931 (0.46)	3,301 (0.50)	1,802 (0.36)
Valvular disease	1,603,393 (5.31)	1,297,184 (5.08)	307,599 (6.60)	60,689 (8.08)	29,228 (5.16)	30,107 (6.80)	53,771 (8.44)	45,756 (6.93)	50,195 (10.03)
Anemia	6,147,849 (20.36)	4,716,338 (18.47)	1,431,734 (30.72)	191,832 (25.54)	176,048 (31.08)	146,685 (33.13)	173,355 (27.21)	306,559 (46.43)	115,252 (23.03)
COPD	4,924,922 (16.31)	3,919,642 (15.35)	1,006,222 (21.59)	137,753 (18.34)	306,611 (54.13)	80,404 (18.16)	122,705 (19.26)	106,566 (16.14)	101,290 (20.24)
Coagulation disorder	1,890,252 (6.26)	1,452,949 (5.69)	438,562 (9.41)	51,376 (6.84)	47,977 (8.47)	32,410 (7.32)	52,370 (8.22)	119,837 (18.15)	39,936 (7.98)
CKD 3-5	3,427,214 (11.35)	2,801,204 (10.97)	625,452 (13.42)	84,875 (11.30)	54,887 (9.69)	62,960 (14.22)	114,423 (17.96)	99,699 (15.10)	76,818 (15.35)
ESRD	1,081,007 (3.58)	947,353 (3.71)	134,691 (2.89)	16,825 (2.24)	9,176 (1.62)	12,397 (2.80)	20,897 (3.28)	24,430 (3.70)	12,161 (2.43)

*SD, standard deviation; VA, Veteran Affairs; PVD, peripheral vascular disease; HLD, hyperlipidemia; CVA, cerebrovascular disease; TIA, transient ischemia attack; CHF, congestive heart failure; HFrEF, heart failure with reduced ejection fraction; STEMI, ST segment elevation myocardial infarction, NSTEMI, non-ST segment elevation myocardial infarction; UA, unstable angina; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end stage renal disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft. *$p < 0.05$.*

(58.15%) were female; 21,043,399 (67.69%) were Caucasian; 4,659,200 (15.43%) had cancer (of whom 2,117,606 [45.45%] was active); 1,159,516 (3.84%) underwent an inpatient PCI, and 661,286 (2.19%) died that hospitalization (**Table 1**). Among all hospitalized patients, 19.45% had CAD, 2.67% had UA/NSTEMI, and 0.75% had STEMI. The most common primary malignancies in patients in whom PCI was performed were prostate (2.34%), breast (1.83%), skin (1.74%), gastrointestinal (1.54%), and hematological (1.48%) cancers.

PCI Sub-group Bivariable Analyses

Among PCI patients, 11.07% had cancer, 0.07% had metastatic disease and he top primary malignancies in which multi- vs. single-vessel PCI was performed at significantly higher proportion compared with other malignancies included breast (2.09%, $p < 0.001$), hematological (1.66%, $p < 0.001$), gastrointestinal (1.66%, $p < 0.001$), colon (1.02%, $p = 0.001$), and lung cancers (1.02%, $p < 0.001$).

There was notable mortality, cost, and length of stay differences according to primary malignancy type, active vs. prior malignancy, and metastasis (**Table 2**). Among PCI patients, the highest mortality by primary malignancy was for prostate (14.87%), lung (14.27%), breast (10.88%), and skin (10.88%) cancers. There was significantly higher mortality in cancer vs. non-cancer patients with NSTEMI/UA (9.34 vs. 6.78%, $p < 0.001$) and STEMI (17.70 vs. 10.83%, $p < 0.001$). Among PCI patients grouped by primary malignancy, the highest mean length of stay (in days) was for bone/connective tissue (11.5, SD 19.25), liver/bile (9.73, SD 11.53), and pancreatic cancers (9.45, SD 10.12; $p < 0.001$), and the highest mean costs were for liver/biliary cancer ($187,742, SD 308,824.00), bone/connective tissue cancer ($164,922.70, SD 223,373.20), and leukemia ($142,577.30, SD 179,511.40; $p < 0.001$).

Overall Sample Multivariable Regression Analyses by PCI

In machine learning-backed multivariable regression fully adjusted for age, race, income, metastases, and mortality risk by DRG, PCI was associated with a significantly reduced odds of mortality for all patients among all adult inpatients regardless of cancer status (OR 0.77, 95%CI 0.75–0.79; $p < 0.001$) and specifically for cancer patients (OR 0.82, 95%CI 0.75–0.89; $p < 0.001$). This was confirmed by propensity score adjustment while significantly reducing their total hospital costs (beta USD$ −8,668.94, 95%CI −9,553.59 to −7,784.28; $p < 0.001$) independent of the length of stay.

CAD and Active Cancer Sub-group Multivariable Regression Analyses by PCI

Results were similar in sub-group analysis among CAD patients and separately in prior and active cancer patients (with greater mortality reductions in patients with active [OR 0.63, 95%CI 0.56–0.71; $p < 0.001$] rather than prior malignancies [OR 0.72, 95%CI 0.65–0.79; $p < 0.001$]) (**Figure 1**). In the CAD sub-group with stratified analysis by ACS (UA/NSTEMI and STEMI) and active or prior malignancy, PCI vs. medical management significantly reduced mortality for all patient

TABLE 2 | Bivariable mortality analysis by myocardial infarction and percutaneous coronary intervention ($N = 30,195,722$).

Ariables (%)	Mortality: 2,448,873 (8.11%)						Cost, median United States dollars ($) 29,143 (range 15,587–56,287)						Length of stay, median days 3 (range 2–5)					
	UA/NSTEMI: 2,155,975 (7.14%)			STEMI: 3,478,547 (11.52%)			UA/NSTEMI: $56,059 (29,194–106,095)			STEMI: $74,861 (46,585–122,465)			UA/NSTEMI: 4 (2–7)			STEMI: 3 (2–5)		
	No PCI: 1,814,469 (84.16%)	PCI: 341,506 (15.84%)	*P*-value	No PCI: 1,946,595 (55.96%)	PCI: 1,531,952 (44.04%)	*P*-Value	No PCI: $39,618 (20,445–83,435)	PCI: $72,680 (44,663–123,811)	*P*-value	No PCI: $38,008 (18,144–89,103)	PCI: $81,960 (55,957–128,357)	*P*-value	No PCI: 4 (2–8)	PCI: 3 (2–7)	*P*-value	No PCI: 4 (2–8)	PCI: 3 (2–4)	*P*-value
No cancer	11.30	2.35	<0.001	26.75	6.41	<0.001	39,483 (20,232–83,797)	72,608 (44,549–123,803)	<0.001	37,676 (17,780–90,558)	81,959 (55,892–128,242)	<0.001	4 (2–8)	3 (2–6)	<0.001	4 (2–8)	3 (2–4)	<0.001
Cancer	13.32	3.02	<0.001	32.12	8.90	<0.001	40,406 (21,485–81,527)	73,137 (45,496–123,817)	<0.001	39,688 (20,153–81,272)	81,989 (56,660–129,395)	<0.001	5 (3–8)	4 (2–7)	<0.001	4 (2–8)	3 (2–5)	<0.001
Breast																		
History	9.84	1.73	<0.001	27.57	8.24	<0.001	37,036 (20,468–64,145)	67,733 (41,300–111,708)	<0.001	33,348 (15,839–70,403)	80,544 (57,881–119,920)	<0.001	4 (2–7)	3 (2–6)	<0.001	4 (2–7)	3 (2–5)	0.062
Active	14.52	0.79	<0.001	39.47	16.67	0.030	39,795 (20,321–76,507)	73,325 (46,953–111,954)	<0.001	52,914 (27,204–118,261)	77,385 (51,906–118,105)	0.100	5 (2–8)	4 (2–7)	0.095	5 (3–12)	3 (2–5)	0.013
Metastatic	19.76	1.64	<0.001	42.86	28.57	0.260	37,059 (22,154–74,875)	85,280 (38,977–128,409)	<0.001	46,331 (24,845–113,660)	81,841 (49,000–135,190)	0.020	5 (2–8)	4 (2–7)	0.269	5 (3–11)	4 (2–8)	0.345
Lung						<0.001			<0.001									
History	11.30	3.57	<0.001	31.58	11.39	<0.001	38,672 (21,271–74,078)	72,994 (47,883–112,613)	<0.001	34,548 (20,597–66,873)	80,058 (57,488–135,796)	<0.001	5 (3–8)	4 (2–6)	0.006	4 (2–7)	3 (2–6)	0.549
Active	22.82	9.13	<0.001	39.59	21.19	<0.001	47,512 (24,626–91,404)	74,196 (49,782–116,071)	<0.001	40,498 (19,516–78,998)	99,581 (57,526–163,505)	<0.001	5 (3–9)	5 (3–9)	0.755	4 (2–8)	4 (2–9)	0.491
Metastatic	23.27	8.16	0.001	36.80	25.86	0.001	47,053 (24,626–88,410)	77,798 (54,411–127,294)	<0.001	38,647 (16,107–75,284)	97,537 (51,849–134,818)	<0.001	5 (3–9)	5 (3–8)	0.558	4 (2–8)	4 (2–8)	0.812
Prostate						0.144			<0.001									
History	10.16	2.32	<0.001	27.88	5.89	<0.001	34,605 (19,043–68,583)	74,589 (45,658–126,691)	<0.001	34,537 (16,899–67,835)	79,883 (54,925–126,777)	<0.001	4 (2–7)	3 (2–6)	<0.001	4 (2–7)	3 (2–5)	0.004
Active	13.59	3.45	<0.001	34.67	8.08	<0.001	39,712 (23,881–81,389)	85,479 (50,212–142,427)	<0.001	40,704 (24,864–84,969)	79,438 (55,561–137,324)	<0.001	5 (3–9)	4 (2–8)	0.007	6 (2–10)	3 (2–7)	0.004
Metastatic	14.84	4.08	0.004	31.03	18.75	<0.001	43,516 (25,273–79,595)	76,375 (47,744–137,167)	<0.001	32,685 (23,843–70,702)	67,627 (55,648–117,526)	<0.001	5 (3–9)	4 (2–9)	0.060	4 (2–9)	3 (2–6)	0.272
Colon						<0.001												
History	11.39	2.53	<0.001	27.21	8.50	<0.001	37,129 (20,418–72,128)	72,120 (44,556–114,526)	<0.001	35,246 (15,955–64,534)	81,350 (55,422–112,388)	<0.001	4 (3–8)	4 (2–7)	<0.001	4 (2–7)	3 (2–5)	0.003

(Continued)

TABLE 2 | Continued

Ariables (%)	Mortality: 2,448,873 (8.11%)						Cost, median United States dollars ($) 29,143 (range 15,587–56,287)						Length of stay, median days 3 (range 2–5)					
	UA/NSTEMI: 2,155,975 (7.14%)			STEMI: 3,478,547 (11.52%)			UA/NSTEMI: $56,059 (29,194–106,095)			STEMI: $74,861 (46,585–122,465)			UA/NSTEMI: 4 (2–7)			STEMI: 3 (2–5)		
	No PCI: 1,814,469 (84.16%)	PCI: 341,506 (15.84%)	*P*-value	No PCI: 1,946,595 (55.96%)	PCI: 1,531,952 (44.04%)	*P*-Value	No PCI: $39,618 (20,445–83,435)	PCI: $72,680 (44,663–123,811)	*P*-value	No PCI: $38,008 (18,144–89,103)	PCI: $81,960 (55,957–128,357)	*P*-value	No PCI: 4 (2–8)	PCI: 3 (2–7)	*P*-value	No PCI: 4 (2–8)	PCI: 3 (2–4)	*P*-value
Active	18.58	6.06	0.003	30.00	19.35	0.288	76,802 (35,376–148,370)	104,675 (55,870–183,304)	0.002	50,822 (23,120–108,955)	113,139 (64,982–175,087)	0.005	8 (4–13)	7 (3–12)	0.070	5 (2–12)	5 (2–15)	0.643
Metastatic	18.23	6.12	0.037	32.43	8.70	0.035	51,511 (26,892–112,133)	86,090 (50,970–174,804)	0.005	49,372 (23,120–78,839)	82,888 (64,982–175,087)	0.002	6 (3–11)	6 (2–10)	0.482	5 (3–9)	4 (2–14)	0.789
Skin									<0.001									
History	8.80	2.73	<0.001	29.66	6.73	<0.001	31832 (17,940–61,004)	69,272 (43,558–110,059)	<0.001	36,652 (17,940–73,450)	77,655 (53,331–117,858)	<0.001	4 (2–7)	3 (2–6)	<0.001	4 (1–7)	3 (2–4)	0.115
Active	15.69	5.19	0.022	18.75	14.29	0.715	46,991 (21,979–91,548)	84,049 (41,616–133,584)	<0.001	41,314 (27,015–75,622)	87,643 (53,654–125,188)	0.010	5 (3–10)	4 (2–7)	0.012	5 (3–6)	2 (2–4)	0.188
Metastatic	20.65	21.74	0.909	33.33	0.00	0.052	46,493 (21,381–83,185)	97,682 (73,386–148,753)	<0.001	59,576 (30,926–79,217)	91,565 (54,585–136,663)	0.101	5 (2–8)	7 (4–9)	0.175	6 (3–10)	5 (3–8)	0.589
Hematologic									<0.001									
History	11.58	3.45	<0.001	18.75	7.10	0.011	36,401 (19,411–70,237)	65,043 (41,059–121,736)	<0.001	40,818 (19,449–81,060)	81,527 (53,788–121,246)	<0.001	4 (2–7)	3 (2–6)	0.002	4 (3–7)	3 (2–5)	0.004
Active	18.07	7.69	<0.001	44.83	10.47	<0.001	51,713 (26,013–118,492)	85,932 (49,276–159,541)	<0.001	53,261 (24,470–147,175)	99,786 (63,124–162,734)	<0.001	5 (3–11)	5 (2–9)	0.001	5 (2–13)	3 (2–7)	0.099
Metastatic	21.35	11.76	0.364	36.84	33.33	0.907	63,282 (29,464–135,134)	81,999 (42,492–148,753)	0.18	57,441 (36,396–128,357)	59,088 (37,016–297,917)	0.738	6 (3–12)	6 (5–10)	0.330	5 (3–11)	3 (3–21)	0.962

STEMI, ST segment elevation myocardial infarction, NSTEMI, non-ST segment elevation myocardial infarction; UA, unstable angina.

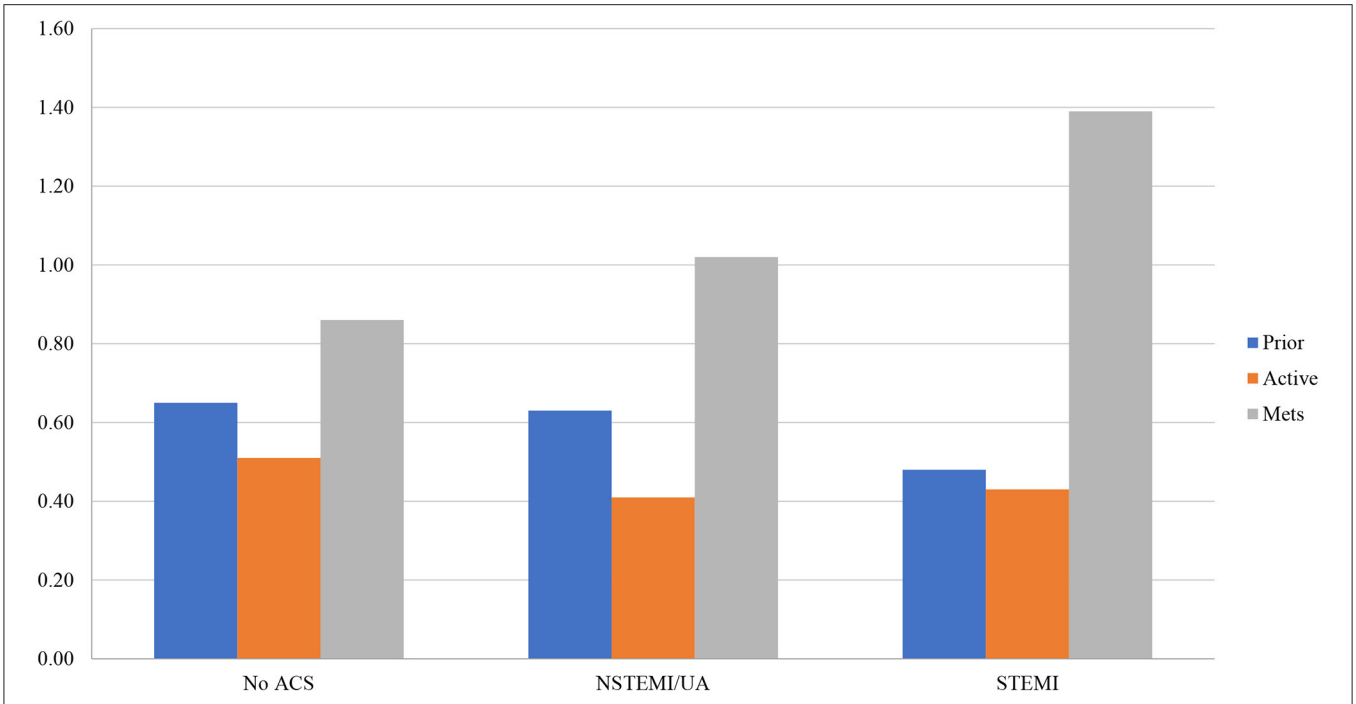

FIGURE 1 | Propensity score-fully adjusted mortality odds ratios by ACS and active or prior malignancy ($N = 30{,}195{,}722$). Fully adjusted for age, race, income, metastases, and mortality risk by Disease Related Group; mets, metastasis; ACS, acute coronary syndrome, NSTEMI, non-ST segment myocardial infarction; UA, unstable angina; STEMI, ST segment myocardial infarction.

groups (**Figure 1**). Active vs. prior malignancy had mortality reductions across no ACS, UA/NSTEMI, and STEMI groups. The greatest mortality reductions among all groups were patients with active malignancy and UA/NSTEMI (OR 0.41, 95%CI 0.26–0.65; $p < 0.001$) and active malignancy with STEMI (OR 0.43, 95%CI 0.31–0.59; $p < 0.001$).

Primary Malignancy Sub-group Multivariable Regression Analyses by PCI

In sub-group analysis by primary malignancy among those with cancer, PCI was associated with a significantly reduced odds of mortality only in patients with head and neck vs. non-head and neck cancers (OR 0.34, 95%CI 0.17–0.66; $p = 0.002$), Hodgkin lymphoma vs. cancers other than Hodgkin lymphoma (OR 0.35, 95%CI 0.14–0.87; $p = 0.025$), and leukemia vs. cancers other than leukemia (OR 0.64, 95%CI 0.48–0.86; $p = 0.003$) (**Figure 2**). PCI in cancer patients with metastatic disease was associated with reduced mortality but not significantly (OR 0.86, 95%CI 0.71–1.04; $p = 0.110$). Similarly, PCI also was associated with non-significantly reduced mortality in patients with non-solid vs. solid tumors (OR 0.85, 95%CI 0.71–1.02; $p = 0.079$). There were no significant disparities by income or race among PCI subjects.

DISCUSSION

This propensity score adjusted nationally representative analysis of over 30 million hospitalized adults suggests that PCI does not increase inpatient mortality (primary endpoint) nor total costs (secondary endpoint) among patients with cancer regardless of whether they had concurrent non-ACS, UA/NSTEMI, or STEMI indications (with particular primary malignancies driving more of the above associations than others). These results may support offering PCI when deemed appropriate by clinicians to cancer patients who have traditionally been excluded from or underrepresented in cardiovascular randomized trials (which may account for some of the current hesitation with considering more readily such invasive treatment options). The above clinical findings may thus allow more informed clinician-patient discussions about treatment options at a time when such cardio-oncology patients with both CAD and cancer represent a sizeable and growing portion of the PCI patient population nationally (as this analysis of over 1 million PCI procedures detected more than 1 in 10 being performed in such patients with both cancer and heart disease).

The most common primary malignancies nationally per our study were prostate, gastrointestinal, breast, skin cancers, lung and hematological. Prostate and skin cancers were the most common primary malignancies in which single-vessel PCI was performed as they can be viewed as more favorable PCI candidates, and were clinical practice is often parallel to non-cancer patients. Conversely, patients with lung, breast, gastrointestinal, and hematological cancers are the cancer patient sub-groups in which multivessel PCI was performed at a higher proportion than single-vessel PCI probably due to time constraints, taking advantage of the window of opportunity and complete revascularization. Also, in lung cancer patients the additional CAD burden can be explained by the higher prevalence of cardiovascular risk factors (such as smoking)

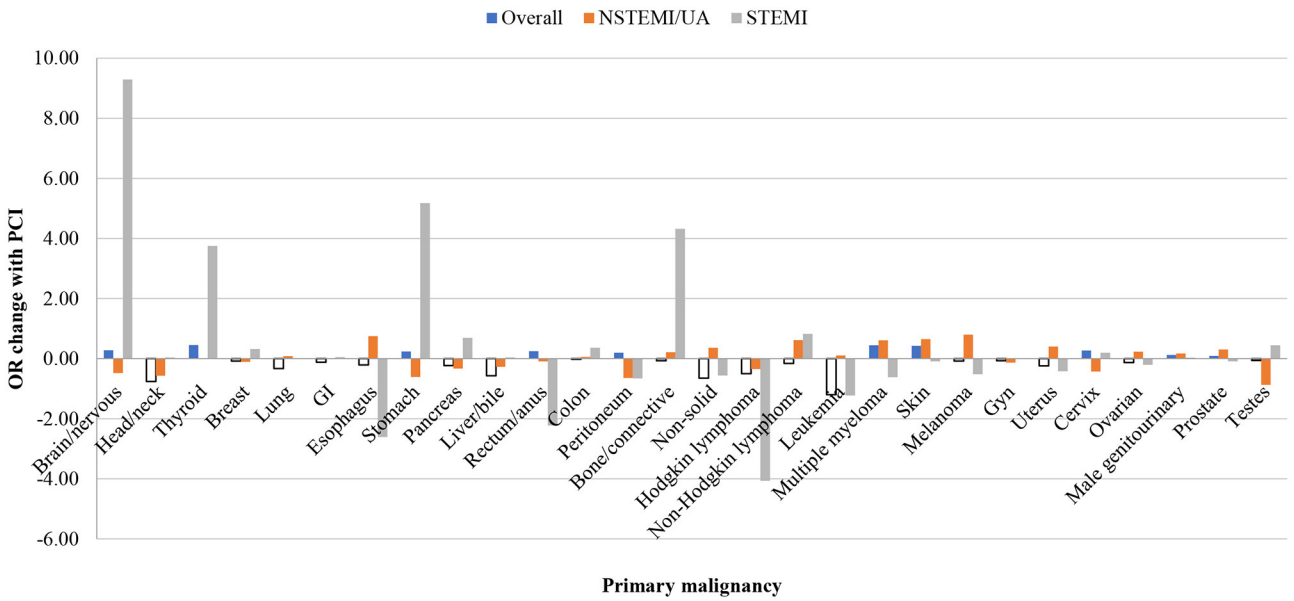

FIGURE 2 | Propensity score adjusted inpatient mortality odds ratio change with ACS and PCI by primary malignancy in fully adjusted multivariable regression (N = 30,195,722). Multivariable regression fully adjusted for age, race, income, metastases, and mortality risk by Diagnosis Related Group (DRG); ACS, acute coronary syndrome, NSTEMI, non-ST segment myocardial infarction; UA, unstable angina; STEMI, ST segment myocardial infarction; PCI, percutaneous coronary intervention); GI, gastrointestinal; gyn, gynecological.

and the cancer treatments that promote early atherosclerosis (including radiation therapy) (4, 5, 15–17). Prior studies of NIS data, as well as our analysis, have shown that PCI in the setting of lung cancer was associated with a higher risk of inpatient mortality when compared to other primary malignancies (20). The short interval to initiation of cancer treatment due to the aggressive nature of majority of these tumors could be utilized for a more comprehensive cardiovascular risk stratification/evaluation and to optimize medical management in an attempt to minimize cardiovascular morbidity and mortality.

VEGF inhibitors (bevacizumab, sunitinib, sorafenib, pazopanib), novel immunotherapies can be associated with vascular toxicity, enhanced inflammation of atherosclerotic plaques, destabilization of pre-existing plaques, and promotion of plaque rupture (41–47). Our study provides an overall picture of the impact of such cancer treatments, but the lack of data granularity prohibits more rigorous understanding of the impact of cancer treatments on CAD burden and PCI outcomes. Regardless, our results are consistent with prior studies that support the safety and efficacy of PCI in cancer patient (9, 21, 25, 28, 30).

The primary organ site and stage including presence or absence of metastatic disease are the main driver of outcomes in a cancer patient population. Metastatic patients have higher risk for inpatient mortality probably due to the greater extent of their oncologic disease. In our analysis, 1 in 20 cancer patients who underwent PCI had metastatic disease, and the intervention still appeared to reduce mortality.

Additionally our analysis also demonstrated that cancer patients who received PCI had decreased total hospital costs of ∼$8,000–9,000, independent of their inpatient length of stay, clinical acuity, mortality risk (as calculated by DRGs), and other factors rigorously tested in propensity score adjustment. The inherent cost of the procedure could potentially be reduced by their immediate symptomatic improvement and therefore decreased laboratory and imaging tests to identify the cause of symptoms. It appears that there could be a financial incentive for hospital systems to specifically encourage early cooperation and planning between cardiology and oncology teams regarding the timing and choice of cancer therapies and coronary revascularization decisions. Our data support the idea that cancer patients could benefit from cardiovascular evaluation and revascularization from such cardio-oncology teams.

This study does have notable limitations which indicate the results should be interpreted cautiously. This is a non-randomized study without longitudinal follow-up that relies upon accuracy of ICD10 coding by providers (i.e., coronary artery disease burden, prior detailed cancer treatment regiments, and overall vs. cardiovascular specific mortality) and a selection bias is possible. By utilizing a large nationally representative dataset and propensity score and machine learning supported analyses with aggressive regression model performance optimization, we attempted to minimize the impact of such limitations and produce the most robust results possible on the association between PCI outcomes and cancer.

CONCLUSIONS

This nationally representative multicenter comprehensive analysis of inpatient mortality and total costs of PCI in all eligible hospitalized patients with and without cancer (including

sub-group analysis by CAD, cancer by primary organ site, active vs. prior cancer, and ACS) suggests a significant and independent inpatient mortality and cost benefit for PCI vs. medical management particularly for cancer patients. As there is a unique cancer and coronary artery disease interaction, certain cancer types have a more pronounced mortality benefit compared to others. This study also suggests that PCI was considered in cancer patients regardless of their primary malignancy type, active or prior malignancy status, and ACS status and did not suggest a significant increase in LOS or cost. Our analysis may support future randomized trials to assess the safety and optimal clinical application of coronary revascularization of onco-cardiology patients with both CAD and cancer, while possibly highlighting the current utility of multi-disciplinary teams for this growing and complex patient population.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The dataset is available for purchase through the United States Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (HCUP). Requests to access these datasets should be directed to HCUP, HCUPDistributor@ahrq.gov.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

DM created the study design and analyzed the data. DM and SL drafted the manuscript. DM, SL, SP, NP, KC, KM, JL-M, MM, and CI interpreted the data, revised the manuscript, and consented to its publication. All authors contributed to the article and approved the submitted version.

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Prognostic Factors and Overall Survival After Pericardiocentesis in Patients With Cancer and Thrombocytopenia

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Background: Pericardiocentesis is an important diagnostic and therapeutic tool for cancer-associated pericardial effusion. Limited safety and outcomes data exists regarding the management of malignancy-related pericardial effusion in patients with thrombocytopenia.

Objectives: Our study aimed to analyze prognostic factors and overall survival (OS) after pericardiocentesis in thrombocytopenic cancer patients.

Methods and Results: A retrospective review of 136 thrombocytopenic cancer patients who underwent primary percutaneous pericardiocentesis was performed. Degree of thrombocytopenia was classified by platelet count recorded on day of pericardiocentesis: 75–149 $\times$ 10^3 cells/μL (41%); 50–74 $\times$ 10^3 cells/μL (10%); 25–49 $\times$ 10^3 cells/μL (24%); <25 $\times$ 10^3 cells/μL (25%). Median OS was 2.6 months and median follow-up was 37.4 months. Kaplan-Meier survival analysis showed significant OS differences among thrombocytopenia severity groups ($p = 0.023$), and worse OS with platelets <100 vs. $\geq$100 $\times$ 10^3 cells/μL ($p = 0.031$). By univariate analysis, thrombocytopenia severity was associated with increased risk of death (HR 0.993; 95% CI 0.989–0.997; $p = 0.002$). Poor prognostic factors for OS were advanced cancer, malignant effusion, elevated international normalized ratio (INR), quantity of platelet transfusions, and platelet transfusion resistance. However, thrombocytopenia severity became insignificant for OS ($p = 0.802$), after adjusting for advanced cancer and INR.

Conclusions: For patients with malignancy-related large pericardial effusion and thrombocytopenia, pericardiocentesis is a feasible intervention and should be considered due to low complication rates. There is no absolute contraindication to pericardiocentesis in case of hemodynamic instability, even with severe thrombocytopenia.

Keywords: pericardial effusion, pericardiocentesis, thrombocytopenia, safety, cancer

INTRODUCTION

Cancer causes pericardial disease by direct structural infiltration or indirectly via chemotherapy, radiotherapy, immunotherapy, or opportunistic infections (1, 2). Pericardial effusion (PE) is associated with malignancy in up to 20% of cases in autopsy studies, and 33% of patients with symptomatic PE have concomitant cancer in a large retrospective review (3–5). Pericardiocentesis is an important diagnostic and therapeutic tool for the cardio-oncologist as large PE manifesting with tachycardia, dyspnea, chest pain, cardiac tamponade, or cardiogenic shock are common (6). According to the European Society of Cardiology 2015 guidelines, in cardiac tamponade with underlying malignancy requiring therapeutic pericardiocentesis, extended pericardial drainage is indicated (class IB level recommendation) (7).

Limited data and safety outcomes exist regarding the management of malignancy-related PE in patients with thrombocytopenia (platelet count $<150 \times 10^3$ cells/μL). In thrombocytopenic patients, platelet count has an imprecise association with increased risk of bleeding. Prior study found increased risk of bleeding in those with platelet counts ≤5,000 cells/μL compared to those with platelet counts ≥81,000 cells/μL, although there was otherwise no clear correlation of decreased bleeding risk with increased platelet counts (8). There is no platelet count threshold at which the risk of bleeding cannot be accounted for (9), and hemorrhagic complications directly impact survivorship among patients with malignancy (10). Thrombocytopenia often carries prohibitive surgical risk and is a relative contraindication for percutaneous pericardiocentesis (11). Traditional approach included attempts to correct thrombocytopenia with prophylactic platelet transfusion with a platelet count goal $>50 \times 10^3$ cells/μL (12).

Our study analyzed the prognostic factors and overall survival (OS) of pericardiocentesis in thrombocytopenic patients with diagnosis of malignancy and attempted to determine the utility of platelet count and hemostatic evaluations in predicting bleeding risk, hypocoaguable state, and mortality among thrombocytopenic cancer patients undergoing pericardiocentesis. To our knowledge, this was the first retrospective survivorship analysis of this particular patient population after primary percutaneous pericardiocentesis.

MATERIALS AND METHODS

The Institutional Review Board of The University of Texas MD Anderson Cancer Center (MDACC) approved this study with a waiver for written informed consent. In December 2018, a retrospective review of the MDACC cardiac catherization laboratory registry for cancer patients with platelet counts $<150 \times 10^3$ cells/μL who underwent primary percutaneous pericardiocentesis between October 1, 2009 to November 30, 2018 was performed. In total, 136 patients met the criteria above and were included in this study. Severity of thrombocytopenia was classified based on platelet count recorded for each patient on the day of pericardiocentesis based on NCI-CTCAE version 5 criteria (13): grade 1 ($75–149 \times 10^3$ cells/μL), grade 2 ($50–74 \times 10^3$ cells/μL), grade 3 ($25–49 \times 10^3$ cells/μL), and grade 4 ($<25 \times 10^3$ cells/μL). Recorded data included patient demographics, cancer history, and serological test results obtained 24 h peri-procedurally (**Table 1**) and echocardiographic data with evidence of increased pericardial pressure or cardiac tamponade physiology. Patients then underwent percutaneous pericardiocentesis with an indwelling pigtail catheter placement (5F Cook pericardial drain) preferably for 3–5 days. The catheter was removed if fluid drainage dropped below 25–50 mL with no residual effusion seen by follow-up echocardiography.

Recording a successful pericardiocentesis required an accurate technique with meticulous hemostasis, equipment availability (7 and 12 cm Cook micropuncture kits), image guidance (when possible a "triple safety" approach consisting in ultrasound-guided needle advancement, fluoroscopy, and echocardiography), and proficiency in subxiphoid and apical approach. Percutaneous pericardiocentesis was performed by using the shortest distance to the pericardial cavity from the subxiphoid or intercostal space, and using the 5-F micropuncture kit (Micropuncture Introducer Kit, Silhouette Transitionless Push-Plus Design, Cook Medical, Bloomington, Indiana) in order to reduce the bleeding risk, with intercostal site entry (lateral) being the preferred approach. Based on body habitus, skin and breast anatomy, scarring from previous surgeries, mediastinal shift from underlying malignancy or abdominal distension, lateral approach expanded between 4 and 6th intercostal space and from midclavicular to midaxillary line. In procedures where only echocardiographic guidance was available, or in patients with concomitant pericardial and pleural effusion or ascites, upon accessing the pericarial space, position was confirmed with agitated saline injection, followed by advancement of micropuncture dilator and additional confirmation with "microbubbles," and completed with the advancement of the multi-hole pigtail catheter under fluoroscopic guidance and suturing in place. In complex (unstable, challenging) patients where both echocardiographic and fluoroscopic guidance were available, to avoid incidental needle displacement and increase in procedural time, if fluid was serous, the pericardial space was secured advancing the micropuncture guidewire with fluoroscopic confirmation of the intrapericardial position prior to advancement. Fluid samples were sent to pathology and microbiology for analysis and results were documented.

Patient demographical characteristics were summarized using mean (SD) and median (minimum-maximum) for continuous variables and counts (%) for categorical variables. Overall survival (OS, time interval from procedure (pericardiocentesis) to death or last follow up) was calculated. Univariate and multivariate Cox proportional hazards regression analyses were conducted to identify variables that were associated with

Abbreviations: PE, pericardial effusion; PLADO, prophylactic platelet dose on transfusion outcomes trial; OS, overall survival; MDACC, MD Anderson Cancer Center; CI, confidence interval; CS, cumulative survival; TEG, Thromboelastography; INR, international normalized ratio; HR, hazard ratio; MA, maximum amplitude.

TABLE 1 | Descriptive statistics of patient characteristics.

Categorical variable		*N* (%)	Continuous variable	Mean ± SD, Median (Min, Max)	*N*
Gender	Male	82 (60.3%)	Age (years)	53.27 ± 17.68, 56.16 (17.86, 84.77)	136
	Female	54 (39.7%)	Weight (kg)	77.54 ± 19, 75.8 (43.6, 134.5)	136
Race	White	82 (60.3%)	Height (cm)	169.76 ± 13.24, 170.1 (76, 196)	136
	Hispanic	18 (13.2%)	BMI (kg/m^2)	27.67 ± 13.42, 26.27 (16.73, 165)	136
	African American	19 (14%)	BSA (m^2)	1.89 ± 0.25, 1.89 (1.4, 2.51)	136
	Other	17 (12.5%)	Troponin I (ng/mL)	6.36 ± 50.15, 0.03 (0, 492)	103
Cancer type	Solid	42 (30.9%)	Troponin T (ng/mL)	21.13 ± 14.56, 19.5 (6, 43)	8
	Hematologic	98 (69.1%)	BNP (pg/mL)	509.05 ± 847.69, 241 (1.49, 5,479)	101
Primary cancer	Breast	4 (2.9%)	NT-proBNP (pg/mL)	737 ± 523.03, 650 (212, 1,582)	7
	Gastrointestinal	7 (5.1%)	Serum creatinine (mg/dL)	1.23 ± 1.11, 0.94 (0.3, 10.63)	136
	Genitourinary	3 (2.2%)	WBC ($cells/mL^3$)	5.51 ± 6.69, 3.55 (0, 41)	136
	Gynecologic	4 (2.9%)	Hemoglobin (g/dL)	9.48 ± 1.65, 9.1 (6.7, 14.6)	136
	Head and Neck	1 (0.7%)	pRBC administered within 24 h (units)	0.21 ± 0.49, 0 (0, 2)	23
	Leukemia	65 (47.8%)	Platelet count (day 0) (K/mL)	64.46 ± 45.07, 51 (6, 147)	136
	Lung	16 (11.8%)	Grade 1 (75–149 × 10^3 cells/μL)		55
	Lymphoma	29 (21.3%)	Grade 2 (50–74 × 10^3 cells/μL)		14
	Melanoma	1 (0.7%)	Grade 3 (25-49 × 10^3 cells/μL)		33
	Renal	1 (0.7%)	Grade 4 (0–24 × 10^3 cells/μL)		34
	Sarcoma	4 (2.9%)	Platelet administered within 24 h (units)	1.57 ± 3.42, 0 (0, 23)	37
	Thymus	1 (0.7%)	INR	1.31 ± 0.28, 1.26 (0.87, 3.05)	136
Advanced cancer		105 (77.2%)	LVEF (%) by TTE	55.23 ± 9.37, 55 (25, 70)	136
History of radiotherapy		44 (32.4%)			
Chemotherapy within 1 month		92 (67.6%)			
Tobacco smoker within 1 year		41 (30.1%)			
Hypertension		57 (41.9%)			
Dyslipidemia		87 (64%)			
Chronic lung disease		13 (9.6%)			
Diabetes mellitus		15 (11%)			
CKD, dialysis-dependent		2 (1.5%)			
Cerebrovascular disease		7 (5.1%)			
Coronary artery disease		6 (4.4%)			
Chronic heart failure		12 (12.6%)			
Family history premature CAD		8 (5.9%)			
Aspirin use only		14 (10.3%)			
Clopidogrel use only		3 (2.2%)			
DOAC use only		9 (6.6%)			
Platelet transfusion refractoriness		27 (19.9%)			
Cardiac tamponade on TTE		68 (50%)			
Complications		5 (3.7%)			
Procedural guidance modality	Echocardiogram	131 (96.3%)			
	Fluoroscopy	61 (44.9%)			
	Combined	96 (70.6%)			
Aspirated fluid appearance	Serous	57 (41.9%)			
	Hemorrhagic	79 (58.1%)			
Malignant aspirated fluid		56 (41.2%)			

CKD, chronic kidney disease; CAD, coronary artery disease; DOAC, direct oral anticoagulant; TTE, transthoracic echocardiogram.

increased risk of death. Kaplan-Meier survival plots were generated and log-rank test was used to compare among subgroups in OS. Estimated median follow-up using reverse Kaplan-Meier method was used, considering the event of death as a censor, so that unobservable follow-up time of each subject was interpreted as follow-up time. A $p < 0.05$ indicated a statistical significance. SAS 9.4 (SAS Institute INC, Cary, NC) was used for data analysis.

TABLE 2 | Univariate analysis for impact on overall survival.

Categorical variable		Hazard ratio (95% CI)	*p*-value
Gender	Male	1	
	Female	0.838 (0.565–1.243)	0.3796
Race	White	1	
	Hispanic	0.986 (0.541–1.798)	0.964
	African American	1.067 (0.605–1.883)	0.8223
	Other	1.148 (0.616–2.136)	0.6643
Cancer type	Solid	1	
	Hematologic	0.753 (0.492–1.154)	0.1931
Primary cancer	Breast	1.704 (0.524–5.537)	0.3755
	Gastrointestinal	0.517 (0.187–1.430)	0.2038
	Genitourinary	0.815 (0.198–3.354)	0.7768
	Gynecologic	1.492 (0.463–4.811)	0.5032
	Head and Neck	2.117 (0.289–15.491)	0.4601
	Leukemia	1	
	Lung	1.471 (0.813–2.660)	0.202
	Lymphoma	0.520 (0.296–0.911)	**0.0223**
	Melanoma	0.000 (0.000)	0.9867
	Renal	6.707 (0.886–50.760)	0.0653
	Sarcoma	1.126 (0.350–3.621)	0.8419
	Thymus	0.000 (0.000)	0.9903
Advanced cancer		10.717 (4.345–26.433)	**<0.0001**
History of radiotherapy		1.351 (0.892–2.046)	0.1549
Chemotherapy within 1 month		1.538 (0.892–2.396)	0.0565
Tobacco smoker within 1 year		1.382 (0.988–2.108)	0.1336
Hypertension		0.662 (0.445–0.984)	**0.0416**
Dyslipidemia		0.791 (0.525–1.192)	0.2624
Chronic lung disease		0.938 (0.488–1.802)	0.8467
Diabetes mellitus		0.643 (0.334–1.239)	0.1869
CKD, dialysis–dependent		2.673 (0.654–10.922)	0.1709
cerebrovascular disease		0.483 (0.153–1.530)	0.2164
Coronary artery disease		0.763 (0.280–2.077)	0.5959
Chronic heart failure		1.069 (0.606–1.886)	0.8182
Family history premature CAD		0.615 (0.249–1.520)	0.2926
Aspirin use only		0.543 (0.281–1.049)	0.0691
Clopidogrel use only		0.275 (0.038–1.980)	0.2001
DOAC use only		1.023 (0.448–2.337)	0.9569
Platelet transfusion refractoriness		1.874 (1.201–2.925)	**0.0057**
Cardiac tamponade on TTE		1.269 (0.857–1.879)	0.2337
Complications		0.707 (0.224–2.232)	0.5541
Procedural guidance modality	Echocardiogram	0.634 (0.257–1.563)	0.3224
	Fluoroscopy	0.944 (0.638–1.399)	0.775
	Combined	1.108 (0.712–1.725)	0.6481
Aspirated fluid appearance	Serous	1	
	Hemorrhagic	0.814 (0.546–1.214)	0.3131
Malignant aspirated fluid		1.659 (1.117–2.465)	**0.0122**
Age (years)		1.003 (0.992–1.014)	0.6026
Weight (kg)		0.999 (0.988–1.009)	0.816
Height (cm)		0.988 (0.974–1.002)	0.1027
BMI (kg/m^2)		1.008 (0.994–1.022)	0.2675
BSA (m^2)		0.826 (0.368–1.855)	0.6427
Troponin I (ng/mL)		0.996 (0.988–1.005)	0.3961
Troponin T (ng/mL)		1.018 (0.959–1.081)	0.5521
BNP (pg/mL)		1.000 (1.000–1.000)	0.8847
NT–proBNP (pg/mL)		1.000 (0.998–1.002)	0.8009
Serum creatinine (mg/dL)		1.000 (0.857–1.166)	1
WBC (cells/mL^3)		1.008 (0.975–1.042)	0.6452
Hemoglobin (g/dL)		1.015 (0.901–1.143)	0.8121
pRBC administered within 24 h (units)		1.297 (0.880–1.913)	0.0.1886
Platelet count (day 0) (K/mL)		0.993 (0.989–0.997)	**0.0021**
Grade 1 (75–149 × 10^3 cells/μL)		1	
Grade 2 (50–74 × 10^3 cells/μL)		1.276 (0.592–2.753)	0.5336
Grade 3 (25–49 × 10^3 cells/μL)		1.530 (0.928–2.522)	0.0959
Grade 4 (0–24 × 10^3 cells/μL)		2.102 (1.288–3.431)	**0.0029**
Platelet administered within 24 h (units)		1.055 (1.003–1.110)	**0.0374**
INR		2.583 (1.279–5.219)	**0.0082**
LVEF (%) by TTE		1.010 (0.987–1.033)	0.3888

SD, standard deviation; CI, confidence interval; BMI, body mass index; BSA, body surface index; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro brain natriuretic peptide; WBC, white blood cell: pRBC, packed red blood cell INR, international normalized ratio; LVEF, left ventricular ejection fraction; TTE, transthoracic echocardiogram. Boldface indicates statistical significance.

RESULTS

Our study included 136 patients with malignancy stratified by grade of severity of thrombocytopenia: 41% grade 1 (75–149 × 10^3 cells/μL); 10% grade 2 (50–74 × 10^3 cells/μL); 24% grade 3 (25–49 × 10^3 cells/μL); 25% grade 4 (<25 × 10^3 cells/μL) (**Tables 1**, **2**). Of the 136 patients, 35 survived during the follow-up period. After pericardiocentesis, median OS using reverse Kaplan-Meier method was 2.6 months with a median follow-up of 21.4 months (95% confidence interval (CI) 0.2–106.8 months). Significant OS differences were observed across thrombocytopenia grades recorded on day 0 ($p = 0.023$, **Figure 1**). Evaluation of patients based on platelet counts <100 × 10^3 cells/μL or ≥100 × 10^3 cells/μL showed a statistical significance in OS ($p = 0.031$). However, there were more patients with platelet count ≥100 × 10^3 cells/μL without advanced cancer than with advanced cancer (54.84 vs. 22.86%, $p = 0.0007$).

Variables showing significant association with OS based on univariate Cox models include elevated INR, platelet count on day of procedure, thrombocytopenia severity grade on day of procedure, platelet transfusion within 24 h of

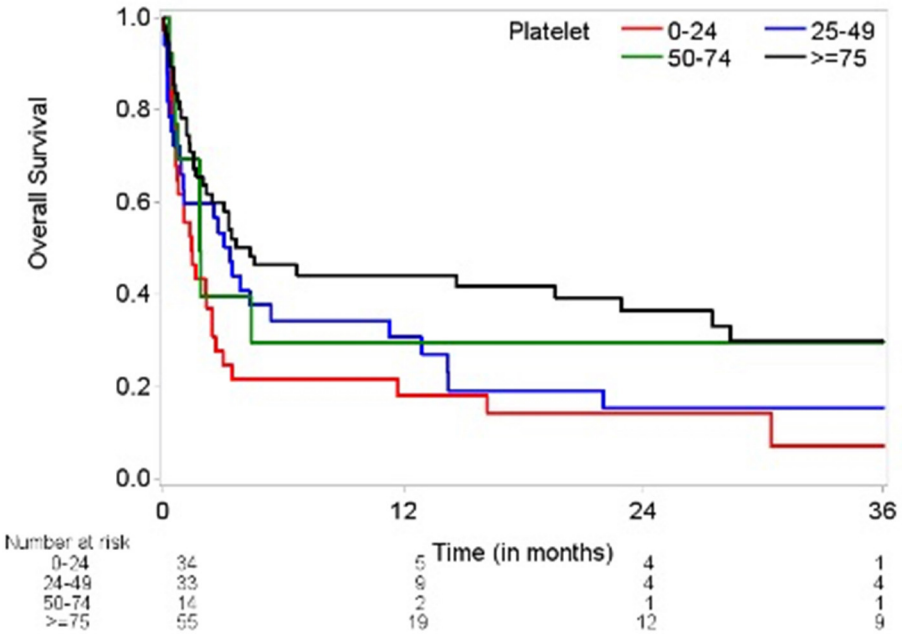

FIGURE 1 | Kaplan-Meier plot of overall survival by thrombocytopenia severity (log-rank test $p = 0.0234$). Time (months) on the *x*-axis marks time elapsed from pericardiocentesis. Overall survival (percentage) on the *y*-axis. Number at risk delineates the remainder of surviving patients at each time point in each group based on degree of thrombocytopenia and platelet count.

procedure, advanced cancer status, malignant fluid composition, and platelet resistance. Factors that did not show significant associations with OS included hemoglobin level, quantity of red blood cell transfusions, anticoagulant therapy, age, race, gender, cardiac tamponade, heart failure, prior radiotherapy, or recent chemotherapy.

The increased recorded platelet count as a continuous variable on procedure day was significantly associated with decreased risk of death (hazard ratio (HR) 0.993; 95% CI 0.989–0.997; $p = 0.002$). Thrombocytopenia grade 4 (HR 2.10; 95% CI 1.29–3.43; $p = 0.003$) comparing to grade 1 was associated with increased risk of death. Poor prognostic factors for OS were advanced cancer, malignant effusion, elevated INR, quantity of platelet transfusions, and platelet transfusion resistance. Adjusting for INR (HR 2.739; 95% CI 1.382–5.428; $p = 0.004$) and advanced cancer status (HR 10.865; 95% CI 4.328–27.277; $p < 0.0001$), thrombocytopenia severity grade on day of procedure ($p = 0.802$) became insignificant (**Table 3**). Based on the current data, the majority of patients had advanced cancer [105 (77%) with advanced cancer vs. 31 (23%) with non-advanced cancer] and the majority of patients with higher thrombocytopenia grade had advanced cancer (85–88% with advanced cancer for grades 2, 3, and 4). Including 105 patients with advanced cancer, thrombocytopenia grade was not significantly associated with OS in a univariate Cox model ($p = 0.736$) and in a multivariate Cox model ($p = 0.887$), adjusting for INR (HR 2.588; 95% CI 1.261–5.311; $p = 0.010$). Marginally significant association was observed in platelet count (as a continuous variable) in a univariate Cox model (HR 0.981; 95% CI 0.960–1.003; $p = 0.087$) and a multivariate Cox model (HR 0.980; 95% CI 0.958–1.002; $p = 0.077$), adjusting for INR (HR 65.396; 95% CI 0.986–4335.876; $p = 0.051$) including patients with non-advanced cancer. However, this multivariate Cox model included 5 events which are not large enough number of events to provide reliable HR estimates.

TABLE 3 | Overall survival by multivariate analysis including INR and advanced cancer status.

Variable	Level	Hazard ratio (95% CI)	*p*-value
INR	ln 1-unit change	2.739 (1.382–5.428)	**0.0039**
Platelet count (day 0) (K/mL)	Grade 1 (75–149 × 10^3 cells/μL)	1.000	
	Grade 2 (50–74 × 10^3 cells/μL)	0.872 (0.403–1.885)	0.7270
	Grade 3 (25–49 × 10^3 cells/μL)	0.861 (0.518–1.431)	0.5646
	Grade 4 (0–24 × 10^3 cells/μL)	1.112 (0.667–1.855)	0.6845
Advanced cancer	Yes	10.865 (4.328–27.277)	**<0.001**

INR, international normalized ratio. Boldface indicates statistical significance.

Pericardiocentesis was performed via subxiphoid (16, 12%) and left apical (120, 88%) approaches. One patient with grade 1 thrombocytopenia developed a hematoma at the pericardial drain site. In addition to the hematoma, other periprocedural issues involved shoulder pain (1 patient), and transient pericarditis (3 patients). Of these 5 patients, the 3 patients with pericarditis survived past 2 months. Three out

of 6 (50%) patients who died within 60 days all suffered from advanced malignancy and coagulopathy with elevated INR. Other than the one patient with hematoma, there were no significant periprocedural bleeding complications, regardless of platelet count.

Pericardial window was performed in 6 patients, four of whom survived past 1 month. Platelet counts on day 0 for patients undergoing pericardial window ranged from 12×10^3 to 106×10^3 cells/μL. The two patients who did not survive had additional neutropenia and one elevated international normalized ratio (INR) level. All had advanced cancer staging (4 leukemia, 1 lymphoma, 1 lung cancer) with recurrent PEs after subsequent pericardiocentesis.

Pre-procedural platelet transfusions were administered for 36 patients (26%), 27 of whom were determined to have platelet transfusion refractoriness, defined as post-transfusion platelet count increment $< 10 \times 10^3$ cells/μL within 24 h after platelet transfusion.

Thromboelastography (TEG) was performed in 8 patients prior to pericardiocentesis, among patients in all four grades of thrombocytopenia. TEG results revealed hypocoagulability in 4 patients (2 with grade 1, 2 with grade 3, 1 with grade 4); 3 TEGs revealed normal clotting function (2 with grade 3, 1 with grade 4), and 1 revealed hypercoagulability (grade 1) (**Table 4**). Five of the patients with performed TEGs presented in cardiac tamponade. Only one patient with TEG evaluation received pre-procedural platelet transfusion (patient had hypocoaguable TEG result, with grade I thrombocytopenia).

TABLE 4 | Thromboelastography (TEG) interpretation, by platelet group.

Platelet group ($n = 8$)	Hypocoaguable TEG	Normal TEG	Hypercoagulable TEG
Grade 1 (platelet count 75–149 $\times 10^3$ cells/μL)	1		1
Grade 2 (platelet count 50–75 $\times 10^3$ cells/μL)			
Grade 3 (platelet count 25–49 $\times 10^3$ cells/μL)	2	2	
Grade 4 (platelet count 0–24 $\times 10^3$ cells/μL)	1	1	

TEG, interpretation based on pathologist review.

DISCUSSION

Patients with PE and underlying malignancy typically present less acutely without hemodynamic compromise, and face decreased OS compared to those without malignancy (1). The only serological marker shown to have a statistically significant negative influence on OS was elevated INR, indicating underlying coagulopathy may worsen overall prognosis. INR was elevated for several non-specific reasons in these patients, however, including anticoagulation, liver dysfunction, malnutrition, vitamin K deficiency. Patients with elevated INR tended to be very ill, and the severity of their disease likely contributed to the correlation with trends for worse OS. Similarly, advanced cancer status was heavily correlated with degree of thrombocytopenia, and likely a confounding variable for OS as highlighted in **Table 3**. After multivariate analysis, thrombocytopenia severity was not

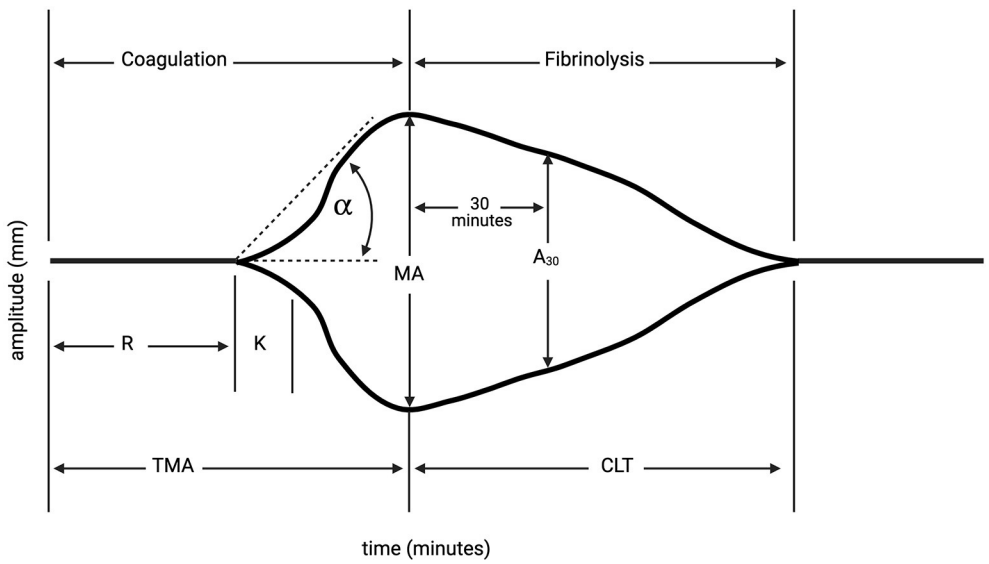

FIGURE 2 | Thromboelastography (TEG). TEG is a hemostatic blood test which dynamically evaluates platelet function and clotting efficacy of whole blood. Reaction time (R) is latency from start of test to initial fibrin formation, and is dependent on clotting factors (normal: 4–8 min). Kinetics (K) is the duration taken to achieve clot strength of amplitude 20 millimeters (mm) (normal: 1–4 min). Alpha (α) measures the speed of fibrin cross-linking, dependent on fibrinogen (normal: 47–74°). Maximum amplitude measures ultimate strength and stability of fibrin clot (mm) (normal: 55–73 mm). Time to reach maximum amplitude (TMA); percentage decrease in amplitude 30-min post-MA (A_{30}); Clot lysis time (CLT). At our institution, hypocoagulability on TEG is defined as a prolonged reaction time (R-time, minutes to clot formation), low alpha angle (measures clot kinetics), and low maximum amplitude (MA, millimeters, measures clot strength). Created with Biorender.com.

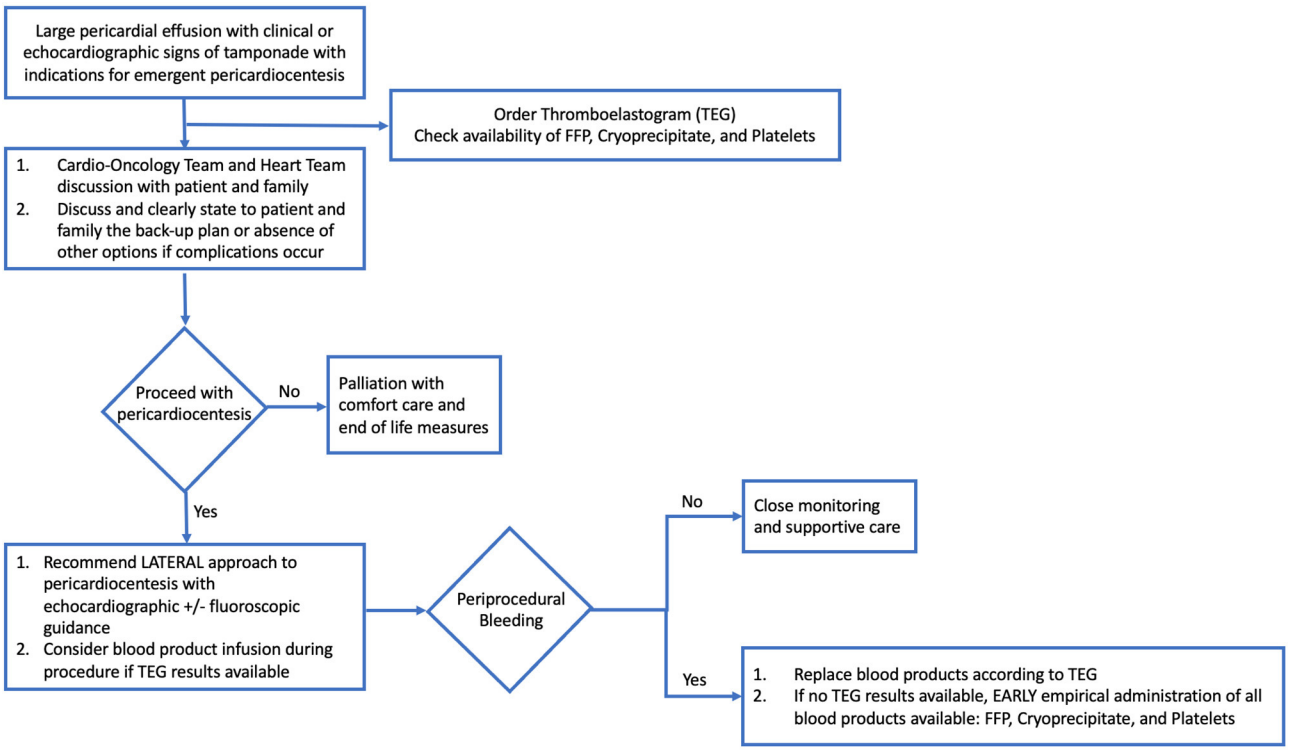

FIGURE 3 | Flow-Chart: Approach to large pericardial effusion in patient with malignancy. Hemodynamically significant pericardial effusion in a patient with malignancy is a complex clinical scenario, one which requires appropriate clinical coordination, laboratory evaluation, and preparation. Important factors include a multidisciplinary discussion with Cardio-Oncology Team, Heart Team, patient and family members to discuss risks, benefits, and back-up options for complications, as well as consideration of palliation and comfort care measures. If proceeding with pericardiocentesis, recommended procedural approach is lateral and with echocardiographic ± fluoroscopic guidance, plus consideration of blood product administration based on laboratory results and thromboelastogram results. In the setting of periprocedural bleeding, early replacement of blood products according to TEG results or empiric administration of all blood products available is of paramount importance, in addition to achieving hemostasis and ongoing supportive care.

significantly associated with OS when advanced cancer and elevated INR were also accounted for.

Worse OS was associated with advanced carcinoma stage and malignant etiology of effusion. However, chemotherapy, radiotherapy, or concomitant infection did not show statistical significance in respective effects on OS. At 1 year post-pericardiocentesis, increased mortality was noted in patients with thrombocytopenia grades 2, 3, and 4 that also correlated with cancer severity and was attributed to natural progression of cancer.

Approach to the pericardial space has evolved; the preferred approach in thrombocytopenic patients is lateral with intercostal site entry between 4 and 6th intercostal spaces and from midclavicular to midaxillary line, unless there are adhesions between the left ventricular apex and pericardial sac or technical barriers to access (skin infections, scars from previous interventions, implants, additional pleural effusion) or the access to the pericardial space is through reduced amount of tissue and avoids hepatic structure or the loculated pocket is accessible only subxiphoid (14). A large study at our institution of pericardiocentesis in malignant PE yielded procedural site selection rates of subxiphoid approach in 63% and lateral intercostal approach in 37% of patients, with low complication rates (12).

TEG, a hemostatic blood test which dynamically evaluates platelet function and clotting efficacy of whole blood (**Figure 2**), can be a helpful tool to determine bleeding risk in thrombocytopenic cancer patients prior to pericardiocentesis in stable patients (15, 16). In thrombocytopenic patients, platelet function rather than platelet count often correlates with bleeding, and hemostasis appears to be affected more than platelet adhesion (17, 18). TEG results in thrombocytopenic cancer patients with PE may provide a more comprehensive risk stratification before pericardiocentesis, and may help determine the appropriate blood product administration when hemorrhagic complications arise, approach already established for the coronary procedures (19).

In terms of intervention modality, an initial surgical approach with pericardial window could potentially provide superior results compared to percutaneous procedures due to decreased PE recurrence rates (1). When balancing the increased safety from combining echocardiographic and/or fluoroscopic guidance during percutaneous pericardiocentesis with the increased bleeding risk in thrombocytopenic patients

with open surgical procedures, the clinical decision has gradually inclined toward the less-invasive approach without any apparent impact on long-term outcomes. Complication rates in this study were consistent with the low incidences reported in prior image-guided studies in non-thrombocytopenic patients, of anywhere between 4 and 20% (7, 20–23). The decreased rate of complication we assume is due to using micropuncture technique and both echocardiographic and fluoroscopic guidance, and in comlex cases even triple-guidance with additional ultrasound-guided access.

In thrombocytopenia grades 3 and 4, mortality rate only increased after 1 year and only one patient with grade 4 thrombocytopenia had peri-procedural complications. In patients with extreme thrombocytopenia we found value in having a detailed discussion with the patient and family reflecting the lack of a surgical rescue option if certain complications occur, therefore a "no plan B situations" explanation is of paramount importance before the procedure. Especially in cases of hemodynamic instability, there are no absolute contraindications for pericardiocentesis in that it may be a necessary life-saving procedure, even in patients with severe thrombocytopenia and coagulopathy (24).

In cardiology and medicine, it is imperative to consider the ratio of risk to benefit in considering interventional diagnostic and therapeutic procedures. This study found that the greater the severity of thrombocytopenia, the greater the risk for intervention. In the case of pericardiocentesis with thrombocytopenia, the procedural risk increases as the platelet count decreases. More severe thrombocytopenia may be associated with more platelet transfusion refractoriness, less surgical back-up available, and lower overall survival. However, in patients with advanced malignancy, it is sometimes pertinent to proceed with higher risk procedures to achieve desired benefit due to the severity of disease and need for intervention. It is of utmost importance, therefore, for the cardio-oncology team to weigh risk and benefits and have the discussion with patients when performing diagnostic and therapeutic interventions such as pericardiocentesis (**Figure 3**). The low rate of periprocedural complications in our study may well be attributed to the consideration of these risks and benefits, and careful appropriate procedural technique.

Limitations

Study limitations included a small sample size and the retrospective nature of data collection. A process of randomization of patients to pericardiocentesis, pericardial window, or medical therapy alone is challenging to imagine, more so to execute. Furthermore, the entry site during pericardiocentesis was ultimately dependent on patient's anatomy, ability to lie flat and interventionalists level of comfort with the approach. The use of TEG in a very small number of patients limits the ability to draw strong inferences from its interpretation. Future analysis of TEG in this patient population could be a helpful risk stratification tool. Finally, determining the utility of peri-procedural platelet transfusion is difficult since certain malignancies and their treatment can add complexity to an already coagulopathic clinical challenge.

CONCLUSIONS

In a high-risk patient population with cancer-related large pericardial effusion and thrombocytopenia, pericardiocentesis is a feasible intervention with low complication rates when appropriate equipment and technique are used. Furthermore, there is no absolute contraindication to pericardiocentesis in cases of hemodynamic instability, even with severe thrombocytopenia. The grade of thrombocytopenia reflects disease severity; however, no significant association was observed with respect to OS when adjusting for advanced cancer status and INR. Further studies will be needed to refine the role of grade of thrombocytopenia in non-advanced cancer patients, and platelet transfusions and platelet function tests in multivariate analysis in this patient population.

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 Institutional Review Board of the University of Texas MD Anderson Cancer Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

NW and ML wrote the manuscript. NP, JL-M, MC, KM, and CI conceived the study, performed data analysis, and reviewed and approved the final manuscript product. NW, ML, CG, AS, TD, DB, and JS performed data collection and analysis and reviewed, edited, and approved the final manuscript product. All authors contributed to the article and approved the submitted version.

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frontiers in Cardiovascular Medicine

REVIEW
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Epigenetic Mechanisms Involved in the Cardiovascular Toxicity of Anticancer Drugs

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The cardiovascular toxicity of anticancer drugs promotes the development of cardiovascular diseases. Therefore, cardiovascular toxicity is an important safety issue that must be considered when developing medications and therapeutic applications to treat cancer. Among anticancer drugs, members of the anthracycline family, such as doxorubicin, daunorubicin and mitoxantrone, are known to cause cardiotoxicity and even heart failure. Using human-induced pluripotent stem cell-derived cardiomyocytes in combination with "Omic" technologies, we identified several cardiotoxicity mechanisms and signal transduction pathways. Moreover, these drugs acted as cardiovascular toxicants through a syndrome of mechanisms, including epigenetic ones. Herein, we discuss the main cardiovascular toxicity mechanisms, with an emphasis on those associated with reactive oxygen species and mitochondria that contribute to cardiotoxic epigenetic modifications. We also discuss how to mitigate the cardiotoxic effects of anticancer drugs using available pharmaceutical "weapons."

Keywords: induced pluripotent stem cells, hiPSCs, cardiotoxicity, heart failure, genomics biomarkers, anthracyclines, anticancer therapy, epigenetic mechanisms

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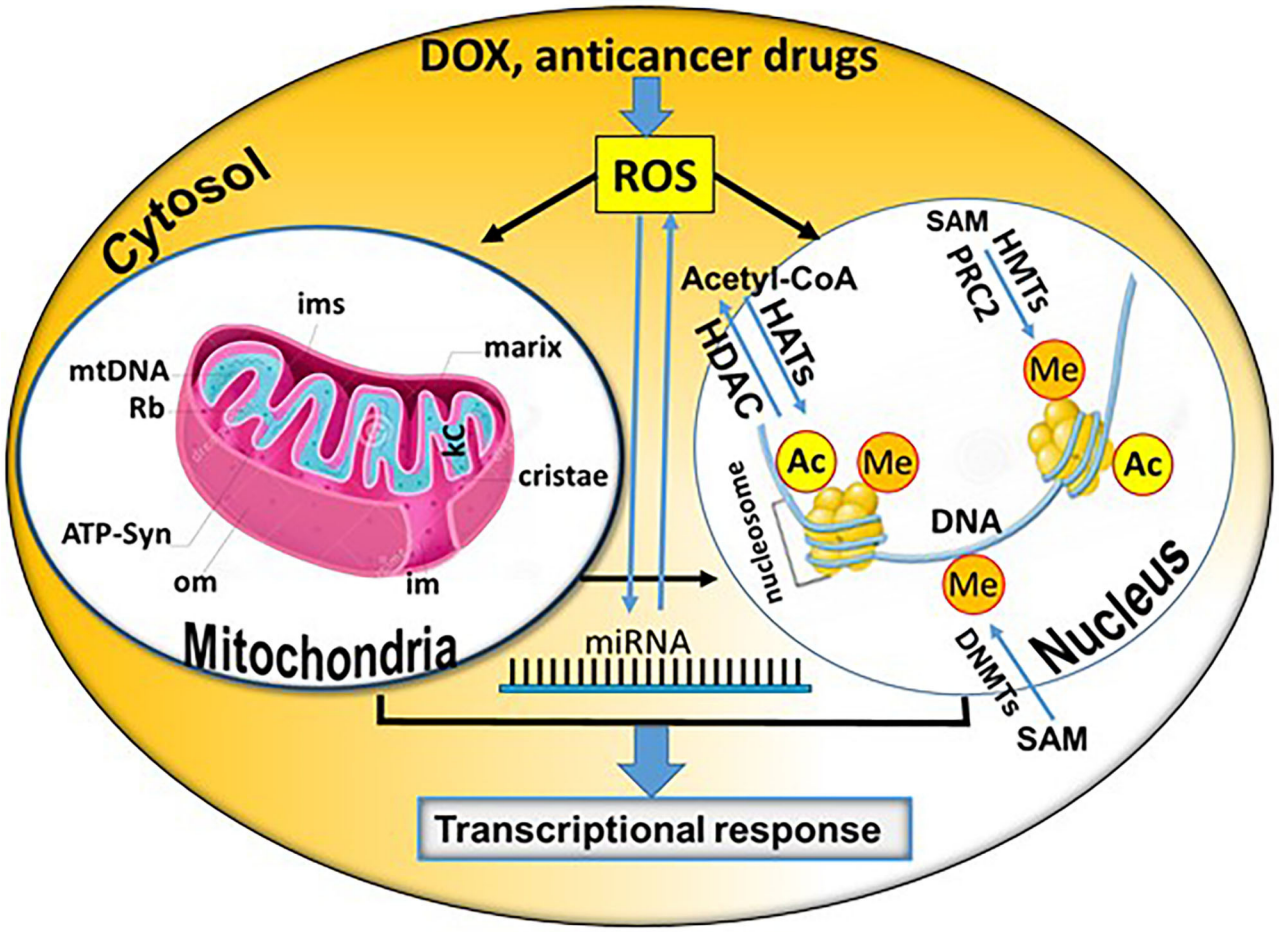
INTRODUCTION

Doxorubicin (DOX; brand name: Adriamycin) was one of the first anthracyclines isolated from *Streptomyces* actinobacterial strains. It is the most commonly prescribed chemotherapy drug to treat breast, ovarian and gastrointestinal cancers, sarcomas, leukemia, non-Hodgkin's and Hodgkin's lymphomas, multiple myeloma and various other cancers, because it shows beneficial therapeutic effects (1). One of its main mechanisms of anticancer activity involves DNA interference, preventing DNA replication and proliferation of the target cancer cells. Moreover, it has been found to interfere, not only with the nuclear DNA, but also with mitochondrial DNA (mtDNA), affecting the energy metabolism (through depletion of adenosine triphosphate; ATP) of several specific cells, including cardiomyocytes (CMs) (2). Another anticancer mechanism of DOX against tumors is the inhibition of topoisomerase IIa (TopIIa), a nuclear enzyme capable of breaking down and reassembling DNA strands in a controlled manner.

DOX acts by producing reactive oxygen species (ROS), causing oxidative stress, damaging cell structures and activating cell death pathways. Patients' responses to this medication are not linear. Indeed, some patients appear to be tolerant to high doses of DOX, while others manifest heart attacks at low-dose (3). ROS play a significant role in the development of cardiovascular diseases



Graphical Abstract | Summary of potential direct and indirect epigenetic mechanisms contributing to the cardiotoxicity of doxorubicin (DOX) and other anticancer drugs (Rb, Ribosomes; kc, Krebs Cycle; om, outer membrane; im, inner membrane; ims, intermembrane space; miRNA, microRNA; SAM, S-adenosyl-L-methionine; Ac, acetylation; Me, methylation; DNMTs, DNA methyltransferases; CoA, coenzyme A; HATs, histone acetyltransferases; HDACs, histone deacetylases; PRC2, RNA polymerase II (RNAPII) can initiate the gene expression process in euchromatin. The polycomb repressive complex 2; HMTs, histone methyltransferases). The core mitochondrion and nucleosome shown in the figure were obtained from Dreamstime.com (https://de.dreamstime.com/) and modified accordingly.

(CVDs), including arrhythmia, cardiomyopathy and heart failure (4, 5). Aside from ROS and other peroxide radical-mediated pathways, DOX induces mitochondrial DNA damage and imbalances calcium and/or iron homeostasis (6). One main pathway through antineoplastic drugs is the generation of ROS (7, 8). This process increases oxidative stress, killing cancerous cells, but also generates toxic mediators that affect intact cells by acting on diverse cellular molecules, such as DNA or proteins. Oxidative stress has been implicated as one of the main cellular events related to CM damage. Several factors may be involved in cancer-related cachexia and cardiac impairment. Pro-inflammatory cytokines, such as IL-6, IL-1β and TNF-α, are the main contributors to heart failure. In addition to inflammation, it is worth mentioning that redox regulation is also associated with cancer progression, where elevated levels of ROS are found in most types of tumors (7, 8). Tumors release pro-inflammatory cytokines that can result in oxidative stress, suggesting that an inseparable relationship exists between the production of ROS and an inflammatory status. The tumor itself releases inflammatory cytokines, which are likely important for inducing a ROS niche, favoring new mutations. The C-reactive protein can predict cardiovascular mortality and is commonly used as a biomarker for acute and chronic inflammation (7, 8). In cancer cells, aside from the inhibition of TopIIa activity, DOX also induces cell death, related to redox metabolism. DOX undergoes redox cycling, catalyzed by the cytochrome P540 system. The product of this reaction is the DOX-semiquinone radical (9). This radical causes oxidative damage of tumor cells through the release of iron from its cells. The DOX-iron complexes catalyze oxygen and hydrogen peroxide into potent ROS, which trigger important antitumor responses in cancer cells. Very often, the misbalance between antitumor and adverse effects results in heart injury (9, 10).

Anticancer treatment is not only accompanied by cardiotoxicity, but also vascular toxicity. Common examples of anticancer drugs inducing acute vasospasm are 5-fluorouracil

(5-FU) and *per os* administration of capecitabine. These mechanisms suggest activation of the protein kinase C signaling pathway, which leads to imbalanced calcium regulation, causing a dramatic reduction in contractility of vascular smooth muscle cells in the vessels. Arterial vasospasm is manifested by endothelial dysfunction related to the toxic effects of 5-FU on endothelial cells. Patients who have pre-existing endothelial dysfunction, such as those with coronary artery diseases, are at greater risk of developing vasospasm from 5-FU than those who do not. In addition, thymidine phosphorylase, which catalyzes the last step in the conversion of capecitabine to 5-FU, is expressed in atherosclerotic plaques. Therefore, its administration can lead to high local concentrations of 5-FU and increased risk (80%) of developing vasospasm. CVDs that usually occur are angina pectoris (45%), followed by myocardial infarction (22%), arrhythmias (23%), ventricular fibrillation, as well as cases of cardiac arrest and sudden cardiac death (11).

In contrast, paclitaxel therapy has been associated with acute coronary syndrome. Myocardial infarction and myocardial ischemia have been observed up to 14 days after starting paclitaxel therapy. Increased Rho kinase activity in vascular smooth muscle cells of the coronary artery are thought to be associated with angiospasms caused by paclitaxel. Several alkaloids (vinblastine, bleomycin and cisplatin) have been associated with endothelial toxicity that may cause an acute coronary ischemia. These drugs are usually prescribed in combination, although more than 2/3 of patients develop angina pectoris during chemotherapy. Cisplatin can cause acute thrombosis as well as acute vasoconstriction in cancer patients, with severe effects observed even two decades after its administration. In fact, the probability that these patients will develop coronary artery diseases is seven times higher than expected (12).

The most important epigenetic mechanisms involve pathways leading to DNA methylation, post-translational histone modifications and regulation of gene expression via non-coded RNAs, such as microRNAs (miRNAs; alternative name miRs) and long non-coding RNAs (lncRNAs) (**Figures 1**, **2**). In addition, epigenetic chromatin alterations occur, linked to environmental factors as well as different drugs that target epigenetic pathways. Epigenetic mechanisms provide transcriptional control in the regulation of gene expression (13). Evidence suggests that epigenetic modifications are associated with changes in both development and behavior, as well as with genetic disorders and diseases. Typically, during the aging of cells, epigenetic changes occur throughout the genome. This process is known as the "epigenetic clock phenomenon" (14). Epigenetic mechanisms not only regulate genomic expression, but also alter drug absorption, metabolism and excretion. The field of pharmacoepigenetics involves study of the variable epigenetic factors that are responsible for differences in patient-to-patient drug responses, new pharmacological targets, as well as disease prognosis and monitoring of long-term biological responses. This scope was expanded, once genetic factors were found to insufficiently explain the differences observed between patients receiving similar or the same treatment regimens (15). Epigenetic mechanisms represent a stable "cell mnemonic" that allows the spread of gene activity from one generation of cells to another. Given that CVDs are responsible for at least 1/3 of premature deaths worldwide, it is worth emphasizing that epigenetic changes are caused by the cardiotoxicity linked to anticancer drugs. How such epigenetic changes can be translated into clinical practice for the development of innovative and effective biomarkers for CVDs remains a challenge (16).

GENERAL ASPECTS OF THE EPIGENETICS

A cell contains ∼2 meters of DNA within its nucleus, which is organized into chromatin and further into chromosomes. Each human diploid somatic cell contains 23 pairs of chromosomes, and each chromosome contains several hundreds of thousands of nucleosomes (17). Each nucleosome, which is the core unit of the chromatin, is composed of negatively charged DNA, tightly wound around positively charged histone pairs (H2A, H2B, H3 and H4), forming a histone protein octamer. Epigenetics is the study of processes resulting in gene expression without modification of the DNA sequence; these processes modify the phenotype of an individual without changing the genotype (18). Epigenetic (pathological) modifications can also be triggered by environment/lifestyle, age, disease, chemicals, drugs and toxicants (19, 20).

Epigenetic modifications occur physiologically, mainly via methylation of the chromatin DNA and via methylation and acetylation of chromatin-histones (19, 20). DNA methylation occurs via DNA methyltransferases (DNMTs), which enable the transfer of a methyl group from the S-adenosyl-L-methionine (SAM) to the fifth carbon atom of cytosine bases, forming pairs with guanidine bases (called CpG DNA regions) (**Figure 1**). Normally, DNA methylation by DNMTs causes a gene expression silencing (21, 22). Demethylation of the CpG DNA regions occurs passively or via the Ten-Eleven Translocation (TET) pathway, increasing gene expression (23).

Histone acetylation of lysine residues (H3K4, H3K9, H3K18, H3K23m H3K27, H3K36-37, H4K8, H4K12, K4H18 H4K20 and H431), as well as on arginine residues (H3R2, H3R8, H3R17, H3R26, H4R3), is catalyzed via the histone acetyltransferase (HAT) enzymes (several isoforms), which induce the transfer of acetyl residues from acetyl-coenzyme A (CoA) to the ε-amino of lysine residues. Deacetylation of a ε-N-acetyl lysine amino acid from histones occurs via histone deacetylases (HDACs) (24, 25) (**Figure 2A**). Histone methylation is catalyzed by histone methyltransferases (HMTs), with transfer of methyl groups from SAM to lysine and arginine amino acid residues (26, 27) (**Figure 2B**). Notably, methylation of histones does not alter the charge of the histones, but rather the volume and hydrophobicity of the histones. Alteration of these parameters facilitates binding of effector-specific molecules, forming chromatin-binding complexes. These induce modifications of the chromatin structure (26, 27). Methylation of histone H3 lysine 4 (H3K4me), H3K36me and H3K79me leads to transcriptional activation, whereas methylation of H3K9me, H3K27me3 and H4K20me leads to transcriptional repression via modification of euchromatin (open chromatin; less condensed chromatin) to heterochromatin (highly condensed chromatin) (27). In contrast to heterochromatin, RNA polymerase II (RNAPII) can initiate the gene expression process in euchromatin. The polycomb

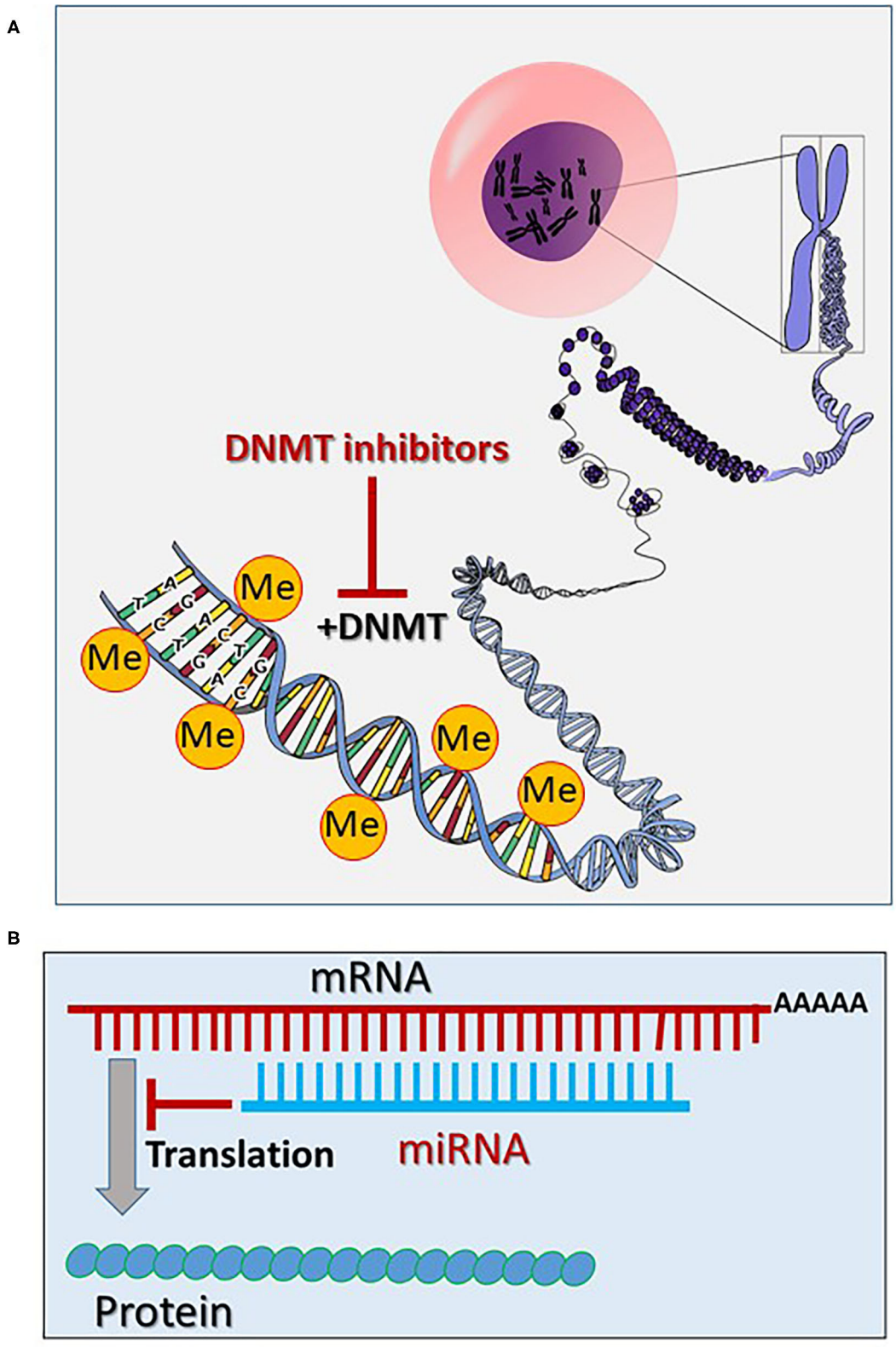


FIGURE 1 | (A) Epigenetic mechanisms via methylation of the chromatin DNA (the core figure was obtained from Open Clipart-Vectors; https://pixabay.com/de/users/openclipart-vectors-30363/) and modified accordingly (see section General Aspects of the Epigenetics). **(B)** Inhibition of the mRNA translation via targeting and degradation of the mRNA by microRNAs (miRNAs) (see section General Aspects of the Epigenetics). (Me, methyl; DNMT, DNA methyltransferase).

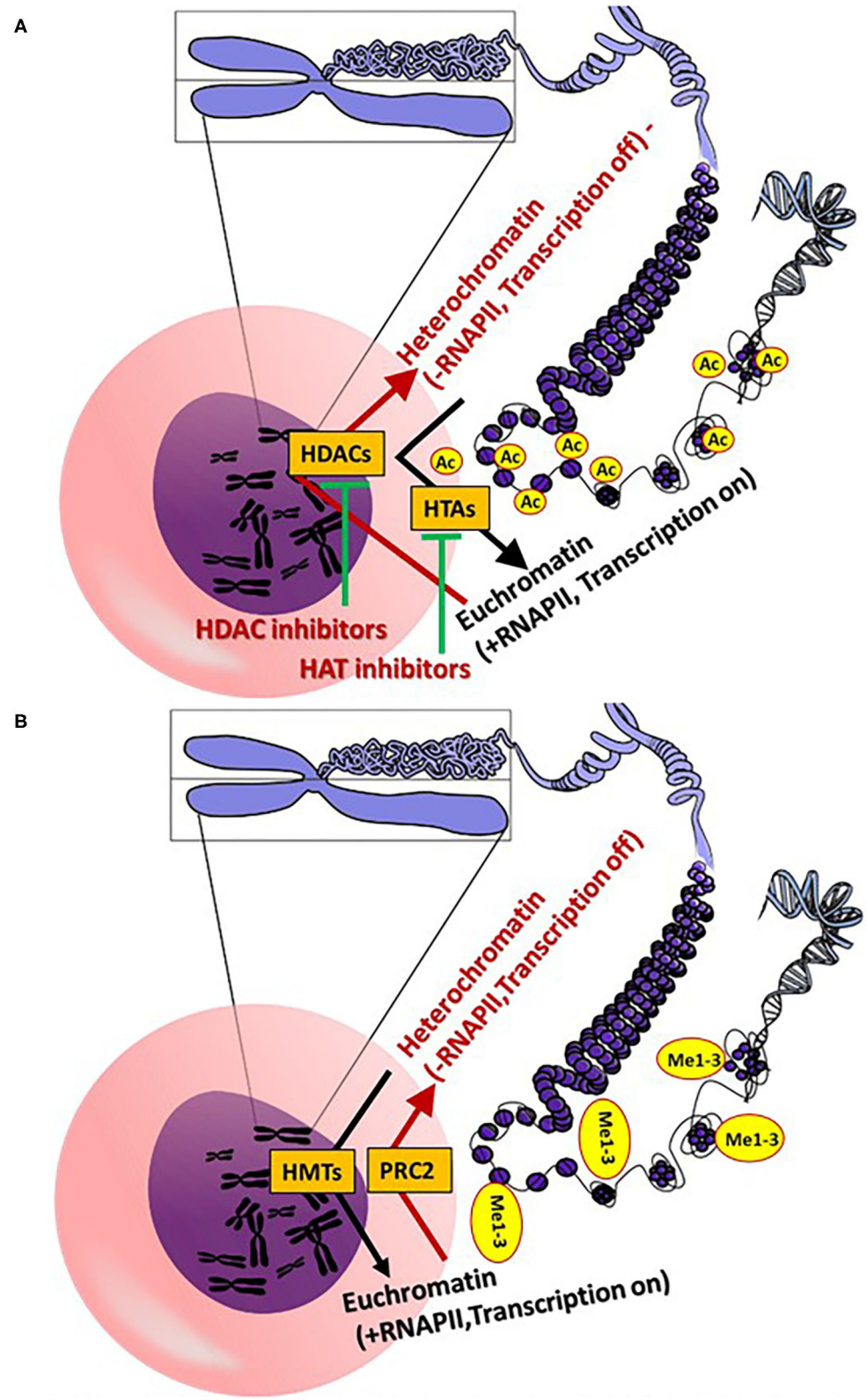


FIGURE 2 | (A) General epigenetic action mechanisms of histone acetylation and deacetylation. **(B)** Epigenetic action mechanisms of histone methylation [see section General Aspects of the Epigenetics **(A,B)**: Core figure was obtained from OpenClipart-Vectors (https://pixabay.com/de/users/openclipart-vectors-30363/] and modified accordingly. (Me, methyl; HDAC, histone deacetylases; RNAPII, RNA polymerase II; PRC 2, polycomb repressive complex 2; HMTs, histone methyltransferases; HTAs).

repressive complex 2 (PRC2; a multi-subunit protein complex) catalyzes tri-methylation of H3K27 to H3K27me3 to regulate the development of multicellular organisms (28). Another key epigenetic regulation of gene expression occurs via histone acetylation and deacetylation of lysine residues (24, 25). In contrast to deacetylation, histone acetylation induces a less tightly packed chromatin (euchromatin), elevating gene expression via RNAPII.

Promising cancer (and cardiovascular) therapeutics that target epigenetics are currently being developed (27, 29, 30). These so-called epi-drugs are small chemical molecules, which act as inhibitors to key epigenetic enzymes, such as DNMTs (e.g., 5-aza-2-deoxycytidine), HATs (curcumin) and HDACs (vorinostat) (29) (**Figures 1**, **2**). Clinical trials with 100 epi-drugs are ongoing, although six epi-drugs have already been approved by the US Food and Drug Administration (FDA) (27) (**Table 1**). Other epigenetic modulators are miRNAs, which regulate gene expression without modifying the gene sequence. They act via specific targeting of mRNAs using complementary sequences, leading to degradation of the appropriate mRNA, which affects protein levels (**Figure 1B**). In addition, the expression of miRNAs can also be regulated by epigenetic mechanisms, including DNA methylation and histone methylation and/or histone acetylation (31). Several miRNA-targeted therapeutics have reached clinical phase trials for treating of cancer and hepatic diseases (32).

DIRECT AND INDIRECT EPIGENETIC DYSFUNCTIONS CAUSED BY DOXORUBICIN

Manifestations of DOX's cardio toxicity include the development of fibrotic lesions, disordering of the CMs and significant deregulation of the transcription processes. Interestingly, even at low doses of DOX, changes occur to the transcriptional profile of many HDACs, which are known epigenetic regulators of cardiac configuration (33). Therefore, a novel cardio protective therapy, based on targeting HDAC enzyme activity during DOX therapy, remains an attractive goal (34). Pathological processes leading to heart dysfunction and heart failure are caused by a cascade of rapid post-translational modifications, governed by a strong epigenetic mechanism. This is most likely caused by HDACs, which play a key role in histone or protein deacetylation, and consequently, in controlling total gene expression (12). When it comes to anticancer treatment with DOX, there are many examples of how epigenetic aspects affect the response of cancer cells to drugs. For example, estrogen enhances the sensitivity of breast cancer cells to both DOX and cisplatin via a self-induced hypermethylation mechanism. More recently, it has been reported that mutations in SETD2, a trimethyltransferase-3-lysine-36 (H3K36me3), have led to increased resistance to chemotherapy through *in vitro* and *in vivo* leukemia models. In terms of cardiotoxicity, there has been a growing interest in sirtuin proteins (SIRTs), a category of NAD^+-dependent deacetylases that catalyze the deacetylation of many proteins, including histones. These proteins have been shown to play an important role in cardioprotection against the cardiotoxicity induced by DOX (35). ROS has been discussed as a key modifier of the epigenetic landscape, mediating the adverse effects of ROS on cancer and CVDs (36, 37). In this context, ROS affect DNA methylation, histone modifications (acetylation and methylation) and non-coding RNA expression [extensively reviewed by (36)]. Consequently, changes in the epigenetic landscape result in abnormal gene expression in both the nucleus and mitochondria, mediating development of CVDs.

Disruption of normal mitochondrial function has been shown to be one of the leading causes of heart injury, consistent with the fact that mitochondria are responsible for producing about 90% of the ATP metabolized by CMs. It is well-known that, in addition to its high affinity for DNA, DOX and other anthracyclines interact with cardiolipine, a mitochondrial negatively charged phospholipid. The interaction of DOX with cardiolipine causes a reversal of the electron transport chain, because cardiolipine is required for normal electron transport chain function and activity, as well as healthy functioning of the cell's respiratory chain (38). Changes in DNA methylation levels are particularly

TABLE 1 | Epi-drugs approved by the US Food and Drug Administration against cancer and bipolar disorders (27).

Therapeutic compound/drug name	Therapeutic target	Epidrug class/biological effect	Interventional clinical trials status	Number of studies	Same pathologies/disorder investigated
Azacitidine (5-Azacytidine)/Vidaza	DNMT1	DNA Methylation Inhibitor	FDA-approved		Myelodysplastic Syndrome
Decitabine (5-aza-2'-deoxycytidine)/Dacogen	DNMT1	DNA Methylation Inhibitor	FDA-approved		Myelodysplastic Syndrome
Belinostat/Beleodaq	HDACs	Histone Deacetylation Inhibitor	FDA-approved		Relapsed or refractory peripheral T-cell Lymphoma
Romidepsin/Istodax	HDACs	Histone Deacetylation Inhibitor	FDA-approved		Cutaneous T-cell Lymphoma.
Panobinostat (Hydroxamic Acid)/Farydak	HDACs	Histone Deacetylation Inhibitor	FDA-approved		Multiple Myeloma
Valproic acid/depakene and Stavzor	HDACs	Histone Deacetylation Inhibitor	FDA-approved		Bipolar disorder, Adjunctive Therapy in Multiple Seizure

HDACs: Histone deacetylases; DNMT: DNA methyltransferase.

evident in the kelch-like family member 29 (Klhl29) and the Nicotinamide mononucleotide adenylyltransferase 2 (Nmnat2) gene, where they are associated with changes in mRNA gene expression. It is important to note that DOX may lose an electron catalyzed by the dehydrogenation of mitochondrial NADH, causing formation of free radicals. Oxidative stress, in turn, damages proteins, DNA and membranes, and is also involved in the induction of mitochondrial permeability. The increased permeability of the internal mitochondrial membrane leads to depolarization and deregulation of mitochondrial energy production (38). The epigenetic remodeling caused by DOX may be responsible for disrupting mitochondrial energy metabolism, but the opposite may also be valid, because the formation of most of the metabolites needed for epigenetic chromatin changes is associated with mitochondrial pathways that are affected by redox cell reactions. DOX can suppress the expression of genes required for oxidation of beta fatty acids and ATP-producing mitochondrial enzymes, explaining the reduced formation of epigenetic modifiers of mitochondrial metabolites, such as acetyl-CoA, acetylcarnitine and ATP (3). A different pattern of protein acetylation has been found in cardiac mitochondrial fractions of rats receiving DOX, accompanied by increased activity of HDACs, suggesting a mutation-predisposition between mitochondrial dysfunction and epigenetic alterations connected with DOX-induced cardio toxicity. Finally, the selective toxicity of DOX in cardiac mitochondria, in contrast to the liver, may be related to the rate of renewal of the mitochondrial cycle. In the heart, this renewal cycle is about 14 days, while in the liver it is only 2–4 days. Thus, liver mitochondria recover faster after DOX toxicity. Mitochondria also act as a source of metabolites and other factors, which are epigenetic modifiers. One of the main epigenetic modifiers is SAM, which is synthesized from ATP (produced in mitochondria) and methionine. The reaction is catalyzed by the enzyme methionine adenosyl transferase (MAT) (39). SAM serves as a general substrate for DNA and histone methylation. Thus, it is believed that mitochondrial disruption induced by DOX and other anticancer drugs may be the main cause for epigenetic changes in the CMs' chromatin (40, 41). The mitochondrial damage caused by DOX is cumulative and persistent, similar to that observed clinically for congestive heart failure (42). Recently, the so-called "mitochondrial memory" or the irreversible nature of DOX in mitochondrial toxicity has been studied in animals (42). When DOX (2 mg/kg) injections were performed weekly, they resulted in cumulative, dose-dependent increases in concentrations of 8-hydroxyguanosine, both in nuclear (nDNA) and mtDNA (34). DOX concentrations were 50% higher in cardiac mtDNA than in liver mtDNA, and remained elevated for 4 weeks after the last DOX injection (34). Therefore, DOX appears to be selectively detrimental to the heart. DOX interrupted cardiac mitochondrial biogenesis, and reduced mtDNA levels as well as variable cross-sectional transcripts for multiple mitochondrial genes encoded by both nuclear and mitochondrial genomes. The transcription of genes involved in lipid metabolism and epigenetic formation were also affected. Transcription of mtDNA is paramount to functional mitochondrial biogenesis. Thus, quantification of the transcription levels of genes involved in this process can be used as a parameter for prediction of abnormal mitochondrial functions. One of the main predictive genes is the peroxisome proliferator-activated receptor γ coactivator 1-alpha (PGC-1α), which is the main regulator of mitochondrial biogenesis. Typically, its meta-transcript levels decrease when abnormal mitochondrial functions occur (42). Likewise, the transcript encoding for the mitochondrial transcription factor A (TFAM), which controls mtDNA transcription, integrity and copying, also is a sensitive indicator of abnormal mitochondrial function. It was also found to be reduced (3). Because of DOX-induced reduction of TFAM, a reduction in the quality and quantity of mtDNA occurred. Typically, DOX reduces mtDNA by 50%. Furthermore, there is a selective reduction in the enzymatic activity of cytochrome oxidase (COX; a complex of multiple subunits, encoded by both nDNA and mtDNA) vs. the activity of electrical dehydrogenase (SDH) encoded entirely by nDNA. This again points to a mitochondrial transfer imbalance (43, 44). A reduction in ATP synthesis would be expected because of such imbalance. Indeed, ATP synthesis in hiPSCs-derived CMs is significantly reduced after cell treatment with etoposide and DOX (43, 45, 46). As reduction of mitochondria biogenesis and mitochondria functionality is severely affected by DOX, in turn, the mitochondria-dependent synthesis of SAM will be significantly reduced. We expect that epigenetic modifications of DNA and histones also will be imbalanced.

Excessive ROS production affects the expression of miRNAs and *vice versa* (5, 47, 48). In this context, inhibition of miR-25 in animal CMs exerted beneficial effects on the DOX-induced apoptosis, ROS production and DNA damage related to targeting of the phosphatase and tensin homolog deleted on chromosome 10 (PTEN) (49). In general, changes in miRNA expression mainly occur via the Nrf2, calcineurin/nuclear factor of activated T cell (NFAT), or via the nuclear factor kappa B (NF-κB) pathways (5). ROS-induced heart injury clearly affects the expression of many miRNAs. To date, several circulating miRNAs (miRNA-499, miRNA-199, miRNA-21, miRNA-144, miRNA-208a, miRNA-34a) have been reported to be potential biomarkers of ROS-associated CVDs (5).

Cardiovascular toxicity is manifested by elevated levels of the classical biomarkers in the blood, such as cardiac troponin I (cTnI) and cardiac troponin T (cTnT). These elevated levels are well-correlated with myocardial injury and act as important plasma biomarkers for the diagnosis of cardiac damage in clinical and preclinical studies. However, high levels of these biomarkers occur only after heart damage. Unfortunately, these biomarkers can only be detected a few hours after myocardial infarction and after treatment with cardiotoxic drugs. Therefore, identification of novel pharmacogenetic early biomarkers capable of predicting cardiac damage are urgently needed. For example, altered expression of miRNAs was recently found *in vivo* and *in vitro* in a study to develop early biomarkers for DOX cardiotoxicity. One of the most important epigenetic mechanisms is the gene regulation induced by the miRNAs and lncRNAs. In this context, after exposure of mice to different cumulative doses, pre-apoptotic miR-34a was detected in large concentrations, indicative of the first stages of myocardial alteration (50).

For the development of more human-related toxicity testing systems *in vitro*, human embryonic stem cells and

human-induced pluripotent stem cells (hiPSCs) have been used to predict the adverse effects of different compounds on genome and epigenome levels (51). Recently, genomic biomarkers have been identified after brief treatment of CMs derived from hiPSCs (hiPSC-CMs) with different anticancer drugs, such as anthracyclines and etoposide (43, 46, 52, 53). Gene ontology analysis of the differential gene expression indicates that processes regulating the contraction of CMs were inhibited by several anticancer drugs, whereas processes promoting apoptosis of the CMs (stress response, pathway p53 signaling) were up regulated (43, 45, 46, 52, 53). In addition, 14 miRNAs were identified as genomic biomarkers for cardiotoxicity after treatment of human CMs with DOX (52) and etoposide (43). Interestingly, among the genomic cardiotoxicity biomarkers identified under *in vitro* conditions, several were also identified in patients suffering heart failure (53). Furthermore, metabolite signatures of DOX-induced toxicity in hiPSC-CMs have been identified. Repeated exposure of human CMs to DOX caused reductions in the use of pyruvate and acetate, and accumulation of formate in the culture medium (54).

PREVENTION OF CARDIO TOXICITY INDUCED BY ANTICANCER THERAPY

Several compounds mitigate anticancer drug-induced cardio toxicity. Rutin (a poly phenolic flavonoid) may be a protective agent against cardio toxicity of anticancer drugs via antioxidant and anti-inflammatory mechanisms. Analysis of the hearts of mice that had undergone cardio toxicity from DOX included inhibition of overactive autophagy and apoptosis mediated by Ak strain transforming activation. Rutin caused a reduction in cardiac fibrosis and morphological changes in the heart linked to treatment with DOX (55). Resveratrol, another poly phenolic flavonoid, has been shown to reduce cardio toxicity linked to DOX by increasing mitochondrial biogenesis. This in turn stimulates the heme oxygenase (HO)/CO system, which acts as cytoprotective in several different tissues and cell types (56, 57). Dexrazoxane is the only FDA-approved protective treatment for DOX cardio toxicity. Its mechanism of cardio protection involves an indirect antioxidant effect via formation of iron complexes. Inhibition of cardiac topoisomerase II-β, as well as the inhibition of DNA cleavages caused by DOX, also are considered cardio protective mechanisms. Likewise, carvedilol, a non-selective β -blocker, appears to improve cardiac mitochondrial function, resulting in increased calcium-loading capacity during DOX therapy (33). Finally, studies have shown that HDAC inhibitors are effective in reducing cardiac hypertrophy under pathological conditions and in weakening the structural remodeling after myocardial infarction. A detailed map of chromatin modification-induced by two HDAC inhibitors, chostatin A (TSA) and suberoylanilide hydroxamic acid (SAHA), has been described in a model of human aortic endothelial cells. HDAC inhibitors mitigate the cytotoxic effect of DOX on the heart. Repeated animal studies showed that treatment of patients with SAHA (an inhibitor of class I and II HDACs) led to a significant improvement in cardiac function (58). The novel butyrate derivative phenylalanine-butyramide protects from doxorubicin-induced cardio toxicity in mice probably via involving HDAC associated mechanisms (59). Till know detail epigenetic mechanisms involved in cardio toxicity were reported by doxorubicin and other anthracyclines only on miRNA level (52).

There are some evidence that female animal hearts are protected due to 17-β-estradiol from the doxorubicin-induced cardio toxicity through the increased levels of ROS and apoptosis in male hearts. However, potential clinical cardio-protective benefits of females hearts are controversial discussed (60).

CONCLUSIONS

Undoubtedly, anticancer treatments cause a persistent and long-term cardiovascular toxicity, leading to CVDs. Thus, an understanding of the toxicity pathways induced by anticancer therapeutics is a priority and precondition to developing safer and better therapeutic drugs for treatment and to ensure a better quality of life for cancer patients. In the last decade, it was recognized that targeting of epigenetic regulators, such as HDACs, prevents severe cardiovascular toxicity during anticancer treatment. Therefore, promising efforts are ongoing to develop epigenetic drugs, targeting HDACs, to prevent the severe side effects of the anticancer drugs. Classical biomarkers, such as elevated concentrations of troponins in the blood, can only be detected after myocardial infarction and cardio toxicity. Human-relevant test systems based on pluripotent stem cell-derived CMs significantly contributed to the identification of several key cardio toxicity mechanisms, involving both genetic and epigenetic pathways. These studies also lead to identification of genetic and epigenetic markers, such as miRNAs, which may be applied as early biomarkers for predicting and preventing cardiac damage induced by anticancer treatment. Mitochondrial dysfunctions in CMs induced by the anticancer drugs via classical and epigenetic pathways are key cardio toxicity mechanisms. Furthermore, epigenetic remodeling, mediated by anticancer drugs, may disrupt the mitochondrial energy metabolism. We conclude that several genetic and epigenetic targets of anticancer therapeutics have now been identified for preventing or ameliorating cardiovascular toxicity. However, clinical studies still need to confirm the beneficial nature of these so-called epi-drugs.

AUTHOR CONTRIBUTIONS

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frontiers in Cardiovascular Medicine

CASE REPORT
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Case Report: Giant Biatrial Myxoma Mimicking Malignant Cardiac Tumor in a Patient With a Hepatic Angiomatous Mass

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Cardiac myxomas, primarily originating from the left atrium, are the most prevalent types of benign cardiac tumors; however, biatrial myxomas are extremely rare. Herein, we present a rare case of a 55-year old male with exertional dyspnea and intermittent chest discomfort due to a giant biatrial mass with concomitant atrial fibrillation and hepatic hemangioma. The giant tumor with its peduncle at the interatrial septum involved both atria; however, bulging through the tricuspid valve to the right ventricle during systole. Hence, excision of the giant cardiac tumor (which grossly composed of three parts: stiff, fleshy, and soft) and Cox-Maze IV procedure was performed with the resected specimen measuring 100 × 80 × 40 mm. The patient who was in a stable condition was discharged home on the 12th post-operative day. Thus, given the excellent post-operative results achieved, surgical treatment in large multi-cavitary benign cardiac tumors is feasible and should be considered a potentially curative therapy.

Keywords: giant biatrial myxoma, malignant, surgery, atrial fibrillation, Cox-Maze IV procedure

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BACKGROUND

Cardiac myxoma, mostly found within the left atrium, is the most prevalent primary cardiac tumor in adults (1). Cardiac myxomas accounts for 30–50% of all primary tumors of the heart with an annual incidence of 0.5 per million populations (2, 3). The majority (60–88%) occurin the left atrium, with a smaller proportion in the right atrium (4–28%) and in rare cases in left ventricular (8%), right ventricular (2.5–6.1%), biatrial (<2.5%), or multiple locations (2.5%) (4, 5). Myxomas developing in three to four heart chambers are extremely rare and usually considered malignant cardiac tumors, especially when tumors located in other organs were detected (6–8). We report a case of a biatrial tumor, which occupies both atria and right ventricle with concomitant atrial fibrillation and hepatic hemangioma.

CASE PRESENTATION

A 55-year-old man with a 2-year history of shortness of breath after slight activity with over 2 weeks of severe chest pain (without any anginal characteristics) was referred to our center. Occasional dizziness with no headaches, fever, or cough was dictated with a body temperature of 36.1°C and

blood pressure of 135/111 mmHg at resting conditions. Physical examination revealed that the pulse was 78 bpm, while the heart rate was 97b pm with an irregular heart rhythm. The first heart sound (S1) intensity varied, and a regurgitant murmur was heard at the apex. There were no other notable clinical findings and family history of cardiovascular disease following medical history and physical examination. Laboratory tests revealed that the N-terminal brain natriuretic peptide precursor (NT-ProBNP) was increased (1421.0 pg/ml), while CK, CK-MB, and cTnT were normal.

Electrocardiography revealed atrial fibrillation with inverted T-waves. Transthoracic echocardiography demonstrated a giant biatrial mass with 44.06 mm × 109.44 mm in the right atrium (**Figure 1A**) and 17.85 mm × 23.87 mm in the left atrium (**Figure 1B**). Notably, the blood flowed through the tumor tissue's space with severe mechanical hemodynamic obstacles (**Figure 1C**). The diameters of RV, LA, and RA were 46, 43, and 57, respectively. The left ventricular systolic function was impaired with an ejection fraction of 42%. Mild mitral and tricuspid regurgitation were also detected.

Thoracic and abdominal computer tomography (CT) showed a biatrial mass (**Figure 2A**) and an angiomatous mass in the right posterior lobe of the liver (**Figures 2B–D**, arrows). Cardiac magnetic resonance imaging (MRI) was also performed, which showed a giant biatrial mass involving the tricuspid valve and the atrial septum. The tumor was unevenly enhanced on a contrast scan, suggesting a high possibility of a malignant tumor (**Figure 2E**). A Positron Emission Tomography-CT (PET-CT) scan was also performed, which detected an FDG-avid lesion in the right atrium. No other FDG-avid lesions are demonstrated. The possibility of a malignant tumor of mesenchymal origin was considered, given the MRI and CT scan results combined with an enhanced PET-CT scan (a giant soft tissue-like mass with increased glucose metabolism in the right atrium) (**Figure 2F**).

Likewise, the possibility of a malignant tumor of mesenchymal origin was considered, given the blade-like low-density foci in the right liver as shown in the enhanced CT scan. A slightly enlarged lymph node with a slight increase in glucose metabolism in the left axilla and bilateral hilar was considered reactive lymph node hyperplasia. After extensive discussions with the patient

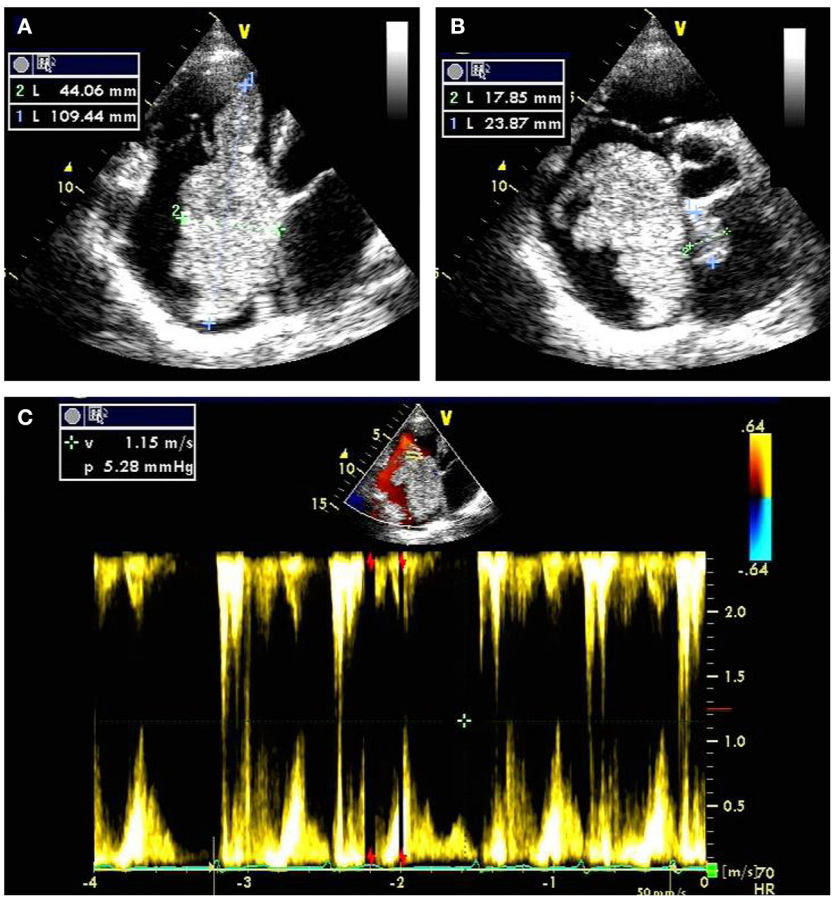

FIGURE 1 | Transthoracic echocardiography preoperatively showing a giant biatrial mass with the size of 44.06 mm × 109.44 mm in the right atrium **(A)** and 17.85 mm × 23.87 mm in the left atrium **(B)**; Color Doppler flow imaging showing severe mechanical hemodynamic obstacles in the right atrium primarily occupied by the giant tumor tissue **(C)**.

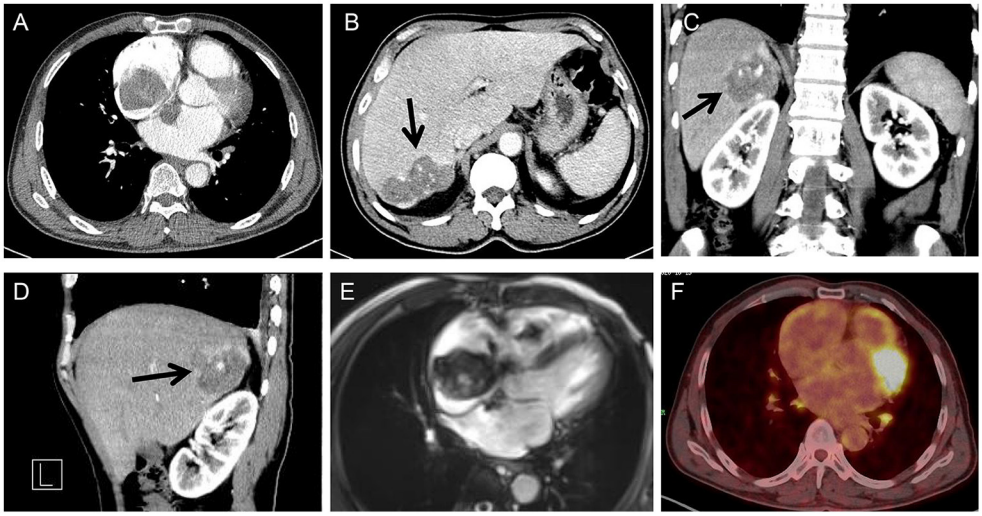

FIGURE 2 | Cardiac CT showing a biatrial mass with the atrial septum infiltrated **(A)**; Abdominal CT showing an angiomatous mass in the right posterior lobe of the liver (arrow) (transverse view) **(B)**, coronal **(C)**, and sagittal **(D)** plane; cardiac MRI showing a giant biatrial mass with tricuspid valve involved **(E)**; PET-CT showing a giant mass with increased glucose metabolism in the right atrium **(F)**.

and his family, excision of the giant cardiac tumor, tricuspid valvuloplasty, and Cox-Maze-IV procedure was scheduled.

A standard median sternotomy incision was performed, and on opening the pericardium, a massive right atrium was visualized (**Figure 3A**). The aorta was then cannulated. Separate cannulas were placed in the superior vena cava (SVC) and inferior vena cava (IVC). After full heparinization, cardiopulmonary bypass (CPB) was routinely applied. The aorta was cross-clamped, and a cold cardioplegic solution (Del Nido) was instilled via the aortic root to arrest the heart. Following the right atrium's opening, a careful exploration of the abnormalities was completed (**Figure 3B**). Together with the involved septum, the biatrial tumor was removed (**Figures 3C,D**). The resected mass from the right atrium was grossly composed of two parts; a cutaneous soft tissue-like mass and a peanut-shell shape-like mass (**Figure 3D**, arrows).

Radiofrequency ablation with Cox-Maze-IV procedure, reconstructing the atrial septum with a suitable bovine pericardial patch, and tricuspid valvuloplasty with the implantation of a prosthetic ring (size 32, Sorin sovering band) were sequentially performed. After careful hemostasis and closing of the wound in layers, the patient was carefully transferred to the intensive care unit (ICU) in a stable condition. Early post-operative management, including continuous arterial blood pressure monitoring and ventilation, was created to stabilize circulation. Transthoracic echocardiography and electrocardiogram were performed to capture any hint of residual tumor or arrhythmias, especially A-V block.

Pathology results confirmed the primary diagnosis of cardiac myxoma and showed interstitial fibrous hyperplasia with vitrification and calcification, hemorrhage, necrosis, and plasmacytes infiltrates (**Figures 4A,B**). The patient recovered

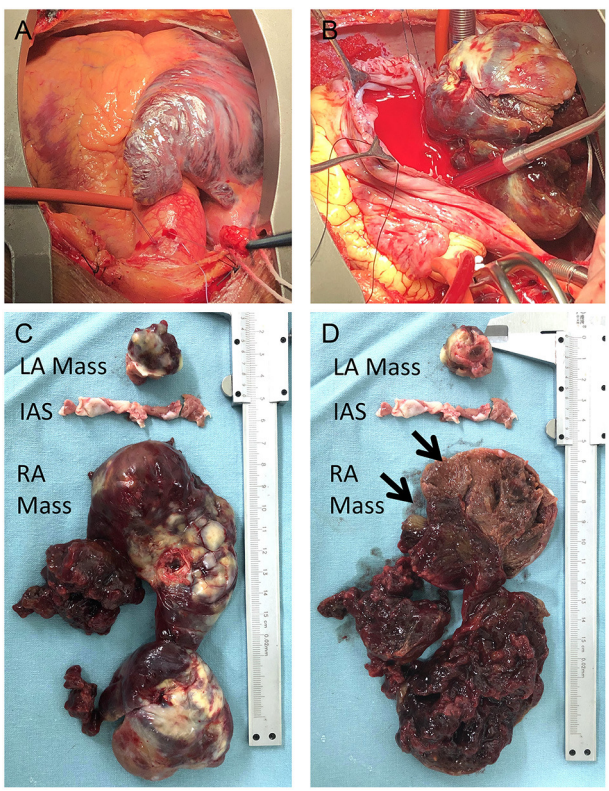

FIGURE 3 | Intraoperative view of the tumor: right atrium was enlarged **(A)** with the tumor inside the chamber; The right side of the tumor was visualized with the opening of the right atrium **(B)**; the biatrial mass together with the infiltrated septum was resected **(C,D)**; the right atrial lesion was grossly composed of two parts (**D**, arrows).

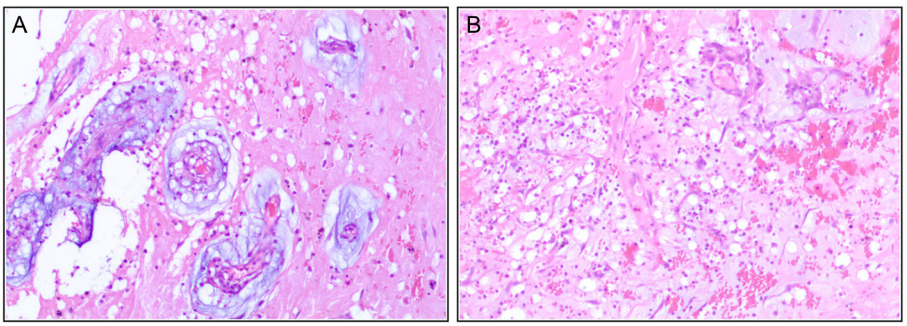

FIGURE 4 | Immunohistochemistry post-operatively confirm the diagnosis of the cardiac myxoma with interstitial fibrous hyperplasia **(A)**, hemorrhage **(B)**, necrosis, and plasmacytes infiltrate.

with sinus rhythm without further complications and was discharged on the eighth post-operative day in a stable condition with recommended subsequent follow-up.

DISCUSSION AND CONCLUSIONS

Cardiac myxoma is the most prevalent primary tumor within the heart cavity. It is believed to be benign, with some complex manifestations with malignant tendencies (8, 9). Typical myxomas are isolated, single, smooth surface, spherical, pedicled, variable in size (∼1–8 cm in diameter, mean 5 cm), 90% located in the left atrium, attached to the atrial septal fossa ovale, and extending into the affected chamber of the heart (1). In extreme cases, the cavity can be filled by the tumor mass (6). The tumor may prolapse toward the ventricle during diastole, as shown in the present case. However, because symptoms may mimic other cardiac conditions, the preoperative diagnosis of myxoma becomes difficult (10, 11). Besides, giant biatrial myxomas involving the right ventricular cavity are extremely rare (12).

A thrombus, liquefied viscose tissue, and a liquefied viscose mesenchymal tumor, including the heart's lymphoma, are the most common differential diagnosis of cardiac myxoma (13). Myxoma looks similar to thrombosis, especially a globular thrombosis in the atrium. However, myxoma and thrombosis are two different kinds of pathology. Significantly, the thrombus's surface is not covered with cells, and its mechanization process starts from within its wall. On the contrary, the non-degenerative parts and the myxoma proximal pedicle are covered with cells, while tissue necrosis and fibrinoid degeneration are in the distal part. Notably, the myxomatoid mesenchymal tumor of the heart is most easily mixed with myxoma. In the presented case, the mesenchymal origin was indicated mainly based on the location (left and right atrium), the blade-like low-density foci in the right liver as shown in the enhanced CT scan. However, other histologies should also be considered. The final result from the pathology would confirmed the diagnosis. Thus, adequate histologic sections, comprehensive observation, and cell identification are crucial for accurate diagnosis (13–15).

Interestingly, studies show that cardiac myxoma may present with possible malignant degeneration and malignant clinical behavior (8, 9, 16, 17). Besides, cardiac myxoma can be preoperatively misdiagnosed as malignant tumors, especially when extra-cardiac tumor-like anomalies are detected (14). Hepatic malignant mass was recently reported to coexist with cardiac myxoma (18). However, the final diagnosis of the angiomatous liver mass in the reported case was unknown. Unfortunately, given the patient's financial status and the lack of basic health insurance, a further clinical investigation was not carried out, which would have identified the asymptomatic angiomatous liver mass. Myxomas in males are very rare but can be seen in the setting of Carney Complex, an autosomal disorder due to mutation of the PRKA R1A subunit of PKA. Patients with these mutations have other features like spotty skin pigmentation, endocrine tumors, peripheral nerve tumors, and a familial predisposition (19). In the presented case, the patient had no adrenal tumors or skin freckles. He denied any previous medical or family history. It is believed that patients with cardiac tumors, both malignant and benign tumors, should undergo surgery in a timely fashion in a specialized center (6). If the myxoma is huge, the blood can only flow through the tumor tissue's space, leading to severely unstable hemodynamics due to mechanical obstacles.

It is critically essential to note that cardiac myxoma tissues are loose and fragile and easy to break off from the tumor (20). Thus, surgical resection should be considered once cardiac myxoma is diagnosed. Notably, the prognosis after surgery is usually excellent in the case of benign tumors (21), even when the involved myxoma is multi-cavitary (4, 22).

It is worth noting that, before the aorta is occluded during the operation, intracardiac and extracardiac exploration should be avoided. The atrial septum or atrial wall, endocardia, and myocardium at the tumor pedicle should be removed entirely. If the heart valves are invaded and cannot be repaired, then valvular replacement should be performed. Valvular annuloplasty should be performed if annular insufficiency from the enlargement was observed. Also, a patch repair should be performed if an extensive range of atrial septal resection could not be avoided. After tumor removal, the heart cavity should be flushed thoroughly to prevent tumoral debris from remaining in the heart chamber. Also, surgery must include resection of all abnormal tissues (23).

In the case herein, the patient had suspected malignant cardiac tumor and other cardiac lesions, including atrial fibrillation, valvular stenosis, or insufficiency. Thus, total resection with radiofrequency ablation and valvuloplasty for the giant tumor was performed to maximize the patient's benefit. Significantly, follow-up with echocardiography should be continued to detect recurrence and long-term effect.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the study protocol was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University, Changsha, China. The patients/participants provided their written informed consent to participate in this study. 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

CF drafted the manuscript. CF and LL designed the study. HZha, CI, ZJ, and LS revised the manuscript. ZJ, HT, and HZhu were responsible for the collection of data or analysis. All authors read and approved the final manuscript.

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REVIEW
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Immune Checkpoint Inhibitors and Atherosclerotic Vascular Events in Cancer Patients

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In clinical trials and meta-analysis, atherosclerotic vascular events (AVEs) during treatment with immune-checkpoint inhibitors (ICIs) have been reported with low incidence. However, preclinical data suggest that these drugs can promote atherosclerosis inflammation and progression of atherosclerosis plaques, and there is now growing and convincing evidence from retrospective studies that ICIs increase the risk of atherosclerotic vascular events including arterial thrombosis, myocardial infarction and ischemic stroke. Prospective studies are needed to increase knowledge on long-term effect of ICIs or their combinations with other cardio-toxic drugs, but in the meantime a careful assessment and optimization of cardiovascular risk factors among patients treated with ICIs is advisable.

Keywords: arterial thrombosis, ischemic stroke, myocardial infarction, atherosclerosis, PD-L1, PD-1, CTLA-4, acute vascular events

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have extended survival across many tumor types and their use in cancer treatment has been increasing over time (1). ICIs are monoclonal antibodies targeting immune checkpoints, proteins that play a negative regulatory function within the immune system (2). Currently approved ICIs are directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), the programmed death 1 (PD-1) and one of its ligands, the programmed death ligand 1 (PD-L1) (3). By binding their target, ICIs release the brakes that cancer cells place on the immune system, thus unleashing the immune cells against the tumor. On the other hand, however, ICIs are characterized by a peculiar toxicity profile consisting of immune-related adverse events (irAEs) that may potentially affect any organ or system, including the cardiovascular system (4, 5).

Initially, atherosclerotic vascular events (AVEs) such as arterial thrombosis, coronary artery disease (CAD), acute coronary syndrome (ACS), myocardial infarction (MI) and ischemic stroke were not specifically recognized as irAEs and therefore not usually considered as a possible toxicity of ICIs. However, there is now growing preclinical and clinical evidence suggesting a possible correlation between ICIs and AVEs. In the present review we summarize and discuss the available literature on this topic.

MATERIALS AND METHODS

For the present review, the PubMed database was searched from the inception to 31st January, 2021, using the following terms: ("CTLA-4" OR "PD-1" OR "PD-L1" OR "immune checkpoint*"

OR "immune checkpoint inhibitor*" OR "anti-CTLA-4" OR "anti-PD-1" OR "anti-PD-L1" OR "ipilimumab" OR "tremelimumab" OR "nivolumab" OR "pembrolizumab" OR "atezolizumab" OR "durvalumab" OR "cemiplimab") AND ("atherosclerosis" OR "atherosclerotic plaque" OR "vascular event*" OR "arterial thrombosis" OR "coronary artery disease" OR "acute coronary syndrome" or "myocardial infarction" OR "ischemic stroke").

IMMUNE SYSTEM AND ATHEROSCLEROSIS

Atherosclerosis is a complex disease process initiated by the retention in the arterial walls of low-density lipoprotein (LDL)-cholesterol, that may undergo oxidative modification leading to the formation of oxidide LDL (oxLDL). The accumulation of oxLDL may elicit an innate inflammatory response with the recruitment of circulating monocytes that, infiltrating arterial walls, differentiate into macrophages and at a later stage transform into foam cells that eventually die creating a core area in the plaque that consists of necrotic cells and cholesterol crystals (6).

As the atherosclerotic plaque grows, accumulation of immune cells and particularly T cells occurs at the shoulder regions of the lesion. In this context of chronic inflammation, adaptive immune response plays a crucial role, and T-cells that recognize autoantigenic components of LDL regulate plaque development (6). Particularly, T helper type 1 cells (Th1) produce interferon-γ (IFNγ), which promotes macrophage activation and counteracts cap formation by enhancing collagen degradation and inhibiting smooth muscle cell proliferation, thus leading to vulnerable plaques that on hemodynamic assaults may undergo rupture with endothelial dysfunction and thrombus apposition, thus leading to acute events such as myocardial infarction or stroke (7). On the other hand, regulatory T cells (Treg) limit Th1 responses in the plaque and T helper type 17 cells (Th17) promotes plaque stability by enhancing collagen deposition, leading to increased cap formation (6).

T cell functions are finely regulated by immune checkpoints, including CTLA-4 and PD-1 that represent now targets for cancer immunotherapy. CTLA-4 is mainly involved in the priming phase of T cell activation, whereas PD-1 is involved in the effector phase (3). When the naïve T cells recognize the antigens presented by antigen presenting cells (APCs) in the lymph nodes through their T cell receptor (TCR), to be fully activated they need a second costimulatory signal that is provided by the interaction of CD28 expressed on the T cell membrane with the B7-1 (CD80) or B7-2 (CD86) molecules on the surface of APCs. CTLA-4 is upregulated on the T-cell membrane shortly after T-cell activation, and the binding of CTLA-4 to B7 molecules provides inhibitory signals for the T cell and induces Treg responses, thereby limiting inflammation and preventing autoimmunity. PD-1 inhibitory receptor is expressed by exhausted T cells after long-term exposure to antigens and exerts a negative regulation when it binds to one of its ligands, PD-L1, or PD-L2, present in inflamed tissues such as atherosclerotic lesions, or tumor microenvironment.

PRECLINICAL STUDIES

Results from preclinical studies suggest that the blockade of CTLA-4 or PD-1/PD-L1 pathway plays a relevant role in promoting progression of the atherosclerotic lesions (**Table 1**) (11, 12). A short-term treatment with an anti-CTLA-4 antibody led to endothelial activation, accelerated the progression of atherosclerosis by inducing a predominantly T cell-driven inflammation, and resulted in the formation of plaques with larger necrotic cores and less collagen in an *in vivo* atherosclerosis experimental model based on hypercholesterolemic, low-density lipoprotein receptor (LDL-R) knock-out mice ($ldlr^{-/-}$ mice) (11).

Regarding PD-1/PD-L1, several preclinical studies showed that PD-1 exerts significant atheroprotective effects, PD-1/PD-L1 pathway downregulates the proatherogenic Tcell response, and PD-1/PD-L1 deficiency promotes atherosclerosis (**Figure 1**) (8–10, 12). Particularly, an *in vivo* study showed that $ldlr^{-/-}$ mice receiving high-cholesterol diet for 10 weeks had increased PD-L1 and B7-1 expression in dendritic cells (DCs) from the iliac lymph nodes, and increased PD-L1 and PD-L2 expression in peritoneal macrophages, compared with mice receiving control-diet (8). In this study, modified mice lacking for both LDL-R and PD-L1/2 genes ($pdl^{-/-}$ $ldlr^{-/-}$ mice) developed a significant increase in the aortic atherosclerotic burden after 10 weeks of high-cholesterol diet, with a 2-fold increase of plaques in aortic root and a 3-fold increase of plaques in aortic arch and descending aorta, when compared with the control group ($ldlr^{-/-}$ mice). In comparison with the control group, $pdl^{-/-}$ $ldlr^{-/-}$ mice had also increased smooth muscle cells and collagen deposition in the plaques, increased $CD4^+$ and $CD8^+$ T-cells and macrophages in the intima, increased $CD4^+$ T-cells with activation phenotype ($CD25^+CD62L^{lo}$) in the iliac lymph nodes, and increased serum TNF-a levels. Furthermore, macrophages and DCs taken from $pd1^{-/-}$ $ldlr^{-/-}$ mice led to increased $CD4^+$ T cell proliferation *in vitro* as compared with those taken from control mice (8). A subsequent study reported that the administration of an anti-PD-1 antibody to $ldlr^{-/-}$ mice fed with high-cholesterol diet resulted into enhanced lesional inflammation characterized by increased $CD4^+$ and $CD8^+$ T-cells, associated with more $CD44^+$ and IFN-g-producing $CD4^+$ and $CD8^+$ T-cells in the iliac lymph nodes, as compared with $ldlr^{-/-}$ mice not receiving the anti-PD-1 antibody (9). Overall, these data suggest that PD-1/PD-L1 axis has an important role in downregulating atherosclerosis by limiting APC-dependent T-cell activation, and that PD-1/PD-L1 blockade may contribute to atherosclerosis progression in murine models through increased activation of $CD4^+$ and $CD8^+$ T-cells.

Anti-CTLA-4 and anti-PD-1/PD-L1 antibodies may alter the composition of atherosclerotic plaque not only in experimental murine models but also in humans. In fact, an autopsy study evaluating the inflammatory infiltrate in coronary artery atherosclerotic plaques from cancer patients reported a

TABLE 1 | Preclinical studies.

References	Model	Main findings
Gotsman et al. (8)	hypercholesterolemic *pdl*$^{-/-}$ *ldlr*$^{-/-}$ mice and *ldlr*$^{-/-}$ controls	PD-L1/2 deficiency led to: • increased atherosclerotic burden throughout the aorta • increased numbers of lesional CD4^{+} and CD8^{+} T-cells. Increase numbers of activated CD+ T-cells in iliac lymphadenopathy • higher levels of serum TNF-α • more effective APCs in activating CD4^{+} T cells
Bu et al. (9)	hypercholesterolemic *pdl*$^{-/-}$ *ldlr*$^{-/-}$ mice, *ldlr*$^{-/-}$ mice treated with anti-PD-1, and *ldlr*$^{-/-}$ controls	PD-L1/2 deficiency led to: • larger atherosclerotic lesions with more abundant CD4^{+} and CD8^{+} T-cells and macrophages • higher levels of serum TNF-α • more proliferation of iliac lymph nodes T-cells to oxLDL • more cytotoxic activity of CD8^{+} T-cells Anti-PD-1 led to: • increased plaque inflammation with more lesional T-cells • more activated T-cells in paraortic lymph nodes
Cochain et al. (10)	hypercholesterolemic *pdl*$^{-/-}$ *ldlr*$^{-/-}$ mice and *ldlr*$^{-/-}$ controls	PD-L1/2 deficiency led to: • increased systemic CD4^{+} and CD8^{+} T-cell activation • expansion of both pro-atherogenic IFNγ-secreting T_{H1} and atheroprotective Foxp3^{+} T_{regs} • massive infiltration of T cells in atherosclerotic lesions • aggravated hypercholesterolemia and exacerbated atherosclerotic lesion development
Poels et al. (11)	Hypercholesterolemic *ldrl*$^{-/-}$ mice, treated with anti-CTLA-4 or control.	Anti-CTLA-4 led to: • 2.0-fold increase in the plaque area in the aortic area • more advanced morphological phenotype and an increased T cell/macrophage ratio in the plaque • activated T-cell profile in the blood and lymphoid organs

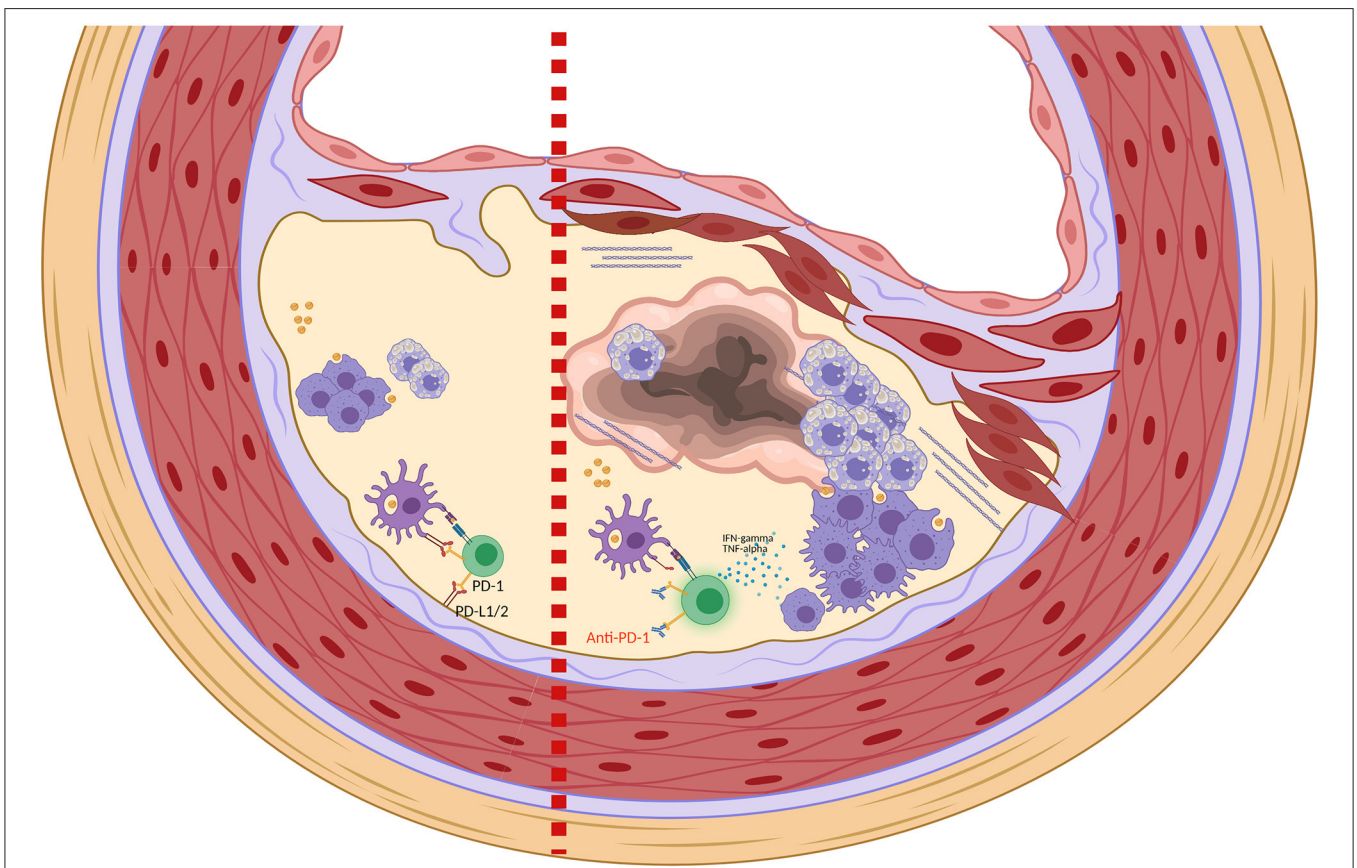

FIGURE 1 | Role of PD-1 and PD-1 blockade in the homeostasis of atherosclerotic plaque. Left side: Binding of PD-1 expressed on T-cells with PD-L1/PD-L2 expressed on DCs and in microenvironment contribute to the inactivation of T-cells and to the maintenance of an immunosuppressive plaque microenvironment. Right side: Anti-PD-1 leads to T-cells activation with production of proinflammatory cytokines such as TNF-α and IFNγ. TNF-α and IFNγ promote smooth muscle cell proliferation, collagen deposition and activation of macrophages that increase the phagocytosis of LDL with transformation into foam cells (8, 9). These changes in the plaque structure ultimately lead to the formation of a necrotic core and plaque instability (Picture created with Biorender.com).

significant increase in T-cells/macrophages ratio in patients who had been recently treated with ICIs compared to those who had not treated with ICIs (13). It was postulated that the ICI-induced switch from a macrophage-predominant to a lymphocyte-predominant plaque may lead to atherosclerosis progression and plaque instability (14), although the lymphocytes/macrophages ratio may not represent the best parameter to describe the quality of the immune infiltrate in atherosclerotic plaques, given that different types of lymphocytes may exert different roles in the atherosclerosis progression (6). In fact, a study evaluating carotid plaques from 29 patients undergoing endarterectomy reported a higher number of $CD4^+$ and $CD8^+$ T cells but a lower number of Tregs in unstable lesions compared with stable lesions (15). More preclinical and translational studies aiming to obtain a better qualitative characterization of the immune infiltrates in atherosclerotic plaques after ICIs exposure would be helpful to elucidate the role of ICIs on the atherosclerotic process.

CASE REPORTS

Several cases of AVEs during treatment with ICIs in cancer patients have been reported (**Table 2**). In 2017, a case of ACS due to right coronary artery occlusion was described in a patient with metastatic NSCLC achieving a complete response to the anti-PD-1 antibody nivolumab (17). Although the patient had pre-existing cardiovascular factors including dyslipidemia treated with atorvastatin and smoking history, the concomitant development of multiple irAEs including fever, erythema multiforme, thyroid dysfunction, and interstitial pneumonia suggested a role for nivolumab in the development of ACS. Since then, other reports of ACS possibly related to anti-PD-1 have been published (18–20). Particularly, one patient with metastatic giant cell bone tumor treated with pembrolizumab experienced 2 subsequent events of non-ST elevation myocardial infarction (NSTEMI), with finding at serial coronary angiography of progressive stenosis of the left circumflex artery 2 months apart (20). Such a rapid progression of atherosclerosis is consistent with data deriving from mice models indicating a role for PD-1 blockade in atherosclerosis progression (9). Although atherosclerosis progression remains one the most likely underlying mechanisms of ICI-related ACS or MI, other speculations on the pathogenesis include a coronary spasm possibly secondary to systemic inflammatory response syndrome induced by ICIs (18), or T cell mediated coronary vessel vasculitis in the absence of atherosclerosis (5).

In 2017, four cases of arterial thrombosis in cancer patients treated with anti-PD-1 antibodies were described (16). One of these patients underwent Fogarty arterial embolectomy, and histological examination revealed that $CD8^+$ T cells were present in the superficial arterial wall, and the thrombus fragments contained large aggregates of entrapped leucocytes, including numerous neutrophils, monocytes and macrophages, with rare T cells and B cells, but no tumor cells were detected. PD-L1 was not expressed in entrapped leucocytes or vascular lining cells (9). The presence of $CD8^+$ T-cells in the arterial wall of this patient is consistent with preclinical findings of an increased amount of $CD8^+$ T-cells in atherosclerotic lesions of hypercolesterolemic $ldl^{-/-}$ mice receiving anti-PD-1 antibodies (9), thus suggesting that andi-PD-1 drugs may result in an impairment of T-cell regulation leading to atherosclerotic plaque instability and rupture (21).

RETROSPECTIVE STUDIES

Only few retrospective studies have investigated the association between ICIs and AVEs (**Table 3**). In particular, an Israeli mono-institutional retrospective study on 1,215 cancer patients treated with ICIs from 2015 to 2018 reported 37 acute vascular events (3%), including cerebrovascular accident, transient ischemic attack, MI, ACS, embolic event, pulmonary emboli (21). In this study, the incidence of vascular events was significantly higher within the first 6 months (31 events, 1,215 patients at risk) than 7–12 months after ICIs initiation (6 events, 822 patients at risk), with an odd-ratio of 3.49 (95% CI 1.45–8.41, $p = 0.002$). Among the 31 patients with an early acute vascular event, 90% had ≥ 2 cardiovascular risk factors (smoking history, diabetes mellitus, hypertension, hyperlipidemia, male sex, past history of acute vascular events, and renal failure) and 55% had $\geq$3 risk factors. A multivariable analysis identified non-small cell lung cancer (NSCLC), history of acute vascular events and dyslipidemia as significant risk factors for AVEs during treatment with ICIs (23). Not unexpectedly, patients who developed an early vascular event had worse median overall survival (OS) than those who did not (3 vs. 14 months; HR 3.01, 95% CI 2.07–4.39, $p < 0.0001$), and in 25% of cases death occurred within 1 month from the vascular event.

A matched cohort study of the Massachusets General Hospital included 2,462 cancer patients treated with ICIs from 2008 to 2012, and 2462 controls matched by age, history of cardiovascular events and cancer type, with the aim to evaluate whether exposure to ICIs was associated with AVEs defined as myocardial infarction, coronary revascularization and ischemic stroke (23). Results from this study showed that there was a 3-fold higher risk for AVEs after starting an ICI (HR 3.3, 95% CI 2.0–5.5; $p < 0.001$), in a multivariable model that included known cardiovascular risk factors (male sex, age, body mass index, hypertension, diabetes mellitus, chronic kidney disease, smoking, prior history of a CV event, statin use, aspirin use, hemoglobin, and low-density lipoprotein). Particularly, the use of ICIs was associated with a higher risk for MI (univariable HR 7.2, 95% CI 4.5–11.5; $p < 0.001$), coronary revascularization [univariable HR, 3.0 (95% CI, 1.9–4.8); $P < 0.001$], and ischemic stroke [univariable HR, 4.6 (95% CI, 2.9–7.2); $P < 0.001$] (23). In the same study, a case-crossover analysis of the cohort of patients treated with ICIs showed a significantly increased incidence of AVEs in the 2-year period after ICIs initiation compared to the 2-year period before (119 patients with AVEs, 4.2% vs. 66 patients with AVEs, 2.32%; HR 4.78, 95% CI 3.50–6.53, $p < 0.001$). Interestingly, in an imaging sub-study on 40 melanoma patients treated with ICIs, there was a >3-fold increase in the rate of atherosclerotic plaque progression after ICIs initiation (from 2.1% per year pre- to 6.7% per year post-ICI). As compared with non-statin

TABLE 2 | Case reports.

References	Age, sex, cancer	ICI	CV risk factor	AVE	Associated irAEs	Tumor response	Treatment	Outcome
Boutros et al. (16)	71 yo, M, stage IV melanoma	Pembrolizumab	NR	Arterial thrombosis (left leg)	Diabetes	Partial response	arterial embolectomy, foot amputation	Resolution ICI discontinued
	69 yo, F	Pembrolizumab	Dyslipidemia	Pulmonary embolism with bilateral lobar artery thrombosis	–	Completer response	Anticoagulation was initiated and intravenous thrombolysis	Resolution ICI discontinued
	78 yo, M	Pembrolizumab	NR	Arterial thrombosis (right common iliac artery, external and internal iliac Arteries and peripheral bilateral artery disease)	–	Partial response	Antiplatelet drug; patient refused bypass graft	NR ICI discontinued
	53 yo, M	Ipilimumab/Nivolumab	History of smoking	Stenosis of the left subclavian artery related to an atherosclerotic plaque with a floating arterial thrombus	Pneumonitis	Progressive disease	Anticoagulant, antiplatelet, and statin therapy	NR ICIs discontinued
Tomita et al. (17)	61 yo, M, stage IV NSCLC,	Nivolumab	Dyslipidemia, history of smoking	ACS	Thyroiditis, erythema multiforme, pneumonitis	Complete response	Stenting	Resolution
Nykl et al. (18)	71 yo, M, stage IV NSCLC,	Pembrolizumab	–	Temporary coronary spasm with inferior STEMI	Systemic inflammation response syndrome	NR	Acetylsalicylic acid, clopidogrel, heparin, and vasopressor support	Resolution ICI restarted
Ferreira et al. (19)	60 yo, F, stage IV NSCLC	Nivolumab	History of smoking	Temporary coronary spasm with ACS	–	Stable disease	Acetylsalicylic acid, clopidogrel, verapamil	Resolution ICI discontinued
	72 yo, M, stage IV melanoma	Nivolumab	NR	ACS	NR	–	Oxygen, nitrates, bisoprolol, eplerenone, furosemide	Death
	53 yo, F, Hodgkin Lymphoma	Nivolumab	NR	Fugitive repolarization disorders	NR	Partial response	Steroids	NR
Kwan et al. (20)	71 yo, M, stage IV giant cell bone tumor	Pembrolizumab	Hypertension, type 2 diabetes, history of smoking, peripheral artery disease	NSTEMI	Primary biliary cholangitis	Stable disease	Atherectomy, stenting, acetylsalicylic acid, clopidogrel, and atorvastatin	Resolution

users, patients receiving statins had lower yearly rates of plaque progression of total aortic plaque volume (5.2 vs. 8.3%, $p = 0.04$) and non-calcific plaque (3.1 vs. 7.0%, $p = 0.04$) (23).

In contrast with these results, a smaller retrospective study reported an improvement of atherosclerosis with nivolumab (22). Among 38 cancer patients included in the study, 11 had atherosclerotic disease with complicated aortic plaques at baseline. Of them, 3 (27.3%) showed a significant shrinkage of atherosclerotic plaques during nivolumab treatment, 7 (63.6%) had no significant changes and 1 (9.1%) had a modest worsening of the atherosclerotic lesions. Interestingly, one of the 3 patients achieving an atherosclerosis improvement, after intervening chemotherapy received subsequently the anti-PD-L1 antibody atezolizumab and again had a new reduction in aortic plaques until nearly complete resolution (22, 24). All the 3 patients with plaques reduction developed irAEs while on nivolumab,

TABLE 3 | Retrospective studies.

References	Study design	*n*	Main findings
Gelsomino et al. (22)	Retrospective, mono-institutional	38	• 11 (29%) patients with atherosclerotic disease and complicated plaques at baseline • Of them, 3 patients (27.3%) had improvement, 7 patients (63.6%) had no changes, 1 patient (9.1%) had modest worsening of plaques after ICIs
Bar et al. (21)	Retrospective, mono-institutional, single cohort	1,215	• Incidence of AVEs within 6 months of ICIs: 2.6% (95% CI 1.8–3.6) • AVEs more frequent within 6 months than from 7 to 12 months of ICIs: OR 3.49 (95% CI 1.45–8.41, $p = 0.002$) • 90% of patients with AVEs had ≥2 CV risk factors • No difference in terms of response to ICIs or associated irAEs between pts who had or had not AVEs • Worse OS in pts with AVEs (3 vs. 14 months, HR 3.01, 95% CI 2.07–4.39, $p < 0.0001$)
Drobni et al. (23)	Retrospective, mono-institutional, matched 2-cohort study, with a case-crossover analysis and imaging sub-study	2,842 (ICIs)/2,842 (no ICIs)	• Matched cohort: higher risk of AVEs in ICIs vs. no-ICIs cohort (HR 3.3, 95% CI 2.0–5.5 $p < 0.001$) • Case-crossover: higher incidence of AVEs at 2 year after ICIs vs. 2 year before ICIs (adjusted HR 4.8, 95% CI 3.6–6.5, $p < 0.001$) • Imaging: Increased rate of progression of aortic plaque volume, from 2.1%/y before ICIs to 6.7%/y after ICIs

thus suggesting that the atherosclerosis improvement could have been related to a strong nivolumab-induced activation of their immune system. The biological mechanisms leading to the atherosclerosis improvement seen in this study are still unknown, but it has been hypothesized that PD-1/PD-L1 blockade may contribute to restore a protective role of T-cells on atheromatous plaques, impaired by plaque-associated macrophages and dendritic cells with hyperexpression of PD-L1. At this regard, a parallel histological study on archival surgical specimens of arteries with atherosclerotic lesions from non-cancer patients revealed that DCs with PD-L1 hyperexpression were observed in complicated plaques only, but not in early plaques (22). Therefore, it cannot be excluded that immuno-modulating agents such as ICIs could both promote or inhibit atherosclerosis. The reason why the pro-atherogenic or anti-atherogenic effect can prevail in the individual patient is unknown, but it possibly can involve several aspects of the plaque microenvironment including the severity of inflammation and the relative concentration of different cytokines. The plaque microenvironment could possibly vary not only between early and advanced plaques as demonstrated by histological studies (22), but also among different individuals and under different circumstances. A biological rationale for the atheroprotective effect of ICIs could be found in findings from a preclinical study reporting that PD-L1/PD-L2 deficiency in murine models may result not only in increased pro-atherogenic Th1 cells but also in increased anti-atherogenic Treg cells (10).

PROSPECTIVE STUDIES AND META-ANALYSES

Data from prospective studies and meta-analysis suggested that AVEs are a rare event during treatment with ICIs. In fact, ICI-related AVEs have been only sporadically reported in prospective clinical trials. Particularly, few cases of MI were described in patients treated with atezolizumab for urothelial cancer (25) and with pembrolizumab for NSCLC (26).

TABLE 4 | Meta-analyses.

References	*N* patients (*n* studies); cancer	Main findings
Nso et al. (27)	4,622 (26); various cancers	• Incidence of MI: 0.4% (95% CI 0.1–0.8%)
Solinas et al. (28)	20,273 (68); various cancers	• Incidence of arterial thromboembolic events: 1.1% (95% CI 0.5–2.1%) • Incidence of stroke: 1.1% (95% CI 0.65–1.45%) • Incidence of MI: 0.7% (95% CI 0.15–1.15%),
Hu et al. (29)	4,828 (22), NSCLC	• Incidence of MI: 1.0% (95% CI, 0–3.8%) • Incidence of stroke: 2.0% (95% CI, 0–13.0%)

In a meta-analysis evaluating the incidence of cardiovascular irAEs in cancer patients treated with ICIs, the incidence of MI was as low as 0.4% (95% CI 0.0–0.07%), although this result could be an under-estimation given that the 26 studies included were not specifically designed to evaluate the incidence of cardiovascular toxicity and only 6 out of 26 reported the incidence of MI as an irAE (27). Similarly, another meta-analysis reported a low rate also for arterial thromboembolic events (1.1%, 95% CI 0.5–2.1%) among over 20,000 cancer patients treated with ICIs in 68 studies (**Table 4**) (28).

The primary site of cancer may represent a risk factor itself for the development of AVEs. As reported before, patients with lung cancer treated with ICIs seem to have higher incidence of

AVEs. In fact, a meta-analysis of 22 trials on NSCLC patients treated with ICIs reported an 1.0% incidence rate of MI (95% CI, 0–3.8%) and 2.0% of stroke (95% CI, 0–13.0%) (29). Consistently with this report, a *post-hoc* analysis of a prospective observational study reported high incidence of arterial thromboembolic events among 217 NSCLC patients treated with ICIs (16 events, 6.5%) (30). Interestingly, in this study patients receiving antiplatelet treatment experienced longer progression-free survival (6.4 vs. 3.4 months; HR 0.67, 95% CI 0.48–0.92; $p = 0.015$) and a trend toward better OS (11.2 vs. 9.6 months; HR 0.78, 95% CI 0.55–1.09; $p = 0.14$) (30).

DISCUSSION

In prospective clinical trials and meta-analysis, the incidence of AVEs during treatment with ICIs was relatively low (31). However, because AVEs have not been typically considered as irAEs, until recently they could have been under-reported in clinical trials and, consequently, also in meta-analysis. Therefore, their actual incidence could be under-estimated (32). The same has already happened for other ICI-related cardiovascular toxicities, such as myocarditis. Immune-related myocarditis, in fact, has been under-reported until 2016, when two cases of fulminant myocarditis were described (33). Since then, the reporting of such events has been increasing, possibly due to increased awareness among clinicians and more detailed cardiac assessments detecting evidence of milder cardiovascular toxicity (31).

Patients enrolled in clinical trials are usually a highly selected population, and elderly patients who may have subclinical atherosclerosis, as well as those with high cardiovascular risk or history of cardiovascular disease, have been often excluded or under-represented in clinical trials investigating ICIs (21, 23). This argument could contribute in part to explain why the incidence of AVEs is low in prospective clinical trials, but becomes meaningfully higher in real-word retrospective studies (3–4%) enrolling patients with higher cardiovascular risk (21). It is known that cardiovascular risk factors, particularly dyslipidemia and history of acute vascular events, may increase the risk for AVEs among cancer patients treated with ICIs, as clearly showed by real-word evidence (23).

In a recently published, well-designed matched cohort retrospective study, treatment with ICIs significantly increased the risk for AVEs and the atherosclerotic plaques volume. This finding is consistent with preclinical data showing that CTLA-4 and PD-1 blockade accelerates the progression of atherosclerotic plaques (22, 24). However, there is also conflicting evidence deriving from a smaller retrospective study that suggested instead an atheroprotective role for anti-PD-1/PD-L1 agents (34, 35). These contrasting observations underline that the interactions among cancer, atherosclerosis, and immune system are still far from being comprehensively understood, therefore further basic and clinical research in this field is urgently needed. The possible role of the microenvironment in modulating the adaptive immune response within the atherosclerotic plaques may offer interesting insights for research, since strategies aiming to manipulate the plaque microenvironment may potentially improve the cardiovascular safety profile of ICIs.

The research on the correlation between ICIs and AVEs is now particularly important, since several combinations of ICIs with other drugs such as anti-angiogenesis agents, that potentially increase the risk for arterial thrombosis and acute vascular events, have been recently introduced in clinical practice (36). Although clinical trials investigating these combinations did not report a significant excess of AVEs, it should be kept in mind that atherosclerosis-related complications may develop gradually over years or even decades, and the post-marketing surveillance is still limited to have sufficient data on long-term adverse events. Moreover, beyond anti-CTLA-4 and anti-PD-1/PD-L1 antibodies, different ICIs are currently under clinical investigation, including antibodies directed against checkpoints that may have a role in regulating the atherosclerosis process and maintaining cardiovascular homeostasis, such as the T-cell immunoglobulin and mucin-domain (TIM) proteins, T cell immunoglobulin and ITIM domain (TIGIT), and OX40 (23, 30).

Some prospective studies designed with the aim to collect data on AVEs and other cardiovascular toxicities among cancer patients receiving ICIs are currently ongoing (NCT04586894, NCT03709771, NCT04115410), and their results will probably provide better knowledge on the correlation between ICIs and AVEs. However, research efforts should be also directed to translational studies aiming to identify novel circulating biomarkers or possibly immunogenomic factors that may predict for cardiovascular toxicity of ICIs (37).

Taken into account the available evidence, it would be advisable that cancer patients who are candidates to receive ICIs are carefully assessed for known cardiovascular risk factors based on easy-to-use scoring systems such as the Systemic Coronary Risk Estimation (SCORE) (37). Baseline assessment and periodical monitoring of body weight, blood pressure, cholesterol, and glycemia should be performed in all cancer patients receiving ICIs. An optimization of cardiovascular risk factors and medical therapy for primary or secondary prevention before, during and after ICIs should be considered. Patients should be always supported for smoking cessation and adoption of healthy lifestyle and healthy diet, although it can be often difficult for cancer patients, especially those with metastatic disease, to do regular physical activity or follow a strict diet. In addition to behavior changes, medical therapy such as lipid-lowering drugs, blood pressure-lowering drugs, oral blood glucose-lowering drugs or insulin, and anti-platelet agents should be appropriately used to manage cardiovascular risk factors including dyslipidemia, diabetes mellitus and hypertension, according to well-established guidelines (37).

This approach will require ever closer cooperation between oncologists and cardiologist in the near future.

AUTHOR CONTRIBUTIONS

AI wrote the draft. All authors critically revised and approved the manuscript.

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Coronary Stent Healing in Cancer Patients—An Optical Coherence Tomography Perspective

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Objective: This study assessed stent healing patterns and cardiovascular outcomes by optical coherence tomography (OCT) in cancer patients after drug-eluting stent (DES) placement.

Background: Cancer treatment, owing to its cytotoxic and antiproliferative effects, could delay stent healing and increase stent thrombosis risk, especially when dual antiplatelet therapy (DAPT) is discontinued early for oncological treatment. OCT can assess stent endothelialization and other healing parameters, which may provide clinical guidance in these challenging scenarios.

Methods: This single-center retrospective study enrolled all cancer patients who underwent OCT for assessment of vascular healing patterns after prior DES placement from November 2009 to November 2018. Primary study endpoints were stent healing parameters, including stent coverage, apposition, degree of expansion, neointimal hyperplasia heterogeneity, in-stent restenosis, stent thrombosis, and overall survival (OS).

Results: A total of 67 patients were included in this study. Mean time between DES placement and OCT evaluation was 154 ± 82 days. Stent healing matched published values for DES in non-cancer patients ($P \geq 0.063$). At 1 year, the OS was 86% (95% confidence interval [CI]: 78–96%) with 0% incidence of acute coronary syndrome. Advanced cancers and active chemotherapies were associated with inferior OS ($P = 0.024$, hazard ratio [HR]: 3.50, 95% CI: 1.18–10.42 and $P = 0.026$, HR: 2.65, 95% CI: 1.13–6.22, respectively), while stent healing parameters were unassociated with OS. Forty-one patients (61%) had DAPT duration ≤6 months.

Conclusions: Stent healing of contemporary DES appears similar in cancer and non-cancer patients. Cardiovascular risk of cancer patients after DES placement can be managed to facilitate timely cancer therapies, as the underlying malignancy and active chemotherapy ultimately determine survival.

Keywords: stent healing, cardio-oncology, dual antiplatelet therapy discontinuation, acute coronary syndrome, optical coherence tomography

INTRODUCTION

Approximately 30% of patients with cardiovascular disease have a current cancer diagnosis with 10% of percutaneous coronary interventions (PCI) occurring in cancer patients (1, 2). Thrombocytopenia and bleeding risk related to malignancies or their treatment as well as the need for timely surgical interventions may require premature dual antiplatelet therapy (DAPT) discontinuation, specifically P_2Y_{12} inhibitors, more often in this patient population. However, discontinuing DAPT prematurely can increase stent thrombotic risk in an already prothrombotic cancer patient population. These competing concerns present a challenging dilemma of when to discontinue DAPT in cancer patients with concomitant coronary artery disease.

Optical coherence tomography (OCT) has been used to guide DAPT discontinuation decisions in cancer patients (3) by offering high resolution and detailed visualization of stented coronary artery segments (4), restenosis, and other stent healing parameters (5–7). Therefore, the current study utilized OCT to accomplish its objectives. The objectives of this study were to evaluate stent healing in cancer patients with previous PCI and drug-eluting stent (DES) implantation, decipher whether stent healing differed from patients without cancer based on published data, assess the impact of cancer stage and active chemotherapy on stent healing, and evaluate the impact of early (<6 months) DAPT discontinuation on overall survival (OS).

MATERIALS AND METHODS

Study Design and Patient Selection

We conducted a single-center, retrospective study of patients with a cancer diagnosis treated at The University of Texas MD Anderson Cancer Center in Houston, Texas, who received coronary stents placed between November 2009 through November 2018. Patients who were treated with PCI with DES implantation, received DAPT, and subsequently underwent OCT evaluation for clinical indications were eligible for inclusion. Clinical indications included abbreviated DAPT course, shortness of breath, acute coronary syndrome, cardiomyopathy, positive biomarkers indicating cancer therapy causing myocarditis, non-specific troponin elevation, and abnormal ECG. OCT at the time of DES implantation was not performed. The local institutional review board approved the study protocol ("A Retrospective Review of Cardiac Catheterization Data in a Cancer Population"); no informed consent was required due to the study's retrospective nature.

Patients' baseline demographics and clinical data were recorded at the time of cardiac catheterization: age, sex, BMI, cardiovascular risk factors (hypertension, smoking history, dyslipidemia, diabetes mellitus, coronary artery disease, and peripheral artery disease), and clinical history including stent number and territory, as well as laboratory data with complete blood counts, creatinine levels, and fasting lipid panel results (8–10).

The antiplatelet regimen was individualized by the operators based on OCT images and evaluation by the cardio-oncology team. Antiplatelet medications were recorded throughout the cancer treatment. Decisions concerning DAPT discontinuation were made based on available literature (3). Patients with a history of mediastinal radiation therapy were excluded to avoid the possible confounding factor of radiation-induced heart disease. Since most PCIs occurred in outside hospital facilities, patients with an unknown stent brand or type, stent placement with multiple stent brands, and undocumented date of stent placement were excluded.

Stratification of Cancer Diagnosis

Cancers were stratified into early and advanced-stage based on staging guidelines and literature-documented risk factors associated with poor prognosis. Overall, advanced cancer was defined as the presence of metastasis, stage III or higher in solid tumors, relapsed and/or refractory disease, or history of stem cell transplant in hematological malignancies. All cancers where treatment was not with curative intent were considered palliative. When all treatments were exhausted and no active treatment was provided, patients were considered hospice. All patients included in this study had at least 50% or greater probability of a 1-year survival. Sources for this literature survey are provided in the **Supplementary Material**.

Aims and Outcomes of the Study

The primary endpoints of the study were stent healing parameters as determined by completeness of strut coverage (11) and apposition (12), degree of expansion (13), neointimal hyperplasia heterogeneity (14), in-stent restenosis (15), stent thrombosis (16), and OS. All parameters recorded have been demonstrated to correlate with OS or with other stent healing parameters (11–16). The 12-month incidence of acute coronary syndrome (ACS) was also recorded. Mean neointimal hyperplasia was also calculated as a secondary assessment of strut and stent coverage. Outcomes were compared to values reported in the literature for populations with cardiovascular disease but without a cancer diagnosis (17–22).

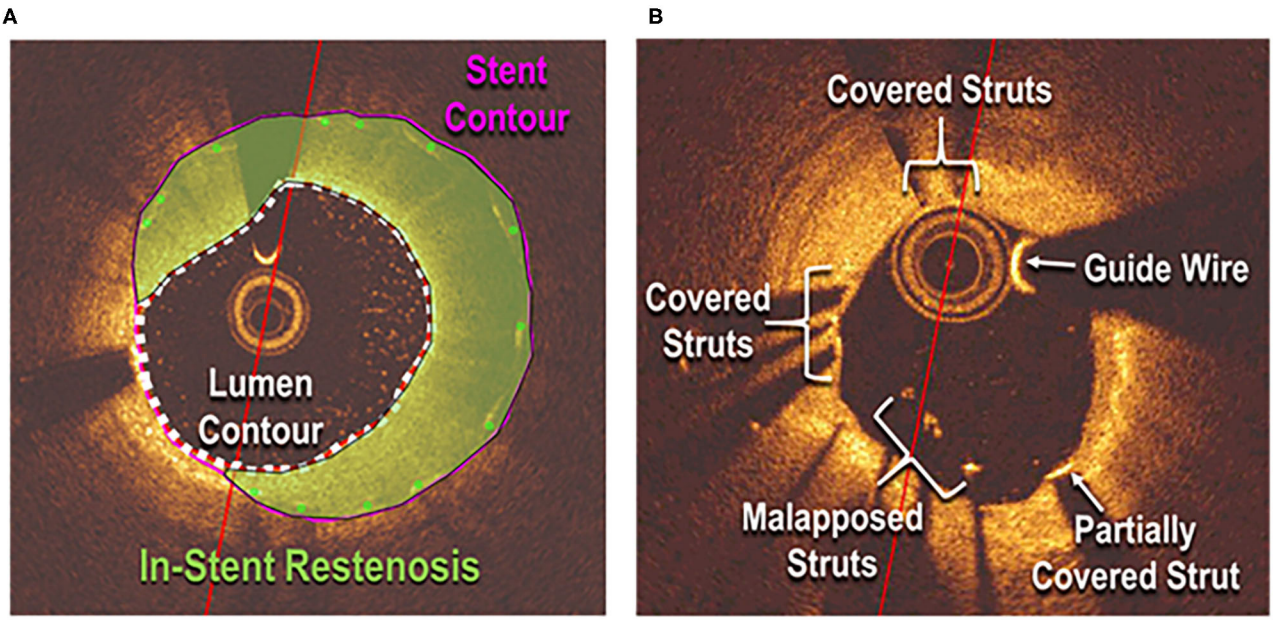

FIGURE 1 | Sample assessment of stent healing parameters. Stent **(A)** and strut **(B)** measurements.

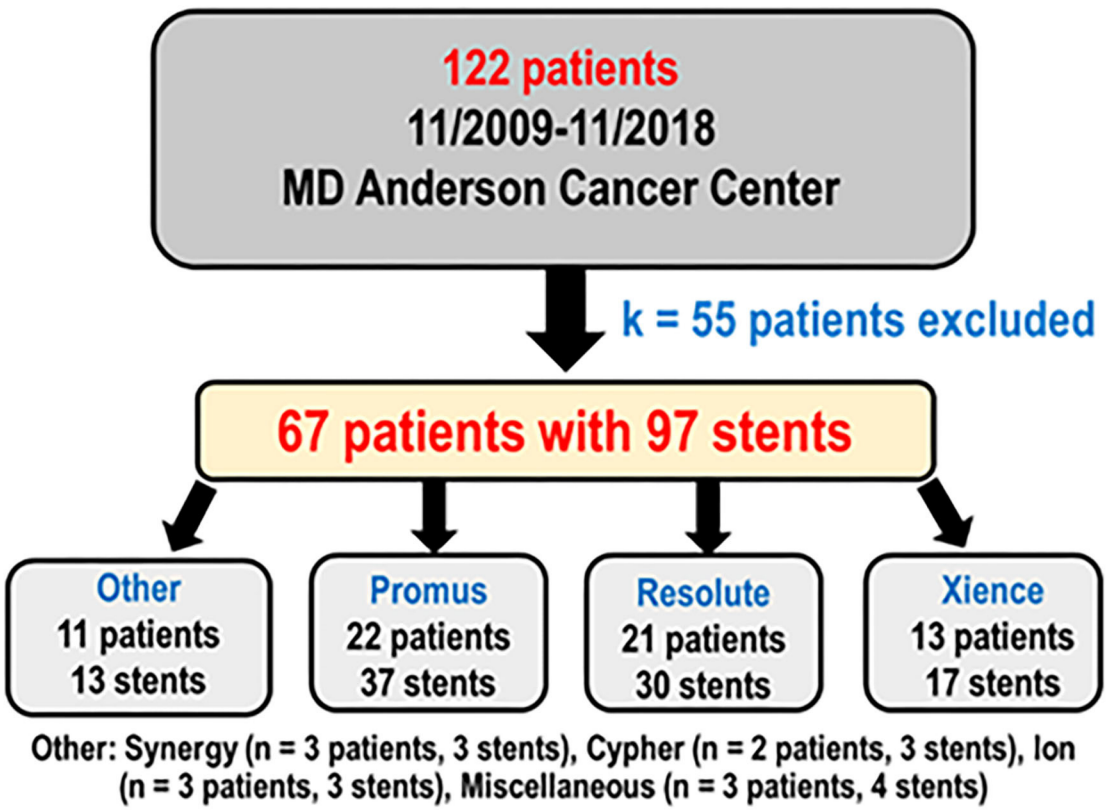

FIGURE 2 | Study design and stent brand distribution.

TABLE 1 | Descriptive data for the study cohort ($N = 67$).

Covariates	Mean ± standard deviation, median (Min, Max), or No. (valid %)
Demographics	
Age, y	65.72 ± 9.04, 66 (41, 84)
Body mass index, kg/m^2	29.9 ± 6.22 28.7 (20.35, 48.78)
Men	55 (82.09)
Women	12 (17.91)
Cardiovascular risk factors	
Smoking	39 (58.21)
Hypertension	61 (91.04)
Systolic blood pressure, mmHg	135.17 ± 21.3, 132 (92, 198)
Diastolic blood pressure, mmHg	73.08 ± 11.25, 72 (49, 102)
Dyslipidemia	63 (94.03)
Diabetes	23 (34.33)
Family history of coronary artery disease	27 (40.30)
Clinical history	
Heart failure	12 (17.91)
Ejection fraction, %	55.91 ± 10.09, 57.5 (19, 70)
Coronary artery disease	64 (95.52)
Myocardial infarction	26 (38.81)
Coronary artery bypass graft	8 (11.94)
Previous number of stents	
1	44 (65.67)
2	15 (22.39)
3	8 (11.94)
Peripheral artery disease	13 (19.40)
Chronic renal insufficiency	12 (17.91)
Indications for OCT analysis	
Abbreviated DAPT course	49 (73.13)
Shortness of breath	12 (17.91)
Acute coronary syndrome	11 (16.42)
Cardiomyopathy	2 (2.99)
Positive biomarkers of cancer therapy causing myocarditis	1 (1.49)
Non-specific troponin elevation	1 (1.49)
Abnormal ECG	5 (7.46)
Cancer data	
Solid	57 (85.07)
Hematologic	10 (14.93)
Advanced	40 (59.70)
Chemotherapy	13 (19.40)
Active	13 (19.40)
History of chemotherapy	8 (11.90)
Laboratory data	
Absolute neutrophil count, cells/μL	4.66 ± 2.3, 4.16 (0, 15.59)
Hemoglobin, g/dL	12.83 ± 1.77, 12.9 (9.6, 17.4)
Platelet count, × 10^3/μL	212.58 ± 82.67, 201.5 (9, 439)
Creatinine pre-OCT, mg/dL	1.23 ± 1.19, 0.98 (0.48, 8.68)
Creatinine post-OCT, mg/dL	1.21 ± 0.98, 0.99 (0.57, 7.42)
Triglycerides, mg/dL	130.55 ± 49.64, 122 (47, 236)
Total cholesterol, mg/dL	145.66 ± 39.31, 138.5 (91, 239)
High-density lipoprotein, mg/dL	44.02 ± 13.64, 40 (26, 76)
Low-density lipoprotein, mg/dL	79.51 ± 36.71, 71 (36, 192)
DAPT characteristics*	
Remained on aspirin	59 (88.06)
Remained on P2Y12 inhibitor: Remained on clopidogrel	2 (2.99)
Remained on ticagrelor	2 (2.99)
Complete discontinuation	5 (7.46)
Single antiplatelet treatment	55 (82.09)
Dual antiplatelet treatment	4 (5.97)
Not recorded	3 (4.48)
Subsequent events	
Acute coronary syndrome	0.00 (0.00)
Death	25 (37.31)

DAPT, dual antiplatelet therapy; OCT, optical coherence tomography.
**DAPT discontinuation occurred at <6 mo post-placement in 41 out of 67 patients (61%).*

OCT Analysis

A C7 Dragonfly OCT catheter and C7-XR OCT intravascular imaging system (St. Jude Medical, St. Paul, MN) were used to obtain OCT data (3). OCT images were analyzed in a semi-automated fashion using the proprietary software QCU-CMS, developed by Dijkstra et al. (Leiden University Medical Center) (23). Manual corrections for detection errors were performed by two independent observers (M.K.A. and C.A.I.). Strut apposition and coverage were detected by whether the strut was located above, at, or below the lumen contour (**Figure 1**). Data were excluded from analysis if during pullback adequate blood clearance was not obtained or stent struts were not clearly identified. Follow-up was obtained through review of hospital and clinic records.

Statistical Analysis

OS was defined as the time from OCT measurement to death or last contact and was estimated by the Kaplan-Meier method. The log-rank test was used to analyze differences in OS between patients with early-stage and advanced cancer diagnoses. Parameters affecting OS were established with Cox regression. An ANOVA variance analysis with a linear mixed-effect model was used to assess the relationship between stent brand, patient demographics, clinical characteristics, and stent healing parameters to account for patients with multiple stents. The Wilcoxon signed rank test was used to compare stent measurements with corresponding published values in patients without a cancer diagnosis. Studies from which published values were derived are cited in the manuscript. Comparisons were made only if the number of days from DES placement to OCT fell within the time range from which the published value was derived to ensure validity. A 2-sided $P < 0.05$ was considered statistically significant. SAS version 9.4 and S-Plus version 8.04 were used to carry out the computations for all analyses.

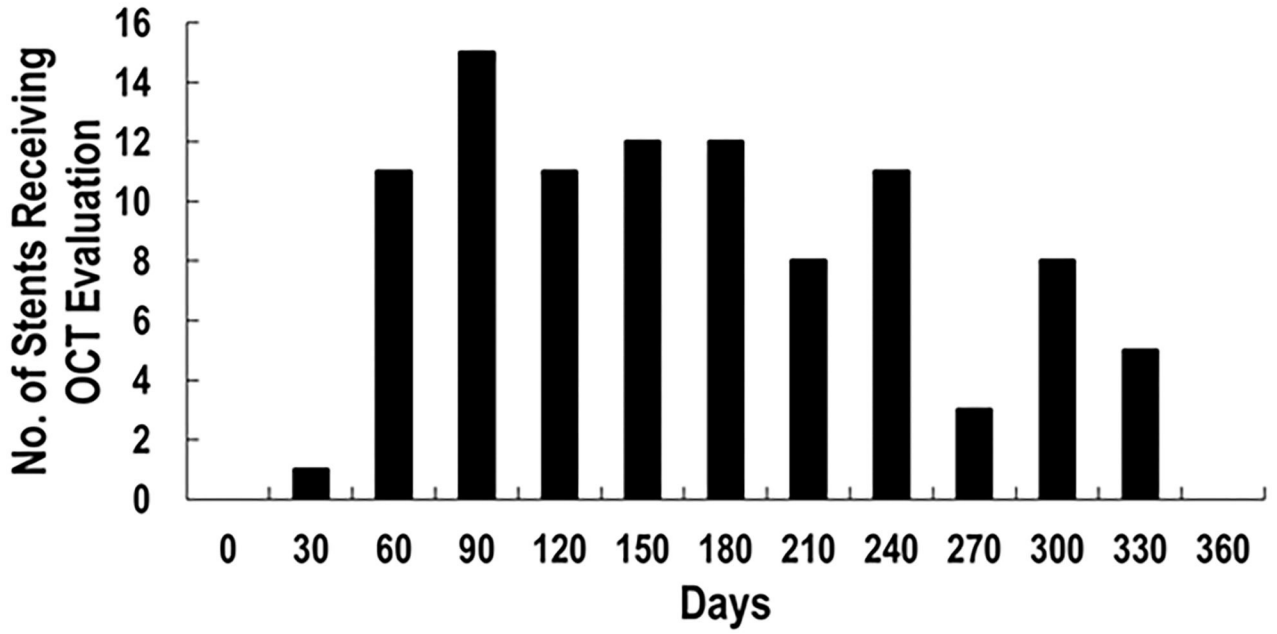

FIGURE 3 | Distribution of days between stent placement and OCT evaluation.

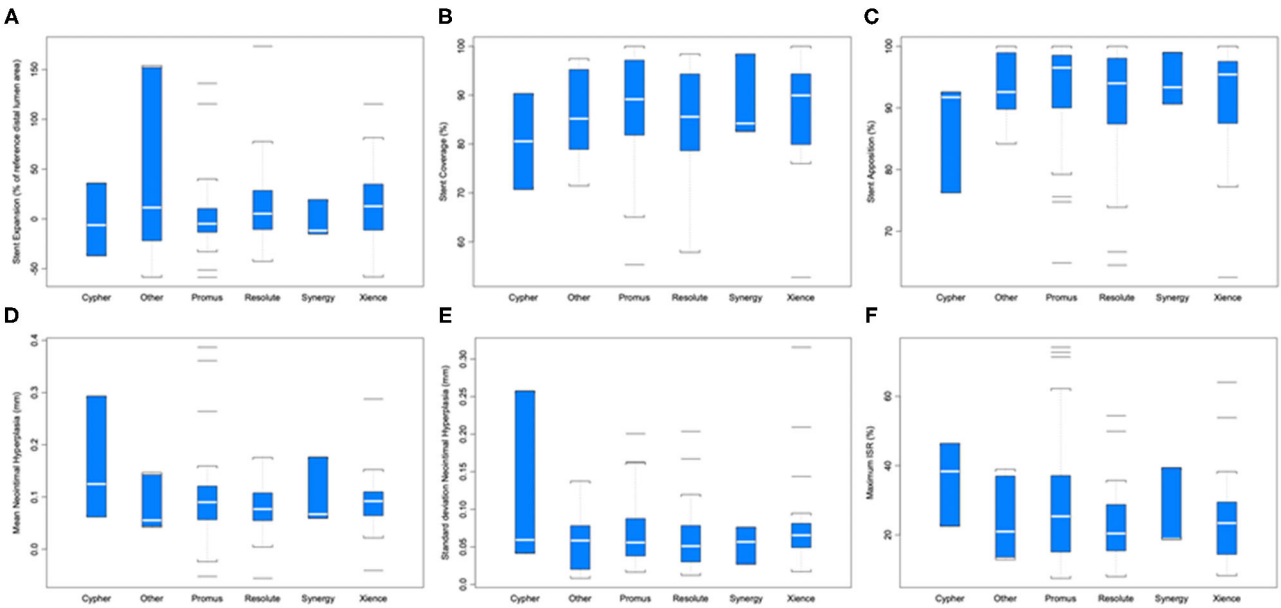

FIGURE 4 | Stent healing parameters by different stent brands. **(A)** Stent expansion ($P = 0.502$). **(B)** Stent coverage ($P = 0.707$). **(C)** Stent apposition ($P = 0.210$). **(D)** Mean neointimal hyperplasia (mm) ($P = 0.736$). **(E)** Standard deviation of neointimal hyperplasia ($P = 0.591$). **(F)** Maximum in-stent restenosis (ISR; $P = 0.204$).

RESULTS

Study Population

One hundred twenty-two patients had coronary stents placed from November 2009 through November 2018 and underwent OCT as part of their clinical care. After 55 patients with incomplete data were excluded, there were 67 patients with 97 stents analyzed (**Figure 2**) with more than 15,000 strut cross sections. Baseline demographics are presented in **Table 1**. Patients were predominantly male (82.09%) with high prevalence of cardiovascular risk factors: hypertension (91.04%), smoking (58.21%), dyslipidemia (94.03%), diabetes (34.33%), and family

TABLE 2 | Descriptive OCT stent measurements ($N = 97$ stents in 67 patients).

Covariates	Strut coverage, %	Strut apposition, %	Strut expansion, %	Mean neointimal hyperplasia, mm	Neointimal hyperplasia heterogeneity, mm	In-stent restenosis, %
Demographics						
Men	85.45 ± 11.78	91.45 ± 9.3	5.13 ± 36.54	0.1 ± 0.06	0.07 ± 0.05	12.03 ± 9.53
Cardiovascular risk factors						
Smoking	86.45 ± 9.88	93.17 ± 7.16	7.56 ± 38.57	0.09 ± 0.04	0.06 ± 0.04*	11.45 ± 5.14
Hypertension	85.96 ± 11.12	91.68 ± 8.95	8.91 ± 41.9	0.1 ± 0.07	0.07 ± 0.06*	12.22 ± 9.28
Dyslipidemia	85.71 ± 11.28	91.71 ± 8.93	10.33 ± 43.28	0.09 ± 0.07	0.07 ± 0.05	12.15 ± 9.16
Diabetes	87.03 ± 9.72	92.37 ± 8.27	−3.05 ± 31.71*	0.1 ± 0.06	0.07 ± 0.05	12.76 ± 6.83
Family history of coronary artery disease	85.16 ± 11.89	91.24 ± 9.11	8.92 ± 43.02	0.1 ± 0.09	0.07 ± 0.06	13.6 ± 10.79
History						
Heart failure	86.54 ± 11.57	92.25 ± 7.56	1.06 ± 44.49	0.11 ± 0.06	0.07 ± 0.04	15.05 ± 9.07
Coronary artery disease	85.95 ± 11.16	92.04 ± 8.79	10.1 ± 43.72	0.09 ± 0.07	0.07 ± 0.05*	12.03 ± 9.04
Myocardial infarction	87.09 ± 9.51	93.37 ± 6.16	10.3 ± 44.34	0.11 ± 0.09	0.08 ± 0.06	14.11 ± 10.06
Coronary artery bypass graft	80.31 ± 10.66	89.39 ± 9.07	21.09 ± 50.62	0.06 ± 0.06	0.06 ± 0.03	8.22 ± 8.2
Indications for OCT analysis**						
Abbreviated DAPT course	85.21 ± 11.45	91.22 ± 9.31	12.88 ± 45.98	0.09 ± 0.07	0.07 ± 0.04	11.54 ± 9.39
Shortness of breath	89.89 ± 9.51	94.77 ± 6.72	0.57 ± 43.65	0.12 ± 0.07	0.07 ± 0.06	14.70 ± 8.64
Acute coronary syndrome	82.61 ± 9.76	90.46 ± 6.62	10.43 ± 44.39	0.10 ± 0.07	0.09 ± 0.08	11.95 ± 6.18
Cardiomyopathy	81.81 ± 11.47	85.59 ± 9.42	−5.22 ± 7.46*	0.12 ± 0.06	0.09 ± 0.04	16.37 ± 9.17
Abnormal ECG	93.50 ± 4.75*	97.19 ± 2.20*	−1.71 ± 23.11	0.12 ± 0.08	0.07 ± 0.06	16.66 ± 12.30
Cancer data						
History of chemotherapy	81.52 ± 13.56	89.70 ± 10.26	11.09 ± 56.38	0.08 ± 0.08	0.07 ± 0.05	10.30 ± 12.46
Active chemotherapy	84.24 ± 13.8	90.29 ± 10.66	7.29 ± 47.64	0.09 ± 0.08	0.08 ± 0.06	12.55 ± 11.69
Advanced	86.77 ± 10.99	92.55 ± 8.4	9.4 ± 44.16	0.1 ± 0.08	0.07 ± 0.06	13.31 ± 10.03
Antiplatelet medications						
Remained on aspirin	85.8 ± 11.33	91.53 ± 9.1*	11.15 ± 46.04	0.1 ± 0.08	0.07 ± 0.06*	12.19 ± 9.52
Remained on clopidogrel	87.35 ± 1.96	91.53 ± 1.36	5.92 ± 25.31	0.14 ± 0.01*	0.09 ± 0.03	18.7 ± 5.13*
Remained on ticagrelor	86.51 ± 11.22	93.34 ± 5.73	45.27 ± 45.93	0.1 ± 0.08	0.07 ± 0.02	11.01 ± 7.89

*$P < 0.05$, used to determine association with stent parameter.

**Non-specific troponin elevation and positive biomarkers indicating cancer therapy causing myocarditis were not included in this analysis due to small sample sizes of only 1 patient for each of these groups.

history of coronary artery disease (40.30%). Thirteen of these patients (19.40%) were undergoing active chemotherapy; 8 of these 13 patients had history of chemotherapy (11.94%). The mean time between stent placement and OCT evaluation was 154 ± 82 days (**Figure 3**). Forty-nine of 67 patients (73%) underwent OCT to evaluate the possibility of an abbreviated DAPT course. Forty-one of 67 patients (61%) [with 59 of 97 stents (61%)] had DAPT discontinued for cancer treatment <6 months after stent placement. The mean time between stent implantation and DAPT discontinuation for this subset was 105 ± 45 days.

Strut and Stent Parameters

Strut coverage, completeness of apposition, and degree of expansion, as well as neointimal hyperplasia and maximum in-stent restenosis are reported in **Figure 4**. ANOVA with linear mixed-effect model demonstrated equivalent stent healing among stent brands ($P \geq 0.204$). Cancer prognosis was not associated with stent healing (early vs. advanced; $P \geq 0.095$). Active chemotherapy and history of chemotherapy did not impact stent healing ($P \geq 0.194$); chemotherapies in this patient population included cisplatin, docetaxel, FOLFIRINOX regimen, carboplatin, pembrolizumab, pemetrexed, MVAC regimen, cabazitaxel, melphalan, R-CHOP regimen, ibrutinib, cytarabine, and bevacizumab.

The impact of baseline characteristics and their association with stent healing are presented in **Table 2**. Stratified comparisons to literature values by follow-up duration of OCT after DES placement and stent brand (Resolute, Promus, and Xience stents) were performed with results noted in **Table 3** (17–22). For inclusion in a particular comparison, the follow-up duration of OCT needed to fall within the follow-up duration of stents included in the published study that generated a literature value. Stent healing in our cohort of cancer patients was similar to published data from patients with only cardiovascular disease ($P \geq 0.063$).

Clinical Outcomes

The median follow-up time was 2.5 years. Median OS was 3.4 years (95% confidence interval [CI]: 2.3–4.5 years). Long-term survival was driven by cancer-related mortality. The OS at 1

TABLE 3 | Stent healing comparison with literature values.

Stent parameter	Promus (17)				Resolute (18–20)				Xience (17, 21, 22)			
	Mean ± SD cancer patients	Mean ± SD literature	*P*	Time (days)	Mean ± SD cancer patients	Mean ± SD literature	*P*	Time (days)	Mean ± SD cancer patients	Mean ± SD literature	*P*	Time (days)
Stent coverage (%)	89.49 ± 12.38	97 ± 7	0.313	241–360	79.09 ± 15.61	95.5 ± 5.5	0.063	31–60	82.15 ± 3.15	73.3 ± 21.3	0.5	31–60
Stent apposition (%)	96.28 ± 5.26	99.8 ± 0.8	0.125	241–360	87.81 ± 12.94	98.1 ± 1.9	0.125	31–60	99.24 ± 0.47	98.7 ± 2.8	0.5	241–360
Mean neointimal hyperplasia (mm)	0.13 ± 0.12	0.105 ± 0.082	1.0	241–360	0.06 ± 0.08	0.07 ± 0.01	1.0	31–60	0.13 ± 0.04	0.091 ± 0.08	0.5	241–360
In-stent restenosis (%)	NA	NA	NA	NA	NA	NA	NA	NA	33.37 ± 6.29	36.8 ± 15.6	0.625	91–180

year from stent placement was 86% and further decreased to 57% at 3 years (**Figure 5**). The cause of death for all patients was cancer. Neither stent thrombosis nor ACS occurred in the analyzed cohort of patients. Deep venous thrombosis incidence at 1 year was 11.9% (eight patients).

Factors Associated With Survival

A univariate Cox regression was conducted to determine which patient characteristics, stent parameters, and strut parameters correlated with OS (**Table 4**). Of all characteristics noted, only cancer prognosis (early vs. advanced), active chemotherapy, and aspirin discontinuation correlated with OS. Continued use of aspirin was associated with longer OS (hazard ratio [HR]: 0.18, 95% CI: 0.04–0.88, $P = 0.034$). Patients on active chemotherapy had a higher mortality with an HR of 2.65 (95% CI: 1.13–6.22, $P = 0.026$). Patients with an advanced cancer stage had a higher mortality with an HR of 3.50 (95% CI: 1.18–10.42, $P = 0.024$). None of the stent healing parameters, including strut coverage, strut apposition, stent expansion, in-stent restenosis, mean neointimal hyperplasia, and heterogeneity of neointimal hyperplasia, correlated with OS ($P \geq 0.098$). Differences in OS between early and advanced cancers were significantly different as per the log-rank test ($P = 0.017$; **Figure 6**).

DISCUSSION

While past studies have used parameters associated with stent healing to guide DAPT discontinuation in cancer patients (3), this is the first study to compare stent healing in cancer patients who underwent intravascular imaging with OCT after DES implantation to a non-cancer population. With the increased incidence of patients with concomitant cardiovascular disease and cancer due to shared risk factors and population aging, the question of how to manage patients with PCI has increased relevance; stent healing is an important part of this question.

Past literature based on animal and *in-vitro* human cell and tissue studies has generated an expectation of delayed stent healing in cancer patients. Tissue factor (24), von Willebrand factor (25), and ADP (26) have been deemed common metabolites contributing to stent thrombosis and cancer pathogenesis; therefore, one would naturally expect that heightened levels of these metabolites from cancer pathogenesis would delay stent healing by contributing to stent thrombosis. However, the accelerated healing kinetics of contemporary DES (27) appear unaffected by vascular toxicities of cancer therapies and biological deterioration from cancer progression. The time scale of stent healing for contemporary DES has shortened to the extent that stent healing is now minimally impacted by cancer pathogenesis. When zooming in on the stent healing process, the rather short time interval required for healing for DES appears very close to a biological plateau minimally impacted by cancer or its treatments.

OCT evaluation is a valuable and effective tool to analyze stent healing and drives a convergence and a quantitative approach where unique clinical characteristics and treatments would make any form of randomization impractical. In addition to the numerous patient characteristics that affect stent thrombosis and

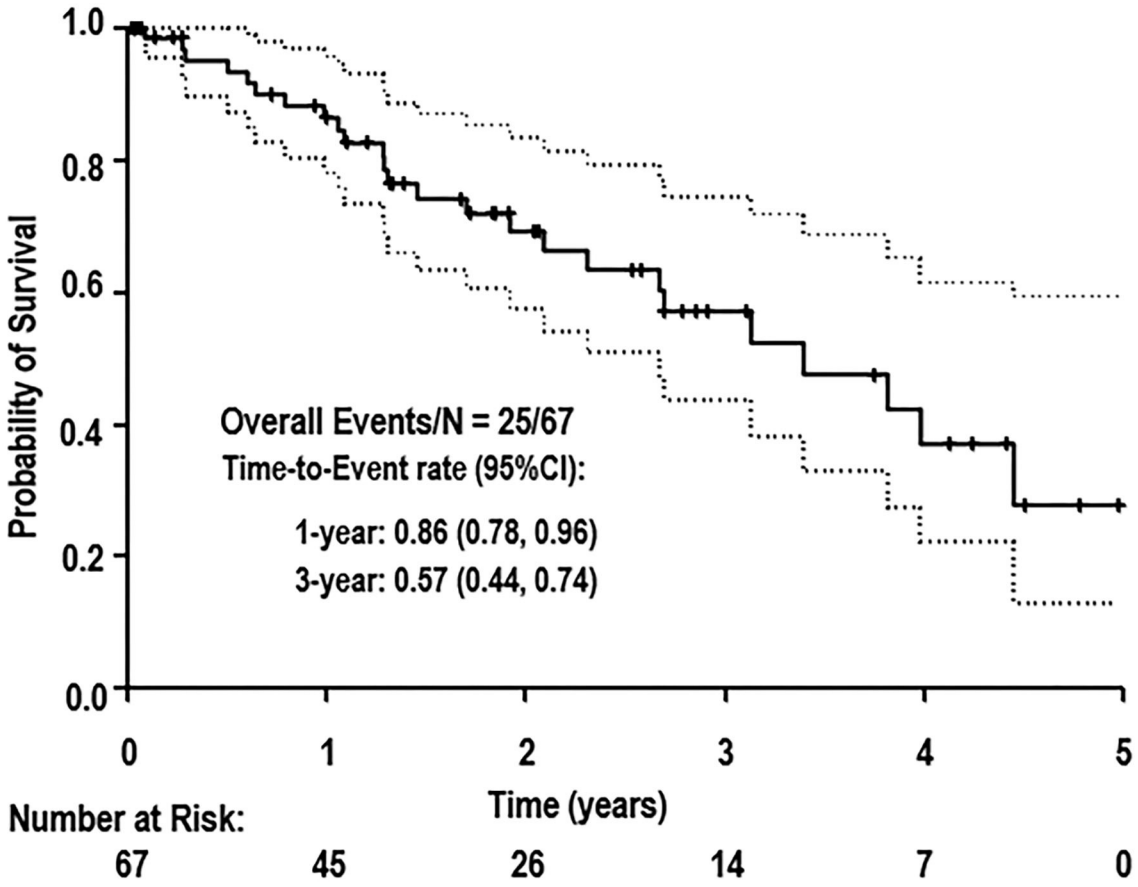

FIGURE 5 | Overall survival of studied population. Survival at 1 and 3 years provided.

in-stent restenosis including age (28), coronary artery disease (29), lack of appropriate statin use (30), low high-density lipoprotein (31), plasma-oxidized low-density lipoprotein (32), diabetes mellitus (33), renal failure (34), prior myocardial infarction (35), prior PCI (35), family history of cardiovascular disease (36), and low ejection fraction (37), increased additional complexity is brought by stent characteristics: polymer, platform, and eluting medication; (38) operator variability; (39) and the prothrombotic nature of the malignancy (40). From 2009 to 2011, a study by Shafiq et al. indicated a 69% variation in the likelihood of DES implantation among physicians in similar hospital settings caring for patients with identical characteristics (39). Since P_2Y_{12} inhibitor discontinuation decisions in the cancer population rely on stent healing parameters (3), a study based purely on clinical characteristics to address the risk of P_2Y_{12} inhibitor discontinuation also represents an impossible task.

A randomized control trial of 117,762 patients conducted in 2012 indicated differences in restenosis and thrombosis between stent brands (41). While assessment of the impact of stent brand in thrombosis incidence is difficult due to the small sample size and absent events, all stent healing parameters trended similarly regardless of stent brand. Of note, in-stent restenosis was similar among brands. Despite differences in platform, polymer, and eluting medication, overall advancements in stent technology may have abated these once clinically significant differences (42).

Since advances in stent technology have reduced the time scale of stent healing, the finding that cancer no longer or minimally impacts stent healing in newer-generation DES is increasingly plausible. Of note, stent healing was also unassociated with active chemotherapy. Ultimately, these findings can generate optimism and increase involvement to address cardiovascular comorbidities and improve resilience to cancer treatment challenges by permitting cancer pathogenesis and stent healing to be treated as two independent processes. Supporting this notion is the non-negligible incidence of deep venous thrombosis consistent with malignancy-based hypercoagulability despite routine prophylaxis and zero stent thrombosis.

This idea elicits the question of whether patients may receive cancer treatment independent of stent healing by discontinuing the P_2Y_{12} inhibitor to manage bleeding risk. Our OCT study demonstrated the relative safety of premature P_2Y_{12} discontinuation independent of cancer stage or treatment. Zero ACS events occurred at 1 year, including no stent thrombosis despite more than half of this patient population discontinuing DAPT at <6 months and the prothrombotic nature of cancer and cancer treatments (43). These results observed for patients with cancer are similar to non-cancer patients (44). A recent randomized control trial that included both cancer and non-cancer patients with indications for remaining on DAPT for only 1 month is also consistent with these results (45). In our study,

TABLE 4 | Cox proportional Hazard model to determine associations of baseline characteristics and stent healing parameters with survival.

Parameter	Classification Method	*P*	Hazard Ratio (95% CI)
Demographics			
Sex	Female vs. Male	0.144	0.12 (0.01–2.08)
Age	Per year increase	0.643	1.01 (0.96–1.06)
Cardiovascular risk factors			
Smoking	Yes vs. No	0.836	1.09 (0.49–2.41)
Hypertension	Yes vs. No	0.902	1.14 (0.15–8.70)
Dyslipidemia	Yes vs. No	0.792	0.76 (0.10–5.85)
Diabetes	Yes vs. No	0.348	1.48 (0.65–3.35)
Family history of coronary artery disease	Yes vs. No	0.828	0.91 (0.40–2.07)
History			
Heart failure	Yes vs. No	0.099	2.11 (0.87–5.11)
Coronary artery disease	Yes vs. No	0.437	2.22 (0.30–16.59)
Myocardial infarction	Yes vs. No	0.092	0.43 (0.16–1.15)
Coronary artery bypass graft	Yes vs. No	0.694	1.28 (0.38–4.31)
Peripheral artery disease	Yes vs. No	0.613	0.78 (0.29–2.08)
Chronic renal insufficiency	Yes vs. No	0.428	1.51 (0.55–4.13)
Indications for OCT analysis**			
Abbreviated DAPT course	Yes vs. No	0.110	0.48 (0.20–1.18)
Shortness of breath	Yes vs. No	0.054	2.44 (0.98–6.07)
Acute coronary syndrome	Yes vs. No	0.319	1.76 (0.58–5.38)
Cardiomyopathy	Yes vs. No	0.237	2.42 (0.56–10.46)
Abnormal ECG	Yes vs. No	0.499	1.67 (0.38–7.43)
Cancer Data			
History of chemotherapy	Yes vs. No	0.072	2.72 (0.92–8.08)
Active chemotherapy	Yes vs. No	0.026*	2.65 (1.13–6.22)
Advanced (cancer types in **Supplemental Material**)	Advanced vs. early–stage	0.024*	3.50 (1.18–10.42)
Antiplatelet medications			
Remained on aspirin	Yes vs. No	0.034*	0.18 (0.04–0.88)
Remained on clopidogrel	Yes vs. No	0.353	2.62 (0.34–20.12)
Remained on ticagrelor	Yes vs. No	0.658	0.50 (0.02–10.89)
Stent healing parameters			
Maximum in-stent restenosis, %	Per unit increase	0.720	1.00 (0.97–1.02)
Mean neointimal hyperplasia, mm	Per unit increase	0.400	0.08 (0.00–28.95)
†$\log_2$(Neointimal hyperplasia heterogeneity, mm)	Per fold increase	0.651	0.91 (0.61–1.36)
Mean strut expansion, %	Per unit increase	0.125	0.99 (0.98–1.00)
Mean strut coverage, %	Per unit increase	0.119	0.98 (0.95–1.01)
Mean strut apposition, %	Per unit increase	0.098	0.97 (0.93–1.01)

$P < 0.05$, used to determine association with overall survival, NR, not reached.

***Non-specific troponin elevation and positive biomarkers indicating cancer therapy causing myocarditis were not included in this analysis due to small sample sizes of only 1 patient for each of these groups.*

†*Log_2 transformation of the original variables required due to right-skewed distribution.*

neither P_2Y_{12} inhibitor discontinuation decisions themselves nor the stent healing parameters used to generate these decisions impacted OS. Therefore, cancer status and active chemotherapy, due to their association with OS, should be prioritized when evaluating risks associated with P_2Y_{12} inhibitor discontinuation. Emergent cancer treatments should not be delayed merely due to DAPT discontinuation guidelines.

One may ask why not continue the traditional practice of stenting with bare metal stents (BMS) in cancer patients to circumvent the question of premature P_2Y_{12} discontinuation? While BMS provide rapid endothelization, shorter DAPT duration, and relatively low stent thrombosis risk compared to the first-generation of DES (46), second- and third-generation DES have demonstrated even lower stent thrombosis risk than BMS (47). With a contemporary almost default stenting with DES, we have witnessed an accelerated decrease of DAPT duration over the last 5 years as stent designs have improved. While European Society of Cardiology (ESC) guidelines permit 1-month DAPT with DES for specific indications, current American Heart Association (AHA)/American College of

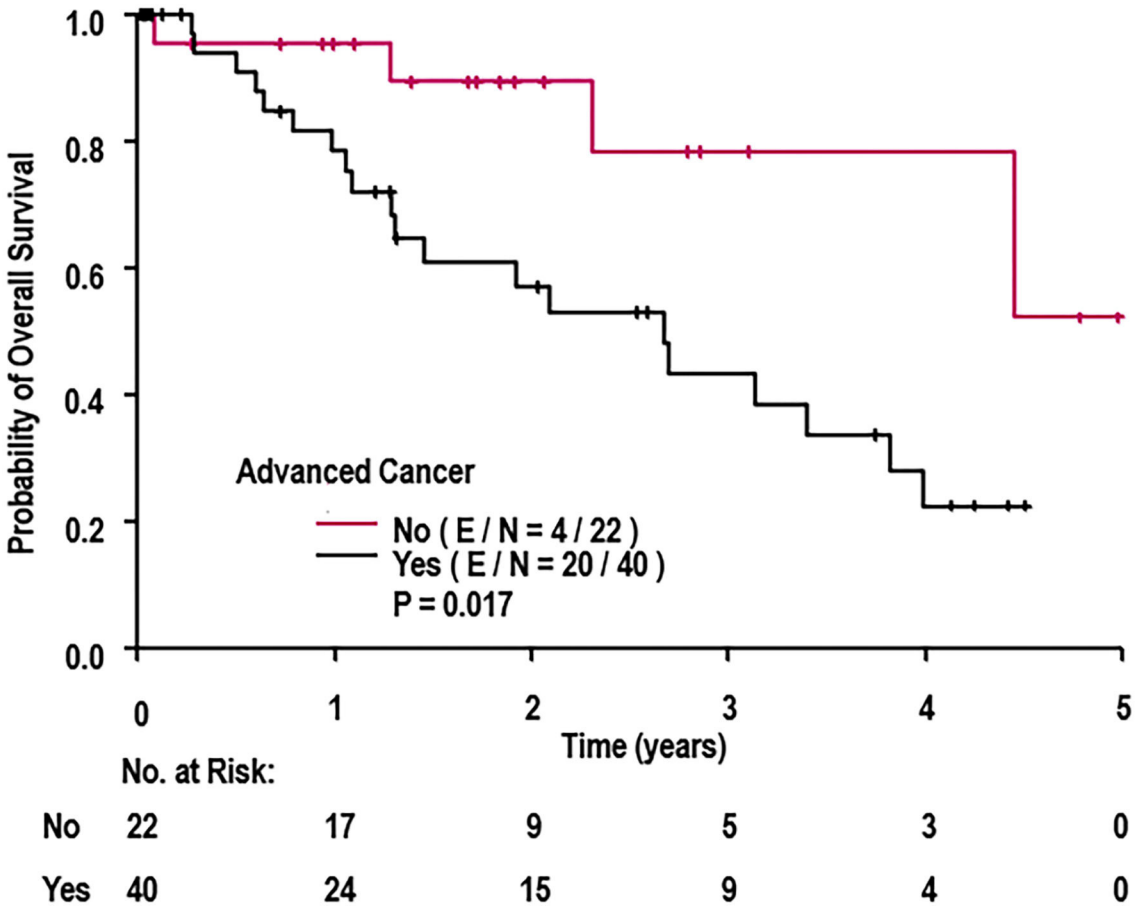

FIGURE 6 | Overall survival of cohort when stratified by cancer prognosis (early vs. advanced). E, events; N, number of patients; OS, overall survival. *P*-value determined from log-rank test.

Cardiology (ACC) guidelines still indicate that DAPT can be shortened to 3–6 months in patients with increased bleeding risk (48). However, in our cohort of cancer patients, more than half the patients discontinued DAPT <6 months (mean duration 3–4 months) after stent placement. Examination of the two most commonly used P_2Y_{12} inhibitors, clopidogrel and ticagrelor, indicates that their discontinuation had no effect on survival. While continuation of aspirin was associated with strut apposition and appeared to improve OS, it may have also been associated with cancer prognosis (early vs. advanced). While recognizing that patients with greater cardiovascular risk benefit from longer DAPT (>12 months) (49), each cancer patient with cardiovascular burden should have a personalized approach to DAPT discontinuation that accounts for cancer status and prognosis.

Limitations

A major limitation of this study is the lack of a control group when comparing stent healing of cancer patients; the center at which this study was conducted treats only patients with a cancer diagnosis. Therefore, a sample cohort with purely cardiovascular pathologies who could be directly compared to the studied population under identical conditions could not be constructed. Ultimately, populations from various published studies were used as comparison groups.

Another limitation concerns the stents used in this study. An ideal scenario for a cancer patient who requires PCI would include 4 or preferably 2 weeks of DAPT, with overall low or absent thrombotic risk and minimal in-stent restenosis during a proinflammatory and prothrombotic treatment. Select stents are approaching these goals; however, they are too recent to be included in this study (45).

Ideally, immediate status of stent healing and placement can serve as an important indicator of late stent healing status. However, since the center at which this study was conducted is a tertiary care center, DES implantation occurred at outside hospitals in which OCT was not conducted immediately after stent implantation. Therefore, information regarding initial stent status and its relationship to OS in this population is unavailable. Nevertheless, in a study published in the *Journal of American College of Cardiology* in 2020, no difference in survivorship was observed when comparing cancer patients with intravenous ultrasound or OCT taken during DES placement vs. cancer patients receiving OCT follow-up after DES placement (50).

Additionally, while our study addressed the relative safety of early P_2Y_{12} inhibition discontinuation irrespective of cancer stage and treatment, our time frame was insufficient to address the interesting aspect of prolonged (>1 year) P_2Y_{12} inhibition and its impact on cancer or cardiovascular mortality (51). One previous study examining prolonged P_2Y_{12} inhibition in cancer patients suggests that it had no effect on cancer or mortality (51).

While cause of death was appropriately established based on the medical record, the retrospective nature of this study primarily establishes associations; causations of additional or aggregate findings are challenging to validate. Furthermore, the time from stent placement to OCT in the studied population was 154 ± 82 days, implying that these conclusions regarding stent healing can only be applied for healing occurring during this time frame. Future studies should assess stent healing *via* OCT evaluation beyond this limited time frame. Additionally, OCT devices are currently unable to specifically pinpoint fibrin deposition, which would be prothrombotic despite appearing as covered and healed stent struts (52). Finally, published values were not available for all measured parameters of each individual stent brand.

CONCLUSIONS

Cancer patients with coronary artery disease receiving DES appear to have a primarily cancer-driven prognosis; therefore, decisions concerning DAPT and especially P_2Y_{12} inhibitor discontinuation should prioritize cancer treatment and active chemotherapy considerations over thrombotic risk. The comparable stent healing visualized by OCT between cancer and non-cancer patients regardless of stent brand and the P_2Y_{12} inhibitor discontinuation not impacting survival should encourage a personalized approach to stent healing management that accounts for cancer status and prognosis. Emergent cancer treatments should be prioritized since cancer status and active chemotherapy ultimately determine OS.

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 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

MKA participated in conception and design, analysis, interpretation of data, drafting of the manuscript, and revising it critically. JH, KM, MC, and JL-M participated in conception of study and revising the manuscript critically. DVB, TD, VZ, and HA participated in revising the manuscript critically. BP, HL, GT, and JD participated in analysis and interpretation of data. TH and MF participated in analysis, interpretation of data, and revising the manuscript critically. MP participated in drafting of the manuscript. DM participated in study design and revising the manuscript critically. CI participated in conception and design, analysis, interpretation of data, and revising the manuscript critically. All authors contributed to the article and approved the submitted version.

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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.2021.665303/full#supplementary-material

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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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Portrait of Italian Cardio-Oncology: Results of a Nationwide Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) Survey

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Aims: Cardio-oncology has achieved a pivotal role in science, but real world data on its clinical impact are still limited.

Methods: A questionnaire was sent out to all cardio-oncology services across Italy ($n = 120$). The questionnaire was made up of 28 questions divided into four blocks: (A) general information on hospitals and service, (B) the inner organization of cardio-oncology and its relationships with out-of-hospital cardiologists and general practitioners, (C) educational needs and referral guidelines, and (D) activities/specific workload.

Results: Ninety-six out of 120 (80%) completed the questionnaire; 9.4% were cancer centers while 90.6% were general hospitals. A cardio-oncology team was present in 56% of the cancer centers and in 20% only of general hospitals, and a cardio-oncology pathway was active in 55% of cancer centers and in just 14% of the general hospitals. Relationships with out-of-hospital cardiologists and general practitioners were lacking. The guidelines of reference were ESC and ANMCO/AIOM. Patients receiving anthracycline chemotherapy underwent scheduled monitoring by means of echocardiography in 58% of cases. Routine use of cardiac damage biomarkers was overall low, ranging from 22 to 33% while the use of global longitudinal strain reached 44%.

Conclusions: Italian cardio-oncology showed a growing influence on clinical practice but still has room for improvement. Cardio-oncology teams are still scarce, and the application of dedicated paths is poor. The need for specific training has been highlighted.

Keywords: cardio-oncology, anthracyclines, trastuzumab, global longitudinal strain, cardiac biomarker, healthcare

INTRODUCTION

After a long period of being overlooked, cardio-oncology (CO) is now playing a major role in the clinical scenario of both cardiology and oncology. The leading cardiology and medical oncology organizations have recently released guidelines and recommendations (1–3) on the subject. In addition, they have provided advice on how to set up a CO program (4, 5). Accordingly, an increasing number of national cardiology societies have published CO reports (6–8), and the number of Internet searches on CO related topics has increased (9). Recommendations and guidelines are fundamental tools for cardiologists who intend to provide the best care to cancer patients and fulfill the scientific need for CO. CO being a relatively new discipline, guideline indications do not directly or automatically apply to clinical daily practice. Recently, a survey on cardiac imaging in CO highlighted considerable gaps between guidelines and everyday clinical practice (10).

The lack of specific clinical pathways and of clinicians' confidence makes the widespread application of the guidelines slower and more difficult. Moreover, the quantity of real world data on the clinical application of these recommendations is limited. On these grounds, we conducted an Italian nationwide survey on the behalf of the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) to paint a detailed picture of the daily behaviors of professionals dealing with cardiac care in cancer patients.

METHODS AND MATERIALS

On July 18th, 2019, a CO questionnaire was uploaded on the ANMCO website on the behalf of Cardio-Oncology Task Force. Deadline for submission was set on January 22th, 2020. An invitation email was sent out to the regional ANMCO presidents, regional CO delegates (identified by the presidents), and the referral cardiologists of each CO service all across Italy. A complete list of CO facilities was available based on the results of the two previous ANMCO surveys in 2017 and 2019. The ANMCO database of CO services was the only one available, and it covers the national territory with few exceptions, so survey results could offer a reliable picture of real-world Italian CO practice. Before compilation, each participant signed up and clearly identified the center for which he or she worked. Completed questionnaires were double-checked to avoid duplicates from the same center.

The aims of the survey were to characterize the activity of CO services across Italy; to explore their network of cancer-treating physicians, general practitioners and out-of-hospital cardiologists; and to analyze their educational needs.

The questionnaire was composed of 28 single or multiple-choice questions divided into four functional domains: (A) general information on hospitals and service (questions 1–4); (B) the inner organization of cardio-oncology and its relationships with out-of-hospital cardiologists and general practitioners (questions 5–13); (C) educational needs and referral guidelines (Questions 14–16); and (D) activity (questions 17–28).

The first block of questions aimed to analyze the types of hospitals in which the cardio-oncology services operate and the inner organization of the oncology referral department. Questions about service-related cancer patients (type of cancer and provenance) were also a part of this block. The second part inquired about the organization of the cardio-oncology service. It was asked about the frequency and the modalities (direct case-by-case phone calls, written advice, etc.) of the relationships between clinicians and general practitioners of the surrounding area. Questions regarding the relationship with out-of-hospital cardiologists were also included in this block while the relationships with out-of-hospital oncologists and hematologists were not part of the survey. The third part explored the educational needs of cardio-oncology service staff; both nurses and physicians were questioned about their interest on specific (additional) training by means of an ANMCO educational focused activity. Moreover, they were asked about their referral guidelines.

The fourth one focused on CO workload. Clinicians were asked about the categories of patients receiving potentially cardio-toxic drugs who underwent regular cardiac follow-up; how they performed risk assessment for cardiac toxicity of anthracyclines; the timeline of cardiological evaluation of patients receiving anthracyclines or trastuzumab; and how they managed new cardiac toxicity and/or new drugs. Information about the use of cardiac damage biomarkers and global longitudinal strain (GLS) in early detection of left-ventricular ejection fraction decrease were also part of this section.

The survey did not require approval by the Local Ethical Committee because it is based on physicians' opinions and administrative data only, without direct patient data collection.

Because of the descriptive aim of the survey, no formal statistical design was set up. Data are presented as percentages of the whole number of answers received for each single or multiple question. Multiple answers were possible for some questions.

RESULTS

On the deadline, 80% of centers (96 out of 120) completed the online questionnaire and were therefore included in this report. The geographical distribution of the centers that completed the survey is shown in **Figure 1**.

Domain A: General Information on Hospitals and Service

Nine out of 96 hospitals (9.4%) were cancer centers, while in the large majority of cases (87 out of 96, 90.6%) CO operated in a general hospital. Twelve out of 87 (13.8%) hospitals in the general hospital category could be classified as tertiary referral establishments. At a glance, an uneven distribution appears with a slight prevalence of participating centers of the northern and central regions of Italy (34 in the North vs. 36 in the central and 26 in the southern regions) and a paired, rather than homogenous, availability of CO services.

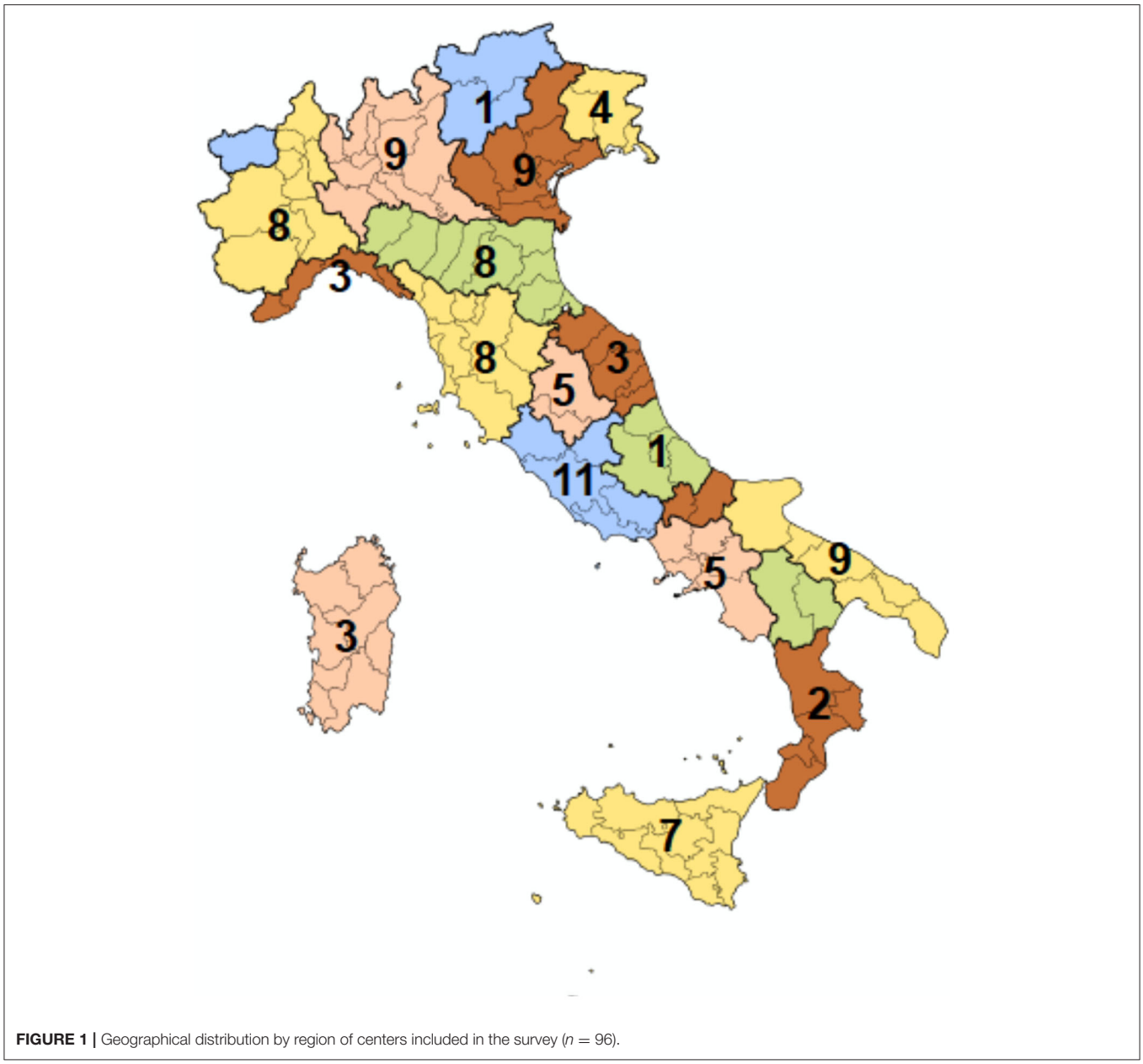

FIGURE 1 | Geographical distribution by region of centers included in the survey ($n = 96$).

As expected, all cancer centers took care of a wide range of cancer patients, including rare ones, but also general hospitals with a cardio-oncology service dealt with more than three cancer types in 77% of cases. Overall, the more frequent cancer type requiring a CO consultation was breast cancer, followed by lung cancer and gastro-intestinal cancer. The differences in CO teams between cancer centers and general hospitals were remarkable. While in five out of nine (56%) cancer centers an official team or a pool of dedicated cardio-oncologists was available, this percentage dropped to 20% (18 out of 87) in general hospitals, leading to an overall percentage of 24% (**Figure 2**, top panel).

Domain B: Inner Organization of Cardio-Oncology and Relationships With Out-of-Hospital Cardiologists and General Practitioners

The differences between cancer centers and general hospitals surfaced when cardiologists were asked about their relationship with oncologists. A shared clinical CO protocol was active (even if with different modalities including multidisciplinary meetings only) in 55% of cancer centers while only 14% of CO services in general hospitals had an organized rule-based clinical pathway (**Figure 2**, bottom panel). Overall, centers suffered because of

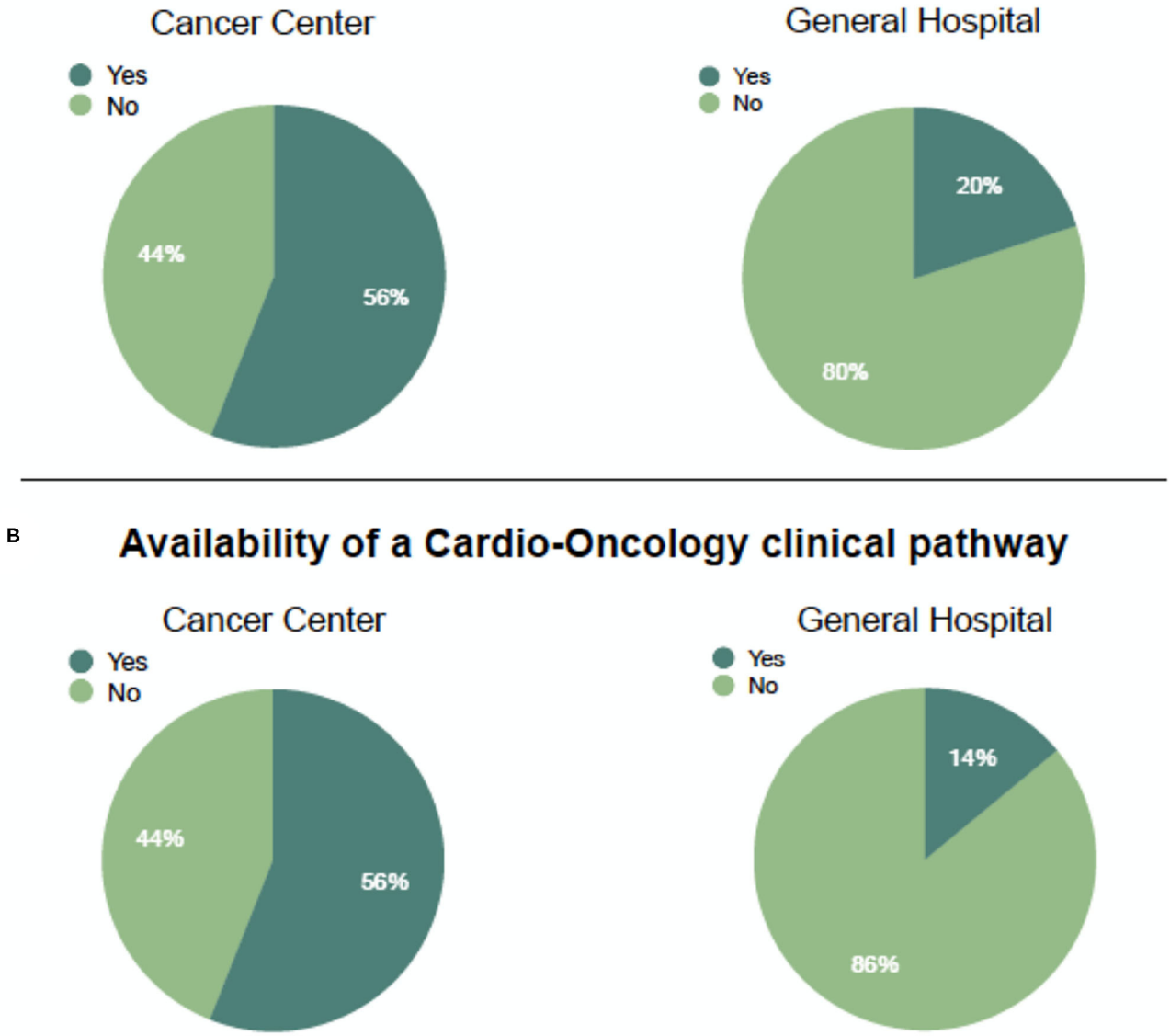

FIGURE 2 | Availability of a cardio-oncology team **(A)** and a dedicated clinical pathway **(B)** in Italian centers having completed the survey, divided by hospital type.

the absence of nurses in the team; only in 27% of responding hospitals was a nurse always on the team. Cooperation with out-of-hospital cardiology services was lacking in both settings. Fifty-eight out of 87 (66.6%) general hospitals and four out of nine (44%) cancer centers did not share information on patients with territorial cardiologists in a planned way. In some cases (22%), information is sent out from cancer centers to external specialists, due to the distance between the patient's home and the center itself. This percentage drops to 10% for general hospitals. In both facilities, information with out-of-hospital cardiologists is shared on a single-case base, limited just to complex ones. When asked about relationships with general practitioners, respondents reported a tighter bond. Communication was frequent in only 9% and occasional in 57% of cases leading to an overall percentage of collaboration of 68%. Information was shared mainly by means of the discharge summary (67%) or by a phone call (41%).

Domain C: Educational Needs and Referral Guidelines

Vocational training paths still represent an unmet need of cardio-oncology staff. An analysis of answers highlighted the willingness to participate in focused CO learning programs in 81.2% (78 out

TABLE 1 | Frequency of routine cardiac evaluations in cancer patients receiving anthracyclines (upper panel) or trastuzumab (lower panel) by center type.

	General hospital	Cancer center
Before and after treatment (*n*/%)	53/87 (60%)	5/9 (55%)
1-year after completion (*n*/%)	39/87 (45%)	4/9 (44%)
3-months schedule	62/87 (71%)	8/9 (89%)

TABLE 2 | Use of cardiac biomarkers (upper panel) and global longitudinal strain (lower panel) in the routine monitoring of cancer patients receiving anthracyclines by center type.

	General hospital	Cancer center
Troponin T or I (*n*/%)	7/87 (8%)	0/9 (0%)
BNP or NT-pro-BNP (*n*/%)	2/87 (2%)	0/9 (0%)
Troponin plus BNP or NT-pro-BNP (*n*/%)	19/87 (22%)	2/9 (22%)
Global longitudinal strain*	37/87 (43%)	4/9 (44%)

*BNP, B-type natriuretic peptide; *Taking together the answers "always" and "depending on the operator" (see text for details).*

of 96) of nurses and in 91.6% (88 out of 96) of clinicians. The reasons for interest in CO training programs were the need for skill improvement (78%) in hospitals where a CO program is already active and initial training in centers lacking a CO team (14%). The guidelines of reference in clinical practice for Italian cardio-oncologists were those of ESC in 64.6% (62 out of 96) and the consensus of ANMCO and AIOM with a similar percentage, 64.6%. American guidelines from ASCO (20%) or cancer-site specific guidelines (21%) were less followed.

Domain D: Activity

The majority of centers (60%) offers a dedicated path to cancer patients for all cardiotoxic drugs with anthacyclines (52%), trastuzumab (51%), immune check-point inhibitors (ICIs) (31%), and tyrosine kinase inhibitors (TKIs) (31%) being the most frequently used drugs. The sound criteria in the literature for the cardiac toxicity of anthracyclines were known and applied constantly (82%). The presence of anthracyclines cardiac toxicity risk factors was checked on an equal basis by cardiologists (42%) or oncologists (43%) but always according to a predefined checklist. The surveillance of cancer patients undergoing treatment with anthracyclines seemed to be quite well-established; overall, 58% of centers routinely performed a scheduled monitoring with echocardiography before and after treatment, with 56% increased frequency in high-risk patients. An end-of-treatment echocardiogram was performed in 68% of cases and 45% performed an additional echocardiogram after 1 year (**Table 1**, upper panel). Trastuzumab treatment was paired with close monitoring; the 3-month control schedule is met in 71% of general hospitals and 89% of cancer centers (**Table 1**, bottom panel).

A low rate of routine utilization of cardiac biomarkers was observed in patients receiving anthracyclines; B-type natriuretic peptide (BNP) and/or NT-pro-BNP alone were routinely used in only 2% of general hospitals, and this percentage slightly rose up to 9% for troponins with a prevalence of troponin T over troponin I. The routine coupled use of these biomarkers reached a percentage of 22% in both general hospitals and cancer centers. Overall, 32% of general hospitals and 22% of cancer centers routinely use any biomarkers to monitor cardiac toxicity of anthracyclines (**Table 2**, upper panel). The use of cardiac biomarkers was slightly more frequent in specific populations as patients at high risk for cardiac toxicity or to those with a suspect of toxicity.

Data on the use of GLS were more reassuring. When we take the answers "always" and "depending on the operator" together, the global percentage of use was 43% and 44% in general hospitals and cancer centers, respectively (**Table 2**, bottom panel).

Patients with a history of coronary artery disease and a planned fluoropyrimide-based treatment underwent a pretreatment exercise stress test or imaging stress tests in 43% of cases, and a similar percentage is subjected to ECG-monitoring during the initials days of therapy. Thrombosis in cancer patients is mainly managed by cardiologists (53%), followed by oncologists (32%) and internal medicine specialists (26%); interestingly, a multidisciplinary approach is reported in 24%.

DISCUSSION

Over the past decade CO has played a major role in the management of cancer patients in Italy. While its role from a scientific and educational point of view has been widely recognized due to the tireless work of scientific societies, the real world impact on daily clinical practice is still too limited. A previous report (11) showed that the percentage of hospitals offering a dedicated CO service was 20% in Tuscany, and the overall national percentage was observed to be slightly higher (24%), and almost half of cancer centers do not have a CO team. As a matter of fact, CO services are still underrepresented and show regional disparities.

Issues on CO availability are not only limited to geographical distribution. The geographical differences we observed, with a slightly higher prevalence of centers with a CO service in the northern and central Italian regions, are not just the natural consequences of the distribution of cancer centers, which are mainly located in these regions.

Clinical CO pathways are lacking in the majority of hospitals, and cooperation among physicians is mainly on a single-case base. Similarly, multidisciplinary meetings are not tightly scheduled. In a minority of centers only one nurse is allocated to the CO team. The relationship among cancer centers, general hospitals, and out-of-hospital facilities was a major focus of the survey. A previous ANMCO report highlighted the need for a multidisciplinary inter-hospital network in order to offer full cardiological assistance to cancer patients (12). Survey results clearly showed that cooperation with out-of-hospital cardiologists or general practitioners, regardless of hospital characteristics, is far from effective. The difference between the rising interest in CO and its low availability observed in Italy was

also outlined in a recent report from the ESC Cardio-Oncology council (4).

The educational work carried out by scientific societies (ESC, ESMO, ASCO, ANMCO/AIOM) to create specific CO guidelines has achieved consistent results. All survey participants declared that they were aware of the existence of specific guidelines, with ESC and ANMCO being the best known and applied. This is undoubtedly related to the increasing attention of both cardiologists and oncologists to CO issues over the last few years and the commitment of scientific societies to seek clinicians' attention with dedicated activities and focused guidelines. The need for specific training is strongly felt by cardiologists and nurses as well as by the wide majority of centers, which are interested in CO courses. Probably, from a national perspective, the classic educational activities (i.e., focused events or dedicated sessions within major congresses) should be coupled with a more specific approach at the local or hospital level. After the pandemic breakout, scientific societies continued to offer specific CO educational programs through web seminars or online competence courses.

In accordance with this educational purpose, ANMCO proposed specific pathways for the management of cardiac toxicity and focused booklets on controversial CO clinical issues. In view of the differences at the hospital level and the sometimes relevant regional distinctions (based on the fact that the Italian health system is regionally based), a single Italian pathway for CO cannot be drawn. A system too rigid could not be universally adopted, so we propose a basic outline to be adapted to local facilities and possibilities.

The cardiac side effects of anthacyclines and trastuzumab have been known since decades (13–15), and specific statements have long been available. At baseline, therapy and post-treatment evaluations are frequently performed in both general hospitals and cancer centers in Italy. In particular, we found a greater percentage of patients undergoing a post-treatment echocardiogram (68% as end-treatment and 45% at 1 year) in comparison with American administrative database evidence, showing that only 29.4% of American patients received an echocardiogram in the year following treatment (16). The relevance of classic and disease-specific cardiovascular risk factors has been clearly understood. A pretreatment check for cardiac toxicity risk factors is routinely performed. Recently, a joint paper from the Heart Failure Association of the European Society of Cardiology and the International Cardio-Oncology Society reaffirms the key role of pretreatment risk factor evaluation (17).

While survey respondents were confident in the clinical management of the cardiac side effects of anticancer drugs, the use of cardiac biomarkers and GLS techniques in monitoring cardiac toxicity is overall poor. The data offer a rather confused and uneven panorama regarding the behavior of different centers for the choice of different biomarkers, with a trend toward their increasing use in higher risk populations or in cases of suspected toxicity. Accordingly, the routine use of GLS seems to have increased over the past few years, but there is still a significant underutilization.

A growing problem in the daily practice of cardio-oncology is the management of cancer-related venous thromboembolism (VTE). The slight prevalence of cardiologists appears to be entrusted with handling VTE, and unfortunately, a multidisciplinary evaluation is rarely carried out. Study limitations should be taken into consideration. This analysis relies only on data from survey participants, which can in some cases be biased by their personal interpretation. The authors have not had direct access to Medical Center databases to check the accuracy of reported data. The general hospital category encompassed a wide range of hospital types, from small peripheral facilities to University hospitals. We did not report any subgroup analysis (e.g., imaging patterns, invasive procedures, and so on) based on hospital size because of both the lack of a clear definition of hospital category and the fact that these categories would be too small. Similarly, we did not run subgroup analysis comparing "general hospital" categories with cancer centers in any secondary item.

The picture of Italian CO, drawn by our survey, is a mixture of dark and light. Progress has undoubtedly been made over the last decade, but the challenges to face in the future are still numerous and complex. The role of national and international guidelines is now well-established, as is the management of older cardio-toxic drugs. Our results indicate two main objectives to be pursued to upgrade the clinical use of CO: (1) specific training provided locally by national scientific societies to both physicians and nurses and (2) closer collaboration at the single hospital level among specialists.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because participating centers do not provide authorization to share them. Requests to access the datasets should be directed to marialaura.canale@uslnordovest.toscana.it.

ETHICS STATEMENT

The survey did not require approval by the Local Ethical Committee because it is based on physicians' opinions and administrative data only, without direct patient data collection.

AUTHOR CONTRIBUTIONS

MC, IP, CL, FC, DG, MG, NM, IB, and FT: study conception and design. MC, AC, IB, IP, CL, FT, SO, and GC: drafting of the manuscript or revising it critically for important intellectual content. MC, AC, FT, GR, SP, LT, IB, LR, GC, and SO: analysis and interpretation of data. All authors final approval of the manuscript.

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A Corrigendum on

Portrait of Italian Cardio-Oncology: Results of a Nationwide Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) Survey

by Canale, M. L., Turazza, F., Lestuzzi, C., Parrini, I., Camerini, A., Russo, G., Colivicchi, F., Gabrielli, D., Gulizia, M. M., Oliva, S., Tarantini, L., Maurea, N., Rigacci, L., Petrolati, S., Casolo, G., and Bisceglia, I. (2021). Front. Cardiovasc. Med. 8:677544. doi: 10.3389/fcvm.2021.677544

In the original article, there were errors in "affiliations 10 and 11. Instead of "Division of Cardiology, Istituto Tumori Giovanni Paolo II, Bari, Italy," it should be "UOSD Cardiologia di Interesse Oncologico - IRCCS Istituto Tumori "GIOVANNI Paolo II" Bari, Bari, Italy."

Instead of "Divisione di Cardiologia, Arcispedale S. Maria Nuova, Reggio-Emilia, Italy," it should be "Division of Cardiology, Arcispedale S. Maria Nuova, Azienda USL – IRCCS di Reggio-Emilia, Reggio-Emilia, Italy."

The authors apologize for these errors and state that they do not change the scientific conclusions of the article in any way. The original article has been updated.

frontiers in Cardiovascular Medicine

CASE REPORT
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Progressive Heart Failure and Death as the Initial Manifestation of NK/T-Cell Lymphoma: A Case Report and Literature Review

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Natural killer/T-cell (NK/T-cell) lymphoma is a rare-type non-Hodgkin lymphoma derived from NK cells or cytotoxic T cells. Here, we present a case of a 40-year-old woman who experienced quick-developed global heart failure and then was diagnosed with NK/T-cell lymphoma through lymphoid biopsy. Neither transthoracic echocardiography nor any radiological images detected a mass in her heart or pericardium. Elevated plasma troponin level and diffused patchy areas of gadolinium late enhancement on cardiac magnetic resonance were compatible with myocarditis. Considering the persistently elevated cytokine level, systemic inflammation symptoms, acute respiratory distress syndrome, and cardiac dysfunction, a cytokine storm secondary to NK/T-cell lymphoma was considered. Due to the refractory malignant arrhythmia, the patient died soon after being admitted to our hospital.

Keywords: NK/T-cell lymphoma, heart failure, cytokine strom, inflammation, myocarditis

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INTRODUCTION

Natural killer (NK)/T-cell lymphoma (NKTL) is a rare and aggressive type of non-Hodgkin lymphoma derived from NK cells or cytotoxic T cells (1). NKTL mostly occurs in the nasal area and upper aerodigestive tract; although extranodal lymphoma was reported in about 30% of non-Hodgkin lymphoma (NHL) (2), cardiac NHL is rarely reported in clinical settings (3, 4).

Compared with diffuse large B-cell lymphomas and T-cell lymphomas, NKTL has a higher tendency to invade heart. Moreover, the presence of cardiac involvement is associated with poor prognosis in patients with lymphoma (5).

Cytokine storm is an umbrella term encompassing several disorders of immune dysregulation characterized by constitutional symptoms, systemic inflammation, and multiple dysfunctions that can lead to multiorgan failure (6). There are multiple clinical causes of cytokine storms, including iatrogenic, pathogen-induced, and monogenic and autoimmune disorders. Of note, hemophagocytic lymphohistiocytosis caused by Epstein–Barr virus (EBV) infection in patients with genetic susceptibility can trigger a cytokine storm (6).

Here, we report a case of an EBV-positive NKTL patient who presented progressive heart failure as an initial manifestation without evidence of cardiac lymphoma infiltration, and a lymphoma-induced cytokine storm was considered the cause of cardiac injury and rapidly deteriorating heart failure.

CASE PRESENTATION

A 40-year-old woman was admitted to our hospital because of fever and orthopnea. A month before her admission, she felt general weakness and was hospitalized. At that time, a laboratory test found increased N-terminal pro-brain natriuretic peptide (Nt-proBNP: 1,562 pg/ml), high-sensitivity troponin (hsTnT: 149 pg/ml), and DNA load of EBV (1,890 copies/ml). The 12-lead electrocardiography demonstrated low voltage in all leads and ST-segment elevation of 2 mm in inferior wall leads and leads of V4, V5, and V6 (**Figure 1**). A transthoracic echocardiogram showed a moderate pericardial effusion, posterior–lateral wall hypokinesis, and normal left ventricular contractility (LVEF = 55%). As acute coronary disease was considered, coronary angiography was performed and revealed normal coronary arteries with no atheromatous finding. Cardiac magnetic resonance (CMR) showed global gadolinium late enhancement and diffuse patchy areas of edema in the interventricular septum and lateral wall of the left ventricle (**Figure 1**). Myocarditis was presumptively diagnosed. The patient was prescribed with prednisone at 40 mg qd, but her condition did not improve and even deteriorated. When she was transferred to our hospital, she had severe heart failure (NYHA IV) and could not lay down more than a few minutes; otherwise, she would be out of breath. On admission, she was found to have a fever, several enlarged cervical lymph nodes measuring 0.5 cm, and enlargement of the liver and spleen. Lab tests revealed that NT-proBNP was more than 35,000 pg/ml and that hsTnT was 699 pg/ml. The patient had elevated IL-5 (18.16 pg/ml), IL-6 (18.16 pg/ml), IL-10 (31.10 pg/ml), and IFNγ (28.46 pg/ml). An echocardiogram showed ventricular wall hypokinesis and moderate mitral and

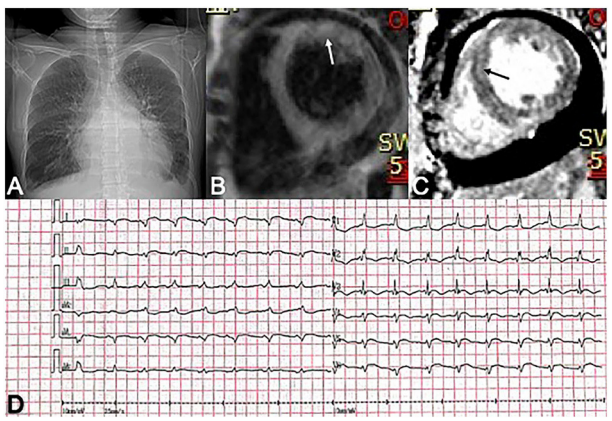

FIGURE 1 | (A) A chest X-ray shows pleural effusion and enlarged heart shadow. **(B,C)** Diffuse patchy areas of edema (white arrow) and heterogeneous delay enhancement (black arrow) in the left ventricle on CMR images. **(D)** ECG demonstrates low voltage in all leads and ST-segment elevations of 2 mm in inferior wall leads and leads of V4, V5, and V6.

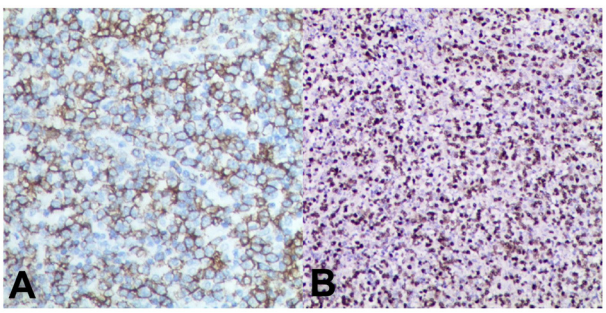

FIGURE 2 | Immunochemistry of lymph nodes derived from the neck area. **(A)** Atypical cells are positive for CD56. **(B)** Cells are also positive for EBV with *in situ* hybridization.

TABLE 1 | Time line.

One month prior to presentation	• General weakness; BP 120/70 mmHg; SO_2 99% (breathing ambient air) • Nt-proBNP: 1,562 pg/ml; hsTnT: 149 pg/ml • ECG: low voltage in all leads and 2 mm in inferior wall leads and V4, V5, and V6 leads • Echocardiogram: moderate pericardial effusion, posterior–lateral wall hypokinesis, LVEF = 55% • CMR: gadolinium late enhancement and diffuse patchy areas of edema in the interventricular septum and lateral wall of the left ventricle • Treatment: sacubitril valsartan 49/51 mg bid p.o.; metoprolol 23.75 mg qd p.o.; prednisone 40 mg qd p.o. for 4 days
Three weeks prior to presentation	• Fever • Treatment: Acyclovir 250 mg q8h p.o.; amoxicillin and clavulanate potassium 1.2 g q8h p.o.
One week prior to presentation	• Dyspnea • Treatment: metoprolol 47.5 mg qd p.o.; spironolactone 20 mg qd p.o.; sacubitril valsartan 49/51 mg bid p.o.; furosemide 20 mg bid p.o.
At presentation	• Quickly aggravated dyspnea presenting as orthopnea and pulmonary edema; BP 101/75 mmHg; SO_2 95% (nasal cannula: 2 L/min) • Nt-proBNP: >35,000 pg/ml; hsTnT: 699 pg/ml • IL-5: 18.16 pg/ml (reference interval: 0–3.1 pg/ml); IL-6: 18.16 pg/ml (0–5.4 pg/ml); IL-10: 31.10 pg/ml (0–12.9 pg/ml)l; IFNγ: 28.46 pg/ml (0–23.1 pg/ml) • Echocardiogram: ventricular wall hypokinesis, moderate mitral and tricuspid regurgitation, LVEF = 43% • Biopsy of lymph nodes revealed NK/T-cell lymphoma • Treatment: sacubitril valsartan 49/51 mg bid p.o.; diuretics (tolvaptan 7.5 mg qd p.o.; furosemide 20 mg bid i.v.; spironolactone 20 mg qd p.o.); vasodilator (nesiritide 0.01 μg/kg/min); inotropic agent (deslanoside 0.2 mg once p.o.)
Three days later	• BP 90/50 mmHg; SO_2 (nasal cannula: 2 L/min); hyperlactacidemia; multiple organ failure • Treatment: transferred to intensive care unit; invasive mechanical ventilation; extracorporeal membrane oxygen; intra-aortic balloon pump; continues renal replacement therapy; tolvaptan 7.5 mg qd; dezocine 5 mg CXWLBBR; deslanoside; inotropic agent (levosimendan, dobutamine, norepinephrine); antiarrhythmic (esmolol hydrochloride, amiodarone hydrochloride)
Ten days later	• Died of heart and respiratory failure

TABLE 2 | Summarization of reported NKTL patients and our case.

Case index	Age/ sex	Race	Primary symptom	Cardiac manifestations	ECG	Echo	Other cardiac imaging	Location of biopsy	Clinical outcome
1	40/F	East Asian	general weakness	myocarditis	ST-segment elevations in inferior wall leads and leads V4, V5, and V6; low voltage in all leads	LVEF = 40%	Global patchy areas of edema, linear late enhancement in the left ventricular lateral wall	Lymph node	Died
2. Shanhui et al J Clin Oncol 2011 Oct	26/M	East Asian	Fever, palpitation, general weakness	Arrhythmia	Wide QRS complex tachycardia	Hypokinetic posterolateral walls, pericardial effusion, LVEF = 41%	Cardiac mass over the left ventricular wall	Endomyocardial, lymph node	Died
3. Yiting et al Case Rep Hematol 2016 July	62/M	Caucasian	Nonspecific respiratory symptoms	Arrhythmia	Ventricular fibrillation	-	-	Autopsy	Died
4. Frank et al Asian Cardiovasc Thorac Ann 2019 Mar	38/M	Asian	Fever, substernal chest pain	Cardiac conduction block	Atrioventricular block	Right atrium mass	Cardiac mass and pericardial nodule with a maximum uptake value	Lung	Unknown
5. Lisa et al Hematol Rep 2011 Aug	54/M	Caucasian	Chest pain and dyspnea on exertion	Cardiac mass	-	Right atrial mass	Right atrial mass	Pericardiophrenic mass	Died
6. Yong-Son et al Inter Med 2014 Oct	23/M	East Asian	Abdominal pain	Myocardial hypertrophy	ST-segment elevation in the V1, V2, and V3 leads	Dilated RV and hypertrophied RV wall, pericardial effusion	Heterogeneous delayed gadolinium enhancement of the RV wall, abnormal hypermetabolic area in RV	Pancreas	Died
7. Ravindran et al Acta Oncol 2009	65/M	Asian	Difficulty in swallowing and sore throat	Cardiomyopathy	Supraventricular tachycardia and atrial fibrillation	LVEF = 25%–30%	Abnormal hypermetabolic area in RA	Nasal cavity and tonsil	Remained in remission

tricuspid regurgitation, LVEF = 43% (additional files). Biopsy of the enlarged cervical lymph nodes was performed, and the histopathology showed atypical T cells with prominent hyperplasia and necrosis and lymph nodes lacking lymphoid follicles with structure destruction. A immunohistochemical study showed that these malignant cells were positive for CD4, CD3ε, CD163, and CD56 (**Figure 2**). EBV *in situ* hybridization was also positive (**Figure 2**). These features were compatible with the diagnosis of NKTL. Positron emission tomography-computed tomography (PET-CT) was not performed as the patient could not lie down.

The patient was refractory to pharmaceutical treatment for heart failure, and her condition deteriorated rapidly (7). She was transferred to the intensive care unit for circulatory and respiratory support and expired 8 days later because of cardiopulmonary failure (**Table 1**).

DISCUSSION

We reported a case of NKTL who presented with a quickly aggravated heart failure, elevated troponin, and diffuse patchy edema, and late gadolinium enhancement of the left ventricle on CMR, which suggested the diagnosis of myocarditis (8). Myocardial injury in lymphoma is uncommon. Previously, infiltration of lymphoma cells into the myocardium was considered as the cause of myocardial dysfunction. Compared with B-cell lymphoma and T-cell lymphoma, NKTL was reported to have a higher incidence of cardiac infiltration (5). In these reported cases of NKTL with cardiac involvement, evidence of lymphoma infiltration, which may manifest as a cardiac mass, abnormal thickening of myocardium, and pericardial effusion, was found by echocardiogram examination, CT/PET-CT, or cardiac MRI (**Table 2**) (9–14). These patients exhibited variable cardiac presentation, and all had a poor prognosis.

However, different from previous reports, there was no clinically detectable evidence of cardiac lymphoma infiltration on echocardiography and on CMR in our reported case. Elevated cTnT and diffuse patchy myocardial LGE were compatible with myocarditis (8). A cytokine storm secondary to NKTL was considered the possible mechanism leading to myocardial injury, malignant arrhythmia, and respiratory failure, which was different from previous reports.

Cytokine storms and cytokine releasing syndrome are life-threatening systemic inflammatory syndromes involving elevated levels of circulating cytokines and immune-cell hyperactivation that can be triggered by various reasons (6). For instance, the Coronavirus Disease 2019 (COVID-19) is characterized as a severe immune response caused by SARS-CoV-2 (the severe acute respiratory syndrome coronavirus 2) infection. Other causes for cytokine storms include autoinflammatory disorders, hemophagocytic lymphohistiocytosis, cancers, and monogenic disorders (6). Hematological malignancy, especially involving peripheral T cells or the NK-cell lineage, is the most common and has the worst prognosis for cytokine storm syndrome (15–17).

NK cells play a pivotal role in modulating the initial response of antigen-presenting cells and attenuate the subsequent activation of antigen-specific T cells, especially cytotoxic T lymphocytes (CTLs) (1). NK-cell dysfunction had been reported to cause the inability to terminate the inflammatory response of CTL and macrophage, ultimately leading to persistent releasing of pro-inflammatory cytokines and cytokine storms. Patients might exhibit acute systemic inflammatory symptoms and multiorgan dysfunction (18–20). Systemically elevated cytokines are known to be cardiotoxic and have the potential to result in profound myocardial injury and arrhythmia, as observed in patients with COVID-19.

CONCLUSION

Our case and summarized previously reported cases in this manuscript suggest that (1) the cardiovascular injury is a significant contributor to the poor prognosis in patients with NKTL. (2) The cardiac injury in NKTL can manifest with a variety of clinical presentations such as cardiac lymphoma, ventricular arrhythmia, and cytokine-mediated myocarditis. (3) CMR and/or PET-CT are more sensitive than echocardiography in detecting cardiac injury in NKTL.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

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

DP identified the case. ZZ and SW conducted the literature search and prepared the first draft of the manuscript. QL contributed to the pathological part of the study. All authors contributed to the articles and approved the submitted version.

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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.2021.685736/full#supplementary-material

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frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
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Cardiac Magnetic Resonance Predicting Outcomes Among Patients at Risk for Cardiac AL Amyloidosis

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Introduction: Patients with systemic AL amyloidosis (AL) should be evaluated for cardiac amyloidosis (CA), as prognosis is strongly related to cardiac involvement. We assessed the characteristics of patients referred to cardiac magnetic resonance (CMR) with suspected CA from a cancer center and determine predictors of mortality/heart failure hospitalizations (HFH).

Methods: Forty-four consecutive patients referred for CMR with suspected CA were retrospectively included. Variables collected included cardiac biomarkers, in addition to echocardiographic and CMR variables. Survival analyses were performed to determine which variables were more predictive of mortality and HFH.

Results: Of the 44 patients included, 55% were females. 73% of patients were diagnosed with CA by CMR; 56% of them had an established diagnosis of AL. Patients with CA by CMR had higher native T1, higher extracellular volume (ECV) fraction, higher T2, less negative GLS by Echo, and higher troponin I and B-type natriuretic peptide (BNP). Kaplan-Meier survival analysis revealed that the following were predictive of mortality: an ECV $\geq$ 0.50 ($p = 0.0098$), CMR LVEF $<$ 50% ($p = 0.0010$), T2/ECV $\leq$ 100 ($p = 0.0001$), and troponin I $>$ 0.03 ($p = 0.0025$). In a stepwise conditional Cox logistic regression model, the only variable predictive of a composite of mortality and HFH was ECV (HR: 1.17, 95% CI = 1.02–1.34 $p = 0.030$).

Conclusion: ECV seems to be an important biomarker that could be a predictor of outcomes in cardiac AL amyloidosis. In combination, CMR and serum cardiac biomarkers might help to establish prognosis in patients with CA.

Keywords: cardiac magnet resonance, CMR, diagnosis, prognosis, cardio-oncology

INTRODUCTION

Patients with multiple myeloma (MM) or monoclonal gammopathy of undetermined significance (MGUS) are at an increased risk of developing AL amyloidosis (AL) (also referred to as primary systemic amyloidosis or primary amyloidosis) (1, 2). AL occurs due to abnormally functioning plasma cells that produce large amounts of the light-chain component of immunoglobulins. Typically, amyloid proteins are soluble in the plasma. However, these proteins may become insoluble after assembling into a misfolded "beta-sheet" conformation (3). Amyloidosis refers to the pathological accumulation of amyloid in the extracellular space of various organs (3, 4).

Amyloid can accumulate in the heart, which is referred to as cardiac amyloidosis (CA) (5–7) and can lead to a restrictive cardiomyopathy. CA can also lead to arrhythmias, heart blocks, or reduced QRS voltages (8, 9). Patients with AL should be evaluated for CA, as the prognosis of AL is greatly influenced by the presence or absence of cardiac involvement (10). In fact, one study demonstrated that cardiac involvement was the single most important determinant of prognosis in patients with evidence of systemic amyloidosis (11).

The gold standard for diagnosing CA is performing myocardial biopsy (3) and analyzing the sample using mass spectrometry (12). However, this procedure is invasive and may fail to detect amyloidosis if the sample is taken from a region without any amyloid deposition (3). Today, various serum biomarkers and imaging findings can assist physicians with the diagnosis and management of CA. Previously, echocardiography was frequently used to identify and prognosticate patient with CA (13–15). More recently, CMR has emerged as an important tool to diagnose and determine the prognosis of patients with CA (14, 16, 17). CMR has demonstrated to have great prognostic value in CA; in particular, T1 mapping and Extracellular volume fraction (ECV) have been validated to be predictive of mortality among patients with CA (18). T2 values have been found prognostic in AL CA (19). However, there is data that suggest that T2 times are no different from controls or not prognostic (20, 21). Thus, the association between native T2 times on CMR and prognosis in CA still remains unclear.

We assessed the characteristics of patients who underwent cardiac magnetic resonance (CMR) for suspicion of CA at a large tertiary cancer center in our pilot study. We also sought to determine which serum and imaging biomarkers were most predictive of heart failure hospitalizations (HFH) and mortality.

METHODS

After obtaining Institutional Review Board approval, we included 44 consecutive patients with suspected AL CA that underwent CMR in this retrospective observational study. Patients included in our cohort had a diagnosis of a hematological malignancy at risk for AL or a diagnosis of AL without a prior diagnosis of CA. They were evaluated by the myeloma department at a large tertiary cancer center, and they were referred for CMR with clinical suspicion of AL CA from March 1, 2009, to March 1, 2018. We retrospectively collected demographic information including age, gender, and body surface area (BSA). From the chart review, we collected past medical history information including the presence of any hematologic diagnosis (MM, MGUS, etc.), hypertension (HTN), diabetes (DM), hyperlipidemia (HLD), atrial fibrillation, stroke (CVA), and transient ischemic attack (TIA). We also recorded the presence of any episodes of ventricular tachycardia (VT), high-degree atrioventricular block, HFH, and survival. Next, we recorded the results of baseline serum tests including brain natriuretic peptide (BNP), troponin I, troponin T, blood urea nitrogen (BUN), creatinine (Cr), and hematocrit (Hct) (recorded nearest to the date of CMR).

Echocardiography

Comprehensive echocardiographic examinations were performed using multiple commercially available equipment (GE Healthcare, Milwaukee, WI, USA; Philips, Amsterdam, The Netherlands) with 3.5-MHz ultrasound probes. Standard views were acquired carefully to avoid foreshortening. When feasible and clinically appropriate, we obtained live global longitudinal strain (GLS) measurements from four-, three-, and two-chamber apical long-axis views acquired at a frame rate of 50–70 frames per second by semiautomatic speckle tracking technique (EchoPAC, GE Medical Systems, Milwaukee, WI, USA).

We recorded echocardiographic information including left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), left ventricular ejection fraction (LVEF), and GLS measurements (when available). Board-certified cardiologists reviewed and interpreted images and measurements.

Cardiovascular Magnetic Resonance

All CMR images were acquired using a 1.5-T MRI scanner which was either Siemens Avanto (Siemens, Erlangen, Germany) or a 1.5-T GE AW (GE, Milwaukee, WI). A standard CMR exam consisted of the following: cine was performed for anatomical and functional assessment using a steady-state free-precession sequence with repetition time, 3.0 ms; echo time, 1.5 ms; in-plane spatial resolution, 1.7 to 2.0 × 1.4 to 1.6 mm; slice thickness, 8 mm; temporal resolution, 35–40 ms. Delayed enhancement (DE) was performed for tissue characterization using a segmented inversion-recovery sequence (12) (in-plane spatial resolution, 1.8 × 1.3 mm; slice thickness, 8 mm; temporal resolution, 160–200 ms) 10–15 min after intravenous contrast administration (gadopentetate dimeglumine, 0.125 mmol/kg). Cine- and DE-CMR images were obtained in matching short- and long-axis planes. Short-axis images were acquired every 1 cm (gap, 4 mm) throughout the entire LV. Long-axis images were obtained in standard two-, three-, and four-chamber orientations. For DE-CMR, inversion times were adjusted to null viable myocardium (13). Modified Look-Locker (MOLLI) T1 5(3)3 for long T1 (native T1) and MOLLI T1 4(1)3(1) for short T1 (post-contrast T1) were acquired in a mid-short-axis segment in patients scanned in Siemens Avanto. Pre-contrast T2 maps were obtained in the same locations as T1 maps using a FLASH sequence with T2 preparation pulses. From automated T1 and T2 maps, measurements were acquired. Native T1, T2, and post-contrast T1 were carefully measured in a global region of interest (ROI) at the mid-ventricular septum; meanwhile in native T1 and

post-contrast T1, an ROI was drawn in blood pool to measure blood T1 times. No T1 and T2 mapping data was available from studies acquired in GE MRI scanners. ECV was calculated with the closest hematocrit value to the day of CMR acquisition. ECV was calculated using the following equation (18):

$$ECV = (1 - Hct)\ x \frac{[R1\ postcontrast\ myo - R1\ precontrast\ myo]}{[R1\ postcontrast\ blood - R1\ preconstrast\ blood]}$$

$$R1 = \frac{1}{T1}$$

A level 3 CMR cardiologist and a cardiac radiologist reviewed the CMR studies. The diagnostic impression from the LGE of each CMR was recorded (in particular, whether or not diagnostic for CA). Next, we recorded information on mortality (and date of death, when applicable) and number of HFH (and dates of admission, when applicable), in addition to the date of first and last office visit at our institution.

We collected CMR variables including left ventricular mass (LV mass), LVEDV, LVESV, LVEF, and pre-contrast and post-contrast native T1 times, respectively, in addition to pre-contrast native T2 times. We also utilized the native T1 times and hematocrit (the closest to the day of CMR) to estimate ECV.

We wanted to explore how T2 contributed to patients' morbidity and mortality. The notion of high T2 values in myocardium representing myocardial edema has a fair amount of bioplausibility in its relationship with mortality in some studies of CA. However, in some studies, it has not shown to be predictive. We evaluated the potential of T2/ECV for prognostication.

Kaplan–Meier and stepwise logistic regression analyses were performed to determine which variables were most predictive of mortality, HFH, and a composite of death and HFH. An event was cataloged as an HFH if during the day of admission the patient had a diagnosis of acute decompensated heart failure confirmed by a cardiologist's note. Group comparisons of CMR, echocardiography, and serum biomarkers between patients with CMR diagnosis of CA and patients without it, helped select the different cutoffs. IBM SPSS Statistics v.24 (IBM, Armonk, NY) and MedCalc 18.9 (MedCalc Software, Belgium) were used for statistical analysis. Significance was determined if $p < 0.05$.

RESULTS

Of the 44 patients included, 55% were females. Hematologic diagnoses at the time of CMR included 16 patients with MM, 20 patients with AL, seven patients with MM and concomitant AL, and 1 patient with lymphocytic lymphoma. 73% of patients were diagnosed with CA by CMR, and 56% of them had an established diagnosis of AL. Mean follow up was 434 days. These patients referred to CMR had at least one abnormal serum biomarker or at least one of the ventricular walls was thicker than 1.1 cm by echocardiogram at the parasternal long axis view.

Patients with CA by CMR had statistically significant higher troponin I and B-type natriuretic peptide (BNP), native T1, native T2, ECV, less negative Echo GLS, and lower T2/ECV ratio (see **Table 1**).

There were 19 total events: 11 deaths and 8 HFH. Kaplan–Meier survival analysis revealed that the following were predictive of mortality: BNP > 300 pg/ml ($p = 0.041$), troponin I > 0.03 ng/ml ($p = 0.002$), an ECV ≥ 0.50 ($p = 0.010$), LVEF (CMR) <50% ($p = 0.001$), and T2/ECV ratio ≤ 100 ($p < 0.001$). The variables predictive of HFH were BNP > 300 pg/ml ($p = 0.008$), troponin I > 0.03 ($p = 0.002$), ECV ≥ 0.50 ($p = 0.002$), and T2/ECV ratio ≤100 ($p < 0.001$) (see **Figures 1–4**). T2 values by themselves were not significantly associated with mortality or HFH; neither were native T1, LVEF by echocardiography, or Echo GLS. In a stepwise conditional Cox logistic regression model including LVEF (CMR),Troponin I, T2/ECV, BNP, and ECV, the only one predictive of a composite of mortality and HFH was ECV (HR: 1.17, 95% CI = 1.02–1.34 $p = 0.030$).

DISCUSSION

ECV and T2/ECV were predictive imaging biomarkers, outperforming traditional serum biomarkers such as troponin I and BNP in this small cohort with low event rates. However, ECV was the most predictive of adverse events in a composite that included HFH and overall mortality per Cox logistic regression. Prior studies have demonstrated that serum cardiac biomarkers have prognostic value in CA (22, 23). In a study performed at the Mayo Clinic, AL amyloid patients with neither of these biomarkers elevated were considered stage I, patients with one of these biomarkers elevated were considered stage II, and patients with both of these biomarkers were considered stage III. The median survivals of these three groups were 26.4, 10.5, and 3.5 months, respectively (22, 23). Our findings were consistent with these results, as patients with CA diagnosed on CMR had elevated levels of troponin I and BNP. Furthermore, troponin I > 0.03 ng/ml was predictive of mortality. Echocardiogram has proven to be a useful tool for identifying and prognosticating CA. The most common feature of CA on echocardiogram is increased left ventricular wall thickness, often > 12 mm (9). Another common feature of CA on echocardiogram is the "speckled" pattern, which occurs because amyloid protein infiltrates are more echogenic than the surrounding myocardium (9). Left atrial enlargement, or either preserved or reduced systolic function (in the clinical setting of congestive heart failure), may also be noted on echocardiogram (24). With respect to GLS, CA demonstrates a typical "apical sparing" pattern (25). A decrease in GLS can be identified before a decrease in LVEF (26), suggesting that it may be a sensitive method for detecting myocardial dysfunction in CA. A GLS value equal or less negative than −14.81% has been demonstrated to predict mortality in patients with AL and a normal ejection fraction (EF) (27). Additionally, a GLS of −17% or more negative has been shown to predict survival among patients with AL amyloidosis undergoing autologous hematopoietic stem cell transplantation

TABLE 1 | Comparative table of patients with AL cardiac amyloidosis by CMR LGE criteria with patients without it.

Variable	*n*	CMR with cardiac amyloidosis	CMR without cardiac amyloidosis	Mann-Whitney *p*-value
Troponin I (ng/mL)	34	0.12 (0.01 to 1.05)	0.03 (0.01 to 0.03)	0.012
BNP (pg/mL)	35	794.40 (82.00 to 3830.00)	130.00 (19.00 to 396.00)	0.007
Echo GLS	30	−12.78 (−21.6 to −4.4)	−17.59 (−22.1 to −12.3)	0.037
Native T1 (ms)	30	1142.60(937.00 to 1251.00)	1057.30 (980.00 to 1144.00)	0.009
T2 (ms)	30	53.30 (41.00 to 60.00)	48.70 (44.00 to 53.00)	0.016
ECV	27	0.48 (0.27 to 0.88)	0.32 (0.22 to 0.52)	0.008
T2/ECV	27	121.42 (56.80 to 182.19)	164.73 (101.61 to 198.69)	0.017

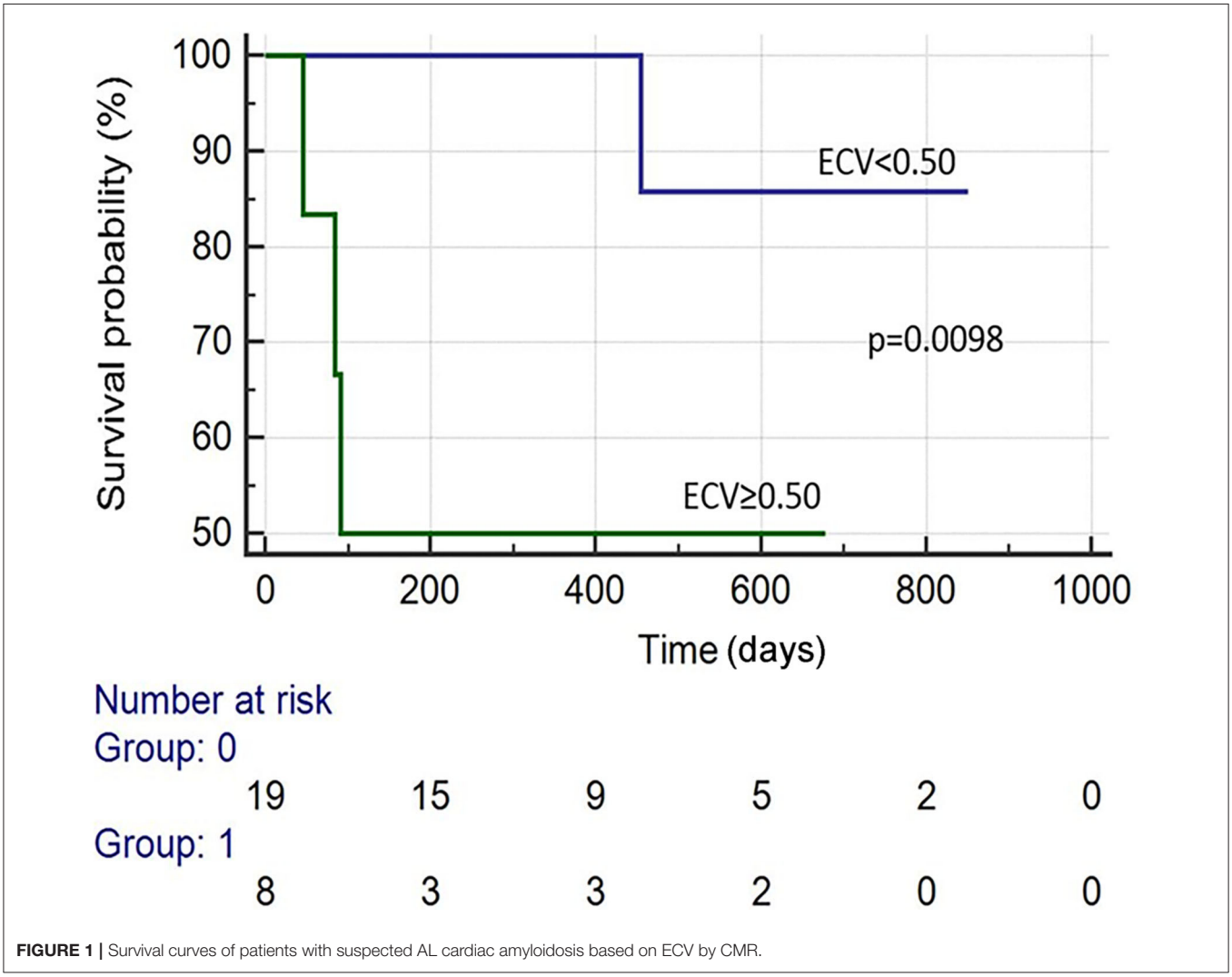

FIGURE 1 | Survival curves of patients with suspected AL cardiac amyloidosis based on ECV by CMR.

(28). Consistent with these findings, our study demonstrated that patients with CA on CMR have less negative GLS on echocardiogram. However, its performance when compared to ECV and T2/ECV was worst and less predictive in a smaller sample size.

A troponin I > 0.03 ng/mL, LVEF < 50% on CMR, and an ECV ≥ 0.50 on CMR were predictors of mortality. However, a T2/ECV ratio ≤100 was also associated with mortality, which has not been previously described in the literature. Further assessment of this ratio in larger studies is suggested. With respect to CMR, parametric imaging with T1 mapping has been shown to be a very useful tool with prognostic value in CA. Myocardial amyloid infiltration and fibrosis can lead to elevated non-contrast or native T1 relaxation times (29). A pre-contrast T1 time of >1,044 ms has been associated with a poor prognosis in AL amyloidosis (30). In our study, patients with CA on CMR had

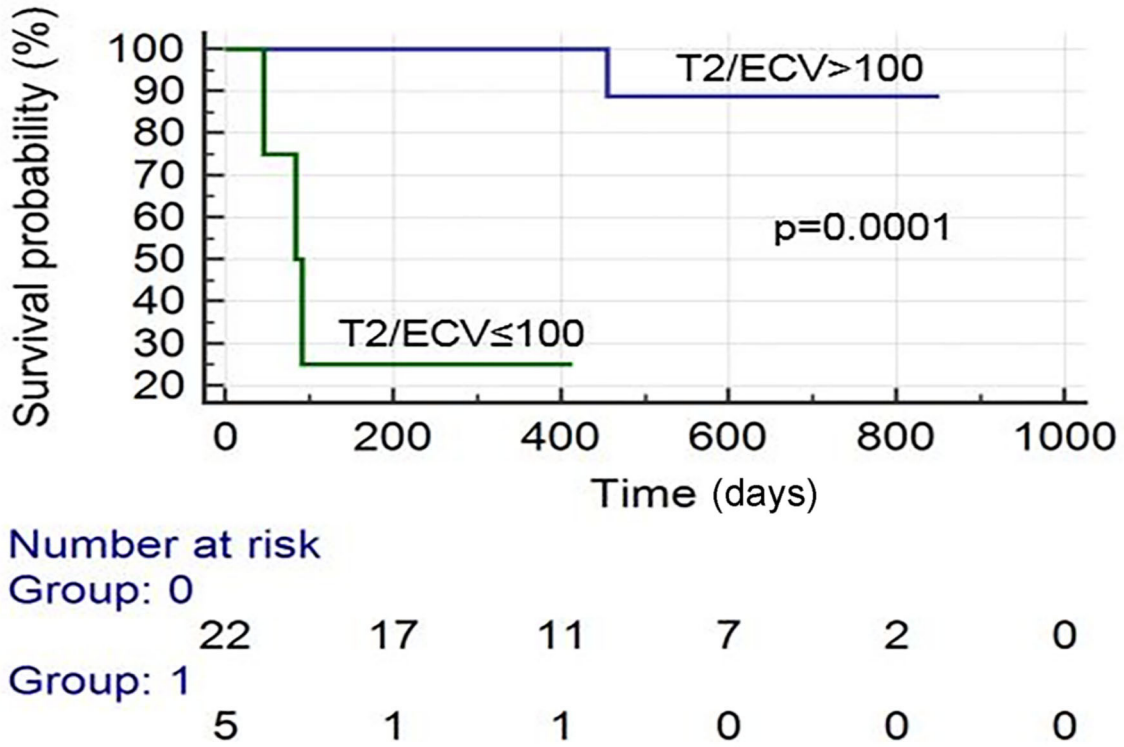

FIGURE 2 | Survival curves of patients with suspected AL cardiac amyloidosis based on T2/ECV by CMR.

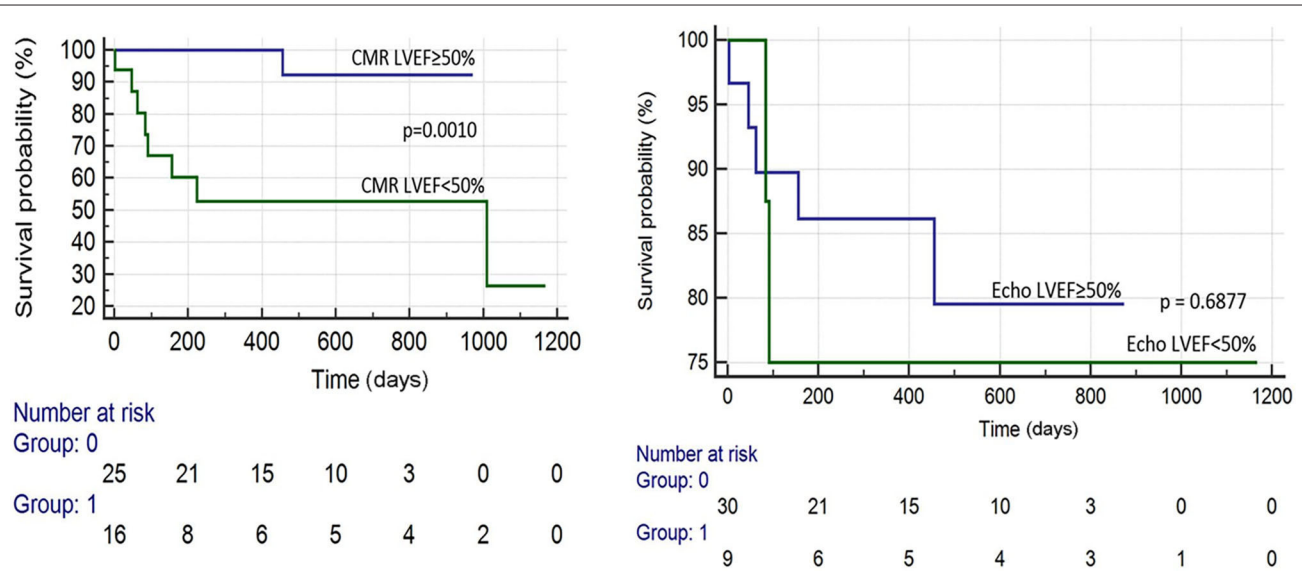

FIGURE 3 | Survival curves by LVEF technique.

an elevated pre-contrast T1 time, but this was not predictive of mortality.

T1 mapping can also be used to estimate ECV, which can be used as a surrogate to *quantify* amyloid burden in myocardium (31). Previous studies have demonstrated that an ECV at equilibrium of >0.45 has been shown to portend a poor prognosis in AL amyloidosis (30). Likewise, we demonstrated that patients with CA on CMR had a higher ECV and that an ECV $\geq$ 0.50 was associated with increased mortality (see **Figure 1**).

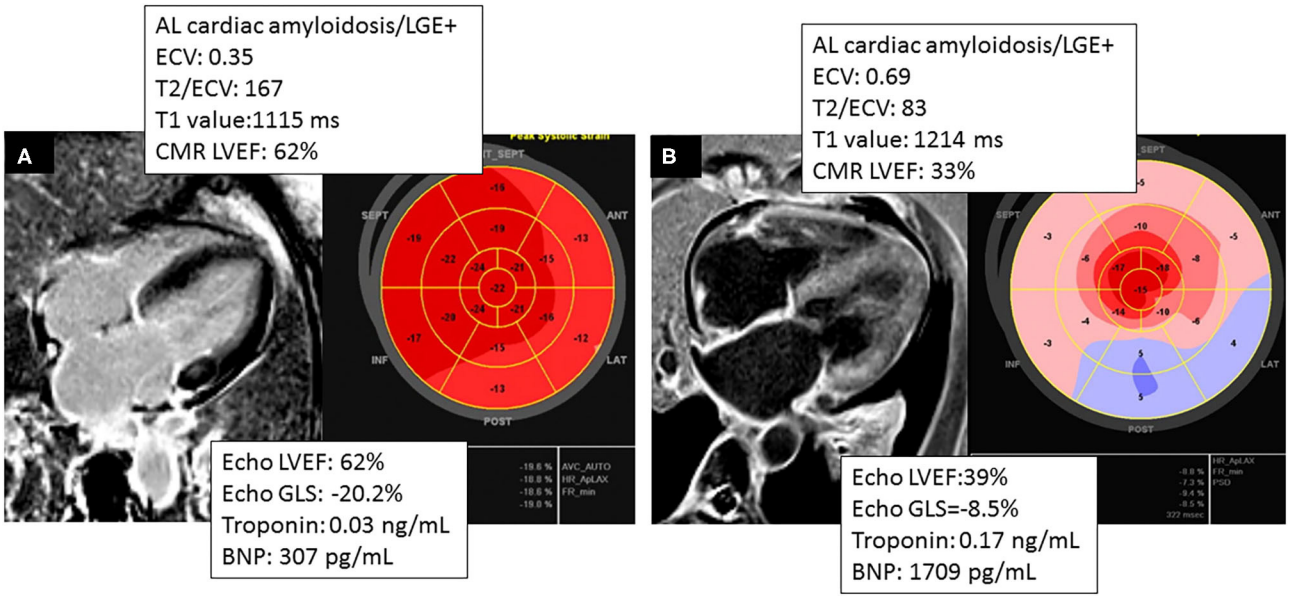

FIGURE 4 | Comparing two different phenotypes of patients with AL cardiac amyloidosis. **(A)** CMR and TTE acquired within 2 months of a patient with AL cardiac amyloidosis with significant burden of disease by CMR (ECV = 0.35) and normal GLS by Echo and concordant LVEF in Echo and CMR. **(B)** Patient that had CMR and TTE acquired within 36 h, showing higher burden of disease by CMR (ECV = 0.69) and concordant LVEF in CMR and TTE.

The role of T2 mapping for the diagnosis and prognosis of CA has not been fully elucidated. One study assessed the mean T2 relaxation times of 49 patients with suspected CA who underwent CMR. There was no difference between the mean T2 relaxation times of those with biopsy-proven amyloidosis vs. those with negative biopsies (20). However, those patients with negative biopsies may have had another cardiomyopathy which may have led to elevated T2 times, or may have had amyloidosis not detected during biopsy (this is possible if an unaffected area of myocardium is biopsied). Our study reveals that native T2 times are indeed elevated among patients with AL CA on CMR, but values did not show prognostic capabilities. T2/ECV may be predictive of both mortality and HFH (see **Figure 2**). However, ECV was the most predictive variable by the Cox logistic regression model. We think that due to limitations in sample size and low event rate, T2/ECV was not a significant predictor by logistic regression and we recommend further studies to assess the potential of this ratio in predicting outcomes.

Interestingly, an LVEF <50% on CMR was predictive of mortality, whereas an LVEF <50% on echocardiography was not predictive of mortality (see **Figure 3**), suggesting that CMR LVEF measurements may have greater utility in determining prognosis among patients with CA (see **Figure 4**).

LIMITATIONS

This study has limitations in sample size and selection bias of referring patients with clinical suspicion of CA. In our single center study, not all subjects underwent T1 and T2 mapping due to limitations in equipment. We acknowledge the limits of the predictive accuracy of our findings given the low event rate in our study. Because of the low event rate, multivariate analysis is limited. The number of subjects in the CMR-positive CA group (73%) far outnumbered the CMR-negative group for CA, which could have biased our results.

CONCLUSION

ECV was the most predictive variable in this pilot study. We consider our findings as tentative. Our results were overall consistent with previous studies that demonstrated prognostic capabilities of cardiac biomarkers (troponin I and BNP) (32). GLS by speckle tracking echocardiography could establish a difference between presence and absence of AL CA by CMR (27) but failed to prognosticate mortality and HFH in our cohort. CMR findings of ECV (30) and T2/ECV prognosticated well in this study, and further studies with larger sample size warranted to assess better ECV and T2/ECV ability to prognosticate in AL CA given our small sample size and low event rate. Our study demonstrates that native T2 times are indeed elevated in AL CA, without effects in prognosis. CMR parametric measurements outperformed echocardiographic measurements such as GLS and LVEF in predicting both mortality and HFH. This study supports the importance of CMR in addition to serum cardiac biomarkers in predicting outcomes among patients suspected or at risk of having AL CA.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by MD Anderson IRB, who provided exemption due to restrospective review. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AA wrote the manuscript. JL-M wrote and planned the manuscript. All the other authors edited the manuscript.

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TAVR in Cancer Patients: Comprehensive Review, Meta-Analysis, and Meta-Regression

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Objectives: This study sought to systematically analyze the available clinical evidence on TAVR therapy in cancer patients with symptomatic severe AS.

Background: Aortic stenosis is the most common valvular heart disease in the world. TAVR has expanded the treatment options for this lethal disease process. The safety and efficacy of TAVR in cancer patients has not yet been reliably established. We thus conducted the largest known multi-center meta-analysis on TAVR and cancer status.

Methods: We performed a literature search using PubMed, EMBASE, and Cochrane Central Register of Controlled Trials from January 2015 to 2020. Studies that compared the use of TAVR in patients with severe symptomatic aortic stenosis and cancer against patients without cancer were included. Meta-regression was also conducted to determine if common clinical factors modified the possible association between cancer status and TAVR mortality.

Results: Five studies with 11,129 patients in the cancer group and 41,706 patients in the control group met inclusion criteria. The short-term mortality in the cancer group was 2.4% compared with 3.3% in the control group (odds ratio: 0.72, 95% confidence interval: 0.63–0.82; $p < 0.0001$). The frequency of stroke was 2.4% compared with 2.7% (odds ratio of 0.87, 95% confidence interval: 0.76–0.99; $p < 0.04$). The frequency of AKI was 14.2% in cancer patients vs. 16.4% (odds ratio of 0.81, 95% confidence interval: 0.76–0.85; $p < 0.04$). The rates of bleeding and need for new pacemaker implantation were not significantly different. Meta-regression demonstrated there was no significant association modifying.

Conclusions: On the basis of the results of this meta-analysis TAVR may be a safe and effective therapeutic option for patients with cancer and symptomatic severe aortic stenosis. Larger, longer, and randomized trials are required to adequately test this above hypothesis.

Keywords: TAVR, cancer, cardio-oncology, meta-analysis, aortic stenosis

INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease in the world with ∼500,000 patients with severe aortic stenosis in the United States alone (1). Symptomatic severe AS is associated with dismal prognosis and an average survival of <3 years if left untreated (2). Initial retrospective data suggested that cancer patients with severe AS who underwent surgical aortic valve replacement (SAVR) experienced improved survival, regardless of cancer status (3). As one of the most important advancements of the past 10+ years, Transcatheter Aortic Valve Replacement (TAVR) has expanded the treatment options for this lethal disease process and it is now FDA-approved for patients with inoperable, high, intermediate, and low risk for surgical aortic valve replacement (SAVR) (4). Patients with cancer often carry a high burden of comorbidity and may be deemed to be ideal candidates for TAVR. However, these patients have been traditionally excluded from TAVR randomized controlled trials (RCT); thus the safety and efficacy of TAVR in cancer patients has not yet been reliably established. Indeed, while conditions associated with cancer and cancer therapy (anemia, thrombocytopenia, bleeding diathesis, thrombophilia, and increased frailty) may argue for a transcatheter approach, they may, at the same time complicate transcatheter interventions. This comprehensive review and meta-analysis seeks to systematically analyze the available clinical evidence on TAVR therapy in cancer patients with symptomatic severe AS.

METHODS

A protocol was prospectively developed detailing the specific objectives, criteria for study selection, approach to assess study quality, outcome and statistical methods. We performed a literature search using Pubmed, EMBASE, Cochrane Central Register of Controlled Trials, and Internet-based sources of Information on clinical trials (clinicaltrials.gov) from January 2015 to January 2020. The Medical Subject Heading (MeSH) terms "transcatheter aortic valve implantation" or "transcatheter aortic valve replacement" combined with "cancer," "malignancy," or "oncology" were used. No language restrictions were applied. Bibliographies of relevant studies and the "Related Articles" link in PubMed were used to identify additional studies. Published abstracts from the annual meetings of the American College of Cardiology, American Heart Association, European Society of Cardiology, Trans Catheter Therapeutics, Society of Coronary Angiography and Intervention, and Euro Percutaneous Coronary Revascularization, were also identified. Studies comparing the use of TAVR in patients with cancer and patients without cancer were included in the meta-analysis. The study received the proper ethical oversight.

Data Extraction

Two investigators (K.M. and C.I.) independently reviewed the studies and reported the results in a structured dataset. Studies were evaluated carefully for duplicate or overlapping data. Disparities between investigators regarding the inclusion of each trial were resolved by consensus by a third independent investigator (M.C.). Eligible trials to be included in our meta-analysis had to meet the following criteria: Studies that compared the use of TAVR in patients with severe symptomatic aortic stenosis and either active malignancy or history of cancer vs. patients without cancer. Prespecified data elements were extracted from each trial as follows: sample size, sex, age, history of coronary artery disease (CAD), hypertension, dyslipidemia, diabetes, atrial fibrillation, stroke or transient ischemic attack (TIA), chronic kidney disease (CKD), Euroscore and STS (Society of Thoracic Surgeons) score. The primary endpoints were short-term mortality, post-operative stroke, acute kidney injury (AKI), bleeding and need for pacemaker implantation.

Statistical Analysis

We used odds ratios (ORs) with 95% confidence intervals (CIs) as the metric of choice for all outcomes. Categorical variables were reported as percentages, and continuous variables as mean SD. Weighted means were used for the pooled estimates of continuous variables. The pooled OR was calculated with the DerSimonian–Lairdmethod for random effects. To assess heterogeneity across studies, we used the Cochran Q *via* a Mantel-Haenszel test based on the pooled OR. Based on the I^2 statistic, values of 25, 50, and 75% were considered as yielding low, moderate, and high heterogeneity, respectively (5–7). Results were considered statistically significant at $p < 0.05$. A funnel plot and the adjusted rank correlation test were used to assess for publication bias with respect to the primary outcome of interest. With the use of a funnel plot, the OR was plotted on a logarithmic scale against its corresponding standard for each study. In the absence of publication bias, one would expect studies of all sizes to be scattered equally right and left of the line showing the pooled estimate of natural log RR. Statistical analyses were performed with RevMan software version 5.3.5 (Cochrane's Informatics and Knowledge Management Department). Meta-regression analyses investigated the effects of study-level characteristics with sex, diabetes, hypertension, dyslipidemia, coronary artery disease, cerebrovascular disease, smoking, chronic kidney disease, atrial fibrillation, and major bleeding represented as proportions with age, European System for Cardiac Operative Risk Evaluation (EuroSCORE), and Society of Thoracic Surgeons (STS) scores represented in their respective standard continuous units. We used the baseline patient traits from the individual studies as independent variables in linear meta-regression on the log-transformed RR of cancer vs. non-cancer on mortality to calculate the variables' meta-regression coefficients with 95% CIs, thus testing if any of the variables were modulators of the effect of cancer vs. non-cancer on mortality. Chemotherapy and anticoagulation were not analyzed given the absence of this data from the respective studies. Meta-regression analysis was performed using Stata version 14.2 (StataCorp LP, College Station, Texas).

RESULTS

Of the 493 citations found, five studies were identified (8–12). Characteristics of the five studies are summarized in

TABLE 1 | Characteristics of included studies.

Study	Studied period	Location	Sample size	Cancer definition	Exclusion	Valve types
Guha et al. (10)	2012–2015	USA NIS National registry	47,295	Any history of malignancy	None	Both
Landes et al. (8)	2008–2016	International 18 TAVR centers	8,497	Active malignancy	None	Both
Berkovitch et al. (9)	2008–2015	Israel Single Center	477	Any history of malignancy	<1 year expectancy	Both
Mangner et al. (11)	2006–2014	Germany Single center	1,821	Any history of malignancy	<1 year expectancy	74.5% Balloon-expandable
Watanabe et al. (12)	2013–2015	Japan Multi-center registry 8 TAVR centers	749	Active malignancy stage >T2 or any malignancy refractory, relapsing, or recurrent	Bicuspid or noncalcified AV, severe AR, or HD dependence	Self-expanding only

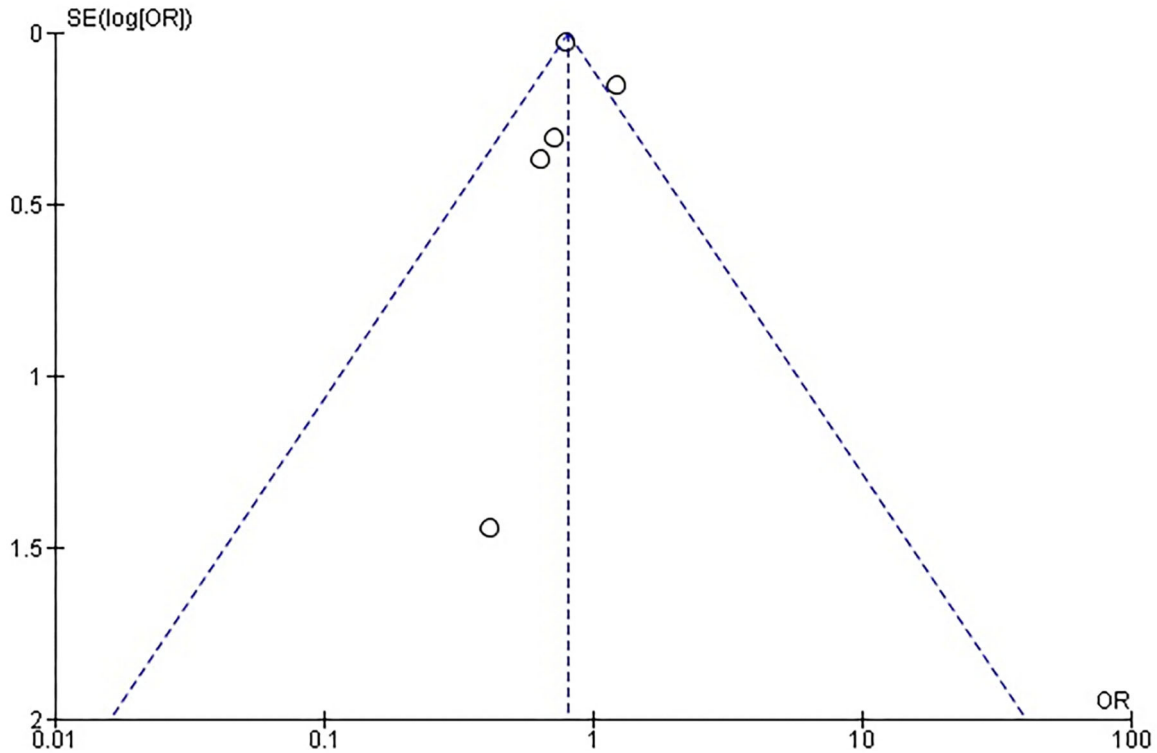

FIGURE 1 | Meta-analysis flow diagram.

Table 1 and **Figure 1**. All studies were observational. The study from Landes et al. was derived from an international registry while the rest were based on national registries from the United States, Germany, Japan, and Israel. Landes and Watanabe included patients with active cancer while Guha, Berkovitch, and Mangner included patients with active or history of malignancy. Berkovitch and Mangner excluded cancer patients with expected survival <1 year, while Watanabe excluded patients with bicuspid or non-calcified aortic valves, severe aortic insufficiency, and patients dependent on dialysis. All studies utilized balloon

TABLE 2 | Baseline characteristics of included studies.

	Study	Guha et al. (11)	Landes et al. (8)	Berkovitch et al. (9)	Mangner et al. (11)	Watanabe et al. (12)
Number of patients	Cancer	10,670	222	91	99	47
	Control	36,625	2,522	386	1,471	702
Male,%	Cancer	57.2%	62.0%	52.0%	42.7%	45.0%
	Control	52.6%	45.0%	52.0%	42.2%	33.0%
Age, years	Cancer	81.1	78.8	79.4	80.5	83
	Control	80.8	81.3	81.8	81	85
CAD, %	Cancer	67.8%	35.0%	47.0%	51.8%	26.0%
	Control	68.8%	17.0%	48.0%	53.1%	24.0%
CVA, %	Cancer	14.0%	11.0%	18.0%	10.8%	11.0%
	Control	13.3%	18.0%	14.0%	9.8%	14.0%
DM2, %	Cancer	38.0%	28.0%	34.0%	39.5%	30.0%
	Control	41.5%	36.0%	40.0%	43.6%	25.0%
HTN, %	Cancer	83.5%	76.0%	82.0%	93.5%	75.0%
	Control	83.8%	92.0%	85.0%	93.6%	75.6%
DLP, %	Cancer	68.8%	57.0%	60.0%	N/A	43.0%
	Control	65.7%	87.0%	75.0%	N/A	43.0%
CKD, %	Cancer	36.9%	N/A	24.0%	30.0%	N/A
	Control	37.9%	N/A	22.0%	34.3%	N/A
Afib, %	Cancer	41.4%	N/A	N/A	40.8%	17.0%
	Control	43.4%	N/A	N/A	44.9%	19.0%
Mean EuroScore	Cancer	N/A	4.2	4.5	N/A	3.10
	Control	N/A	5.4	5.4	N/A	3.9
Mean STS score	Cancer	N/A	4.9	4.6	N/A	5.4
	Control	N/A	6.2	5.7	N/A	7.0

CAD, Coronary artery disease; CVA, Cerebrovascular accident; HTN, Hypertension; DLP, Dyslipidemia; CKD, Chronic kidney disease; Afib, Atrial fibrillation; STS Score, Society of Thoracic Surgeons Score.

expandable and self-expanding except the one from Watanabe which included only balloon expandable valves. The baseline age was comparable in all studies (**Table 2**). The sample of cancer patients who received TAVR included more male patients with higher rates of underlying CAD and dyslipidemia. The control group included patients with higher rates of diabetes, CKD and atrial fibrillation. Patients with cancer had lower mean EuroScore (4.1 vs. 5.1) and STS scores (4.9 vs. 6.3). The clinical outcomes of the included studies are summarized in **Table 3** and **Figures 2A,B**.

Short-Term Mortality

Rates of short-term mortality were reported in all trials (**Figure 2A**). In the study from Guha and Berkovitch, short-term mortality was described as in-hospital deaths. In the rest of the studies, short term mortality was assessed at 30 days. The overall mortality in the cancer group was 2.4% (273 of 11,371) compared with 3.3% (1,391 of 41,706) in the control group. Patients in the cancer group had an odds ratio of 0.72 (95% confidence interval: 0.63 to 0.82; $p < 0.0001$) for short-term mortality compared to the patients without cancer. There was no evidence of statistical heterogeneity among studies ($I^2 = 0\%$; heterogeneity $p = 0.5$). There was no evidence of publication bias for the primary endpoint on visual estimation of the funnel plot (**Supplementary Figure 1**).

Periprocedural Acute Cerebrovascular Event or Transient Ischemic Attack

Rates of CVA/TIA were reported in all trials. Only the study from Guha reported both CVA and TIA, while the rest of the studies described only the rates of CVA. The overall stroke rate was 2.4% (264 of 11,126) compared with 2.7% (1,141 of 41,661) in the control group. Patients in the cancer group had an odds ratio of 0.87 (95% confidence interval: 0.76–0.99; $p < 0.04$) for periprocedural stroke compared to the patients without cancer. There was no evidence of statistical heterogeneity among studies ($I^2 = 0\%$; heterogeneity $p = 0.92$). There was no evidence of publication bias on visual estimation of the funnel plot (**Supplementary Figure 2**).

Acute Kidney Injury

Rates of AKI were reported in all trials. The overall AKI rate was 14.2% (1,614 of 11,372) in cancer patients compared with 16.4% (6,815 of 41,668) in the control group. Patients in the cancer group had an odds ratio of 0.81 (95% confidence interval: 0.76–0.85; $p < 0.04$) for AKI compared to the patients without cancer. There was significant heterogeneity among studies ($I^2 = 49\%$; heterogeneity $p = 0.10$). There was evidence of publication bias on visual estimation of the funnel plot (**Supplementary Figure 3**).

TABLE 3 | Clinical outcomes of included studies.

	Short-term mortality		Stoke		Acute kidney injury		Bleeding		Need for pacemaker	
Study	**Cancer**	**Control**	**Cancer**	**Control**	**Cancer**	**Control**	**Cancer**	**Control**	**Cancer**	**Control**
Guha et al. (10)	2.3	3.2	2.4	2.7	14.3	17.3	19.8	19.2	11.3	10.9
Landes et al. (8)	1.8	3.2	0.9	0.9	3.6	5.5	14.4	6.1	19.4	13.7
Berkovitch et al. (9)	1.1	5.2	2.2	3.4	16.5	21.5	N/A	N/A	15.4	15.6
Mangner et al. (11)	6.0	7.6	4.7	4.7	19.3	16.5	41.9	37.9	29.7	28.4
Watanabe et al. (12)	4.3	2.7	2.1	5.6	0.00	2.4	27.7	36.5	2.1	5.4

Values in %.

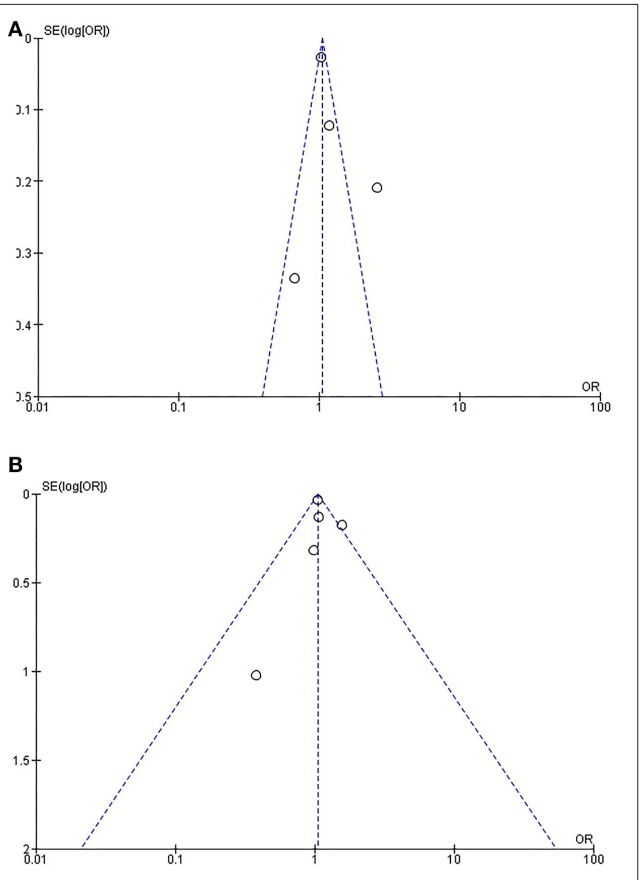

FIGURE 2 | (A) Forest plot meta-analysis. **(B)** Forest plot meta-analysis.

Bleeding

Rates of short-term bleeding were reported in four trials. Guha et al. only reported bleeding necessitating transfusion. The studies from Landes and Watanabe reported any bleeding, while Manger reported all VARC-II bleeding events. The overall bleeding rate was 20.3% (2,298 of 11,280) in cancer patients compared with 19.3% (7,995 of 41,273) in the control group. Patients in the cancer group had an odds ratio of 1.05 (95% confidence interval: 1.00–1.11; $p < 0.06$) for bleeding compared to the patients without cancer. There was significant heterogeneity among studies ($I^2 = 86\%$; heterogeneity $p < 0.0001$), probably due to heterogeneity in the definition of bleeding. There was evidence of publication bias on visual estimation of the funnel plot (**Supplementary Figure 4**).

Need for Pacemaker Implantation

Rates of new pacemaker implantation were reported in all trials. The overall rate of new pacemaker implantation was 12.0% (1,372 of 11,380) in the cancer group compared with 11.6% (4,842 of 41,705) in the control group. Patients in the cancer group had an odds ratio of 1.06 (95% confidence interval: 0.99–1.13; $p < 0.09$) for a new pacemaker implantation need compared to the patients without cancer. There was significant heterogeneity among studies ($I^2 = 31\%$; heterogeneity $p < 0.22$). There was evidence of publication bias on visual estimation of the funnel plot (**Supplementary Figure 5**).

Meta-Regression

The effects of meta-regression coefficients on mortality were not statistically significant for sex, diabetes, hypertension, dyslipidemia, coronary artery disease, cerebrovascular disease, smoking, chronic kidney disease, atrial fibrillation, major bleeding, age, EuroSCORE, nor STS scores (all $p > 0.05$).

DISCUSSION

Cardiovascular disease and cancer are the two leading causes of death in developed countries. Despite the increasing prevalence in both, death rates have been steadily declining with the introduction of technology and novel therapies. Tailoring the most optimal and appropriate management for patients with this double jeopardy can be challenging (13). Most cardiovascular conditions in cancer patients can be now safely assessed and managed in the cardiac catheterization lab (14).

Previously, the clinical dilemma to continue cancer treatment in patients with severe AS vs. delaying cancer treatment and undergo surgical aortic valve replacement (SAVR) often favored the former. However, the few patients that underwent SAVR had dramatically better survival, predominantly from improved resilience to anemia, infections/sepsis, and rapid volume changes from chemotherapeutic regimens or hypotension/volume loss during surgical procedures, not uncommon during the cancer treatment roller-coaster (3). The increased access of cancer patients to TAVR dramatically changed clinical decisions minimizing the delays in cancer care from ∼2 months to 2 weeks

(15). Today most cancer patients undergo AVR before cancer treatment, with the large majority receiving TAVR vs. SAVR. Our meta-analysis tries to answer the next question: what is the procedural and short-term risks of TAVR which may translate to delays in cancer treatment and modified overall survival.

This meta-analysis demonstrates a favorable post-TAVR short-term mortality and remarkable safety. In fact, we observed improved stroke and AKI rates without increased bleeding and need for new pacemaker implantation in cancer patients compared to controls. The convergence of five registries, even after taking into consideration their observational nature, leads to the assertion that there is no longer equipoise but an argument for the application of TAVR in cancer patients. Those results are in contrast to a recent meta-analysis from Bendary et al. (5) which reported higher rates of postprocedural pacemaker, probably due to the non-inclusion of the most recent NIS data from Guha et al.

Valvular disease has been long acknowledged as a serious adverse effect of cancer therapy including radiation and chemotherapy (6, 16). It can potentially occur in >75% of patients who have received RTX (7). Cancer patients are often turned down for surgical AVR due to assumed limited life expectancy or increased risk of bleeding, liver or kidney dysfunction, cognitive dysfunction, scarring from chest radiation or prior open heart surgery (17). Moreover, previous chest radiation therapy results in slower sternal wound healing, aortic root calcification and increased bleeding. Euroscore and STS scores do not take into consideration all the aforementioned factors. However, studies in cancer patients undergoing TAVR after chest radiation do indicate a lower than expected mortality (18). While the current guidelines do not recommend TAVR in patients with life expectancy is <1 year, many cancer survivors do not meet this timeline and even those on active therapy are experiencing continuously improving survival (18–20). There therefore will be a rising need to revisit the option and benefit of TAVR in cancer patients.

Our results are in contrast with the recent metanalysis of Bendary et al., where no difference in short-term mortality was recorded (5). Moreover, these favorable outcomes may not translate to longer term follow up. Indeed, Bendary et al. reported higher 1-year mortality rate in the cancer group, mainly driven by patients in advanced cancer stage. Compared to previous meta-analysis, the addition of the largest study to date from Guha et al., with over 35,000 patients accounts for the significantly different results. In the present study, this short term "cancer paradox" could be partially explained by the lower Euroscores and STS scores in the cancer group. In addition, no differentiation was made between active vs. prior cancer. The favorable outcome on acute kidney injury rates could partially be explained by the lower rates of diabetes and chronic kidney disease in cancer group. There was no difference in the rate of permanent pacemaker implantation between patients with cancer and without cancer. Those results are in contrast to the recent meta-analysis from Bendary et al. which reported higher rates of postprocedural pacemaker, probably due to the lack of inclusion of the most recent NIS data from Guha et al. Interestingly, in the present meta-analysis the presence of cancer was not associated with higher bleeding complications during TAVR. In most centers, today oncologists oversee cancer therapy during TAVR and they often need to temporarily modify cancer therapy or transfuse platelets or other blood products when necessary. Bleeding events is often the most serious concern for cancer patients with severe aortic stenosis referred for surgical aortic valve replacement. Indeed, sternotomy and cardiopulmonary bypass pose an increased risk for bleeding complications in cancer patients. Thus, TAVR represents a viable alternative for those patients.

Limitations

To date there are no randomized controlled trials on the safety and value of TAVR in cancer patients. As with any meta-analysis, the conclusions drawn from such data are subject to the limitations of the original studies. Patient-level data were not available, precluding subgroup analysis. Our meta-analysis is based on observational studies with all associated inherent bias. Without proper randomization, important selection bias exists for cancer patients who received TAVR after decision from regional multi-disciplinary structural teams. This is reflected in the unequal Euroscore and STS scores between the two groups. The increased rates of diabetes, chronic kidney disease, and atrial fibrillation in the control group may partially explain the unfavorable clinical outcomes compared to the cancer group. We only reported short-term outcomes up to 30 days because most cancer patients resume cancer therapy within 2 weeks. It is possible that those favorable outcomes may not translate to intermediate or long-term follow-up. In longer follow-up, it is clinically challenging to assess whether patient outcomes are due to post-operative TAVR complications, cancer therapy or the natural history of the malignancy itself. There was heterogeneity in the description of short-term mortality, stoke or TIA and bleeding rates. Moreover, there was important heterogeneity and publication bias in acute kidney injury, need for pacemaker and bleeding rates. The differences in the definition of bleeding and acute kidney injury may be a possible explanation. The use of different types of TAVR platforms may explain the heterogeneity in the rates of new pacemaker implantation. We did not report procedural outcomes (i.e., rates of transfemoral access, use of more than one valves, conversion to open surgery, coronary obstruction, tamponade, annular rupture, and valve migration) because of the limited data and description in our included manuscripts. Our analysis did not differentiate active cancer with prior cancer history, different types or stages of cancer, type of chemotherapy, radiation therapy or timing of TAVR relative to diagnosis or treatment of cancer. It is probable that those factors may impact clinical outcomes. Our analysis also lacked cost analysis which can vary significantly from cancer vs. non-cancer patients and affect treatment availability and clinical outcomes, and combined with the above lack of clinical long-term endpoints particularly median survival, challenge more confident and comprehensive interpretation of the data and the suitability of cancer vs. non-cancer patients for AS treatments. Thus, it must be stressed that cautious interpretation of these results is required as strictly hypothesis generating only. Yet, the above findings are consistent with a growing body of recent literature including Lind et al. (21) demonstrating in a larger

longitudinal cohort study suggesting that cancer vs. non-cancer have similar short-term complications and survival (though with worse long-term survival which is unclear whether this is due to the underlying cancer).

Given the notable selection bias associated with the above factors, we sought to improve the external and internal validity of the results using the more sophisticated meta-regression technique to demonstrate that common factors typically seen in clinical practice and in the literature to modify the relationship of cancer vs. non-cancer on TAVR mortality did not appear to do so at least in the included studies. This gives some degree of greater confidence that the main findings in this study (that includes a large meta-analysis level of patients with advanced meta-regression techniques) may be genuine hypothesis-generating findings warranting larger, longer, and randomized trials on this topic.

CONCLUSION

This meta-analysis demonstrates lower rates of short-term mortality, stroke and acute kidney injury without higher rates of bleeding and pacemaker implantation in cancer patients who undergo TAVR for the management of symptomatic severe AS, compared to patients without cancer. Larger randomized controlled trials are needed to assess the value of TAVR in different types and stages of cancer and to identify the subgroups with the most benefit.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: PubMed, EMBASE, and Cochrane Central Register of Controlled Trials.

AUTHOR CONTRIBUTIONS

KM, MC, and JH extracted the data. KM and DM performed the analysis. KM, DM, MC, CG, JH, KT, IA, and CI interpreted the results, drafted the manuscript, revised it, and approved its submission. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.641268/full#supplementary-material

Supplementary Figure 1 | Funnel plot for short-term mortality.

Supplementary Figure 2 | Funnel plot for stroke.

Supplementary Figure 3 | Funnel plot for acute kidney injury.

Supplementary Figure 4 | Funnel plot for bleeding.

Supplementary Figure 5 | Funnel Plot for need for pacemaker.

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Diversity of Cardiologic Issues in a Contemporary Cohort of Women With Breast Cancer

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Background: Women with breast cancer (BC) represent a special population particularly exposed to cardiovascular disease (CVD) risk. However, cardiologic assessment in BC is mostly limited to detection of left ventricular dysfunction cardiotoxicity (LVD-CTX) due to anticancer treatments. Our aim was to comprehensively investigate CV profile and events in a contemporary BC cohort.

Methods and Results: Records of BC patients referred for a Cardio-Oncologic evaluation before starting anticancer treatments, between 2016 and 2019, were retrospectively reviewed ($n = 508$). Information regarding prevalence and control of CV risk factors, and novel CVD diagnoses were extracted. Occurrence of LVD-CTX, CV events other than LVD-CTX and mortality was assessed. Mean age of study population was 64 ± 13 years; 287 patients were scheduled to receive anthracycline and 165 anti-HER2 therapy. Overall, 53% of BC women had ≥2 CV risk factors, and 67% had at least one of arterial hypertension, dyslipidaemia or diabetes mellitus not adequately controlled. Eighteen (4%) patients were diagnosed a previously unknown CVD. Over a mean follow-up of 2.5 ± 1 years, 3% of BC patients developed LVD-CTX, 2% suffered from other CV events and 11% died. CV risk factors were not associated with LVD-CTX, except for family history of CAD. On the contrary, patients with other CV events exhibited a worse CV profile. Those who died more commonly experienced CV events other than LVD-CTX ($p = 0.02$).

Conclusions: BC women show a suboptimal CV risk profile and are at risk of CV events not limited to LVD-CTX. A baseline Cardio-Oncologic evaluation was instrumental to implement CV prevention and to optimize CV therapies.

Keywords: women, cardiovascular health, Cardio-Oncology, breast cancer, cardiotoxicity

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BACKGROUND

Awareness toward cardiovascular disease (CVD) remains low among women, even if it is the leading cause of mortality and morbidity in the female sex (1, 2). Patients with breast cancer (BC) represent a special female population particularly exposed to CV risk (2). Indeed, various analyses have highlighted how CVD is becoming a leading threat for health in BC patients, especially in

individuals older than 65 years or with pre-existing CV conditions (3–5). However, in common clinical practice, a focus on CV health in BC women is not routinely undertaken, and cardiologic involvement has been mostly dedicated to cardiotoxicity due to anticancer treatments.

Several BC therapies may indeed cause CV adverse effects, in the short and long-term, and in particular left ventricular dysfunction (LVD) due to anthracyclines and drugs targeting the human epidermal growth factor receptor 2 (HER2) (6, 7). The discipline of Cardio-Oncology was initially devoted to identification and management of cardiotoxicity (8). As traditional CV risk factors predispose to cardiotoxicity (9), and to adverse outcomes after oncologic treatment in cancer survivors (10), the need for CV prevention in oncology has emerged as another important issue (11). Nonetheless, integrated data about these diverse aspects of Cardio-Oncology practice are limited.

We herein present a monocentric experience of early cardiologic evaluation of BC patients in the setting of a structured Cardio-Oncology programme, not exclusively dealing with cardiotoxicity, but dedicated to the diversity of CV issues of BC women. Aim of the present study was to delineate a comprehensive view of CV risk profile assessment and management before anticancer treatment initiation, and occurrence of CV events after treatment in a contemporary cohort of BC patients.

METHODS

We retrospectively reviewed the records of all BC patients referred for a Cardio-Oncologic evaluation before starting anticancer treatment (i.e., baseline evaluation) at the IRCCS Ospedale Policlinico San Martino Cardio-Oncology Outpatient Clinic between 1st January, 2016 and 15th June, 2019. All patients were managed in accordance with the Declaration of Helsinki and signed an informed consent for the processing of personal data for scientific research purpose.

The Cardio-Oncologic evaluation consisted of collection of clinical history, physical examination, 12-lead ECG, and transthoracic echocardiography according to current guidelines (12). CV risk factors were assessed, and lifestyle changes and/or medications recommended if necessary.

The following data were extracted: (i) prevalence of CV risk factors, namely arterial hypertension, dyslipidaemia, smoking, diabetes mellitus and family history of coronary artery disease (CAD); (ii) control of CV risk factors, where inadequate control was defined as previously unknown arterial hypertension or known arterial hypertension with blood pressure (BP) values not at target (13), blood cholesterol levels not at target according to the CV risk profile (14), active smoking, or glycaemic values not at target (15); (iii) novel CVD diagnoses (i.e., any CVD unknown prior to baseline Cardio-Oncologic evaluation).

Since baseline evaluation, all patients were prospectively followed up with regular Cardio-Oncologic and/or oncologic evaluations. Follow up was censored at 15th June, 2020 or at time of death. No patients were lost at follow-up. The following outcomes were assessed: (i) LVD cardiotoxicity; (ii) CV events other than LVD occurring after initiation of anticancer therapy; (iii) all-cause mortality. LVD cardiotoxicity was defined as a drop in LV ejection fraction (EF) of >10% from baseline values and below 53%, according to the 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging Expert Consensus (16). Other CV events were adjudicated based on medical reports.

Statistical Analysis

Continuous variables, reported as mean ± SD or as median and minimum-maximum range for non-normal distributions, were compared by Student's *t*-test or Mann-Whitney test, as appropriate. Categorical variables, reported as percentages, were compared by chi-squared test. When feasible, Cox multivariable regression analysis (variable selection method: backward stepwise elimination) was performed including all candidate variables ($p < 0.10$ in univariate analysis). Incidence rates of events during follow-up were compared with Poisson regression analysis. A two-sided $p < 0.05$ was considered statistically significant. Data were analyzed with SPSS software version 25 (SPSS Inc., Chicago, Illinois).

RESULTS

Study population consisted of 508 women with BC. Their characteristics are shown in **Table 1**, and details about anticancer treatments in **Supplementary Table 1**. Mean age was 64 ± 13 years and 259 (51%) patients were >65 years old. The median number of Cardio-Oncologic evaluations per patient was 2 [1–15]. Two-hundred thirty-five (46%) patients received only one Cardio-Oncologic (i.e., baseline) evaluation.

Baseline Cardio-Oncologic Evaluation

At the time of the baseline Cardio-Oncologic evaluation, 295 (58%) patients were in an adjuvant cancer setting (**Table 1**). Two-hundred eighty-seven (57%) were scheduled to receive anthracycline chemotherapy and 165 (33%) anti-HER2 targeted therapy, with trastuzumab alone (129, 25%) or trastuzumab and pertuzumab (36, 6%). Thirty-nine (8%) patients had a previous exposition to anthracyclines.

Baseline Cardiovascular Profile Assessment

Two-hundred thirty-two (46%) patients had arterial hypertension, 302 (59%) dyslipidaemia, 47 (9%) diabetes mellitus, 185 (36%) were smokers, and 63 (12%) had family history of CAD. Overall, 53% of patients had ≥2 CV risk factors. Pre-existing CVD was infrequent, with peripheral arterial disease (6%) and atrial fibrillation (AF, 5%) being the most common conditions. Inadequate control of CV risk factors was found in 94 hypertensive patients (41% of those with arterial hypertension), 270 dyslipidaemic patients (89%), and 10 diabetic patients (21%). Overall, 340 (67%) BC patients had at least one of these CV risk factors not adequately controlled. Moreover, 109 women were active smokers (59% of those with a history of smoking).

Mean LVEF was 60 ± 3%. One-hundred eleven (22%) patients had left ventricular hypertrophy; 99 (89%) of these patients were hypertensive, and 46 of them had BP values not at target.

TABLE 1 | Characteristics of study population.

	n = 508 (%)
Age (mean ± SD)	64 ± 13
Age >65 years	259 (51)
Oncologic profile	
Cancer setting	
Neoadjuvant	108 (21)
Adjuvant	295 (58)
Advanced	105 (21)
Previous exposure to anthracyclines	39 (8)
Anticancer treatment	
Anthracycline	287 (57)
Epirubicin	274 (54)
Cumulative dose (mean ± SD; mg/mq)	353 ± 68
Doxorubicin	3 (<1)
Liposomal	10 (2)
Anti-HER2	165 (33)
Trastuzumab	129 (25)
Trastuzumab and pertuzumab	36 (7)
Anthracyclines + anti-HER2	91 (18)
Cardio-Oncologic evaluations (median, [range])	2 [1–15]
CV risk profile	
Arterial hypertension	232 (46)
Inadequately controlled	94 (41)
Dyslipidaemia*	302 (59)
Inadequately controlled	270 (89)
Diabetes mellitus	47 (9)
Inadequately controlled	10 (21)
Tobacco smoking	185 (36)
Active	76 (41)
Former	109 (59)
Family history of CAD	63 (12)
≥2 CV risk factors	267 (53)
BMI > 30 kg/mq	69 (14)
Chronic kidney disease	16 (3)
Pre-existing CVD	
CAD	13 (3)
PAD	28 (6)
AF	23 (5)
HF	10 (2)
LVH	111 (22)
Moderate-to-severe VHD	20 (4)
Baseline LVEF	60 ± 3

**In 59 patients, lipid blood values were not available and a diagnosis of dyslipidaemia was based solely on clinical history.*

HER2, human epidermal growth factor receptor 2; CV, cardiovascular; CAD, coronary artery disease; PAD, peripheral artery disease; AF, atrial fibrillation; HF, heart failure; LVH, left ventricular hypertrophy; VHD, valvular heart disease; LVEF, left ventricular ejection fraction.

Novel Cardiovascular Diagnoses

At baseline Cardio-Oncologic evaluation, 18 (4%) BC patients were found to have a previously unknown CVD: 6 moderate-to-severe valvular heart disease, 6 AF, 4 HF (2 with reduced EF and 2 with preserved EF), 1 CAD, and 1 a thoracic aortic aneurysm. Following these diagnoses, an appropriate treatment was started in each case; the oncologic therapeutic strategy did not change due to novel CVD diagnosis.

Clinical Course After Initiation of Anticancer Treatment

Over a mean follow-up of 2.5 ± 1 years, accounting for 1251.4 patient/years, 15 (3%) BC patients developed LVD, 10 (2%) suffered from other CV events and 55 (11%) died (**Figure 1**).

Left Ventricular Dysfunction

Mean time from baseline Cardio-Oncologic evaluation to LVD was 1 ± 0.9 years, and incidence rate was 1.2 per 100 patient/years (95% CI: 0.8–2.0).

Five patients also presented HF symptoms (33%). Mean LVEF at the time of LVD was 42 ± 6%. Of the 15 LVD events, 13 occurred during anti-HER2 therapy (7 patients treated with trastuzumab alone and 6 with trastuzumab and pertuzumab); 1 at the end of treatment with liposomal anthracycline and a cyclin-inhibitor; and 1 as a late asymptomatic LVD 3.5 years after treatment with anthracycline, cyclophosphamide, 5-fluorouracil, and taxanes.

Characteristics of BC patients with and without LVD are reported in **Table 2**. Those who developed LVD were more commonly treated with anti-HER2 therapies (87 vs. 31%, $p < 0.001$) and with anthracyclines in combination with anti-HER2 (53 vs. 17%, $p = 0.002$). They also received more Cardio-Oncologic evaluations (4 [1–8] vs. 2 [1–15], $p = 0.001$, **Figure 2**) and had more frequently a family history of CAD (40 vs. 12%, $p = 0.001$).

Since the vast majority of BC patients had LVD during anti-HER2 therapy, characteristics of patients with and without LVD in this specific subgroup were compared (**Table 2**). Mean time from baseline Cardio-Oncologic evaluation to LVD among anti-HER2 recipients was 0.8 ± 0.4 years. Incidence rate was 3.2 per 100 patient/years (95% CI: 1.9–5.4). Of the 13 anti-HER2 LVD (4 with overt HF), 8 patients were also treated with anthracyclines, and 8 had recovery of LVEF (i.e., returning to baseline values).

BC patients with LVD due to anti-HER2 were more commonly treated with pertuzumab (46 vs. 20%, $p = 0.04$), but there was no association with anthracyclines therapy (62 vs. 55%, $p = 0.77$). CV profile was similar between the two groups except for family history of CAD (46 vs. 11%, $p = 0.003$).

Other Cardiovascular Events

Mean time from baseline Cardio-Oncologic evaluation to CV events other than LVD was 1.1 ± 0.8 years, and incidence rate was 0.8 per 100 patient/years (95% CI: 0.5–1.5).

Details of CV events are reported in **Supplementary Table 2**. Three BC patients had an episode of pulmonary embolism; 2 (treated with anti-vascular endothelial growth factor agents) developed uncontrolled arterial hypertension; 2 were found to have AF; 1 had cardiac tamponade; 1 an episode of takotsubo syndrome and 1 a fatal ischaemic stroke (late after anticancer treatment completion). Anticancer therapy was permanently interrupted only in one pulmonary embolism case.

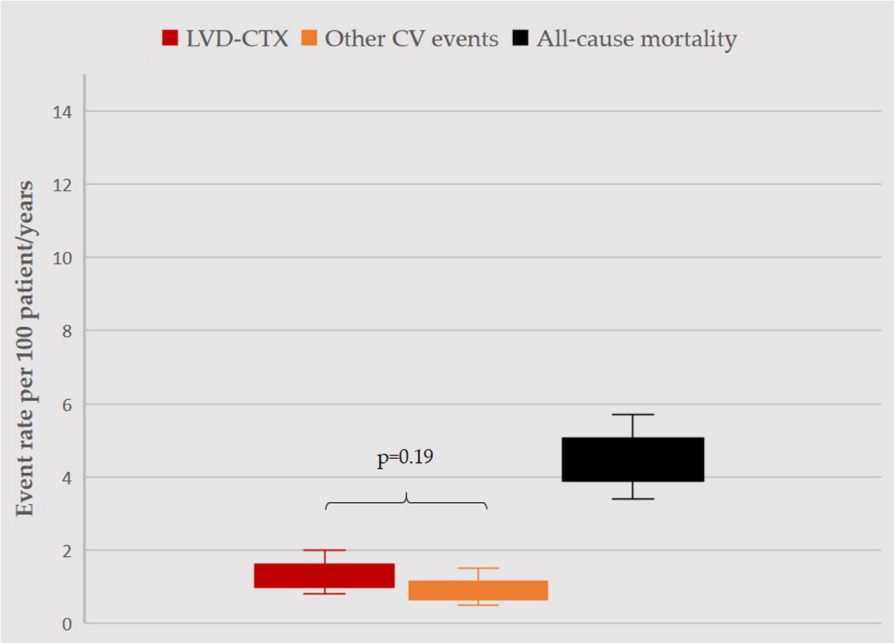

FIGURE 1 | Incidence rate of events during follow-up. Incidence rates per 100 patient/years, with confidence intervals, for LVD (red), other CV events (orange) and mortality (black) are displayed. LVD and other CV events occurred with similar rates ($p = 0.19$). Rate of mortality was significantly higher as compared to other events (in both cases, $p < 0.05$), yet overall survival rate was >95%. For the purpose of this analysis, follow-up was censored at occurrence of any event (1207.2 patient/years). LVD, left ventricular dysfunction; CV, cardiovascular.

Characteristics of patients with and without CV events other than LVD are shown in **Table 3**. Those with events were slightly older ($p = 0.07$), and more commonly in an advanced cancer setting (50%), while those without were in an adjuvant setting (59%, $p = 0.03$). There were no differences in terms of anticancer therapies, but those with CV events more frequently had a previous exposition to anthracyclines (30 vs. 7%, $p = 0.03$). Patients with events had more commonly arterial hypertension (80 vs. 45%, $p = 0.05$) and LVH (50 vs. 21%, $p = 0.05$).

All-Cause Mortality

Mean time from baseline Cardio-Oncologic evaluation to death was 1.5 ± 1.1 years, and incidence rate was 4.4 per 100 patient/years (95% CI: 3.4–5.7); with overall survival rate ranging 95–97% per year.

As shown in **Table 4**, BC patients who died were older (68 ± 11 vs. 63 ± 13 years, $p = 0.01$), with advanced cancer (64 vs 16%, $p < 0.001$) and more frequently with a previous exposition to anthracyclines (24 vs. 7%, $p < 0.001$). AF was more common among those who died (13 vs. 4%, $p = 0.01$).

No LVD events occurred among BC patients who died, whereas CV events other than LVD were significantly more common (7 vs. 1%, $p = 0.02$). At multivariate Cox regression analysis (**Supplementary Table 3**), only an advanced cancer setting (HR 7.80 [4.47–13.62], $p < 0.001$) and AF (HR 4.12 [1.85–9.20], $p = 0.001$) were significantly associated with the risk of death.

DISCUSSION

CV health in BC women is a matter of concern for several reasons: awareness toward CV prevention in females is suboptimal; management of CV risk profile may be overlooked in oncologic patients; anticancer therapies may cause or predispose to CV events, affecting cancer survivorship (2, 17). However, in BC patients, cardiologic attention and involvement is mostly limited to detection and management of LVD due to anthracyclines and anti-HER2 therapies, and an integrated approach caring for bidirectional CV and oncologic needs is often lacking. At our Institution, a baseline cardiologic evaluation in the setting of a structured Cardio-Oncology programme helped assessing this gap in clinical practice and appreciating the diversity of CV issues which may affect BC women, beyond the sole cardiotoxicity.

Usefulness of a Baseline Cardio-Oncologic Evaluation for Cardiovascular Prevention

In this BC cohort, prevalence of CV risk factors was significant, and higher as compared to the European general population (18, 19). Most importantly, CV risk factors control was suboptimal, in particular in the case of dyslipidaemia and arterial hypertension. Overall, the baseline Cardio-Oncologic evaluation allowed to implement CV prevention, recognize unknown CV conditions (even severe valvular heart disease or CAD) and optimize CV profile in the vast majority of BC patients. In a contemporary American BC population receiving trastuzumab

TABLE 2 | Characteristic of BC patients with and without LVD.

Variable	Overall population ($n = 508$)			Anti-HER2 population ($n = 165$)		
	With LVD $n = 15$ (%)	Without LVD $n = 493$ (%)	*p*	With LVD $n = 13$ (%)	Without LVD $n = 152$ (%)	*p*
Age (mean ± SD)	65 ± 11	64 ± 13	0.67	66 ± 11	61 ± 13	0.19
Age >65 years	8 (53)	251 (51)	1	8 (62)	64 (42)	0.25
Cancer setting			0.14			0.20
Neoadjuvant	5 (33)	103 (21)		5 (39)	45 (30)	
Adjuvant	5 (33)	290 (59)		4 (31)	83 (55)	
Advanced	5 (33)	100 (20)		4 (31)	24 (16)	
Previous exposure to anthracyclines	1 (7)	38 (8)	1	1 (8)	6 (4)	0.44
Anticancer treatments						
Anthracyclines	10 (67)	277 (56)	0.60	8 (62)	83 (55)	0.77
Cumulative dose (mean ± SD; mg/mq)	315 ± 42	354 ± 68	0.11	315 ± 42	343 ± 45	0.09
Anti-HER2	13 (87)	152 (31)	**<0.001**	-	-	-
Trastuzumab	7 (47)	122 (25)	0.07	-	-	-
Trastuzumab and pertuzumab	6 (40)	30 (6)	**<0.001**	6 (46)	30 (20)	**0.04**
Anthracyclines+anti-HER2	8 (53)	83 (17)	**0.002**	-	-	**-**
Cardio-Oncologic evaluations (median, [range])	4 [1–8]	2 [1–15]	**0.001**	4 [2–8]	4 [1–15]	0.43
Arterial hypertension	9 (60)	223 (45)	0.30	8 (62)	63 (41)	0.24
Dyslipidaemia	9 (60)	293 (59)	1	7 (54)	82 (54)	1
Diabetes mellitus	3 (20)	44 (9)	0.15	2 (15)	12 (8)	0.30
Tobacco smoking	7 (47)	178 (36)	0.42	6 (47)	54 (36)	0.55
Active	5 (33)	71 (14)	0.06	4 (31)	20 (13)	0.10
Family history of CAD	6 (40)	57 (12)	**0.001**	6 (46)	17 (11)	**0.003**
≥2 CV risk factors	10 (67)	257 (52)	0.30	9 (69)	71 (47)	0.15
BMI > 30 kg/mq	1 (7)	68 (14)	0.71	1 (8)	18 (12)	1
Chronic kidney disease	0 (0)	16 (3)	1	0 (0)	4 (3)	1
Known CV conditions						
CAD	2 (13)	11 (2)	0.06	2 (15)	4 (3)	0.07
PAD	1 (7)	27 (6)	0.58	1 (8)	7 (5)	0.49
AF	1 (7)	22 (5)	0.51	1 (8)	6 (4)	0.44
HF	1 (7)	9 (2)	0.26	1 (8)	2 (1)	0.22
LVH	3 (20)	108 (22)	1	3 (23)	22 (15)	0.42
Moderate-to-severe VHD	1 (7)	19 (4)	0.46	1 (8)	6 (4)	0.44
Baseline LVEF	57 ± 8	60 ± 2	0.14	56 ± 8	60 ± 2	0.11

BC, breast cancer; LVD, left ventricular dysfunction; HER2, human epidermal growth factor receptor 2; CAD, coronary artery disease; CV, cardiovascular; PAD, peripheral artery disease; AF, atrial fibrillation; HF, heart failure; LVH, left ventricular hypertrophy; VHD, valvular heart disease; LVEF, left ventricular ejection fraction. The bold values highlight significant p values.

therapy, cardiologic involvement during oncologic treatment was performed in <30% of cases (20). BC patients undergoing cardiologic evaluations, however, showed improvements in CV risk factor control.

The usefulness of a baseline cardiologic consultation, in terms of assessment of LVEF, in BC patients scheduled to receive anthracycline treatment, has been questioned given that detection of reduced LVEF, and therefore indications for changing chemotherapy strategy, is generally low (21). However, in contemporary care, Cardio-Oncology should not be intended as a simple act of cardiologic clearance to anticancer treatments, rather it should encompass a thorough assessment of CV risk profile (6). Moreover, for many oncologic patients, a baseline Cardio-Oncologic evaluation may represent the first (and even the only, as was the case for several of the BC women in our cohort) occasion to undergo a cardiologic consultation. With non-adherence to CV medications being detrimental for long-term outcome of BC patients, the baseline Cardio-Oncologic evaluation may also be the chance for CV health education and motivational support (20, 22). It is undeniable that such an "holistic" cardiologic approach requires resources and may be perceived as time consuming. Nevertheless, it is reasonable to assume that the implementation of CV prevention in the oncologic setting by the means of Cardio-Oncology would be of great potential, given the high prevalence of CV comorbidity and risk factors, especially in women undertreated with little awareness of their CV risk (1, 2, 4, 11). Moreover, a well-delivered baseline cardiologic assessment

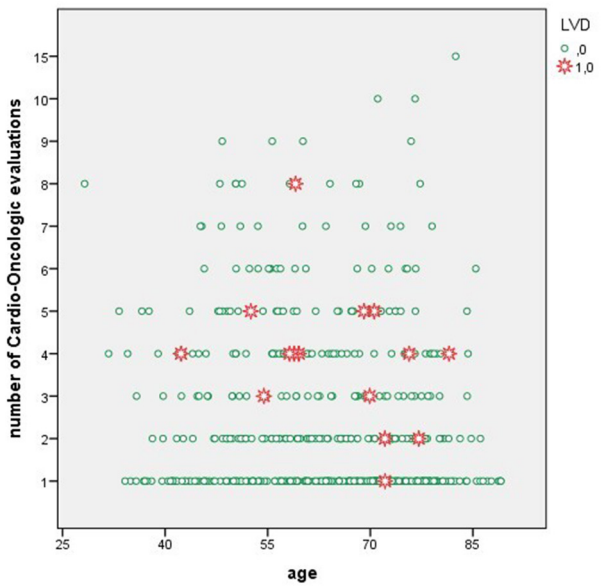

FIGURE 2 | Distribution of LVD events according to number of Cardio-Oncologic evaluations.

may avoid unplanned CV evaluations during the anticancer treatment period.

Insights into Left Ventricular Dysfunction Due to Anticancer Treatment

Few LVD events occurred in our cohort. Contrary to previous reports (23, 24), classic modifiable CV risk factors, and in particular arterial hypertension, were not associated with the occurrence of LVD. It might be speculated that such finding was the straight consequence of CV risk profile optimization secondary to the baseline Cardio-Oncologic evaluation. Since the risk of cardiotoxicity is mainly related to the individual baseline CV risk profile and the intrinsic toxicity of a given drug (9), "blunting" the CV profile may result in reducing cardiotoxicity risk. In a cohort of oncologic patients treated with anti-vascular endothelial growth factor agents, we have shown that an approach based on a structured Cardio-Oncology programme with baseline evaluation and tailored recommendations for BP management resulted in a lack of association between both controlled and uncontrolled arterial hypertension at baseline and the risk of CV events (25). Similarly, in this BC population, modifiable CV risk factors were not associated with LVD occurrence and its risk was mostly driven by the inherent toxicity of anticancer treatments, such as combined anti-HER2 therapy. Taken together, these findings highlight the importance of baseline CV evaluation of BC women, and that of adequate monitoring of patients scheduled to receive at-risk treatments, even in the long-term (6, 7). However, it should be noted that BC patients with LVD in the overall study population underwent a greater number of Cardio-Oncologic evaluation as compared to those without LVD (**Figure 2**), while this result was not found in the anti-HER2 subgroup, likely due to the regular echocardiographic monitoring these patients undergo. Moreover, only a third of patients with LVD had overt HF, and more than a half had complete recovery of LVEF. Analyses from the *Cardiotoxicity of Cancer Therapy study* showed that BC patients treated with anthracyclines and/or anti-HER2 therapies frequently display subclinical, modest, but persistent indexes of LVD, with only partial recovery over time (26, 27). However,

TABLE 3 | Characteristic of BC patients with and without CV events other than LVD.

Variable	With events $n = 10$ (%)	Without event $n = 498$ (%)	p
Age (mean ± SD)	71 ± 12	63 ± 13	0.07
Age >65 years	7 (70)	252 (51)	0.34
Cancer setting			**0.03**
Neoadjuvant	3 (30)	105 (21)	
Adjuvant	2 (20)	293 (59)	
Advanced	5 (50)	100 (20)	
Previous exposure to anthracyclines	3 (30)	36 (7)	**0.03**
Anticancer treatments			
Anthracyclines	4 (40)	283 (57)	0.34
Cumulative dose (mean ± SD; mg/mq; not liposomal)	409 ± 180	352 ± 65	0.57
Anti-HER2	2 (20)	163 (33)	0.51
Only trastuzumab	1 (10)	128 (26)	0.46
Trastuzumab and pertuzumab	1 (10)	35 (7)	0.52
Anthracyclines+anti-HER2	2 (20)	89 (18)	0.70
Number of Cardio-Oncologic evaluations (median, [range])	3 [1–9]	2 [1–15]	0.20
Arterial hypertension	8 (80)	224 (45)	**0.05**
Dyslipidaemia	7 (70)	295 (59)	0.75
Diabetes mellitus	1 (10)	46 (9)	1
Tobacco smoking	3 (30)	182 (37)	0.75
Active	1 (10)	75 (15)	1
Family history of CAD	1 (10)	62 (12)	1
≥2 CV risk factors	7 (70)	260 (52)	0.35
BMI > 30 kg/mq	1 (10)	68 (14)	1
Chronic kidney disease	0 (0)	16 (3)	1
Known CV conditions			
CAD	0 (0)	13 (3)	1
PAD	0 (0)	28 (6)	1
AF	1 (10)	22 (4)	0.37
HF	0 (0)	12 (2)	1
LVH	5 (50)	106 (21)	**0.05**
Moderate-to-severe VHD	0 (0)	20 (4)	1
Mean LVEF	60 ± 3	60 ± 0	0.73
LVD-CTX	0 (0)	15 (3)	1

BC, breast cancer; HER2, human epidermal growth factor receptor 2; CV, cardiovascular; CAD, coronary artery disease; PAD, peripheral artery disease; AF, atrial fibrillation; HF, heart failure; LVH, left ventricular hypertrophy; VHD, valvular heart disease; LVEF, left ventricular ejection fraction; LVD, left ventricular dysfunction. The bold values highlight significant p values.

TABLE 4 | Characteristics of BC patients who died at follow-up and who survived.

Variable	Died $n = 55$ (%)	Survived $n = 453$ (%)	p
Age (mean ± SD)	68 ± 11	63 ± 13	**0.01**
Age >65 years	36 (66)	223 (49)	**0.03**
Cancer setting			**<0.001**
Neoadjuvant	9 (16)	99 (22)	
Adjuvant	11 (20)	284 (63)	
Advanced	35 (64)	70 (16)	
Previous exposure to anthracyclines	13 (24)	26 (6)	**<0.001**
Anticancer treatments			
Anthracyclines	16 (29)	271 (60)	**<0.001**
Cumulative dose (mean ± SD; mg/mq; not liposomal)	344 ± 89	353 ± 67	0.59
Anti-HER2	10 (18)	155 (34)	**0.02**
Only trastuzumab	4 (7)	125 (28)	**<0.001**
Trastuzumab and pertuzumab	6 (11)	30 (7)	0.26
Anthracyclines+anti-HER2	3 (6)	88 (19)	**0.01**
Number of Cardio-Oncology evaluations (median, [range])	2 [1–15]	2 [1–10]	0.74
Arterial hypertension	32 (58)	200 (44)	0.06
Dyslipidaemia	33 (60)	269 (59)	1
Diabetes mellitus	9 (16)	38 (8)	0.08
Tobacco smoking	20 (36)	165 (36)	1
Active	9 (16)	67 (15)	0.69
Family history of CAD	5 (9)	58 (13)	0.52
≥2 CV risk factors	32 (59)	235 (52)	0.40
BMI > 30 kg/mq	7 (13)	62 (14)	1
Chronic kidney disease	2 (4)	14 (3)	0.69
Known CV conditions			
CAD	2 (4)	11 (2)	0.64
PAD	5 (9)	23 (5)	0.21
AF	7 (13)	16 (4)	**0.01**
HF	2 (4)	8 (2)	0.30
LVH	16 (29)	95 (21)	0.17
Moderate-to-severe VHD	3 (6)	17 (4)	0.47
Mean LVEF	59 ± 3	60 ± 3	0.24
LVD	0 (0)	15 (3)	0.39
Other CV events	4 (7)	6 (1)	**0.02**

BC, breast cancer; HER2, human epidermal growth factor receptor 2; CV, cardiovascular; CAD, coronary artery disease; PAD, peripheral artery disease; AF, atrial fibrillation; HF, heart failure; LVH, left ventricular hypertrophy; VHD, valvular heart disease; LVEF, left ventricular ejection fraction; LVD, left ventricular dysfunction. The bold values highlight significant p values.

association of LVD with overt HF is unclear, and studies to understand the long-term significance of modest-but-stable systolic dysfunction are needed (27). Moreover, a recent case-control study of BC patients treated with trastuzumab showed no association between adherence to echocardiographic monitoring and risk of HF (23). Thus, it may be worth to re-evaluate clinical practice in the light of novel findings, in order to understand what would be the best strategy to follow-up BC patients, especially if treated with anti-HER2 therapy, prior, during and after anticancer treatment. In other words, the risk of cardiotoxicity related to this anticancer treatment does not appear to be reduced by a careful echocardiographic monitoring. Strategies differing from the 3/6 months echocardiographic LVEF screening, derived from seminal trials (28), may be worth of investigation in future studies.

Finally, it is of note that the only CV risk factor significantly associated with LVD was family history of CAD. It has been found that sarcomeric gene variants contribute to the risk of developing cancer-therapy induced cardiomyopathy (mostly due to anthracyclines) (29). Our data may indicate that at some extent a genetic background predisposition might also contribute to the development of early LVD due to anti-HER2 therapy, warranting further investigations.

The Burden of Cardiovascular Events Other than Left Ventricular Dysfunction

Beyond LVD, there is a broad spectrum of CV issues that may affect BC women. These CV events are not of secondary importance in the clinical history of BC women, as they may be severe and happen with a similar rate to that of LVD (**Figure 1**). Some of these CV events were clearly related to anticancer therapy (as elevation of BP with anti-vascular endothelial growth factor agents), while other may have been not, and just have resulted from an unfavorable CV profile. Indeed, characteristics of BC patients experiencing these CV events were different from those of patients with LVD. BC women with CV events other than LVD had more commonly advanced cancer (and as such had more frequently a previous exposition to anthracyclines) and a worse CV risk profile, characterized by arterial hypertension with organ damage. The occurrence of these CV events may be the result of the interaction of cardiologic and oncologic comorbidities, which may intersect and favor occurrence of adverse clinical outcomes (2, 30). Consistently, BC patients who did not survive, as compared to survivors, more frequently experienced a CV event other than LVD during their clinical course. In other words, the burden of CV risk factors and CVD extend beyond the risk of LVD, and has a significant impact on the clinical course of oncologic patients (31). As a plausible consequence, in our cohort, AF was the only predictor of mortality – together with advanced cancer, as expected –, reflecting the fact that AF represents a proxy of frailty (32).

All these aspects underline the importance of CV prevention in oncologic patients, and specifically in BC women. Adequate CV risk profile optimization and management exerts beneficial effects not only in the short-term to minimize cardiotoxicity, but also in the long-term clinical course, both from the cardiologic and the oncologic standpoint (2, 11). This consideration acquires even more importance when one considers that mortality was overall low, and therefore the vast majority of our BC cohort would experience extended life expectancy. In such a perspective, CV prevention becomes of paramount importance.

LIMITATIONS

This is a monocentric retrospective study in which BC women with a baseline Cardio-Oncologic evaluation were evaluated. Such approach is not mandatory in our Institution and thus,

though being a minority of cases, some patients might have not undergone a baseline Cardio-Oncologic evaluation. This may partially have represented a selection bias. Moreover, being a retrospective real-world analysis, in our analysis a comparator group is not present (i.e., BC women not undergoing Cardio-Oncologic evaluation). The low number of LVD and other CV events in our cohort may have influenced comparisons between groups with and without events (**Tables 2**, **3**). These results are only of association, should be considered hypothesis-generating and interpreted with caution. Given all these aspects, survival analyses were not performed for these events. Data regarding hormonal therapy and radiotherapy were incomplete and therefore were not included in the analysis.

We recognize these shortcomings of our work. However, to our knowledge, few studies have previously comprehensively assessed CV health of BC women in large cohorts, as we did.

CONCLUSION

BC women show a suboptimal CV risk profile before initiation of anticancer treatments and during their clinical course are at risk of experiencing CV events not limited to LVD. In this cohort, a baseline Cardio-Oncologic evaluation was instrumental to deal with all these aspects, by implementing CV education and prevention strategies, and by optimizing CV therapies when needed. Bearing in mind CV health of BC women since the beginning of oncologic treatment is likely to exert beneficial effects in the short and long-term.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

GT and PS conceived the idea. GT, PA, MS, and PS developed the project. GT, GB, MS, and GG collected data. GT performed statistical analysis. GT wrote the initial draft with the help of PA, PS, and IP. All authors critically revised the manuscript and agreed with the final version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.654728/full#supplementary-material

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Cardiologic Long-Term Follow-Up of Patients Treated With Chest Radiotherapy: When and How?

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Introduction: Radiotherapy may cause valvular (VHD), pericardial, coronary artery disease (CAD), left ventricular dysfunction (LVD), arrhythmias. The risk of radiation induced heart disease (RIHD) increases over time. The current guidelines suggest a screening for RIHD every 5 years in the long-term survivors who had been treated by chest RT.

Methods: We reviewed the clinical and instrumental data of 106 patients diagnosed with RIHD. In one group (Group A: 69 patients) RIHD was diagnosed in an asymptomatic phase through a screening with ECG, echocardiogram and stress test. A second group (37 patients) was seen when RIHD was symptomatic. We compared the characteristics of the two groups at the time of RT, of RIHD detection and at last follow-up.

Results: Overall, 64 patients (60%) had CAD (associated to other RIHD in 18); 39 (36.7%) had LVD (isolated in 20); 24 (22.6%) had VHD (isolated in 10 cases). The interval between the last negative test and the diagnosis of moderate or severe RIHD was <5 years in 26 patients, and <4 years in 18. In group A, 63% of the patients with CAD had silent ischemia. The two groups did not differ with regard to type of tumor, cardiovascular risk factors, use of anthracycline-based chemotherapy, age at RT treatment, radiation dose and interval between RT and toxicity detection. The mean time from RT and RIHD was 16 years in group A and 15 in group B. Interventional therapy at RIHD diagnosis was more frequent in group B (54 vs. 30%, $p < 0.05$). At last follow-up, 27 patients had died (12 of cancer, 9 of cardiac causes, 6 of other causes); mean ejection fraction was 60% in group A and 50% in group B ($p < 0.01$). Patients with ejection fraction ≤50% were 14.5% in group A and 40% in group B ($p < 0.01$).

Conclusions: Clinically relevant RIHD become evident at a mean interval of 16 years after RT. The most frequent clinical manifestations are CAD and LVD. RIHD diagnosis in asymptomatic patients may preserve their cardiac function with timely interventions. We suggest -after 10 years from radiotherapy- a screening every 2–3 years.

Keywords: radiotherapy—adverse effects, long term survivors, lymphoma, radiation-induced heart disease (RIHD), coronary artery disease, valvular heart disease (VHD), left ventricular dysfunction (LVD), cardiotoxicity

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INTRODUCTION

Chest radiotherapy (RT) for mediastinal or lung tumors or also breast cancer (mostly left-sided), is associated with long-term cardiac adverse effects, namely coronary artery disease (CAD), valvular heart disease (VHD), left ventricular dysfunction (LVD), and pericardial disease (1, 2). The risk of radiation-induced heart disease (RIHD) increases over time: the cumulative incidence of RIHD requiring intervention, 20 years after mediastinal irradiation for Hodgkin's lymphoma, is 16% (3, 4). Survivors of childhood and adolescent cancer treated with RT, compared to their siblings, have a 5–6-fold risk of myocardial infarction, pericardial disease, or valvular abnormalities after 30 years of age (5). Cardiologic surveillance is, therefore, recommended every 5 years for cancer survivors treated with chest RTs, mostly for those treated during childhood, or when symptoms appear (6). We will analyze this approach on the basis of our experience at the CRO (National Cancer Institute of Aviano), in the cardio-oncology and long-term survivors clinic.

MATERIALS AND METHODS

We reviewed the clinical and instrumental data of 106 patients under care at the National Cancer Institute (CRO) of Aviano and who were diagnosed with RIHD. The study was approved by the internal review board. In one group (Group A: 69 patients), RIHD was diagnosed in an asymptomatic phase; these pertained to a group of 321 patients undergoing regular screening every 2–5 years with: clinical cardiologic examination, resting ECG, resting echocardiogram (M-mode, two-dimensional, and Doppler), and stress test for a period of 2–44 years (mean 17, median 16), or who were seen occasionally when referred to our outpatient cardiology clinic for routine examinations before surgery. A second group (Group B: 37 patients) was seen, due to complaints of symptoms related to their RIHD.

CAD was diagnosed in the presence of acute coronary syndrome or myocardial infarction or on the basis of provocative tests (treadmill or bicycle stress test, stress echocardiography, myocardial scintigraphy), and coronary angiography (7). LVD was diagnosed in the presence of a $\geq$15% drop in left ventricular ejection fraction (LVEF) from baseline to an absolute value of $\leq$53%, or a >10% drop to a value $\leq$50% (8, 9). Since a baseline echocardiogram before RT was not always available for patients treated before 1990, and in those treated in different hospitals, a LVEF of <45% was considered diagnostic of hypokinetic cardiomyopathy (10). The severity of valvular heart disease was assessed according to current guidelines at the time of the echocardiographic evaluation and integrated with cardiac catheterization and/or surgical data in patients who underwent cardiac surgery (11–13). We considered moderate to severe mitral regurgitation, aortic regurgitation, and/or aortic stenosis as being clinically relevant and considered VHD secondary to RT in the absence of other conditions (e.g., pre-existing valve abnormalities, severe mitral valve prolapse, clinical history of rheumatic heart disease, or bacterial endocarditis) that could be a possible cause.

STATISTICAL ANALYSIS

Given the descriptive aim of the registry, no formal statistical design was set up. Descriptive data are presented as a percentage of the entire number of patients. Time to RIDH was calculated from radiotherapy to the first evidence of cardiac toxicity, while follow-up time was calculated from the time of RIDH to the last visit or death. Continuous variables were expressed as the mean $\pm$ standard deviation of and their differences were tested for significance with the Student's *t*-test. The association between clinical parameters were calculated using contingency table methods and tested for significance using the Pearson's chi-square test. All significance levels were set at a 0.05 value, and *p*-values were two-sided. SPSS software (version 19.00, SPSS, Chicago) was used for all statistical analysis.

RESULTS

Demographics and Treatment Data

The patients were 34 males and 72 females, 8–67 years of age at the time of RT, with 78 who received mediastinal RTs for Hodgkin's lymphoma ($n = 54$) or Non-Hodgkin's lymphoma ($n = 24$), and 27 chest RTs for breast cancer (26 left-side, 1 right-side, including sternum in the RT plan). Cardiovascular risk factors included diabetes in 8 patients, dyslipidemia in 31, hypertension in 12, smoking habits in 4, and family history of CAD in 20. For all patients, an attempt was made to prevent all modifiable cardiovascular risk factors, such as encouraging them to perform regular physical activity, to avoid or stop smoking, and to regularly check blood glucose and lipids (14). To patients with hypertension, diabetes, and dyslipidemia detected during follow-up, appropriate medical therapy was also prescribed: anti-diabetics, statins and/or angiotensin inhibitors or beta-blockers (according to heart rate), and acetylsalicylic acid. In 6 patients, the total radiotherapy dose delivered was unknown. In the others, it ranged from 15 to 60 Gy; a >35 Gy dose—which doubles the risk of RIHD compared to doses of 20–30 Gy (15)—was administered to 77 patients. Anthracycline-based chemotherapy (before or after RT) was given to 68 patients (**Table 1**). Females were represented more in the asymptomatic group (75 vs. 54%, $p < 0.05$). The two groups did not differ with regard to type of tumor, cardiovascular risk factors, use of anthracycline-based chemotherapy, age at RT, and radiation dose (**Table 1**). The RT techniques changed over time (with the extended mantle field RT progressively replaced in the 1990s by modern techniques, such as Involved Fields Radiotherapy IFRT, which significantly reduce radiation burden to the heart and the risk of RIHD) (16–21). We, therefore, also took this variable into consideration. The patients were treated between 1974 and 2010: 79 up to and 27 after 1999. The proportion of patients treated before 2000 (when modern techniques were introduced as standard treatment in our hospital), were similar in the two groups (**Table 1**). The only difference between the two was an increased prevalence of females in the asymptomatic group.

TABLE 1 | Baseline characteristics of the entire study group and of the two groups.

	Total ($n = 106$)	Asymptomatic group ($n = 69$) (%)	Symptomatic group ($n = 37$) (%)	p
Males	34	17 (25%)	17 (46%)	<0.05
Females	72	52 (75%)	20 (54%)	
Hodgkin's	54	33 (48%)	21 (57%)	NS
Non-Hodgkin's	24	15 (22%)	9 (24%)	NS
Breast cancer	27	20 (29%)	7 (19%)	NS
Diabetes	8	4 (5.8%)	4 (11%)	NS
Dyslipidemia	31	19 (27.5%)	12 (32%)	NS
Hypertension	12	7 (10%)	5 (13.5%)	NS
Active smoker	4	1 (1.5%)	3 (8%)	NS
Anthracyclines	79	52 (75%)	27 (73%)	NS
Total dose ≥35 Gy*	84/99*	56/63* (88%)	28/36* (78%)	NS
Treated before 2,000	79	51 (74%)	28 (76%)	NS
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	
Age at RT (years)	38 ± 14.7	39 ± 15	35 ± 15	NS
Radiation dose (Gy)	40 ± 8	41 ± 8	39 ± 9	NS

RT, Radiotherapy; Gy, Grays; RIHD, Radiation Induced Heart Disease; SD, Standard Deviation.
**Data of 7 patients are missing; percentage calculated on the number of patients with complete information.*

TABLE 2 | Characteristics of the patients at time of detection of radiation induced heart disease.

	Total ($n = 106$) (%)	Asymptomatic group ($n = 69$)	Symptomatic group ($n = 37$)	p
Left ventricular dysfunction (LVD)	20 (19%)	16 (23%)	4 (11%)	NS
Cardiac ischemia	46 (43%)	33 (48%)	13 (35%)	NS
Valvular disease	10 (9%)	10 (14.5%)	0	NS
Pericardial constriction	1 (0.9%)	1 (1.5%)	0	NS
LVD + ischemia	10 (9%)	2(3%)	8 (22%)	0.01
Valvular disease + constriction	1 (0.9%)	0	1 (3%)	NS
LVD + valvular disease	5 (4.7%)	2 (3%)	3 (8%)	NS
Ischemic and valvular disease	4 (4%)	0	4 (11%)	NS
LVD + ischemia + valvular disease	4 (4%)	0	4 (11%)	NS
	Min, Max, Median	**Mean ± SD***	**Mean ± SD***	
Age at first RIHD detection (years)	22, 82, 52	55 ± 12	52 ± 13	NS*
Time from RT (years)	0, 35, 16	16 ± 9	15 ± 9	NS*
Interval between a normal test and RIHD	0, 23, 3	4 ± 3.7	3 ± 3.4	NS*

LVD, Left Ventricular Dysfunction; PCI, Percutaneous Coronary Intervention; RT, Radiotherapy; SD, Standard deviation; NS, non-significant.
**P calculated on the mean ± SD.*

Radiation-Induced Heart Disease

Overall, 64 patients (60%) had CAD (isolated in 46, associated to other cardiac diseases in 18); 39 patients (36.7%) had LVD (isolated in 20); 24 (22.6%) had valvular heart disease (isolated in 10 cases). Among patients in the asymptomatic group who had CAD diagnosed with a stress test, 21/32 (63%) had silent ischemia. Isolated LVD was more frequent in the asymptomatic group (23vs. 11%), but the difference was not statistically significant. On the contrary, the association between LVD and myocardial ischemia was significantly more frequent in the symptomatic group (22 vs. 3%, $p < 0.01$). Isolated VHD and pericardial constriction were only detected in asymptomatic patients, while the association of cardiac ischemia and VHD, with or without LVD, was only observed in the symptomatic group. However, due to the small number of cases, the difference was not statistically significant (**Table 2**). In 17 patients with different manifestations of RIHD, a second or third toxicity was diagnosed, 1–18 (median of 7) years apart. The first diagnosis of RIHD was reached at a mean and median time of 16 years from RT (range 0–35 years), without any significant difference between the two groups. RIHD was diagnosed in 5 patients (1 in the asymptomatic group, 4 in the symptomatic group) in the first year after RT. All had been previously treated with anthracyclines, had a normal EF after chemotherapy, and developed LVD shortly after a mediastinal RT with ≥40 Gy. We, therefore, considered that, although these patients might have had subclinical anthracycline myocardial damage, the role of RT was relevant. The mean and median ages at the time of the first clinical evidence of RIHD were 54 and 52 years, respectively. Thirty-six patients presented one or more normal or minimally altered tests relevant to the specific RIHD (e.g., an echocardiogram for LVD and VHD, a provocative test for CAD), obtained before the diagnosis of moderate to severe disease (**Figure 1**). The interval between the last negative test and the diagnosis of moderate or severe RIHD was 0 (2 patients experienced an acute myocardial infarction a few months after a negative treadmill stress test) to 7 years (mean and median time of 3 years). In 26 patients (72%), the interval was <5 years; in 18 (50%) it was <4 years. Among patients with CAD, 22 had a previous negative stress test performed 0–6 years before (at a median time of 3 years); 3 who presented an acute myocardial infarction had a negative stress test within 2 years before the myocardial infarction.

Treatment and Follow-Up

After diagnosis, each patient was treated according to type and severity of their disease and symptoms. Cardiac surgery (either valvular or coronary artery graft), or interventions, such as Transcatheter Valve Replacement (TAVR) or Percutaneous Coronary Intervention (PCI), were indicated in 41 patients (38.7%). The need of interventional therapy was more frequently considered in the symptomatic group (54 vs. 30%, $p < 0.05$). After diagnosis, 11 patients (7 in the asymptomatic group and 4 in the symptomatic group) were lost to follow-up. For those

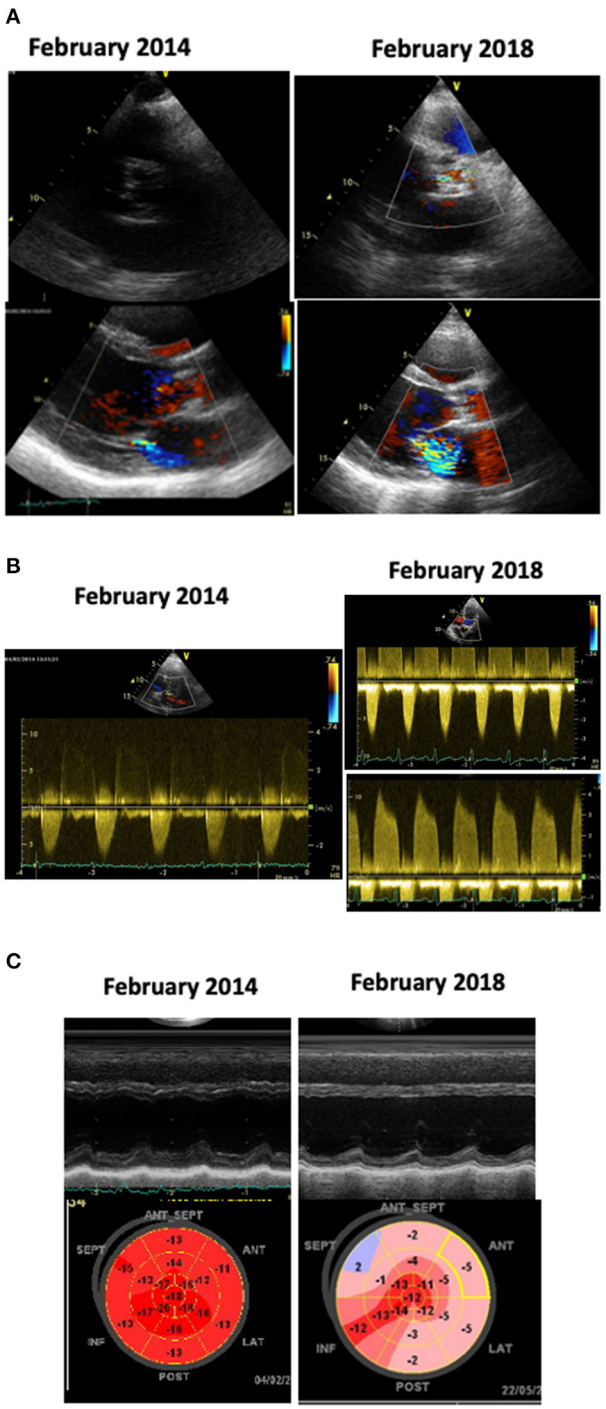

FIGURE 1 | Echocardiograms of a patient treated with anthracyclines chemotherapy and mediastinal RT in 1999, at age 19. He underwent a cardiologic follow-up every 2–3 years. In February, 2014 (images on the left) the echocardiogram detected the new appearance of mild aortic and mitral dysfunction **(A,B)**; the left ventricular (LV) function and Global Longitudinal Strain (GLS) were normal **(C)**; a stress test was negative. We planned yearly check-up, but the patient, who felt completely asymptomatic, skipped the appointments. In February 2018, at age 38, he suddenly experienced a

(Continued)

FIGURE 1 | congestive heart failure. The echocardiogram (images on the right) showed: calcific aortic stenosis, severe mitral regurgitation **(A)**; severe aortic stenosis and moderate aortic regurgitation **(B)**; severe LV dysfunction and abnormal GLS **(C)**. At coronary angiography a 70% stenosis of the left anterior descending coronary artery was detected.

in the asymptomatic group, a mean follow-up of 10 ± 5 years was available; for those in the symptomatic group, the available follow-up was 7 ± 4 years. Overall, 27 patients died (29% of the asymptomatic group and 20% of the symptomatic group—**Table 3**). The causes of death were cardiac-related (heart failure or acute myocardial infarction) in 9 cases, cancer progression or second/third cancer diagnosis in 12, sepsis in 2 cases, and unknown in 4. The left ventricular EF at the last follow-up was 60 ± 10% in the asymptomatic group and 50 ± 13% in the symptomatic group ($p < 0.01$). Patients with an EF < 50% were 14.5% in the asymptomatic group and 40% in the symptomatic group ($p < 0.01$).

DISCUSSION

Our experience confirms previous reports assessing that the prevalence of moderate to severe valvular disease, CAD, and LVD in patients treated with mediastinal or chest RT is high and increases with time after irradiation (22–26). According to these observations, surveillance should be lifelong.

Our retrospective study included patients of different ages, with different tumors and under various radiation treatments. These differences might actually influence the incidence of RIHD in different subgroups (19). The number of patients was too low to allow for a comparison between mediastinal and breast RT, and the aim of the study was only to assess what the best approach for screening might be in patients at risk of RIHD in the real world, in a cardiology clinic, or in general clinical practice.

As previously reported, RT is an independent risk factor of CAD, and the disease is often asymptomatic: this warrants an active screening process (27, 28). Autonomic dysfunction, which is frequent after RT, is similar to the cardiac autonomic cardiopathy observed in diabetes, possibly secondary to direct cardiac nerve damage by RT, and might explain the absence of angina (29–31). In fact, most of our patients with CAD who were in the screening group had silent ischemia, and those in the symptomatic group had a higher prevalence of LVD (with dyspnea as a prevalent symptom). The problem of silent ischemia is particularly relevant because patients have no warning symptoms during physical exertion, and the first symptomatic episode may be an acute myocardial infarction, or an ischemic cardiomyopathy, which may lead to a chronic anatomic and functional defect (32). Therefore, regular screening for cardiac ischemia is highly recommended, regardless of the presence or absence of angina. Screening may be performed as it is for CAD in diabetic patients, using either a physical or pharmacological stress test (preferably with imaging, such as echo-stress, or with myocardial scintigraphy), computed

TABLE 3 | Treatments and outcome after diagnosis.

		Total (*n* = 106) (%)	Asymptomatic group (*n* = 69)	Symptomatic group (*n* = 37)	*p*
Cardiac surgery or PCI		41 (38.7%)	21 (30%)	20 (54%)	0.025
Mean follow-up after diagnosis (years)			10 ± 5	7 ±4	
Death		27	20 (29%)	7 (20%)	NS
Cause of death	Cardiac	9	1	8	
	Cancer	12	4	8	
	Others/unknown	6	3	3	
EF at last follow-up (mean value ± SD)			60 ± 10	50 ± 13	0.024
Patients with EF <50% at last follow-up		25 (23.6%)	10 (14.5%)	15 (40%)	0.01

EF, Ejection Fraction; PCI, Percutaneous Coronary Intervention; SD, Standard Deviation.

tomography calcium score, or other methods (according to the availability of the tests in a given center), as well as balancing diagnostic utility, and cost and risk for the patient (33–36).

The time to progression of VHD and CAD was short in our patients, in contrast with a paper by Donnellan, who found a similar rate of progression in the aortic stenosis gradient in patients with or without previous RT (37). However, follow-up in the Donnellan study was shorter (lasting an average of 3.6 years) than in the present study, and the RT patients still had a more severe change in the aortic valve area and a significantly shorter time from the baseline echocardiogram to symptom onset and aortic valve replacement (AVR). The progression from aortic sclerosis to severe calcific stenosis involves genetic factors, lipoprotein deposition and oxidation, and chronic inflammation. The use of aggressive therapy to lower blood pressure, blood lipids, and to contrast chronic inflammation may slow down this process (38–43). According to our experience, patients who had any sort of aortic or coronary calcification detected during screening (even if subclinical), should undergo a strict follow-up (yearly or every other year), since the disease might worsen in a short period of time.

The higher prevalence of symptomatic patients undergoing valve replacement or revascularization in the present study is explained by the fact that, among the asymptomatic patients, major interventions were only proposed to those with severe disease or those at a high risk of clinical instability (e.g., critical stenosis of a main coronary artery or very severe aortic stenosis), while aggressive medical therapy with strict follow-up and additional tests (such as stress echocardiography or myocardial scintigraphy) were proposed to the others, in order to delay the need for cardiac surgery, TAVR, and/or PCI, which has often been reported to be technically difficult, risky, and with less probability of long-term success in these types of patients (44–51). Another reason to postpone surgery in the asymptomatic patients is that CAD and VHD may often progress at a different rate, requiring further interventions years apart, and we attempted to prevent re-surgery (52).

In terms of EF, the better outcome at follow-up of the asymptomatic patients could be explained by the fact that a timely therapeutic intervention (lowering blood pressure, prescribing statins, anti-inflammatory medication, and anti-ischemic therapy in these patients if needed, as well as performing cardiac surgery or percutaneous interventions for severe valvular disease or CAD) prevented myocardial infarctions and adverse cardiac remodeling, secondary to cardiac ischemia and myocardial fibrosis in patients with CAD, or to pressure overload in patients with VHD (53–56). Therefore, our experience reinforces the concept that RIHD should be recognized and treated before the symptomatic phase. A major problem, which is mostly detected in younger patients, is the fact that they are often reluctant to consider their cardiovascular risk and, therefore, might not adhere to prescriptions, as a reaction to post-traumatic stress, which may lead to denial (57–59).

With regard to the timing of screening tests, it is well-known (through large cohort studies) that the incidence of symptomatic RIHD is very low in the first 10 years after RT and increases rapidly afterwards. This is not limited to patients treated in adult age (who could have a risk linked to their age) but also to those treated in childhood who develop CAD or VHD at a relatively young age. Nevertheless, current guidelines suggest screening every 5 years or when symptoms develop, regardless of the time from RT. According to our experience, an interval of 5 years is too long, since many patients might progress from mild to severe disease during this period, possibly with the event of an acute myocardial infarction or sudden death. Moreover, symptoms such as dyspnea (secondary to VHD or angina equivalent) may be under-assessed and misinterpreted in patients with chronic lung dysfunction, as patients treated with chest RT frequently are (mostly if chemotherapy with bleomycin/or anthracycline were added) (60–63).

Along with regular screening tests, special attention must be given to these patients in relation to their adherence to suggested lifestyles and pharmacologic prescriptions. This behavior must be constantly reinforced. Since oncologists often dismiss patients from follow-up after a time span of 10–15 years from complete recovery, this should be carried out by other physicians: usually general practitioners who tend to their patient for all their various conditions, and cardiologists who conduct the follow-ups. Communication must be tailored to the particular psychological attitude of long-term cancer survivors (64).

CONCLUSIONS

RIHD is an elusive clinical entity in the pre-symptomatic phase and can worsen dramatically in a short period of time. The timely recognition of subclinical RIHD and promptly prescribed therapies may improve the long-term outcome of patients who, after recovering from cancer, are at risk of cardiac events. Screening tests should be more frequent (every 2 or 3 years) after 10 years from RT, and even more frequent (on a yearly basis) in patients with a possible high risk of progression (initial valve disease, coronary calcification, moderate to high risk of CAD). General practitioners and general cardiologists (who may see patients for reasons that do not depend on their cancer history but just for routine check-ups), should be aware of the risk of RIHD, of its often elusive clinical presentation, of the need for and method of screening it, and should care for the many patients who are not followed by a long-term survivors clinic or by an oncocardiologist.

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 Comitato Etico Unico Regionale (CEUR) Friuli Venezia Giulia. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CL, MM, and EC planned the study, recruited and followed the patients, and wrote the paper. MC performed the statistical analysis and contributed in writing the paper. FT contributed in writing the paper. All authors contributed to the article and approved the submitted version.

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Perceptions of the Cardiologists and Oncologists: Initial Step for Establishing Cardio-Oncology Service

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Background: Over the last years, there was no established cardio-oncology service in Iraq and no firm data about the incidence of cardiovascular disease (CVD) among patients with cancer. As an initial step, we decided to conduct a national cardio-oncology online survey for cardiologists, oncologists, and their residents which would help us to understand the expected prevalence, problems, and readiness for collaboration between the two specialties.

Objectives: For evaluating the current national practice in the cardiology and oncology specialty fields and to identify the hidden gaps associated with the development or worsening of CVD among patients with cancer.

Methods: An online survey including 19-question for cardiologists/cardiology residents (CCRs) and 30-question for oncologists/oncology residents (OORs) about cardio-oncology service was sent to them including all Iraqi cities using Google document form during December 2020.

Results: The total number of responses was 164, mainly 62.2% from CCRs while 37.8% from OORs. Hypertension was the main baseline risk factor (71%). A 77.5% of CCRs prescribe cardiovascular drugs vs. 35.5% by OORs. About 76.5% of CCRs and 79% of OORs are facing difficulties in the management of patients with cancer with established CVD. CVD was the leading cause of both hospitalization (30.7%) and mortality (48.4%). About 62.8% of CCRs and 64.5% of OORs have an interest to work in cardio-oncology service.

Conclusion: Based on the perception of cardiologists and oncologists, CVD is the main cause of hospitalization and mortality among patients with cancer. High interest among CCRs and OORs to work in cardio-oncology service. Positive initiatives are available to take the action plan in this emerging field.

Keywords: breast cancer, heart failure, hypertension, risk factor, hospitalization, mortality, online survey

INTRODUCTION

Cardio-oncology is an emerging specialty and service with a team-based approach that includes cardiologists, oncologists, and hematologists working collaboratively for optimizing cardiovascular risk stratification, prevention, and treatment for all patients with cancer and survivors to guide best practice by bridging the gaps in knowledge and needs including supporting patients with cancer to improve continuing of their cancer therapies without interruption by the cardiovascular disease (CVD) (1–4). First cardio-oncology service emerged in 2010 (1, 4), therefore, such essential service was not available worldwide including Iraq. A descriptive study in the United Kingdom including data over 5-year activity from cardio-oncology service reported that baseline CVD and myocardial toxicity are higher than that was documented in previous studies (5). This is why continuing national and international research in the cardio-oncology field is of high importance for a better understanding of the current practice and optimization of cardio-oncology services. In 2019, the Iraqi Cardio-Oncology Program was founded by a senior consultant cardiologist and his mentee the cardiology clinical pharmacist to support the initiation of cardio-oncology services and as an initial step for evaluating the current national practice and uncovering the hidden gaps associated with the development or worsening of CVD especially during a very critical time of COVID-19 era, therefore, it was decided to conduct an online survey. An online survey has several advantages, including low costs, real-time access, not time-consuming, and respondents may be more willing to participate and had documented the need to improve the care of patients (2, 6).

METHODS

Ethical Approval

The study was approved by the Department of Continuing Medical Education at the Iraqi Board for Medical Specializations.

Study Design

An online survey link including 19 questions for cardiologists/cardiology residents (CCRs) and 30 questions for oncologists/oncology residents (OORs) about cardio-oncology service was sent to participants who are working in cardiology and oncology sites in all 18 Iraqi cities using Google document form in December 2020. The link was shared with the participants by sending a message on WhatsApp or Viber applications for responding to the survey voluntarily. The message was sent either individually or by sharing it on WhatsApp or Viber groups for cardiologists, oncologists, and their residents.

Survey Questionnaires

Questions were divided into three categories: (1) about demographics of participants, (2) questions about current practice, and (3) questions about their opinions about cardio-oncology service. Some of the questions in categories two and three were directed only to oncologists [for OORs] related to baseline patients' characteristics and referral. One question was directed only to cardiologists (for CCRs). Other questions were directed to both cardiologists and oncologists. The single choice answer was used, including the "other" option to add unavailable suitable answers of the participants. Multiple choice answers were used for the cardio-oncology team question. Age was typed by the participants. Collected data were filled in excel for double check and analyzed in excel using numbers, percentages, average, and SD for the continuous variables.

TABLE 1 | Demographics of participants.

		Cardiology Total ($N = 102$)	Oncology Total ($N = 62$)
Age (years)		43 ± 6	38 ± 6
		33–65	27–52
Gender	Male	98.0 (100)	59.7 (37)
	Female	2.0 (2)	40.3 (25)
Specialist		63.7 (65)	64.5 (40)
Residents		36.3 (37)	35.5 (22)

Values are mean ± SD, % (n), or range.

Statistical Analysis

The statistical analysis was performed using Excel for Mac, Version 15.13.3.

RESULTS

Demographics of Participants

Most of the responders were male and specialists; cardiologists and oncologists, with age younger than 66 years old. Results are available in **Table 1**.

Questions About Current Practice Regarding Cardio-Oncology Patients

Hypertension (HTN) is the most common baseline CVD among patients with cancer according to the OOR experiences (71%), while heart failure (HF) was the most common one as a result of the CCR responses (60.3%). The results of these questions are available in (**Table 2** and **Figures 1**–**7**).

Questions About Their Opinions About Cardio-Oncology Service

The majority of CCRs (86.3%) and OORs (85.5%) believe that the establishment of cardio-oncology services will improve the outcomes of patients. The details are available in (**Table 3** and **Figure 8**).

DISCUSSION AND CONCLUSION

This survey showed that HTN was the most common preexisting CVD among patients with cancer according to the response of about two-third of OORs, while none of the CCRs mentioned it

TABLE 2 | Questions about current practice regarding patients with cardio-oncology.

1. What is the most common cardiac disease in patients with cancer at presentation?	responses of OORs showed that hypertension is the most common cardiac disease accounting for 71%, followed by HF 12.9%, pericardial effusion 6.5%, ischemic heart disease 6.5%, and arrhythmia 3.2%. While CCRs' responses were HF 60.8%, pericardial effusion 36.3%, arrhythmias 2%, and ischemic heart disease 1% (**Figure 1**).
2. What is the most common type of cancer associated with CVD?	Breast (71.6%), lung (17.7%), and hematologic (5.9%), and colon cancers were the most common types according to the response of CCRs. OORs chose breast (72.6%), lung (21%), prostate (3.2%), and colon cancer (1.6%) as the most common type while (1.6%) had no idea.
3. How often do you check the anticancer agents (question for CCRs)/cardiovascular drug (question for OORs) of patients with cancer with cardiac disease when presenting to you whether at private clinic or hospital?	The response to the option [Drugs were checking as required depending on the symptoms of the patients] was chosen by 48.1% of CCRs and by 82.3% of OORs. Checking drugs each visit was recorded by 46.1 and 9.7% of CCRs and OORs, respectively. While checking at first visit only was the response of (2.9%) of CCRs and (8.1%) by OORs. Among CCRs (2.9%) mentioned that they never check the cancer therapy of the patients.
4. Do you prescribe cardiovascular drugs for patients with cancer?	Only (77.5%) of CCRs mentioned that they are prescribing cardiovascular drugs for cancer patient who are (at risk) of developing the cardiac disease, while (35.5%) of OORs mentioned they are prescribing cardiovascular drugs for patients with cancer.
5. Which is the most cardiovascular drug do you prescribe for patients with cancer?	Responses from all cardiology participants and 48 (77.4%) oncology participants showed that ACEI/ARB are the most frequent cardiovascular drugs to be prescribed, followed by beta-blocker by CCRs and anticoagulant by OORs (**Figure 2**).
6. Do you face any difficulty in taking management action plan among patients with cancer with CVD?	The difficulty was faced among (76.5%) of CCRs when a patient with cancer refers to them to decide to continue or withhold chemotherapy/radiotherapy due to cardiac disease, and (79%) of OORs are facing difficulty in planning management strategy of cancer in a patient with cardiac disease.
7. What's the most common cancer type presents to you suffering from cardiac disease due to chemotherapy and radiotherapy?*	Breast cancer is the most common cancer type associated with CVD induced by both chemotherapy (66.7%) and radiation therapy (52.9%). Results are available in **Figure 3**.
8. What's the most common cardiac disease due to chemotherapy and radiotherapy is developed among your patients?**	HF is the most common CVD induced by chemotherapy (64.5%) and radiation therapy (45.2%).Results are available in **Figure 4**.
9. Do you face any interaction between cardiovascular drugs and anticancer?**	About 40.3% of OORs' responses reveal that they are facing interaction between cardiovascular drugs and anticancer therapy.
10. What's the most complications of chemotherapy do you face in patients with cancer?**	Renal impairment is the most common complication of chemotherapy (32%) while CVD is the sixth one (5%). Results are available in **Figure 5**.
11. Most of patients with cancer presented initially before starting anticancer or radiotherapy categorized under which group? **	Most of the responses (61.3%) categorized patients to have baseline cardiovascular risk factors, while (21%) under the category of established cardiac disease (i.e., history of CVD). Finally, (17.7%) of responses showed that patients with cancer are presented most commonly with no history of CVD.
12. What's the main medical cause for hospitalization and mortality among patients with cancer?**	CVD is the leading cause of hospitalization (30.7%) and mortality (48.4%) according to the response of OORs as shown in **Figures 6**, **7**.
13. Monthly, how many patients with cancer with cardiac disease do deal with approximately?**	An average of 10 patients monthly.
14. Do you refer all newly diagnosed patients with cancer to cardiologist for baseline cardiac evaluation before initiating anticancer or radiotherapy?**	A 62.9% of OORs refer newly diagnosed patients for cardiac evaluation, 37.1% of them do not send their patients.
15. For patients with cancer with cardiac symptoms (dyspnea, palpitation, etc.) do you send the patient for ECG/echocardiography only or for cardiac referral too?**	The majority of responses (79%) indicated that OORs sends such patients for ECG/echocardiography together with cardiac referral, (11.3%) only send for ECG/echocardiography, while (9.7%) send patients directly for a cardiac referral without checking ECG/echocardiography.
16. Do you refer only newly diagnosed patients with cancer with known cardiac disease to cardiologist for baseline cardiac evaluation before initiating anti-cancer or radiotherapy? Or do you refer all newly diagnosed patients with cancer?**	Most of the responders (54.8%) send all patients for baseline cardiac evaluation, however, (37.1%) send only patients with a known history of cardiac disease. The rest of the responders (8.1%) mentioned that they send patients as required, all patients with breast cancer, patients with CVD or risk factors if they will use cardiotoxic chemotherapy, or when using known cardiotoxic agents in all patients with cancer.

**Indicating this question was directed only for CCRs.*

***Indicating this question was directed only for OORs.*

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCRs, cardiologists/cardiology residents; OORs, oncologists/oncology residents; CVD, cardiovascular disease; ECG, electrocardiogram; HF, heart failure.

as a baseline CVD, at the same time OORs reported prescribing angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) mainly for patients with cancer, this may indicate that they are treating HTN in such patients without referring to cardiologists. Published evidence documented that HTN is the most common baseline comorbid disease among patients with cancer with the prevalence of 38–42% before initiation of cancer therapy, however, after initiation of cancer

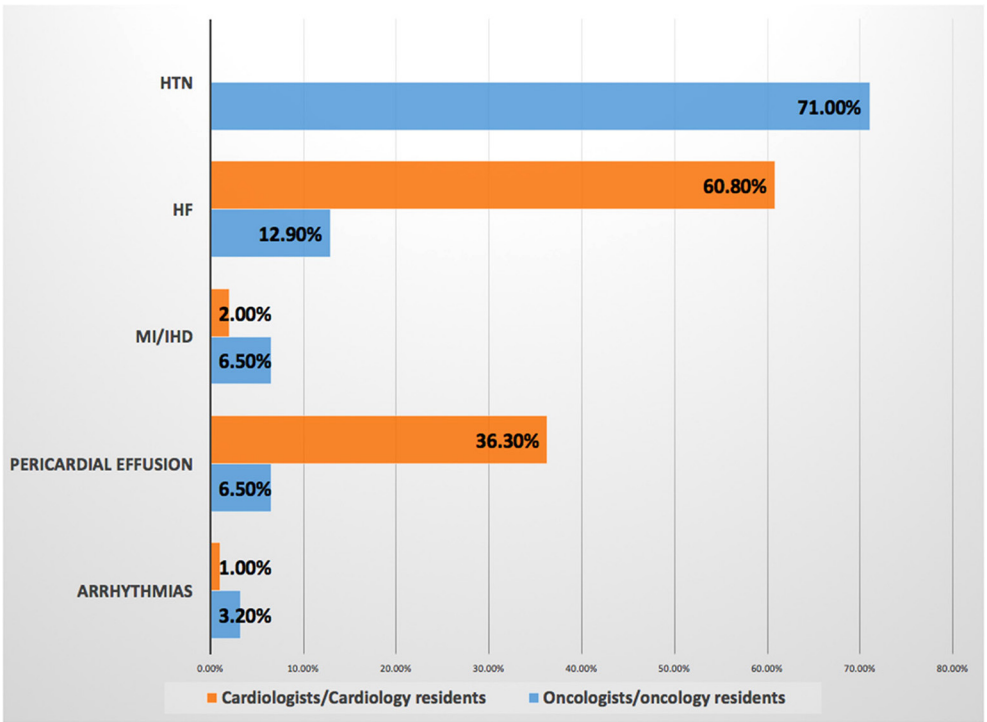

FIGURE 1 | Most common baseline cardiovascular disease among patients with cancer. Prevalence of baseline cardiovascular disease, hypertension is the most common risk factor according to responses of the oncologists/oncology residents. HF, heart failure; HTN, hypertension; IHD, ischemic heart disease; MI, myocardial infarction.

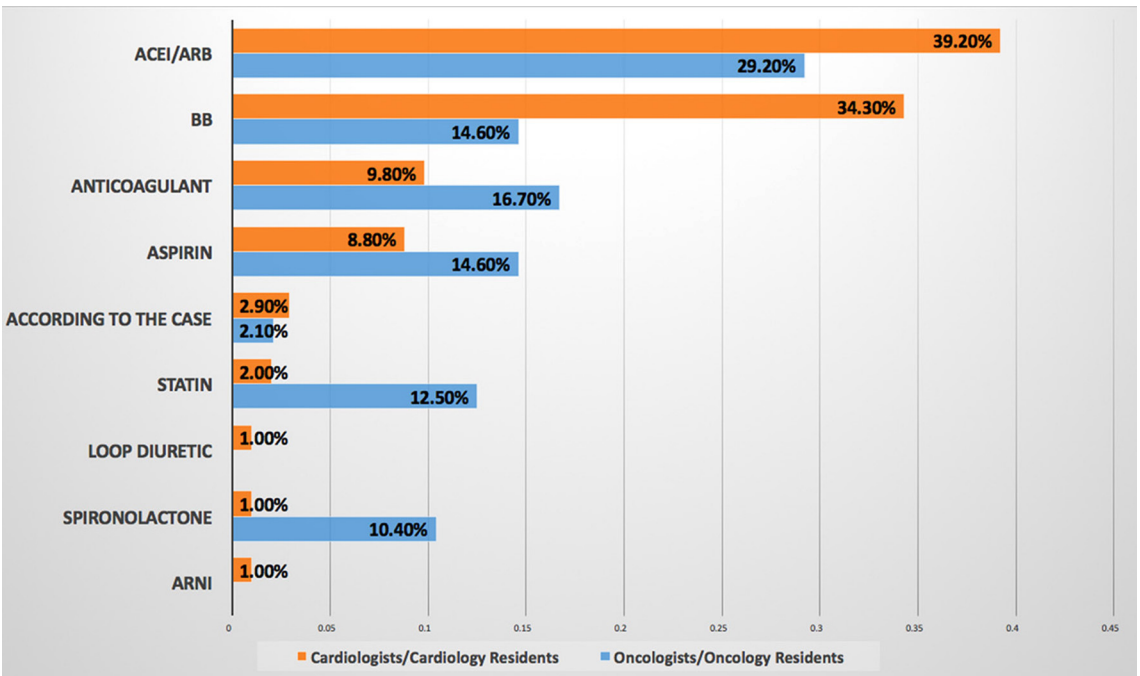

FIGURE 2 | Most commonly prescribed cardiovascular drug for patients with cancer. ACEI/ARB are the most commonly prescribed cardiovascular drug for patients with cancer by both cardiologists/cardiology residents and oncologists/oncology residents. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; ARNI, angiotensin receptor-neprilysin inhibitor.

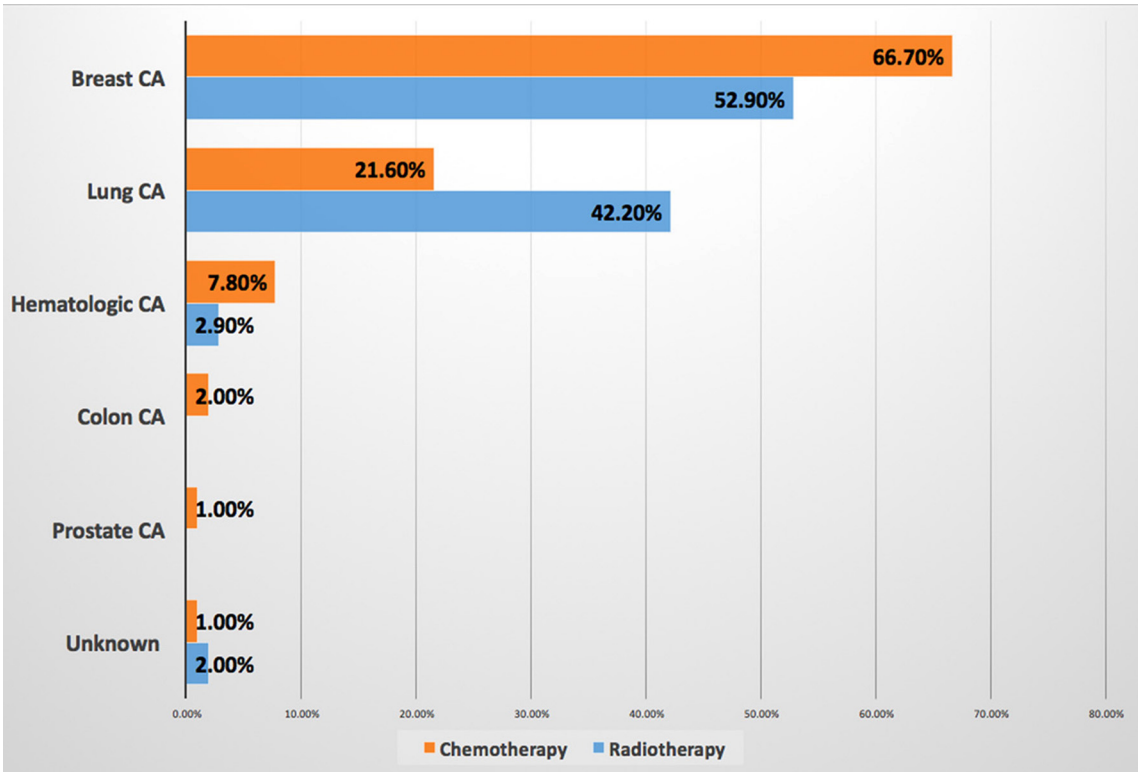

FIGURE 3 | Most cancer types associated with cancer therapy-induced cardiovascular disease. Breast cancer is the most common malignancy associated with CVD induced by both chemotherapy and radiation therapy. CA, cancer; CVD, cardiovascular disease.

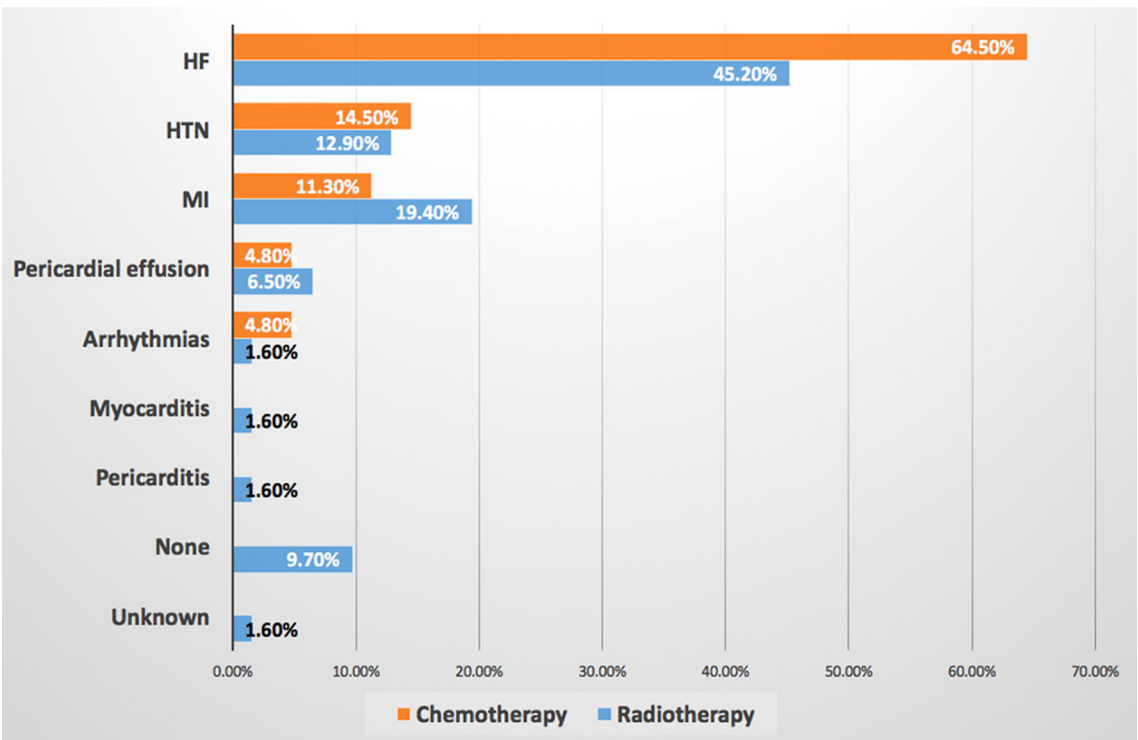

FIGURE 4 | Most common cardiovascular disease induced by chemotherapy and radiotherapy. HF is the most common CVD induced by both chemotherapy and radiation therapy. HF, heart failure; HTN, hypertension; MI, myocardial infarction.

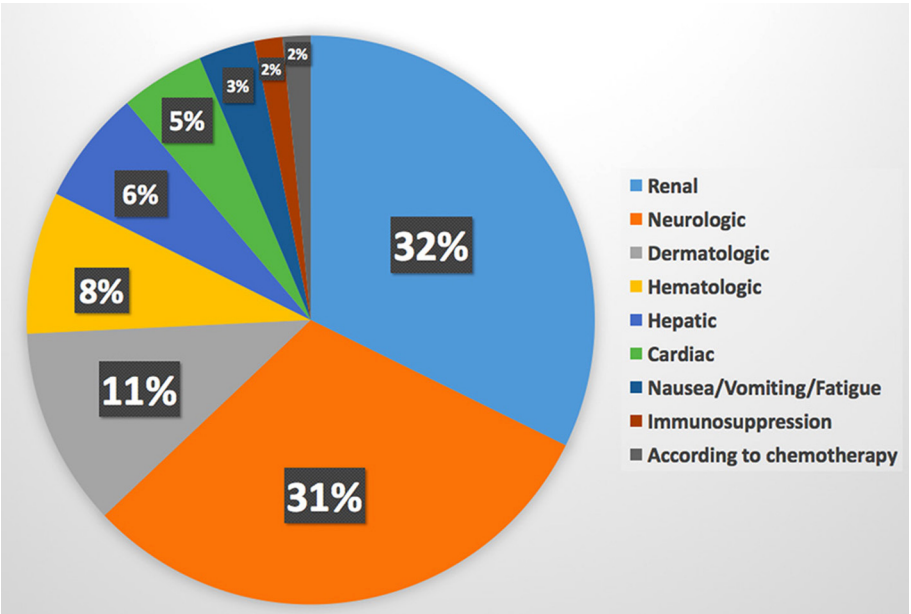

FIGURE 5 | Most common complications of chemotherapy. Cardiovascular disease is the sixth complication of chemotherapy.

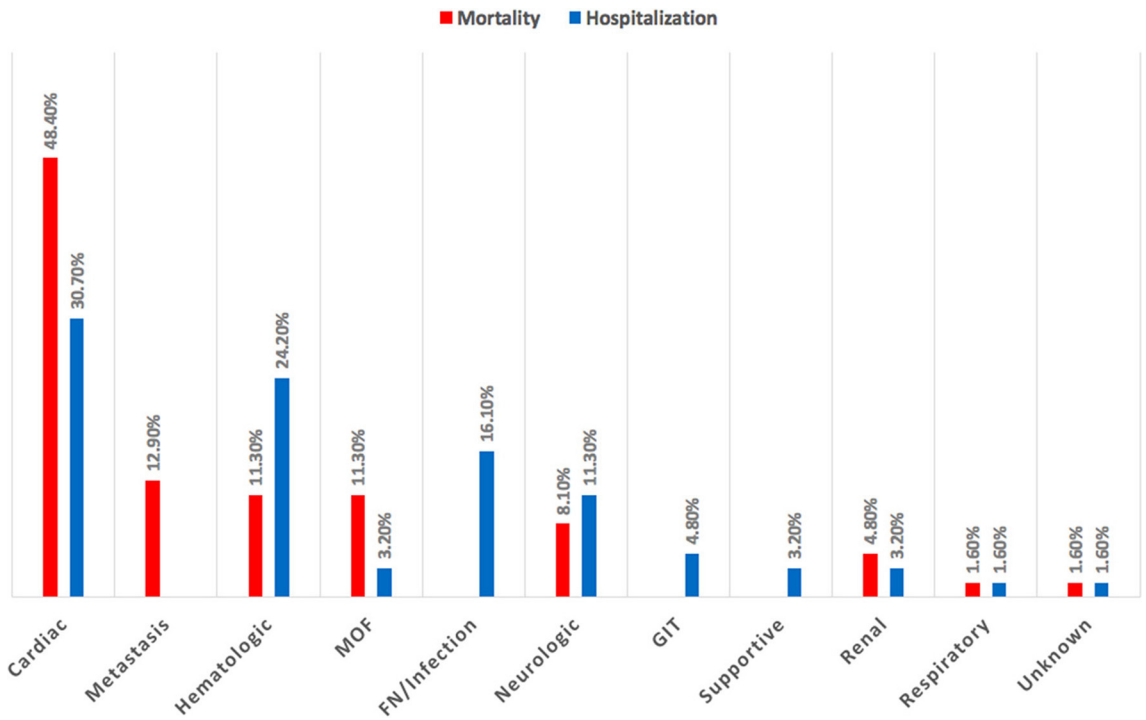

FIGURE 6 | Main medical cause for hospitalization and mortality among patients with cancer. Cardiovascular disease is the leading cause of hospitalization and mortality among patients with cancer. GIT, gastrointestinal tract; MOF, multi-organ failure.

therapy the incidence of *de novo* or worsening HTN ranging between 17 and 80% (6–9). It is known that CVD and cancer are sharing the same risk factors and preventive strategies, and pre-existing CVD in newly diagnosed patients with cancer may attribute to increasing morbidity and mortality, however, limited studies focus light on the prevalence of pretreatment cardiovascular risk factors (10, 11). A recently published JACC perspective can be considered as a roadmap to improve education

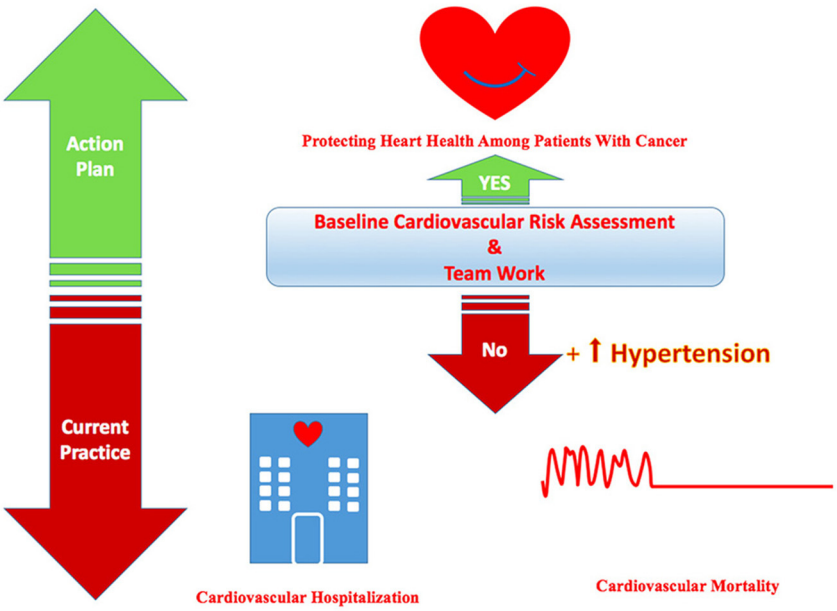

FIGURE 7 | Central illustration showing the current practice and the required action plan to protect heart health among patients with cancer. Hypertension is the most common baseline cardiovascular risk factor among cancer patients according to the current practice which can be the leading cause of cardiovascular hospitalization and mortality. The action plan is required to protect the heart health of cardio-oncology patients by baseline cardiovascular risk assessment and teamwork.

and training in the field of cardio-oncology to prevent CVD among patients with cancer rather than direct treatment (12). Regarding the most common CVD induced by chemotherapy and radiation therapy, both the CCRs and OORs reported HF as the first complication, then CCRs reported HTN as the second cardiac complication followed by myocardial infarction, while OORs reported the second complication is myocardial infarction followed by HTN, therefore, both the CCRs and OORs confirm that HTN incidence is among the first top three complications of cancer therapy. HF is a known complication of cancer and radiation therapies particularly in breast cancer, in addition, chest radiation accelerates atherosclerosis and cardiomyopathies (2, 13–15). Systemic HTN can be associated with both chemotherapies and immunologic therapies thus further increasing the burden of cardiovascular toxicities, it was estimated that novel cancer therapy can induce HTN by 24% (7–13). Moreover, resistant HTN and hypertensive crisis are associated with surgery or radiotherapy involving the head or neck (8). Therefore, treatment of HTN is one of the cornerstones for reducing the major cardiovascular events such as HF and end-stage renal failure in addition to overall mortality (7). The most common cardiovascular drug prescribed was ACEI/ARB as reported by both CCRs and OORs followed by anticoagulant and aspirin prescribed by OORs and beta-blockers prescribed by CCRs, this may be interpreted by the OORs use of ACEI/ARB for treating HTN among patients with cancer as a first-line drug as mentioned above. While ACEI/ARN and BB explain that CCRs prescribe them for patients with cancer who are (at risk) of CVD and patients with HF. In UK-based cardio-oncology service, it was also documented that beta-blockers and ACEI/ARB were the most prescribed drug for the referred cardio-oncology patients (6). Beta-blockers are considered cardioprotective drugs among patients with cancer for their beneficial effect in CVD and for the growing evidence regarding their role in breast cancer as it is associated with a significantly lower rate of metastasis particularly with propranolol, significantly reducing HF incidence during anthracyclines therapy with or without trastuzumab, and reducing of cancer-specific mortality rate among patients with prostate cancer whether using cardioselective or noncardioselective beta-blockers (16). Most of the CCRs and OORs reported that the main cancer type associated with CVD related to chemotherapy and radiation therapy are breast cancer and lung cancer, therefore, focusing attention on these two types of cancer particularly baseline risk factors assessment is important to prevent CVD complications. Current evidence also reported breast cancer as the first type of malignancies associated with CVD and the cause of referral (6, 14). More than two-third of OORs reported facing drug-drug interactions, despite this, they are checking for drug-drug interaction only when it is required depending on symptoms as reported by more than two-third of OORs and by about half of CCRs, i.e., checking after the interactions were taking place and this will increase the incidence of drug-drug interactions. Documented harmful drug-drug interactions among patients with cancer who are receiving oral cancer therapy are very common reaching 46% including 15% major and 83% moderate harmful interactions, 14% of interactions including

TABLE 3 | Questions about cardio-oncology service.

1. For cardio-oncology teamwork for the management of cancer patient, which specialties do you think it is important to be available? (please choose all options you think it is mandatory)	The main selected specialties are shown in (**Figure 8**), with cardiologist being the highest recommended expert to be in the team as responding by CCRs (87.3%) and OORs (72.6%). Other specialties suggested, namely: surgeon, hematologist, radiologist, nuclear medicine specialist, nephrologist, psychologist, pulmonologist, nutritionist, and echocardiographer.
2. Do you think it is important to establish a cardio-oncology service for better outcomes of patients with cancer?	Most of CCRs (86.3%) and OORs (85.5%) believe it is important to establish cardio-oncology service, (12.8%) and (14.5%) of CCRs and OORs; respectively, think it is maybe important to establish such service, while only (1%) of CCRs do not think it is important.
3. If there is a plan to establish cardio-oncology service, where is the best place for it?	Most of CCRs (76.5%) and OORs (66.1%) suggest that the best place for cardio-oncology service to be at the academic center rather than a community center, and regarding the best site for this service, (75.8%) of OORs suggested being at oncology site while (52%) of CCRs preferred to be at a cardiology site.
4. Do you have the interest to work in a cardio-oncology service?	Responses with interest to work in this service including 62.8% of CCRs and 64.5% of OORs.
5. Do you think it is important to include cardio-oncology training among the training curriculum of cardiology/oncology fellowship?	For CCRs, 69.6% of them believe it is important to include cardio-oncology training in the cardiology curriculum, a higher percentage was found among OORs (91.9%) to include such training in the oncology curriculum. Disagreement for including this training was the response of 3.9% of CCRs and 8.1% of OORs. The remaining response from CCRs (26.5%) thinks it may be important to include it in the curriculum.
6. Do you think it is essential to hold a monthly cardio-oncology meeting to discuss challenging cases of heart disease in patients with cancer?	Most CCRs (74.5%) and OORs (90.3%) agreed with the holding of a monthly meeting, (25.5%) of CCRs think it may be essential to hold such meeting, while (9.7%) of OORs find it is not essential.
7. How often do you need the availability of echocardiography and ECG minimally per week for the assessment of patients with cancer?*	Most of OORs' response (40.3%) was 2 days/week, (32.3%) need them once weekly, (9.7%) daily, (8.1%) believe their availability is not necessary, (4.8%) as required, (3.2%) once monthly, and (1.6%) three times monthly.

**Indicating this question was directed only for OORs.*
CCR, cardiologists/cardiology residents; OORs, oncologists/oncology residents.

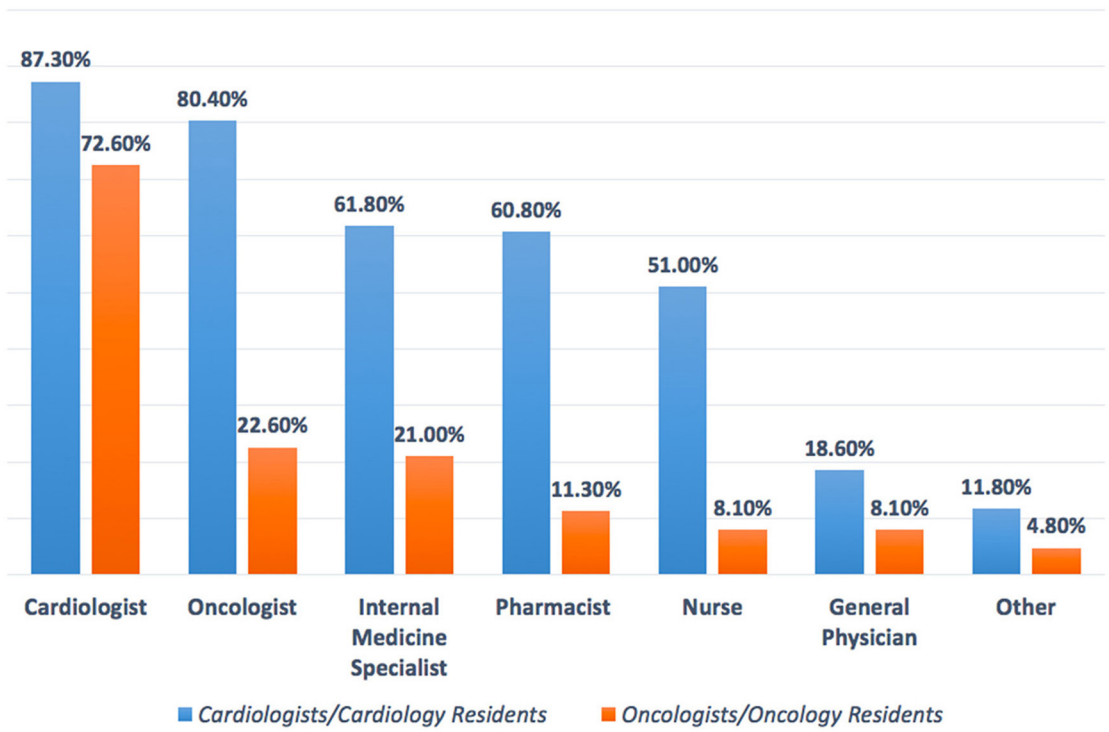

FIGURE 8 | Suggest cardio-oncology team members. Cardiologists, oncologists, internal medicine specialists, and pharmacists are the main specialists in the cardio-oncology team. Oncologists/oncology residents tend to focus mainly on cardiologists as a member of the cardio-oncology team.

cancer therapy and QT interactions (17). According to the OORs response of survey, CVD is the sixth complication of chemotherapy, however, the majority of the response of OORs regarding the main cause of hospitalization and mortality among cardio-oncology patients is CVD, this may be explained by uncontrolled baseline CV risk factors and underestimating of evaluation drug-drug interactions which may increase CVD or risks which exacerbate CVD leading to hospitalization and mortality. Evidence showed that cardiovascular hospitalization is the main cause of prostate cancer and the third cause of noncancer hospitalization among patients with cancer in general and noncancer mortality is highest among patients with colorectal, bladder, kidney, endometrium, breast, prostate, and testis cancers with heart disease being the most common cause (18, 19). Other findings in this study reported more than two-third of CCRs and OORs are facing difficulties while taking management action plans among cardio-oncology patients which necessitates teamwork and availability of guidelines and protocols for the management of cardio-oncology patients. Most CCRs and OORs agreed that the cardio-oncology team should include cardiologists, however, most CCRs believe that the team should include also oncologists, internal medicine specialists, and pharmacists, in addition to other specialties, however, the minority of OORs tend to include other specialties among the cardio-oncology team. It is known that cardiologists have an important role in the prevention of cardiovascular complications among patients with cancer through a comprehensive evaluation of cardiovascular risk factors and physical examination before initiation of cancer therapy (20), however, other specialties are also essential to be included among the cardio-oncology team for better outcomes, for example, the availability of pharmacists to prevent or minimize harmful drug-drug interactions which commonly occur (17). The proposed typical cardio-oncology team includes cardiologists, oncologists, hematologists, general practitioners, pharmacists, nurses, cardiac surgeons, radiologists, clinical laboratory specialists, palliative care team, psychologists, social workers, and data managers, depending on hospital size and organization (20). The current survey discovered several encouraging and strength points for the initiation of cardio-oncology services in Iraq including more than one-half of both CCRs and OORs have the interest to work in cardio-oncology service, most of the CCRs and OORs believe in the importance of holding a monthly cardio-oncology meeting to discuss together challenging cardio-oncology cases, and two-third of CCRs want to include cardio-oncology training in cardiology curriculum and almost all OORs wish to include such training in the oncology curriculum, all these points are promising for the near future improvement in the standard of cardiac services for patients with cancer to achieve the mission of our cardio-oncology program by protecting heart health among cardio-oncology patients.

This study depended on an online survey reflecting the expert opinions, therefore, the real prevalence of baseline cardiovascular risk factors and other results among patients with cancer need to be documented by clinical researchers and registries.

In conclusion, according to the survey-based data depending on the perception of cardiologists and oncologists, CVD is the leading cause of hospitalization and mortality among cardio-oncology patients, despite that CVD may be considered as the sixth rank complications among cancer therapy. There are essential needs to focus on the baseline CV risk stratification among patients with cancer to prevent CVD or CVD worsening by emphasizing on teamwork. There is an increasing interest among cardiologists, oncologists, and their residents in cardio-oncology teamwork and cardio-oncology training. It is time to take the action plan to change the current real practice to bridge the gap in the cardio-oncology service and to support clinical researches and registries in this field.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

HF and IY contributed equally in study design, writing, review, and approve for publication. IY performed the statistical analysis.

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Soluble Urokinase Plasminogen Activator Receptor Is Associated With Subclinical Myocardial Impairment by Speckle Tracking Echocardiography in Lung Cancer Patients

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Background: Plasma cardiac biomarkers have emerged as a cost-effective diagnostic tool aimed at early identification of cardiotoxicity. Soluble urokinase plasminogen activator receptor (suPAR) is a bone marrow cell derived signaling molecule that is associated with cardiovascular disease outcomes.

Objectives: We investigated associations between suPAR and global longitudinal strain (GLS) as a marker of early myocardial impairment in lung cancer patients.

Methods: We retrospectively analyzed 52 patients with stage IV non-small cell lung cancer with normal left ventricular ejection fraction (LVEF >55%) and without known heart disease or end-stage renal disease (ESRD). We studied associations between cardiac biomarkers and echocardiographic measures of systolic and diastolic function. GLS was analyzed using 2D speckle-tracking echocardiography via vendor-independent software (TomTec).

Results: Median plasma suPAR was 7.0 ng/mL (interquartile range: 5.4–9.0). Mean LVEF was 61.9 ± 8.3% and mean GLS was-19.3 ± 2.1%. Inter-observer reproducibility was excellent for GLS as determined by Intraclass Correlation Coefficient analysis, ICC = 0.81 (0.68–0.89). After multivariate analysis, suPAR was the only biomarker associated with GLS ($p = 0.009$). suPAR was also associated with diastolic parameters E velocity ($p = 0.018$), A velocity ($p = 0.017$), and E/E' ratio ($p = 0.033$). Interestingly, suPAR was not associated with LVEF ($p = 0.916$). In addition, suPAR and GLS were found to be age-independent predictors of all-cause mortality, though only GLS remained significant after multivariate adjustment.

Conclusions: In this cohort of stage IV non-small cell lung cancer patients with normal LVEF and without known heart disease or ESRD, suPAR was associated with GLS and diastolic impairment. suPAR is a readily available inexpensive biomarker; further research is required to evaluate the possible role of suPAR in screening for subclinical LV dysfunction in the high-risk oncological population.

Keywords: soluble urokinase plasminogen activator receptor (suPAR), myocardial global longitudinal strain, speckle tracking echocardiography, biomarkers, cancer

INTRODUCTION

Current standards for detecting cancer-therapy induced cardiotoxicity are based on assessment of cardiac function by left ventricular ejection fraction (LVEF) using either transthoracic echocardiography (TTE) or radionuclide multigated acquisition (MUGA) (1, 2). However, the assessment of LVEF lacks the sensitivity needed for detecting early subclinical changes. Newer echocardiographic modalities such as speckle tracking echocardiography (STE) enable earlier diagnosis of subclinical cardiac impairment not detected by conventional echocardiography (3).

Strain imaging, particularly global longitudinal strain (GLS) assessment by STE, has been increasingly utilized to risk stratify patients receiving anthracycline-based chemotherapeutic agents due to its superiority in detecting subclinical cardiac dysfunction (4, 5). STE by GLS therefore detects early derangements in cardiac function prior to a detectable fall in LVEF.

Biomarkers have emerged as a new cost-effective diagnostic tool aimed at early identification of patients more prone to developing cardiotoxicity (6). Soluble urokinase plasminogen activator receptor (suPAR) is gaining increasing attention because it is a circulating signaling molecule from the Ly6/neurotoxin family that is strongly predictive of incident and progressive chronic kidney disease and cancer cell progression (7–10). Mechanistically, suPAR activates podocytes on the kidney filtration barrier causing their functional breakdown (11) yet a mechanistic role for suPAR in cardiovascular diseases is not established. As an indicator of cardiovascular health, suPAR outperforms traditional markers of inflammation such as high sensitivity C-reactive protein (hs-CRP) in prognosticating a range of cardiovascular diseases (12, 13). Given the fundamental role of inflammation in cardiovascular disease (CVD), suPAR may aid in risk prediction and prevention of cardiac disease, particularly in the high-risk oncologic population.

Non-small cell lung cancer (NSCLC) accounts for the majority all lung cancers and is currently the leading cause of cancer-related deaths (14). Lung cancer patients are at increased risk of CVD due to direct cardiac toxicity from antineoplastic agents and radiation therapy, as well as shared cardiovascular risk factors (15). As new targeted therapies improve cancer patient survival, early detection of myocardial dysfunction is of utmost importance.

In the current study, we hypothesize that lung cancer treatment is associated with early/subclinical myocardial impairment as assessed by GLS. We examined the utility of an inexpensive and easily available biomarker (suPAR) in its association with GLS derangements as a marker of subclinical LV dysfunction, in stage IV non-small cell lung cancer patients with normal LVEF and without known heart disease or end-stage renal disease (ESRD).

Abbreviations: CVD, cardiovascular disease; GLS, global longitudinal strain; TTE, transthoracic echocardiography; MUGA, radionuclide multigated acquisition; STE, speckle tracking echocardiography; LVEF, left ventricular ejection fraction; suPAR, soluble urokinase plasminogen activator receptor; CRP, C-reactive protein; NSCLC, non-small cell lung cancer; ESRD, end stage renal disease.

METHODS

Study Population

We selected patients with stage IV NSCLC that previously failed first-line platinum-based therapy and presented to Rush University Medical Center in Chicago, Illinois between January 2005 and December 2015. Serum and clinical data were collected prospectively by the Rush Biorepository Core (16) with written informed patient consent. The study protocol was reviewed and approved by the Institutional Review Board at RUMC.

From a total of 136 patients with stage IV NSCLC whom had serum suPAR measurements available, we excluded patients with (1) incomplete data, (2) known heart disease and/or ESRD, (3) biplane LVEF $<$ 55%, or (4) poor image quality or arrhythmia at the time of echocardiography (**Figure 1**). A total of 52 patients were included in the current study. ESRD was defined as estimated glomerular filtration rate $<$15 ml/min, based on Modification of Diet in Renal Disease method (17). Known heart disease was defined as heart failure; coronary artery disease, including previous myocardial infarction, stable angina, previous percutaneous coronary intervention or coronary artery bypass surgery; congenital heart disease; pacemaker or intracardiac defibrillator implantation.

Outcome Measures

The time of observation was calculated from the date of suPAR draw until death or to the date of last follow-up for those still alive. All-cause mortality was obtained from the Social Security Death Index. Survival times were calculated from the date of suPAR draw to the date of death. Cox regression analysis was performed to predict 5-year all-cause mortality.

Conventional Echocardiography

Comprehensive echocardiographic examinations were carried out and analyzed using General Electric, Vivid 7 Dimension

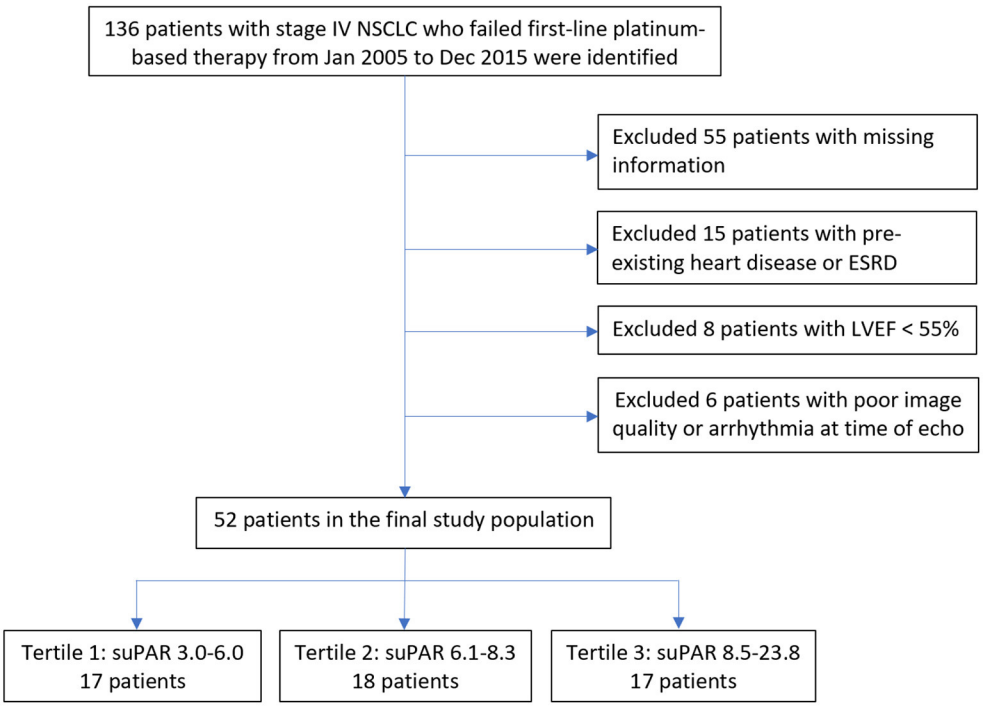

FIGURE 1 | Study population flowchart. Displays the initial study population through the final study population, exclusions included. ESRD, End Stage Renal Disease; LVEF, Left Ventricular Ejection Fraction; NSCLC, Non-Small Cell Lung Cancer; suPAR, soluble urokinase-type Plasminogen Activator Receptor.

imaging system device (GE Vingmed Ultrasound AS, Horten, Norway) with a 3.5 MHz transducer in accordance with the standard recommendations of the American Society of Echocardiography (18). Echocardiography was performed within 90 days of peripheral blood draw. LVEF was measured by biplane Simpson method in apical 4- and 2-chamber views. Three consecutive heart cycles were recorded for each view.

Pulsed-wave Doppler was performed in the apical 4-chamber view to obtain mitral inflow velocities for LV filling pattern evaluation. Peak velocity of early (E) and atrial (A) diastolic filling and deceleration time of E wave (DT) were measured, and the E/A ratio was calculated. Tissue Doppler early diastolic mitral annular velocity ($E^{'}$) was acquired at the lateral annular site and used to calculate E/E' (19, 20). Diastolic function was classified as normal, mild (grade 1, impaired relaxation), moderate (grade 2, pseudonormal), or severe (grade 3, restrictive) (20).

Speckle Tracking Echocardiography

All echocardiographic images were acquired with frame rates of 70–90 frame/s and digitally stored for three cardiac cycles. This method has been described in detail (3) and involves tracking speckles from frame to frame. For the current study, the stored images were retrospectively assessed using 2D STE offline analysis software (2D Cardiac Performance Analysis) developed by TomTec Imaging Systems, GmbH (Munich, Germany). LV GLS was determined by selecting the most representative of the 3 cardiac cycles and marking the endocardium in the standard apical 4-, 2-, and 3- chamber views (**Figure 2**). Automated computation was then performed based on the timing of the aortic valve closure. Images were reviewed and analyzed offline by two independent observers blinded to suPAR levels and clinical characteristics of the study population.

Laboratory Analysis

Collection and Storage of Serum Specimens

Peripheral blood was obtained from each patient using standard phlebotomy techniques, with all samples handled and processed in an identical manner, as previously described (21). A portion of each serum sample used for the Luminex evaluations were supplemented with 25 μL/mL of the Mammalian Protease inhibitor cocktail (Sigma, St. Louis, MO) and 10 μL/mL of 0.5 M EDTA to minimize further proteolysis. Aliquots were archived in a −80°C freezer until testing. No specimen was subjected to more than two freeze-thaw cycles.

Measurement of Serum Biomarker Concentrations

All specimens were evaluated using the Luminex immunobead platform and commercially-available kits, as previously described (21). All assays were performed according to the manufacturer's recommended protocols. All primary data points were collected on a Luminex FLEXMAP 3D® system with concentrations calculated based on 7-point standard curves using a five-parametric fit algorithm in xPONENT® v4.0.3 (Luminex Corp., Austin, TX) as previously described (21). sAXL and suPAR levels were measured using the commercially available MILLIPLEX® MAP Human Angiogenesis Panel 2 (EMD

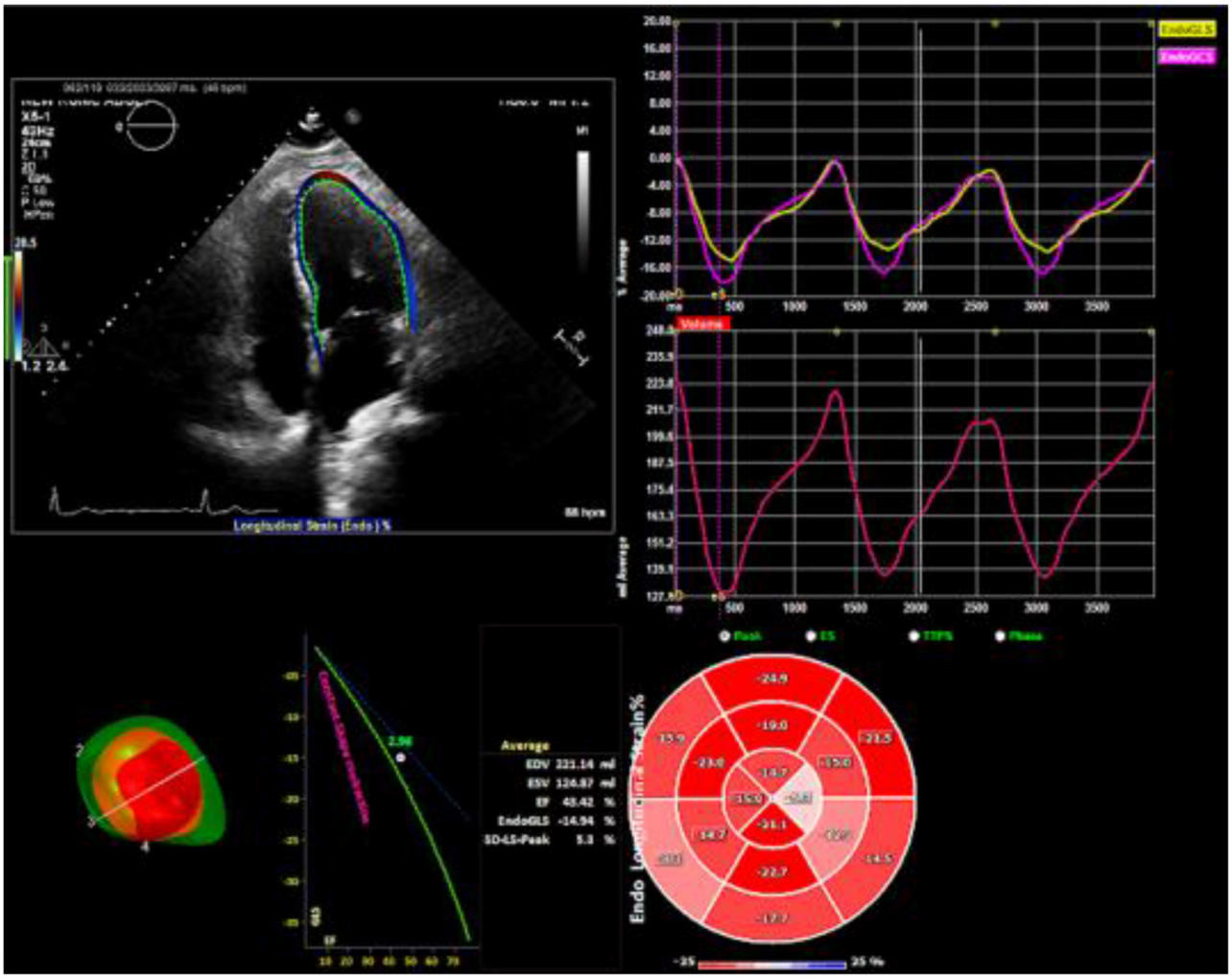

FIGURE 2 | Two-dimensional speckle tracking echocardiography analysis. Strain curves and a color-coded 16-segment bull's eye plot are presented. Color lines indicate regional strain. Values of longitudinal strain are negative (sign –). Endocardial border tracing in apical four-chamber view can be achieved automatically. Global longitudinal strain (GLS) can be calculated from standard apical 4-, 2-, and 3- chamber views.

Millipore Corp., Billerica, MA) for Osteopontin levels. CRP levels were measured using Human Acute Phase 5+4-plex Panel (Bio-Rad Laboratories, Inc., Hercules, CA). Tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels were measured using MILLIPLEX® MAP Human Circulating Cancer Biomarker Panel 1 (EMD Millipore Corp., Billerica, MA). Angiopoietin-2 and Endothelin-1 levels were measured using MILLIPLEX® MAP Human Angiogenesis/Growth Factor Panel 1 (EMD Millipore Corp., Billerica, MA). Resistin levels were measured using Human Diabetes 10-plex (Bio-Rad Laboratories, Inc., Hercules, CA). With a few exceptions, the blood samples were drawn within 6 months of cancer diagnosis; after the patients had failed platinum-based therapy.

Statistical Analysis

For each patient the following data was obtained through electronic medical records: patient demographics, cancer history, cancer therapy, cardiac medication use, cardiac risk factors (e.g., hypertension, diabetes, hyperlipidemia, smoking), and eGFR. Continuous variables were reported as means ± SD while categorical variables were expressed as numbers or ratios. Between-group comparisons were achieved by 1-way ANOVA for continuous variables while chi-square test was used to evaluate dichotomous variables. Due to the skewed distribution of the biomarker levels, a natural logarithm transformation was performed on all biomarkers. The Pearson correlation coefficient was used to assess the correlation between two variables. A value of $p < 0.05$ was considered to be statistically significant. Reproducibility for LV GLS measurement was assessed by intraclass correlation coefficient (ICC) analysis.

Multivariable linear regression analysis was used to test associations between cardiac biomarkers and echocardiographic parameters. With fixed adjustments for age and sex, the forward stepwise selections approach (probability of 0.05 to enter or leave

the model) was used to identify significant variables associated with systolic echocardiographic parameters (LVEF and GLS) and diastolic parameters (DT, E, A, E/A, E', and E/E'). Variables included in the final model were age, sex, BMI, smoking history, systolic blood pressure, diabetes, serum creatinine, and poorly differentiated histology. Potential risk factors for 5-year all-cause mortality were evaluated using Cox proportional hazards models. The multivariate model included age, gender, and additional variables; with a p-value of <0.10 in the univariate Cox analysis. Variables included in the final model were age, gender, diabetes, use of diuretics, and use of beta blockers. All analyses were performed with SPSS version 22 for Windows (SPSS Inc., Chicago, IL, USA). Level of significance was set at $p < 0.05$.

RESULTS

Patient Characteristics

Patient baseline data and echocardiographic parameters are summarized by suPAR tertiles in **Table 1**. The mean age was 62.7 ± 9.4 years, with 27 (52%) females. The median plasma suPAR level was 7.0 (interquartile range: 5.4–9.0). suPAR levels were similar in men and women, and were not associated with age or BMI. Higher suPAR levels were associated with history of smoking, use of diuretics, higher serum creatinine and lower eGFR, CRP, TNF-α, sAXL, and Angiopoietin-2. suPAR levels were not found to be associated with cancer duration, poorly differentiated histology, history of surgical resection, performance status, or radiation therapy.

suPAR and Echocardiographic Parameters

The mean LVEF was 61.9 ± 8.3% and mean GLS was −19.3 ± 2.1%. Inter-observer reproducibility was excellent for GLS, ICC = 0.81 (0.68–0.89). suPAR levels were not associated with LVEF ($p = 0.862$) in unadjusted comparisons (**Figure 3**). Conversely, there was a significant association between suPAR and GLS ($p < 0.001$), which remained statistically significant ($p = 0.009$) in the multivariate adjusted model (**Table 2**). For the echocardiographic parameters, suPAR levels were significantly correlated with diastolic measures E velocity ($p = 0.007$), A velocity ($p = 0.021$), and E/E' ($p = 0.011$), but not with E/A ($p = 0.831$), E' ($p = 0.802$), or DT ($p = 0.801$) in unadjusted comparisons; but only E velocity, A velocity, and E/E' remained significantly associated with suPAR ($p = 0.018$, $p = 0.017$, and $p = 0.033$, respectively) in multivariate analysis.

suPAR, Cardiac Biomarkers, and GLS

Associations between suPAR, cardiac biomarkers, and GLS were examined in unadjusted and adjusted models (**Table 3**). In unadjusted comparisons, suPAR ($p < 0.001$), TNF-α ($p = 0.032$), and sAXL ($p = 0.033$) were significantly correlated with GLS. However, after multivariate adjustment, only suPAR ($p = 0.009$) remained associated with GLS.

Prognostic Value of suPAR and GLS

The median follow-up time was 7.5 months (interquartile range: 3.75–18). At 5 years, 51 patients (98%) were deceased. In univariate Cox regression, the use of diuretics and beta blockers were the only clinical factors associated with all-cause mortality. In unadjusted models, GLS and multiple biomarkers including suPAR, CRP, TNF-α, angiopoietin-2, and resistin were independently associated with all-cause mortality (data not shown). After adjusting for age, suPAR, and GLS remained significantly associated with all-cause mortality. However, in the multivariate model, only GLS remained an independent predictor of all-cause mortality (data not shown).

DISCUSSION

In this study of 52 pretreated stage IV NSCLC patients with normal LVEF and without ESRD, we investigated associations between the biomarker suPAR and GLS as a measure of subclinical LV dysfunction. We also assessed associations between suPAR, other biomarkers, and echocardiographic measures of systolic and diastolic function.

We demonstrated that suPAR was strongly and independently associated with GLS; but not LVEF. In comparison to other cardiac biomarkers, suPAR was the only biomarker associated with GLS after multivariate adjustment. Furthermore, both suPAR and GLS were found to be independent predictors of all-cause mortality, independent of age. These findings suggest that suPAR is a sensitive marker of early myocardial impairment with useful prognostic implications.

CVD is an important cause of morbidity and mortality in the oncological population due to shared cardiovascular risk factors and direct cardiotoxic effects of cancer therapy. However, current standards for monitoring cardiac dysfunction rely on the presence of functional impairment, precluding any chance of preventing its development (1, 2). In the case of anthracycline-associated LVEF impairment, early initiation (within the first month of discovery of LVEF impairment) of standard heart failure therapy was associated with two-thirds chance of full LVEF recovery, compared with a 0% chance of full recovery if treatment was initiated after 6 months (22). Therefore, more sensitive screening modalities are needed for earlier detection of subclinical heart disease and stratification of patients prone to developing myocardial impairment. Several population-based studies have demonstrated a link between suPAR and CVD and mortality in the general population (9). Our study is the first to investigate associations between plasma suPAR levels and subclinical myocardial impairment in the oncological population.

GLS assessed by STE is an emerging technique for detecting and quantifying subclinical LV systolic dysfunction. GLS is established to be the best measure for predicting cardiotoxicity and clinical dysfunction in cancer patients receiving chemotherapy (4). Furthermore, GLS was found to be superior to LVEF in predicting cardiac events and all-cause mortality in patients with previous CVD or chronic kidney disease (5, 23). However, GLS is not routinely used in practice due to lack of standardization across echocardiographic imaging software and hardware; and the relatively time-consuming nature of GLS acquisition with echocardiographic imaging (24, 25); which is also not currently reimbursed in the United States.

TABLE 1 | Baseline characteristics according to suPAR tertiles.

Parameters	All patients ($n = 52$)	Tertile 1 ($n = 17$)	Tertile 2 ($n = 18$)	Tertile 3 ($n = 17$)	*P*-value
suPAR range, pg/mL	2,968–237,980	2,968–6,036	6,090–8,324	8,519–23,798	N/A
Clinical characteristics					
Age, years	62.7 ± 9.4	61.9 ± 9.5	60.9 ± 9.2	65.4 ± 8.2	0.308
Female, *n* (%)	27 (52%)	11 (65%)	11 (61%)	5 (29%)	0.077
African American, *n* (%)	10 (19%)	6 (35%)	2 (11%)	2 (12%)	0.127
Body mass index, kg/m^2	25.0 ± 4.9	24.2 ± 4.8	25.4 ± 5.0	25.4 ± 4.9	0.741
Systolic BP, mmHg	121 ± 18	120 ± 12	118 ± 21	126 ± 19	0.385
Diastolic BP, mmHg	72 ± 12	69 ± 10	71 ± 12	76 ± 12	0.207
Smoking history, pack years	27 ± 29	15 ± 14	24 ± 22	44 ± 40	0.014
eGFR, mL/min	86 ± 28	109 ± 24	86 ± 24	62 ± 15	<0.001
Medical history					
Hypertension, *n* (%)	27 (52%)	7 (41%)	8 (44%)	12 (71%)	0.176
Dyslipidemia, *n* (%)	18 (35%)	6 (35%)	4 (22%)	8 (47%)	0.316
Diabetes, *n* (%)	7 (13%)	2 (12%)	3 (17%)	2 (12%)	0.892
Cancer history					
Cancer duration, months	14 ± 12	15 ± 14	10 ± 8	19 ± 13	0.098
Poorly differentiated, *n* (%)	27 (52%)	10 (59%)	10 (56%)	7 (41%)	0.563
Surgical resection, *n* (%)	27 (52%)	12 (71%)	7 (39%)	8 (47%)	0.159
Radiation therapy, *n* (%)	5 (10%)	1 (6%)	2 (11%)	2 (12%)	0.824
Performance status, grade	0.7 ± 0.6	0.6 ± 0.6	0.7 ± 0.6	0.9 ± 0.7	0.232
Medications					
Diuretics, *n* (%)	13 (25%)	0 (0%)	3 (17%)	10 (59%)	<0.001
Beta blockers, *n* (%)	24 (46%)	5 (29%)	10 (56%)	9 (53%)	0.249
Calcium channel blockers, *n* (%)	17 (33%)	5 (29%)	5 (28%)	7 (41%)	0.672
Ace inhibitors/ARBS, *n* (%)	15 (29%)	3 (18%)	4 (22%)	8 (47%)	0.129
Statins, *n* (%)	19 (37%)	8 (47%)	4 (22%)	7 (41%)	0.290
Biomarkers					
Creatinine, mg/dL	1.0 ± 0.4	0.7 ± 0.2	0.9 ± 0.3	1.2 ± 0.3	<0.001
CRP, mg/L	16.3 ± 17.6	6.8 ± 7.2	14.8 ± 11.7	27.4 ± 23.6	0.001
IL-6, ng/mL	6.6 ± 9.8	4.3 ± 7.8	4.6 ± 5.8	11.2 ± 13.4	0.065
TNF-α, ng/mL	6.0 ± 5.0	4.3 ± 3.5	5.2 ± 2.7	8.6 ± 7.0	0.030
sAXL, pg/mL	1372.1 ± 660.8	1098.8 ± 501.9	1193.2 ± 478.1	1843.8 ± 734.9	0.001
Angiopoietin-2, pg/mL	2,389 ± 1,679	1,590 ± 1,106	2,626 ± 1,951	2,937 ± 1,630	0.046
Resistin	4,982 ± 2,704	4,106 ± 1,891	5,081 ± 2,442	5,755 ± 3,455	0.205
Endothelin-1, pg/mL	18.0 ± 77.3	37.3 ± 135.5	7.4 ± 4.4	10.0 ± 7.0	0.462
Echocardiographic characteristics					
LVEF, %	61.9 ± 8.3	61.7 ± 8.0	62.9 ± 10.0	61.1 ± 6.8	0.805
GLS, %	−19.3 ± 2.1	−20.3 ± 1.9	−19.6 ± 1.6	−17.8 ± 2.1	0.001
E velocity, m/s	0.8 ± 0.2	0.7 ± 0.1	0.8 ± 0.1	0.9 ± 0.2	0.034
A velocity, m/s	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.107
E/A ratio	1.0 ± 0.3	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.3	0.881
E' velocity, cm/s	9.2 ± 1.7	9.5 ± 1.3	9.0 ± 1.4	9.2 ± 1.2	0.698
E/E' ratio	8.8 ± 2.4	7.6 ± 1.5	8.9 ± 1.9	9.9 ± 3.2	0.025
Deceleration time, ms	195 ± 75	202 ± 45	187 ± 56	198 ± 112	0.828

P–values are for unadjusted comparisons (analysis of variance or χ^2) between tertiles of suPAR. Values are presented as mean ± standard deviation or as percentages (%). BP, blood pressure; CRP, C–reactive protein; GFR, glomerular filtration rate; IL−6, interleukin-6; LVEF, left ventricular ejection fraction; sAXL, soluble AXL; TNF-α, tumor necrosis factor-α.

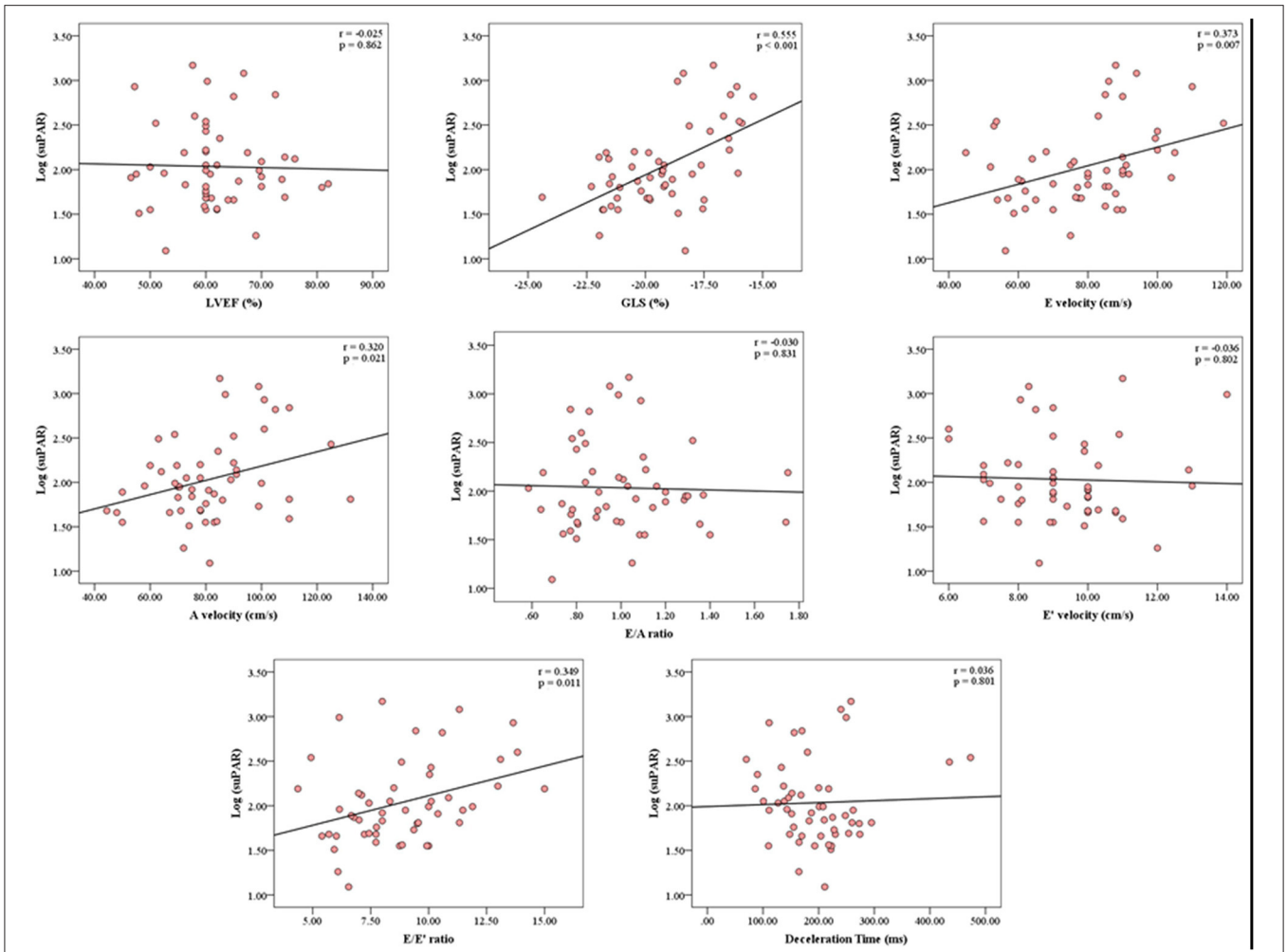

FIGURE 3 | Correlation Analysis between the serum concentration of suPAR and echocardiographic parameters. The correlation analysis graphs demonstrate significant correlations between suPAR levels and GLS, E velocity, A velocity, and E/E'. suPAR levels were not associated with LVEF. GLS, Global Longitudinal Strain; LVEF, Left Ventricular Ejection Fraction; r, Pearson's correlation coefficient; suPAR, soluble urokinase-type Plasminogen Activator Receptor.

Over the last decade, measurement of cardiac-specific biomarkers has emerged as a new cost-effective diagnostic tool aimed at early identification of patients more prone to developing cardiotoxicity (6). suPAR is thought to reflect activation of the inflammatory and immune systems and has been associated with poor clinical outcomes (12, 26, 27). suPAR has been associated with the presence of coronary micro- and macrovascular disease, carotid plaques, stroke, myocardial ischemia, and cardiovascular death, independent of traditional CV risk factors and hs-CRP (9, 13, 28–30). Moreover, suPAR, which has been linked to vascular inflammation, is a better marker for CVD compared with other markers of inflammation such as hs-CRP (12, 13, 31, 32). Despite the observed association between suPAR and several aspects of CVD, it remains unclear whether suPAR is playing a causal role.

In our cohort of stage IV NSCLC patients, the levels of suPAR were noticeably greater than those in similar non-oncological study populations. This is in line with previous studies in cancer patients showing more significant suPAR elevations when compared with healthy controls (9, 33). Urokinase-type plasminogen activator receptor (uPAR) is present in NSCLC tissue (7) and is thought to be released into the plasma leading to increased suPAR levels. Our patient cohort was treated with antineoplastic drugs, including first-line platinum-based therapy, at the time of the study. Therefore, it cannot be determined from the present data whether this treatment may have caused the release of suPAR (e.g., from dead cancer cells) or whether the plasma suPAR levels are independent of antineoplastic treatment. Notably, platinum-based therapy has not been shown to be related to diastology (15) or general LV dysfunction, including LVEF (15, 34). We demonstrated that suPAR levels were not significantly associated with history of radiation therapy, surgical resection, poorly differentiated histology, or cancer duration. We suspect this may be related to the variability of timing of symptom onset to diagnosis in these late stage cancer patients.

In the current study, we examined the relationship between cardiac biomarkers and systolic function in cancer patients with normal LVEF and without ESRD. We demonstrated that suPAR

TABLE 2 | Multivariate linear regression analysis showing association between suPAR and echocardiographic parameters after adjusting for important covariates.

	β (95% CI)	*P*-value
LVEF (%)	0.334 (−6.025 to 6.693)	0.916
GLS (%)	1.710 (0.446–2.975)	0.009
E velocity	14.845 (2.694–26.995)	0.018
A velocity	17.097 (3.193–31.002)	0.017
E/A ratio	−0.057 (−0.268 to 0.154)	0.590
E' velocity	−0.158 (−1.229 to 0.913)	0.767
E/E' ratio	1.721 (0.142–3.301)	0.033
DT	13.625 (−45.388 to 72.637)	0.644

Model adjusts for age, sex, BMI, smoking history, SBP, diabetes, creatinine, and poorly differentiated histology. DT, Deceleration Time; LVEF, Left Ventricular Ejection Fraction; GLS, Global Longitudinal Strain.

TABLE 3 | Univariate and Multivariate associations between biomarkers and GLS.

Biomarker	Univariate		Multivariate	
	r-value	*P*-value	β (95% CI)	*P*-value
suPAR	0.555	<0.001	1.710 (0.446–2.975)	0.009
IL−6	0.122	0.398	0.114 (−0.138 to 0.367)	0.366
TNF-α	0.297	0.032	0.184 (−0.402 to 0.770)	0.532
CRP	0.095	0.504	0.135 (−0.301 to 0.571)	0.536
sAXL	0.295	0.033	0.287 (−0.901 to 1.475)	0.628
Angiopoietin-2	0.117	0.410	0.035 (−0.811 to 0.882)	0.933
Resistin	0.159	0.259	0.001 (−1.163 to 1.164)	0.999
Endothelin−1	0.101	0.478	−0.154 (−0.830 to 0.521)	0.647

Model adjusts for age, sex, BMI, smoking history, SBP, diabetes, creatinine, and poorly differentiated histology. CRP, C-reactive protein; IL-6, interleukin-6; LVEF, Left Ventricular Ejection Fraction; GLS, Global Longitudinal Strain; r-value, Pearson's correlation coefficient; sAXL, soluble AXL; TNF-α, tumor necrosis factor-α.

was the only biomarker associated with GLS after multivariate adjustment. Interestingly, we found no association between suPAR and LVEF, suggesting that suPAR may be more reflective of early myocardial changes. These findings are supported by Theidela et al. in a diabetic population with normal LVEF and without ESRD (35). In contrast, Fujita et al. showed an association between suPAR and LVEF in patients with ischemic heart disease and impaired renal function (36), likely because suPAR levels are elevated in patients with renal disease (10) as was the case in our univariate analysis.

We also examined the relationship between suPAR and diastolic parameters. Consistent with other studies (35, 37) suPAR was significantly associated with diastolic function (E/E') after multivariate adjustment. This could be related to impaired coronary microcirculation and increased arterial stiffness seen in patients with elevated suPAR levels (37–40).

It is noteworthy that in the early results of the Strain Surveillance of Chemotherapy for Improving Cardiovascular Outcomes [SUCCOR] randomized trial (41), there was no significant difference between GLS and LVEF-guided management of potential cardiotoxicity in majority breast cancer patients treated with doxorubicin therapy. Major critiques and flaws of this study were that first, unlike our current study, the mean dose of doxorubicin administered in the SUCCOR trial was <250 mg/m^2, the threshold for cardiotoxicity risk associated with doxorubicin therapy. Second, LVEF and GLS in the SUCCOR trial were in the normal range at baseline and follow-up, with therefore limited power for detection of changes in LVEF or GLS. Third, the first two problems listed above were compounded by the short trial duration of follow-up, which further limited the ability of the study to detect differences between the two groups. Despite these challenges, the SUCCOR trial still demonstrated that fewer patients had cardiotoxicity in the GLS-guided than the LVEF-guided arm; and that among those that received medical therapy for cardiotoxicity risk, there were larger reductions in LVEF at follow-up in the LVEF-guided arm compared with the GLS-guided arm.

The prognostic value of both suPAR and CRP have been well-documented in different types of cancers, including NSCLC (35, 41, 42). Similarly, GLS is a useful prognostic marker in multiple disease processes, including CVD and malignancy (9). In line with previous studies, we demonstrate consistent prognostic value of suPAR, CRP, and GLS in predicting all-cause mortality in our age-adjusted NSCLC cohort. However, after multivariate only GLS and CRP remain independent predictors of all-cause mortality.

Our results suggest that suPAR may be a valid biomarker for subclinical myocardial impairment as the association between suPAR and GLS remained significant even after adjustment of important covariates. Given this observed relationship between suPAR and subclinical myocardial dysfunction, suPAR measurements may therefore be useful in clinical practice in identifying oncological patients at risk of developing heart disease. suPAR as a simple, inexpensive, and readily available test, could be a useful surrogate marker to circumvent the difficulty and costs associated with serial GLS measurements, particularly in cancer survivorship years.

Strengths and Limitations

As a single-center retrospective study, our study cannot provide information on the causal or resultant nature of the relationship between suPAR and early myocardial impairment. Furthermore, as a retrospective study, prior heart disease was determined by the information documented in the electronic medical records, and could not be ascertained. Echocardiographic examination and blood draw for suPAR measurements were not performed simultaneously, which could affect accurate comparisons. Also, because many of the patients were lost to follow-up in the community after cancer therapy, we did not have direct access to cardiovascular events data. We had access to the deaths data because of the cancer registry that meticulously obtains and records death information from the social security death index. Lastly, our small sample size was partly due to missing values which could have induced bias, thus limiting the interpretation of the results. Nonetheless, the robust associations between suPAR and GLS, despite the small sample size, emphasizes the strength of our study findings.

CONCLUSIONS

In patients with stage IV NSCLC with normal LVEF and without known heart disease or end-stage renal disease, suPAR was significantly associated with GLS and markers of diastolic LV myocardial impairment. Additionally, suPAR outperformed other cardiac biomarkers in its association with GLS. Moreover, suPAR and GLS were found to be independent predictors of all-cause mortality, independent of age. suPAR is a readily available and inexpensive marker. In order to limit costs associated with serial echocardiographic imaging, further research is required to evaluate the possible role of suPAR in screening for subclinical LV dysfunction—during treatment and particularly in cancer survivorship years—in the high-risk oncological population.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Rush University Medical Center. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AM, FB, and TO designed and executed the study. JB performed biomarker collection. AM and TO analyzed the data. AM and FB drafted the initial manuscript. TO, JB, and JR revised and discussed the manuscript. All co-authors have contributed to the development of this research project and the writing of this manuscript. All authors read and approved the manuscript for publication.

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Conflict of Interest: JR is a cofounder of TRISAQ which develops drugs against suPAR and in which he has financial interest including stock.

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.

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frontiers in Cardiovascular Medicine

CASE REPORT
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Case Series: Recovery of Chemotherapy-Related Acute Heart Failure by the Combined Use of Sacubitril Valsartan and Wearable Cardioverter Defibrillator: A Novel Winning Combination in Cardio-Oncology

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Effective anticancer treatments have dramatically improved the outcome of patients with cancer, but cardiac toxicity reduces their clinical efficacy in a non-negligible percentage of patients. Sacubitril/valsartan is a new paradigm in the treatment of chronic heart failure, with a reduced ejection fraction due to the enhancement of natriuretic peptides' properties when coupled with a blocking effect on the angiotensin II type 1 (AT1) receptors. As with other clinical conditions of heart failure with potentially reversible declines in cardiac function, a wearable cardioverter defibrillator (WCD) is a valid tool for protection against sudden death until recovery occurs. We report a case series of four patients with chemotherapy-related acute cardiac failure with severely reduced cardiac function. They were successfully treated with sacubitril/valsartan while being protected from malignant arrhythmias using a wearable cardioverter defibrillator until the recovery of cardiac function. Sacubitril/valsartan was confirmed to be effective in anthracycline-related cardiac toxicity and the wearable cardioverter defibrillator should be considered as a support tool even in the oncology patient.

Keywords: sacubitril/valsartan, wearable cardioverter defibrillator, cardio-oncology, heart failure, anthracyclines

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INTRODUCTION

Improvements in anti-cancer global strategy have resulted in better outcomes for a large part of patients with cancer, with many of them experiencing remission or long-term survival. Cardiovascular disease is the second leading cause of death in cancer survivors, preceded only by the cancer-related mortality itself (1). Systolic dysfunction is a well-documented and dose-dependent side effect of anthracyclines, which, in many cases, can be reversed with the introduction of heart failure therapy (2). Angiotensin-converting enzyme (ACE)-inhibitors, or angiotensin receptor blockers, together with beta-blockers, are the cornerstone of treatment of cancer therapy-related cardiac dysfunction (3). Sacubitril/valsartan (S/V) is a combined neprilysin inhibitor and angiotensin AT1 receptor blocker, which is approved for the treatment of chronic heart failure, with a reduced ejection fraction (4). No data from the pivotal PARADIGM-HF trial on cancer therapy-related cardiac dysfunction is available as these patients, although not formally excluded, have not been enrolled. Recently, some retrospective real-world data on S/V use in patients with reduced ejection fraction after chemotherapy showed an improvement in myocardial performance and reverse remodeling, but sound evidence is still lacking (5–8). Patients with heart failure (HF) and reduced ejection fraction (HFrEF) have a major risk of malignant arrhythmias and sudden cardiac death. The use of a wearable cardioverter defibrillator (WCD) is a valid tool for protection against sudden death in cases of potentially reversible cardiac damage. In patients with cancer, a WCD can be useful for those with potentially reversible cardiac toxicity during the implementation of evidence-based medical therapy. Interestingly, planned radiotherapy does not represent a contraindication to WCD since it can be easily removed to avoid interference between ionizing radiation and device function (9).

Cardiac magnetic resonance (CMR) represents the gold standard in cardiac function assessment and can be used for an early-stage screening of heart damage. Its role in tissue characterization can help eliminate other possible causes of myocardial dysfunction when cardiac toxicity is suspected. For this purpose, T1 and T2 mapping, in addition to late gadolinium enhancement (LGE), are very useful tools (10). We collected a case series of four patients with acute heart failure and deeply depressed EF secondary to anthracyclines or carfilzomib cardiotoxicity. We investigated the use of S/V to rescue the cardiac systolic function, together with the use of WCD, while waiting for the effects of medical therapy.

CASES PRESENTATION

Case 1

A 57-yo man with a malignant abdominal desmoid tumor, with long-term anthracyclines treatment (cumulative dose of 600 mg/m^2), and with a regular clinical and echocardiographic follow-up. The patient was hospitalized in November 2019 for acute heart failure with reduced ejection fraction (EF 25%) 1 month after the end of chemotherapy. The event occurred 8 months after the treatment started and 5 months after crossing the threshold dose of 300 mg/m^2. The patient started the anthracyclines therapy after a long period of hospitalization due to complications from abdominal surgery and a significant weight loss. No coronary lesions were detectable on coronary angiography. The CMR findings were an increased biventricular size and a severe biventricular dysfunction, with left systolic ejection fraction (LVEF) of 25% and right ventricle (RV) EF of 40%, increased native T1 signal (1,095 ms vs. normal value of 950 $\pm$ 21 ms) with a marked increase of extracellular volume (ECV) (40% vs. normal value of 26 $\pm$ 4%), but no LGE was found. Laboratory findings showed normal high-sensitive C-reactive protein (hs-CRP) levels and glomerular filtration rate. High-sensitive troponin T (hs-TnT) was elevated at admission time (190 pg/ml), with a slight decline during the in-hospital stay (162 pg/ml). The N-terminal prohormone of natriuretic peptide (NT-proBNP) levels was clearly elevated at baseline (9,752 pg/ml), but we observed a reduction during hospitalization to 7,200 pg/ml at discharge. During the follow-up, the NT-proBNP levels continued to decrease to 530 pg/ml within the year. Given the severe LV dysfunction, the patient was discharged with heart failure therapy (ACE-inhibitor, beta-blocker, anti-aldosterone therapy) and a WCD. At the first follow-up visit 10 days later, ACE-inhibitor was replaced with S/V due to persistent systolic dysfunction. After 3 months, the LVEF increased from 25 to 40% with the reverse remodeling of ventricular size and WCD was discontinued. The patient compliance to WCD was high with a median of 22.4 h/day. No significant arrhythmias were detected. Echocardiography findings were confirmed at 6 months by CMR (LVEF 43% and RVEF 51%), and while the native myocardial T1 signal decreased, it was not yet normal (1,051 vs. 1.095 ms). At the one-year follow-up visit, the LVEF had improved to 45% (**Table 1**).

TABLE 1 | Summary of clinical and imaging characteristics of the presented cases.

	Case 1	Case 2	Case 3	Case 4
Age	57	65	83	65
Cancer site	Desmoid	Breast	Multiple Myeloma	Breast
Drug	Anthra	Anthra Trastuzumab	Carfilzomib	Anthra
total dose (mg/m^2)	600	360 na	na	540
Admission LVEF	25%	30%	25%	25%
LVEF after S/V	45%	48%	48%	46%
Recovery time	3 months	3 months	2 weeks	3 months
Baseline T1 msec	1,095	1,040	1,066	986
T1 after S/V msec	1,051	1,000	na	na
Baseline ECV	40%	na	32%	23%
ECV after S/V	na	28%	na	na
LGE (yes/no)	No	No	Yes (non ischemic)	No

Anthra, anthracyclines; LVEF, left ventricular ejection fraction; S/V, sacubitril/valsartan; ECV, extracellular volume; LGE, late gadolinium enhancement; na, not applicable/not available.

Case 2

A 65-year-old woman, with early left breast cancer, was treated with surgery and radiotherapy in 2006, and adjuvant epirubicin (cumulative dose 360 mg/m^2) plus cyclophosphamide followed by trastuzumab for 1 year, ending in 2007. In September 2020, the patient was hospitalized for acute heart failure, with EF at 30%, and a coronary computed tomography (CT) that documented the absence of coronary artery disease. The patient reported smoking habits and hypertension in her medical history. The Hs-CRP and hs-TnT values and the glomerular filtration rate were all within the normal range, while NT-proBNP levels were elevated at admission (2,636 pg/ml), but during hospitalization, they rapidly decreased to 863 pg/ml at discharge and normalized at 3 months follow-up. The CMR showed an LV dilatation with severe impairment of contractile function (LVEF 32%) and a mild RV failure (RVEF 48%); native myocardial T1 signal was increased (1,040 ms) while LGE was absent. The patient was discharged with WCD and heart failure therapies including beta-blocker, anti-aldosterone therapy, and S/V that was later replaced by ramipril (2.5 mg/day) due to hypotension. After 3 months, the CMR highlighted a normalized left ventricular size and right ventricular function (RVEF 69%), left ventricle systolic function improvement (LVEF 48%), and a native myocardial T1 signal decreased to 1,000 ms with respect to baseline 1,040 ms with normal ECV (28%). No LGE was detectable, but septal edema was still present in the T2 mapping. The WCD was discontinued due to LVEF recovery (**Table 1**). Patient compliance to WCD was high with a median of 23.4 h/day with no significant arrhythmias detected.

Case 3

An 83-year-old man with advanced multiple myeloma was treated with a first-line bortezomib-melfalan-prednisone combination in 2018, and with carfilzomib in December 2020 after the disease relapse. After 1 week since carfilzomib was started, the patient was hospitalized for acute heart failure with severe biventricular dysfunction (LVEF 25%). The patient presented with a reduced glomerular filtration rate and elevated hs-CRP levels (42 mg/L). The filtration rate remained unchanged during the in-hospital stay, while hs-CRP decreased to 18 mg/L. A high-sensitive troponin T was elevated at admission time (130 pg/ml) with a trend in reduction (90 pg/ml). The baseline NT-proBNP levels were clearly elevated (13,735 pg/ml), with a sharp reduction during hospitalization (1,137 pg/ml at discharge). A coronary CT (coronary angiography was excluded due to renal impairment) showed diffuse and severe coronary atherosclerosis without obstructive coronary disease. The patient was started on heart failure therapy with beta-blocker and S/V; after 2 weeks from therapy, introductory CMR was performed and has shown the normal biventricular dimensions and right ventricular function (RVEF 60%), left ventricular systolic function improvement (LVEF 45 vs. 25%), interventricular septal and lateral wall abnormal native T1 signal (1,000 and 1,066 ms, respectively), and an increased ECV (32%) and a mid-wall septal LGE with a non-ischemic pattern. At the one-month follow-up, LVEF had further improved to 48% (**Table 1**).

Case 4

A 65-year-old woman with early left breast cancer was treated with adjuvant anthacycline-based chemotherapy (epirubicin with a cumulative dose of 540 mg/m^2), followed by radiotherapy (dose 50Gy) in 2003. In January 2021, the patient reported dyspnea for mild effort. This patient also reported a history of smoking and hypertension. Chest X-Ray showed a pleural effusion, and the echocardiography documented a dilated left ventricle with severe systolic dysfunction (EF 25%) leading to hospitalization. The admission hs-CRP levels and hs-TnT were slightly elevated but remained in a stable trend during hospitalization. The filtration rate showed a baseline reduction that stayed unchanged during observation. As expected, the NT-proBNP levels were clearly elevated at baseline (15,600 pg/ml) but we observed a sharp and fast reduction (2,300 pg/ml at discharge). No coronary artery disease was found at coronary angiography. CMR confirmed an increased left ventricular size, severe biventricular systolic dysfunction (LVEF 27% and RVEF 29%), and no significant LGE. Heart failure therapy, with beta-blocker and anti-aldosterone therapy plus S/V, was started together with SGLT2 inhibitor empagliflozin for the previously undiagnosed diabetes. The patient was discharged with WCD. At the first follow-up visit 1 month later, LV size was normal, and the ejection fraction improved to 35%. At the three-month follow-up visits, LVEF had improved to 46%, and WCD was discontinued (**Table 1**). Once more, compliance to WCD was high with a median of 23.5 h/day. No significant arrhythmias were detected.

DISCUSSION

In this case series, we investigate the role of early S/V use in chemotherapy-induced cardiomyopathy, coupled with the use of WCD as a bridging therapy while waiting for ventricular function recovery. The CMR played a major role in confirming the echocardiographic data, in ruling out the ischemic etiology, (11) and in better defining the cardiac damage (10).

Chemotherapy-related heart failure may present a wide time range from the start of treatment, and this fact is clearly shown in our case series. In cases 2 and 4, the HF symptoms showed up to 13 and 18 years from anticancer therapy, respectively, while the time interval was shorter for case 1; while in case 3, symptoms appeared just 1 week after the treatment started. In cases with a long time interval, treatment-related cardiac damage acts as an additional cardiovascular risk factor (12). Acute and/or early forms are less characterized, although also include an immune-inflammatory pattern with a widespread cell death-mediated myocardial damage. This hypothesis perfectly fits with case 3. The first case was probably presented with immunosuppression that is related to malnutrition and prolonged hospitalization, which makes the hypothesis of immune-inflammatory myocardial damage less likely. Irrespective of the early or late clinical presentation, while our cases showed a prompt recovery of cardiac function, they should undergo a tailored cardiological follow-up schedule and a multidisciplinary approach if a new oncological treatment is needed.

Chemotherapy-related cardiomyopathy, with functional impairment, may be successfully treated with an HF therapy, particularly when inhibitors of the renin-angiotensin system are used. Although these patients were not enrolled in the PARADIGM-HF trial (4) due to a history of chemotherapy-related HF over the last 12 months, the use of S/V in the setting of cardiac dysfunction secondary to chemotherapy is an intuitive therapeutic opportunity (13). However, all currently available data comes from case reports/series and retrospective analyses, and prospective validation of its use is still lacking. A retrospective multicenter registry showed that S/V was well-tolerated and could improve the myocardial function and the structure in patients with cancer and with chemotherapy cardiomyopathy (6). Positive effects of S/V on cardiac structure and function in chemotherapy-damaged hearts were also reported recently. A group of patients underwent CMR at baseline, and after 3 months from the beginning of S/V therapy, the findings were consistent with the reverse remodeling of LV volumes, improvement of LVEF, and reduction of NTpro-BNP levels (14).

A meta-analysis highlighted the effect of S/V on reverse cardiac remodeling in patients with HfrEF. The patients treated with S/V showed an improved LVEF, as well as improvements in most of the cardiac remodeling indices, like the LV end-diastolic volume, the LV end-systolic volume, the left atrial volume, and the LV mass index, as compared with patients treated with ACEIs or ARBs. Patients appeared to benefit more if treated with S/V as early as possible and for a duration of at least 3 months (15). A possible explanation for the reverse cardiac remodeling effect relies on the possibility that the neprilysin inhibitor fostered the reparative processes. In an experimental rodent model of progressive doxorubicin-induced cardiotoxicity, S/V offered greater protection against LV remodeling and dysfunction compared with valsartan (16).

Cardiac magnetic resonance (CMR) is the gold standard for ventricular dimension and ejection fraction assessment. All our patients had biventricular dysfunction in the acute phase, but, while LV impairment was clearly detected by echocardiography, RV dysfunction was detected only by CMR. However, EF reduction is just a small part of cardio-toxic damage (17). Early diagnosis of myocardial damage is crucial for its reversibility and the CMR seems to be the most effective tool to reach this aim because of its capability of tissue characterization (18). The T1 and T2 mapping CMR can easily highlight the additional signs of myocardial injury. In particular, native T1 values reflect the signals from the intracellular and extracellular compartments as well as intrinsic variances in tissue properties. An increased native T1 is useful for detecting the acute myocardial pathologies that can also occur in cardiotoxicities, such as edema, infarction, myocarditis, and subacute processes like diffuse fibrosis (19).

The reference for non-invasive recognition of focal fibrosis areas is LGE, but a limitation of this technique is the low sensitivity for diffuse fibrosis that is more frequent in patients with cardiotoxicity, especially in anthracycline cardiomyopathy (20). The T1 mapping can be considered as the early tissue markers of ventricular remodeling, whose increase was directly related to the administered dose and was inversely related to the exercise capacity, myocardial mass, and reduction in parietal thickness (21). All our patients had increased native T1 and ECV values, which are related to a diffuse increase in collagen content leading to a change in myocardial extracellular volume and resulting in diffuse fibrosis (22). The T2-weighted imaging can identify the presence of edema, which is secondary to acute myocardial inflammation and injury. Therefore, the increased native T1 and T2 values can detect an early myocardial inflammation, while elevated native T1 but normal T2 demonstrate subsequent interstitial fibrosis and remodeling (23). However, the utility of T2 maps in cardiotoxicity has not been thoroughly studied. Although they are very promising techniques, both have some limitations, mostly related to their dependence on physiological factors (for ex: age, sex, and heart rate) and on CMR protocols. Reference values should be individually validated in every radiological institution (24). In particular T2 maps are an ongoing matter of study in the CMR field and their utility in cardiotoxicity has not been thoroughly studied.

Implantable cardioverter defibrillators (ICDs) are indicated for the primary prevention of sudden cardiac death (SCD) in patients with reduced LV function (LVEF equal to or <35%). A subset of patients with cancer is at risk for SCD due to a variety of cardiac causes, including chemotherapy-induced cardiomyopathy. The data regarding the risk of arrhythmic death in these patients are very limited, but a study on the use of WCD in patients suffering from anthracycline cardiotoxicity showed a risk of malignant arrhythmia at around 7% in 3 months, which is significantly higher than in the general population with heart failure (9). An individual with cancer may have contraindications for permanent defibrillator implantation, including the potential reversibility of cardiomyopathy, an unclear prognosis for 1-year survival, and an increased risk of device infection related to some chemotherapies. Moreover, radiotherapy may interfere with the ICD function, and the presence of ICD can reduce the radiation dosing to the targeted tumor area. The WCD may protect the patients with cancer, who are at risk for SCD until an ICD can be safely implanted or until it has become unnecessary. One of the limitations of the WCD is the possible reduced compliance to continuously wear the device and the lack of pacing in the patients who are pacemaker-dependent (25). However, the median wearing time, reported in the most recent registry data, is higher than 23 h a day (26, 27). An interesting new feature of this technology is the recent integration of sensors that allow the physician to monitor the hemodynamic compensation and the patient's state of health as a whole. The WCD (LifeVest®, ZOLL, Pittsburgh, PA, USA) can obtain information about the average heart rate, the physical activity performed in daily steps, the body positions during days, the body angle, and the body position while the patient is reclined, indirect indices of physical capacity, and state of congestion. Our patients tolerated WCD with high compliance. While there were no spontaneous ventricular tachyarrhythmia events in this pilot evaluation, the use of the WCD in patients, who are actively receiving chemotherapy,

is feasible and acceptable to these patients as demonstrated by the high compliance rates. In patients agreeing to undergo chemotherapy, non-invasively preventing the sudden cardiac death during periods of high short-term risk is appealing. Larger studies will be needed to clearly demonstrate the short-term and long-term benefits of such a strategy.

PATIENT PERSPECTIVE AND CONCLUSIONS

Chemotherapy-induced acute heart failure could represent a potentially life-threatening side effect of many oncology drugs. Besides representing a clinical emergency, it could also negatively affect long-term patient outcome from an oncological point of view. In fact, a steadily impaired EF could limit the anticancer therapeutic options. Prompt and steady recovery of cardiac function has been a 2-fold relevance. All available therapeutic strategies should be implemented to get this goal. The presented case series highlighted the positive role of the early use of S/V in LVEF recovery in this clinical setting. The WCD should be considered in oncology patients when recovery of cardiac function is expected. A prospective evaluation of a larger size of the S/V effect in an oncology population is needed to confirm its retrospective and positive results.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Written informed consent was obtained from all participants for their participation in this study.

AUTHOR CONTRIBUTIONS

MLC, KC, GS, JDM, AC, FS, and EV: study conception and case description. MLC, KC, GS, AC, GC, NM, CT, and IB: drafting of the manuscript or revising it critically for important intellectual content. All authors: final approval of the manuscript.

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Cardio-Oncology: A Myriad of Relationships Between Cardiovascular Disease and Cancer

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Cardiovascular disease (CVD) and cancer are the leading causes of death worldwide. With an increasing number of the elderly population, and early cancer screening and treatment, the number of cancers cases are rising, while the mortality rate is decreasing. However, the number of cancer survivors is increasing yearly. With the prolonged life span of cancer patients, the adverse effects of anti-tumor therapy, especially CVD, have gained enormous attention. The incidence of cardiovascular events such as cardiac injury or cardiovascular toxicity is higher than malignant tumors' recurrence rate. Numerous clinical studies have also shifted their focus from the study of a single disease to the interdisciplinary study of oncology and cardiology. Previous studies have confirmed that anti-tumor therapy can cause CVD. Additionally, the treatment of CVD is also related to the tumors incidence. It is well established that the increased incidence of CVD in cancer patients is probably due to an unmodified unhealthy lifestyle among cancer survivors or cardiotoxicity caused by anti-cancer therapy. Nevertheless, some patients with CVD have a relatively increased cancer risk because CVD and malignant tumors are highly overlapping risk factors, including gender, age, hypertension, diabetes, hyperlipidemia, inflammation, and obesity. With advancements in the diagnosis and treatment, many patients simultaneously suffer from CVD and cancer, and most of them have a poor prognosis. Therefore, clinicians should understand the relationship between CVD and tumors, effectively identify the primary and secondary prevention for these diseases, and follow proper treatment methods.

Keywords: cardiology, oncology, cardiovascular disease, cancer, cardiotoxicity

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INTRODUCTION

Currently, cardiovascular disease (CVD) and cancer have the highest morbidity and mortality worldwide. They are closely related in terms of many factors, including risk factors, pathogenesis, and iatrogenic side effects. The lifetime risk of CVD in people >30 years old is close to 50%, causing ∼17.3 million deaths worldwide each year (1). In 2020, ∼19.3 million people were diagnosed with cancer globally, resulting in approximately 10 million deaths. It is worth noting that the first year of cancer is the period with the highest mortality from cardiovascular complications (2). Therefore, as a severe global public health threat, the relationship between

CVD and cancer is actively being studied and updated. Various exogenous factors and genes have contributed to the onset of these diseases. Anti-cancer treatments have led to an increase in the incidence of CVD. Similarly, antihypertensive drugs (angiotensin converting enzyme inhibitors; ACEI) and aspirin affect the occurrence of different types of cancer. We summarized relevant studies and proposed that CVD and cancer are predisposing factors for each other. Starting from the pathogenesis, this article systematically summarizes the epidemiological status, points out the common occurrence and pathogenic mechanisms of various CVD and cancer, lists anti-cancer drugs, and discusses several cardiovascular side effects induced by anti-cancer therapy. Finally, we provide the latest strategies for the clinical management of such patients.

RELATIONSHIP BETWEEN CANCER AND CARDIOVASCULAR DISEASE

Common Risk Factors

CVD and cancer are multifactorial, with highly overlapping risk factors, including smoking, metabolic syndrome, radiation, age, air pollution, and environmental toxins (3). Recent studies have pointed out that CVD and tumors have direct mutual effects in addition to the above risk factors. CVD can increase the overall incidence of cancer. In patients with early-stage breast cancer, 59% of post-treatment recurrence and 60% of cancer-specific deaths are related to cardiovascular events (4, 5). Heart failure may be a risk factor for tumors by releasing particular heart failure-associated proteins, such as SERPINA3, into the bloodstream, leading to tumor development and growth, while elevated cardiac and inflammatory markers may indicate new cancers, according to an experimental study (6). Hypertension has a similar mechanism to tumors. Hypertension affects the arterial wall through oxidative stress and is related to cell canceration (7). Patients with hypertension have 2-fold higher risk cancer of normal people.

With normal blood pressure, and the incidence of malignant tumors increases with the increase of blood pressure. Active and effective antihypertensive treatment can prevent cardiovascular complications and improve the quality of life in cancer patients. Grossman et al. (8) further showed that high blood pressure increased the risk of cancer death by 23%. Myocardial infarction, as an acute rational stressor that accelerates breast cancer progression, accelerates tumor growth by activating systemic host response; meanwhile, bone marrow cells present an immunosuppressive state, accelerating the division of monocytes, and promoting tumor proliferation (8, 9). In addition, tumors promote the development of CVD. Tumors consume glucose in the body in a form other than insulin, leading to systemic insulin loss, and cardiac atrophy and heart failure, and possibly accelerating tumor progression (10). Moreover, many drugs and radiotherapy in cancer treatment are cardiotoxic, which aggravate the occurrence and development of heart failure, arrhythmia, coronary artery disease, hypertension and other CVD.

Genetic Susceptibility

TET2 is the most common mutated gene associated with increased incidence and mortality due to CVD, which is also the first gene identified as an acquired mutation in individuals without hematological malignancies. Preclinical studies have shown that TET2-deficient cells can accelerate atherosclerosis in mice, promoting the release of IL-1β from macrophages; consequently, perpetuating vascular inflammation and inducing monocyte aggregation at the lesion site to aggravate inflammation (11). Hereditary/familial cardiomyopathy (CMY) is an autosomal dominant monogenic disease with no clear cardiac abnormality (12). Hypertrophic cardiomyopathy (HCM) has the highest incidence among CMY, followed by dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ACM), and restrictive cardiomyopathy (13). In 2012, Truncations of titin (*TTN*) was first proposed as a DCM related gene, which encodes myotin in sarcomere (14). Truncating variants in the *TTN* gene (*TTNtv*), i.e., *TTN* trunk-frame-frame-mutation was detected in 25% of familial cardiomyopathy, 18% of sporadic cardiomyopathy, 10% of perinatal cardiomyopathy, and 25% of alcoholic cardiomyopathy. Patients with *TTNtv* had worse cardiac function (15). *TTNtv* carriers are likely to have cancer treatment-induced cardiomyopathy (CCM). Genetic susceptibility to DCM increases susceptibility to CCM (16). 90% of patients with CCM received anthracyclines. An animal study showed that mice with *TTNtv* showed left ventricular cardiomyocyte elongation and dysfunction after treatment with anthracycline (13). In addition, desmosomes, as the main structure of the connections between cells, inhibit cell motor ability. Mutations in desmosome genes have been detected in various cancers and ACM patients (13). In a study of cardiomyopathy induced by cancer treatment in children, the risk of CCM in Africa is higher than in Europe, possibly due to abnormal expression of putative homeodomain transcription factor 1 (PHTF1) and associated with long-term response to adriamycin therapy (17). Therefore, genetic screening provides guidance to identify patients at high risk for CCM and helps evaluate drugs for prevention and treatment and optimize the treatment of cancer and CVD.

Clonal Hematopoiesis

Clonal hematopoiesis (CH) is defined as the clonal expansion of blood cells in the presence of somatic mutations and is an age-related biological state (18). The concept of clonal hematopoiesis of indeterminate potential (CHIP) was first introduced in 2015 as the presence of somatic mutations associated with hematologic malignancies in the blood or bone marrow of individuals with non-malignant hematologic diseases (19), involved in tumor development and CVD (20). CHIP is a biological state associated with aging that is virtually absent in children and its expression increases with age, mainly in the form of hematopoietic stem cell mutations. CHIP produces clonal white blood cells to populate peripheral blood, and individuals with 2–3 of these somatic mutations in a row are at increased risk of developing leukemia (21). Therefore, CHIP is considered a preclinical state for malignant blood disorders. Notably, CHIP alters innate immune cells to promote lymphoid malignancy and accelerates

solid cancer progression by disrupting acquired immune cell homeostasis (22). In addition, chemotherapy promotes clonal expansion of specific mutations, leading to poor outcomes (23).

CHIP is an independent risk factor for CVD. CHIP increases the risk of atherogenesis and accelerates atherosclerosis and chronic cardiac insufficiency, leading to a poor prognosis for such patients (20). In 2017 Jaiswal et al. (24) enrolled 4,726 participants with coronary heart disease and 3,529 controls and confirmed that the presence of CHIP in peripheral blood cells can lead to a doubling of the risk of developing coronary artery disease. The study also found that the degree of coronary artery calcification and the incidence of coronary events were positively associated with CHIP (24). Atherosclerosis due to CHIP-associated mutations are primarily mediated by inflammation. The presence of CHIP-associated mutations in macrophages stimulates inflammation and changes the levels of inflammatory factors. Moreover, persistent chronic inflammatory state positively feeds back into somatic mutations leading to increased CHIP-associated mutations, promoting the development and progression of atherosclerosis (25–28). This finding also explains the role of CHIP in patients with valvular lesions, where the presence of CHIP has been shown to accelerate valve sclerosis in patients with aortic stenosis and often leads to a poor prognosis, and CHIP increases mortality even after aortic valve replacement (29, 30). Besides, 2021 Pascual et al. (31) observed that CHIP was common in patients with reduced left ventricular ejection fraction (LVEF) and was highly associated with accelerated heart failure progression regardless of etiology.

Multiple Strike Theory

Multiple strike theory (**Figure 1**) is critical in the pathogenesis of cancer and CVD; the more the risk factors, the higher the incidence of disease. Children and adolescents with cancer have a good prognosis after antitumor therapy, while poor prognosis with cardiovascular side effects when the heart is stressed by pregnancy, hypertension, diabetes and hyperthyroidism (3).

First, tumors are associated with the pathogenesis of CVD, including the induction of exogenous factors, such as adverse lifestyle and endogenous factors, namely certain gene mutations, such as *TTNtv*, affecting the occurrence of DCM and CCM. Secondly, both anti-tumor therapy and treatment of CVD may further deteriorate cardiovascular function, cause tumor, and affect the prognosis. These common risk factors, genetic predisposition, therapeutic interventions, and the progressive involvement of certain diseases that stress the heart may contribute to the gradual development of cardiotoxicity during antitumor therapy.

COMMONLY USED DRUGS FOR PATIENTS WITH CARDIOVASCULAR DISEASE MAY AFFECT THE OCCURRENCE OF CANCER

Aspirin

Aspirin is widely used in the primary and secondary prevention of CVD due to its effects on platelet aggregation, atherosclerotic thrombosis, and embolization. Platelet activation prevents tumor cells from elimination by an immune response and promotes their retention in endothelial cells and growth of metastatic cells, as well as contributes to angiogenesis, thereby promoting metastasis (32). Therefore, aspirin can slow the metastatic spread of cancer cells by inhibiting platelet aggregation (33, 34).

During the past 3 decades, studies have shown that regular, low doses (75 to 300 mg) of aspirin reduce the risk of cancer in the general population, with a significant benefit (35). Since 1988, many studies have demonstrated the positive effect of aspirin on colorectal cancer (36, 37). Recent studies have shown that the risk of colorectal cancer is significantly reduced after using aspirin continuously for 5 years and that the protective effect persists at 20 years of follow-up, and a longer duration of aspirin use is related to higher protection (38, 39). Similarly, aspirin may reduce deaths from prostate, biliary, and liver cancers (40–42). However, studies have also suggested that aspirin may accelerate cancer progression in people over 70 years because of its bleeding risk (32, 43). Therefore, aspirin should be used carefully in population with high risk of bleeding, while long-term use is recommended for those at high risk of CVD.

Statins

Statins can reduce blood cholesterol levels by inhibiting the rate-limiting enzyme of the MVA metabolic pathway, namely HMG-CoA reductase (HMGCR), which can significantly reduce morbidity and mortality due to CVD. Meanwhile, statins also inhibit the transport of receptors on the surface of cell membranes, thereby reducing cancer cell growth, survival, migration, metastasis, inflammation, angiogenesis, promoting apoptosis, and having a protective effect on tumors. Statins may also have an anti-cancer effect by depleting cholesterol in certain situations. Lipophilic statins are more effective in inhibiting viral replication, enhancing therapeutic effectiveness, and passively entering the cell membrane, providing a more sustained and effective cholesterol-dependent anti-HCC effect (44, 45).

Previous studies have shown that statins use is associated with a 13–40% reduction in the incidence of cholangiocarcinoma (46, 47). In a large clinical case analysis, statins are associated with a 25% reduction in the risk of extrahepatic cholangiocarcinoma and improved survival for patients with distal cholangiocarcinoma. Moreover, the risk decreases with the duration of statin use (48). A previous study has suggested that statins may prevent cholangiocarcinoma, but due to the low incidence of cholangiocarcinoma, the association between statins and cholangiocarcinoma still needs to be further verified (49). A recent Swedish viral hepatitis cohort study reported a dose-dependent and time-dependent reduction in the risk of liver cancer, all-cause mortality and liver-related mortality in patients with viral hepatitis treated with lipophilic statins (50). Many studies have shown that statins are associated with a lower incidence of colon cancer. Statins also reduce the risk of progression from non-advanced adenomas to colon cancer, especially proximal lesions, and prevent colorectal cancer recurrence after treatment (51). Additionally, inhibition of the HMG-CoA reductase gene is associated with a lower incidence of epithelial ovarian cancer. However, the effect of statins on ovarian cancer has not been determined and needs to be

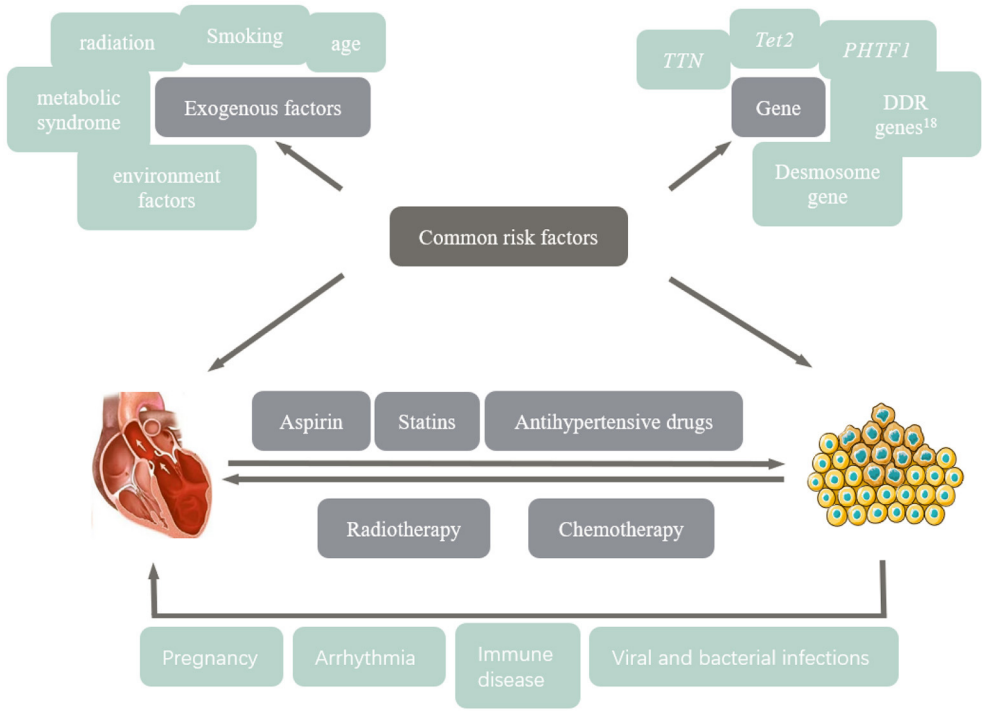

FIGURE 1 | The multiple blow theory is that anti-tumor therapy leads to cardiotoxicity.

further investigated (52). Furthermore, retrospective studies have shown that breast cancer patients receiving both statins and anthracyclines have a lower risk of heart failure than those who do not receive statins; however, the difference is not significant in breast cancer patients receiving trastuzumab (53).

Antihypertensive Drugs

According to statistics, about 37% of cancer patients have hypertension, and the active and effective control of blood pressure by antihypertensive drugs can prevent the occurrence of cardiovascular complications and improve the quality of life in cancer patients (54). At present, the widely using antihypertensive drugs include ACEIs, angiotensin-receptor antagonists (ARBs), β-blockers, calcium antagonists, diuretics, α-blockers and central sympatholytic drugs. The relationship between antihypertensive drugs and cancer has received widespread attention recently, and the interaction between several antihypertensive drugs and malignant tumors is still unclear. A 1,998 article published in The Lancet studied the patients who used blood pressure drugs for more than 3 years. Patients who used ACE inhibitors had the lowest relative risk of developing cancer, while patients who used calcium channel blockers (CCBs), diuretics, and beta-blockers, had no significant effect on cancer risk (55). In recent years, studies have shown that various antihypertensive drugs may be associated with cancer, while renin-angiotensin system inhibitors (RAS inhibitors) may have a more comprehensive protective effect (**Table 1**).

TABLE 1 | Impact of commonly used antihypertensive drugs on cancer risk.

Antihypertensive drugs	Effects on various cancers
Diuretics	Increase the risk of breast and skin cancer; may increase the incidence of urinary cancer
CCBs[a]	Increase the incidence of skin cancer and urinary system cancer
β2 receptor blocker	Reduce the incidence of lung cancer and digestive system tumors, and have different conclusions on the effects of head and neck squamous cell carcinoma, breast cancer, skin cancer and urinary system tumors.
ACEI/ARB[b]	Reduce the incidence of breast cancer, urinary tract cancer, and digestive tract cancer May increase the incidence of lung cancer, especially after using high dose ACEI (56).

[a] *CCBs, Calcium channel blockers;* [b] *ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor antagonists.*

Diuretics

Certain diuretics (such as thiazide diuretics), are considered photosensitive drugs and can increase the risk of skin cancer associated with ultraviolet (UV) light by damaging DNA (57). Thiazide diuretics are associated with insulin resistance, a recognized risk factor for breast cancer (58).

Two large studies from Denmark and Iceland have shown that hydrochlorothiazide is significantly associated with an increased risk of skin cancer, possibly in a dose-dependent relationship (59, 60). However, other studies have shown no significant

relationship between hydrochlorothiazide and the risk of skin cancer, which may be due to individual sensitivity to UV light, which led to different results (61). Since 1980, many studies have shown that diuretics are positively correlated with the risk of breast cancer. The incidence of breast cancer increases by 16% in using diuretics for more than 10 years, and the use of diuretics is highly correlated with the poor prognosis of breast cancer patients (62). A case-control study of hypertensive and non-hypertensive patients on antihypertensive drugs showed that methotrexate, thiazide, and loop diuretics increased the risk of renal cell carcinoma by 40%, with women at a higher risk than men (63, 64). However, high blood pressure itself can cause kidney damage, so more clinical studies are needed to confirm this statement.

Calcium Channel Blockers

To date, available data suggest that CCBs increase the tumors incidence by inhibiting apoptosis or interfering with cell differentiation through calcium triggering signals. Moreover, CCBs reduce intracellular calcium levels and impair the process of programmed cell death. The body is prevented from destroying damaged cells to prevent malignancy, leaving them to replicate when desired (65, 66).

A meta-analysis combining 11 related studies showed that long-term (>9 years) treatment with CCBs increased the incidence of malignancy (67). Rothschild's large population-based study and meta-analysis showed a slightly increased risk of lung and prostate cancer in calcium antagonist users, both in a time-dependent manner (68–70). CCBs were associated with a 1.6-fold increased risk of breast cancer in those who used CCBs for more than 2 years, especially invasive ductal carcinoma and invasive lobular carcinoma of the breast thant hose who had never used antihypertensive drugs (71, 72).

Beta-Receptor Blockers

In recent years, several studies have found that selective beta 2 blockers (β2 blockers) may reduce the recurrence and metastasis of cancer and thus increase overall survival in cancer patients. Selective beta 1 blockers have been shown to have no beneficial effect on cancer (73). Epinephrine and norepinephrine can induce tumor cell invasion and migration, thereby affecting lymph node invasion and metastasis, and this effect is mediated by the β-adrenergic pathway, especially the β2 receptors (74–77). Therefore, beta-blockers compete with epinephrine and norepinephrine for effective beta-adrenergic receptors to reduce the migratory activity of cancer cells and can also alter tumor growth, invasion, apoptosis, and angiogenesis to prevent tumor metastasis (78). Furthermore, the selective β2 receptor blocker propranolol can reduce the expression of the proliferative antigen Ki-67 and increase the phosphorylation of the tumor suppressor gene *P53* in early breast cancer, thus slowing down cell proliferation and inducing cell apoptosis, which has a positive effect on breast cancer pateints (79).

Barron suggested that women who took propranolol in the years before breast cancer diagnosis were significantly less likely to develop T4 tumors in a large population study, with positive lymph nodes (N2/N3), or metastases and significantly lower mortality rate than women who did not take propranolol. Besides, prolonged use of propranolol may reduce T4 tumorigenicity (73). Moreover, propranolol has a protective effect on head and neck cancer, stomach, colon, and prostate cancer, especially when used for more than 1,000 days (46). Inhibition of angiogenesis reduces bacterial translocation; thus, non-selective beta-blockers have been shown to reduce the incidence of liver cancer in patients with cirrhosis (80).

ACEI/ARB

RAS is well known for its control over the body's internal environment stability. Recently, there have been many studies reported RAS involvement in the complex carcinogenic mechanism. It is associated with proliferation signaling, resistance to cell death, induction of angiogenesis, energy metabolism reprogramming, inflammation, cell migration, invasion, and metastasis, thereby promoting vascular endothelial growth factor-mediated angiogenesis in malignant tumors and increasing proliferation of malignant tumor cells (81, 82). Therefore, using drugs that inhibit the RAS (mainly ACEI and ARB) can slow the rate of tumor growth. Furthermore, the risk of most cancers also decreases by using for long time (83).

A recent retrospective study of 73,170 patients with breast cancer patients using ARB improved patient's survival rate and reduced mortality. Patients who used other antihypertensive drugs also had reduced mortality, but cannot rule out it is due to blood pressure control or have positive effects on cancer (84). Similarly, compared with other antihypertensive drugs, patients on ACEI have a lower incidence of prostate cancer; hence, ACEI may improve their survival rate (85, 86). RAS inhibitors slow the progression of gastrointestinal cancer. Using ACEI over 3 years was associated with a 29% reduction in the risk of esophageal adenocarcinoma, and high daily doses were associated with a 45% risk reduction (87). RAS inhibitors have been linked to a protective effect against pancreatic cancer, with a 39% risk reduction after 1–3 years of use, but no significant effect on long-term use (88). A case-control study of patients with hypertension suggested that RAS inhibitors reduced the incidence of colon cancer, with long-term use decreasing the risk by 16 and a 25% reduction after 5 years of use. The greater the dose, the more significant the positive effect (89). The dose of ACEI is inversely proportional to the size of adenomatous polyps.

However, ACEI increases the incidence of lung cancer in patients with hypertension. The existing research points out that bradykinin (BK, a 9-peptide substance with cardioprotective effects) was found in lung cancer tissue and substance P. Many tumor cells expressed higher levels of BK and the related receptors that directly release vascular endothelial growth factor that stimulate the growth of cancer cells and angiogenesis, leading to increased risk of lung cancer. Additionally, ACEI promotes the buildup of these two chemicals in the lungs (90, 91).

Hicks et al. (92) in 2018 conducted a study, which included more than 90,000 patients with hypertension, was followed for 13 years to compare ACEI use and lung cancer incidence. This study confirmed that ACEIs could lead to an increased incidence of lung cancer. Lin et al. (93) further compared lung cancer incidence in hypertensive patients using ACEIs vs. ARBs and

found that lung cancer incidence was significantly higher in patients using ACEIs than in those using ARBs. Moreover, they found that the higher the dose and longer the duration of ACEI use, the higher the incidence of lung cancer. Kumar et al. (94) and Hsu et al. (95) subsequent studies support this view. There are different conclusions, a 2021 study by Lee et al. (96) concluded that there was no significant difference in the effect of ACEI and ARB on lung cancer. Similarly, a meta-analysis, enrolled 13 observational studies with 458,686 ACEI users, conducted by Batais et al. (97) suggested that ACEIs were not associated with an increased risk of lung cancer. Although most studies reported a negative effect of ACEIs on lung cancer, more prospective studies are needed to confirm the effect of antihypertensive drugs on cancer incidence and progression.

Different cancer stages or different types of cancer have different responses to RAS blockers. As the only antihypertensive drugs that have definite effects on cancer, RAS blockers should be used carefully in clinical practice to achieve treatment optimization.

Other Drugs

A retrospective study suggested that in patients with atrial fibrillation (AF), oral anticoagulants, gastrointestinal bleeding, urogenital bleeding, and bronchopulmonary bleeding often increased the risk of cancer, and there is a strong correlation with the severity of bleeding. It is worth mentioning that this new cancer is often detected within 6 months after bleeding, but this may be related to more frequent follow-ups. In any case, patients with AF receiving oral anticoagulants should be alert to the occurrence of cancer once they have bleeding in the above-mentioned organs (98).

EARLY-ONSET AND HIGH-INCIDENCE CARDIOVASCULAR RISKS OF CANCER PATIENTS AND THEIR MANAGEMENT STRATEGIES

Cancer Treatment Is Prone to Cardiovascular Disease

Cardiotoxicity due to antineoplastic therapy is induced by multiple factors, mainly including oxidative stress (99) [OS; including mitochondrial functional impairment (100), myocardial apoptosis (101, 102)], microtubule dysfunction (103, 104), and disruption of myocardial immune homeostasis (105, 106).

OS refers to an imbalance in the body's oxidative and antioxidant systems that tend toward oxidation, causing abnormalities in the body's biochemical and physiological processes and damaging endothelial tissue (107). Oxidants of oxidative stress refer to reactive oxygen species (ROS) or nitrogen substances (RNS) as well as free radicals. The direct effects of both inflammation and ROS are mediated by the activation of macrophages in the arterial wall (108). Neutrophils and monocytes/macrophages are the main sources of ROS, and oxidative stress increases the production of chemokines (MCP-1, CSF-1) and adhesion molecules (ICAM-1), tending to shift the redox balance toward a peroxidized state by promoting the aggregation of these cells (109). Since the heart has a weak antioxidant capacity (102), high concentrations of ROS predispose cardiomyocytes to mitochondrial damage and lipid peroxidation, affecting myocardial function. High oxidative status in elderly patients could explain the high incidence of cancer in elderly patients; therefore, chronic inflammation and oxidative stress should also be considered risk factors for cancer in the elderly (110). Drugs that mediate cardiotoxicity through oxidative stress are mainly anthracyclines and anti-epidermal growth factor receptor 2 (ErbB2) drugs, which increase the production of ROS and RNS, inhibit oxidative phosphorylation (111), lead to mitochondrial damage in cardiomyocytes (110), and ultimately result in irreversible myocardial damage. Mitochondria are important target tissues, and patients receiving tyrosine kinase inhibitors (TKI) can also suffer from cardiac complications due to impaired mitochondrial function that lead to cell death (106). Paclitaxel alters the process of cell division by affecting microtubule function, and it also affects the level of histamine in the body and stimulates the development of cardiotoxicity (106). Notably, immune checkpoint inhibitors (e.g., PD-1) mainly affect immune regulation, i.e., they influence T-cell effector function by inhibiting T-cell downstream signaling and hinder the immune organ from fighting against cancer cells (112, 113). Therefore, immune checkpoint inhibitors have been used in solid and hematological cancers to enhance the immune system's potential to fight cancer cells (114). Although existing studies suggest that immune checkpoint inhibitors are less likely to be cardiotoxic, immunotherapy may cause life-threatening events in patients (cardiac arrest, fulminant myocarditis, shock) by disrupting immune homeostasis in the myocardium (115, 116).

Cardiac Dysfunction

In patients with antineoplastic therapy-induced congestive heart failure, a reduction in LVEF of more than 10% and <50% is diagnostic of cancer therapy-induced cardiac insufficiency (cancer therapy drug-associated cardiac insufficiency/CTRCD). CTRCD usually appears months to years after treatment and is reversible in 75% of patients after withdrawal; however, it may affect long-term prognosis in 25% of patients, especially in patients with left bundle branch block. Most of these patients have no obvious symptoms, left ventricular dysfunction was diagnosed in some patients, while only a small number of patients develop symptomatic heart failure (117).

The most common anti-cancer drug that causes heart failure is anthracycline, the main treatment drug for many lymphomas, soft tissue sarcomas, and breast cancer, causing about 43% of those at risk (118). The main mechanism is the irreversible damage of cardiomyocytes with a high density of mitochondria, which induces myocardial remodeling and leads to cardiomyopathy (119). This is followed by TKI and immunotherapy, but the damage to the heart muscle is temporary and reversible. Previous studies suggested that the targeted drug trastuzumab may also increase the risk of cardiomyopathy by four times, and that when combined with anthracyclines, the risk increases by seven times (120, 121).

Women receiving anthracyclines are less likely than men to have cardiac insufficiency secondary to chemotherapy (122). The mechanism of cardiac insufficiency caused by anthracyclines is mainly due to oxidative stress-mediated oxidative damage in cardiomyocytes and abnormal mitochondrial function (123), which is less reported in female individuals (122). Notably, the occurrence of cardiac insufficiency complications in pediatric cancer patients does not appear to be significantly correlated with gender, as pediatric and postmenopausal females are more likely to develop cardiac insufficiency from antineoplastic therapy, suggesting that estrogen modulates abnormal oxidative stress in cancer patients receiving anthracyclines (124, 125). Estrogen enhances myocardial resistance to ischemia/reperfusion injury, i.e., attenuates abnormal oxidative stress and apoptosis (126). Thus, estrogens are cardioprotective. Sex differences in cardiotoxicity are not only present in anthracycline treatment but also cardiotoxicity caused by paclitaxel and tyrosine kinase inhibitors. The cardiotoxicity produced by different drugs differed concerning age and gender (**Table 2**). Sex-related genes are also involved in regulating the development of chemotherapy-related cardiac insufficiency (139). However, there are few studies related to the effect of gender on the efficacy and complications of antitumor therapy, and more gender- and age-specific studies are needed in the future to clarify the effectiveness of antitumor therapy and provide more theoretical support for clinical use.

Coronary Artery Disease (Acute Vasospasm and Atherosclerosis)

With the increasing number of cancer survivors, vascular toxicity has become the second most widely concerned disease after cardiac toxicity. In addition to the high incidence of venous thromboembolism, arterial toxicity has also attracted attention due to the increase of cancer patients, the prolonged life span, and the continuous progress of cancer treatment. A case study of children's study points out that had not been treated for cancer patients with systemic inflammation and increased risk of atherosclerosis, and a diagnosis of age is smaller, the higher their risk of dying from heart disease, 2 years after another child study, points out that accepting radiotherapy or chemotherapy and survival over the age of 35 patients compared with a normal person five times the risk of myocardial infarction (AMI) (140, 141). However, the overall incidence of myocardial infarction is not high. Arterial thromboembolism is also common in pancreatic, gastric, and lung cancer patients, like venous thromboembolism. Among all patients with vascular complications, lung cancer patients have the highest mortality rate and colon cancer patients have the highest bleeding risk (142, 143). Patients with metastatic cancer complicated with acute myocardial infarction have a poor prognosis, and the cause of death is usually associated with hemorrhage and reinfarction (144).

Ischemic heart disease is critical cardiotoxicity in patients treated with 5-fluorouracil during antitumor therapy. Vascular endothelial growth factor inhibitors can cause coronary spasms and even acute myocardial infarction due to endotheliotropic and erosion of monolayer vascular endothelial cells (145, 146). Paclitaxel can cause acute coronary spasms and even myocardial infarction (147). In such patients, the ST segment elevation rapidly reduces after immediate administration of nitrates. Due to its endothelial toxicity, which is not easy to eliminate, cisplatin can also cause coronary artery diseases, and the toxicity increases with the increase of its dose (148). Existing findings show that radiation therapy can change vascular reactivity and vascular spasm and possible acute severe endothelial injury and acute myocardial infarction (MI). The prolonged radiation exposure time is proportional to the risk of myocardial infarction. Due to the cancer patients own existence of cardiovascular risk factors and the role of anti-cancer treatment, prolonged endothelial cells to rebuild (149, 150). Protecting the heart from radiation may significantly reduce the risk of coronary atherosclerotic heart disease (151).

Arrhythmias

Various arrhythmias may occur in cancer patients during anti-cancer treatment. Inflammatory infiltration of the heart may result in pericarditis or cardiomyopathy that involves the cardiac conduction system and results in the atrioventricular block, prolonged QT interval, and AF. Radiotherapy causes radiation injury and promotes myocardial fibrosis, resulting in an atrioventricular block and AF, but rarely causes ventricular arrhythmias (152), so it may become an alternative therapy for invasive ventricular ablation of ventricular arrhythmias. The arrhythmias induced by antitumor therapy may also be related to drug interactions, drug accumulation, and electrolyte disturbance. The common arrhythmias in cancer patients mainly include AF, prolonged QT interval, ventricular arrhythmias, and cardiac arrest (152).

In 1993, the first arrhythmia caused by antineoplastic therapy was proposed, about 30% of patients who used chemotherapy drug paclitaxel developed asymptomatic bradycardia (104). Later studies suggested that thalidomide, palazonib, sunitinib, and crizotinib may also cause bradycardia. About 72% of patients treated with the chemothermic arsenic trioxide extended their QT interval from baseline by more than 30 ms, with half of those exceeding 60 ms (153). Many targeted drugs cause prolongation of the QT interval (154, 155). Generally, the prolonged QT interval resolves gradually as the drugs are metabolized. However, if the upper limit is exceeded, antitumor drugs should be discontinued to avoid torsade de points ventricular tachycardia. AF is closely linked to cancer, and they share the same risk factors: obesity and inflammation. A study showed a 20% increase in the incidence of cancer within 1 year of AF onset. AF occurred as a cardiotoxic complication of antitumor therapy with anthracycline, ibrutinib, melphalan, and paclitaxel (156, 157).

Thrombotic Disease and Peripheral Vascular Disease

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is second only to disease progression as the leading cause of death in cancer patients. Pulmonary embolism occurred in half of untreated DVT patients. About one-third of untreated pulmonary embolism patients die, most of whom have recurrent thromboembolism (158, 159). Compared with normal people, the incidence of VTE

TABLE 2 | Differences in cardiotoxicity due to antineoplastic drugs.

Antiblastic drugs	Major symptoms	Age differences	Gender differences
Anthracyclines	Cardiac insufficiency	No age difference in the development of congestive heart failure (CHF) in metastatic breast cancer patients >40 years of age treated with adriamycin (127). Increased incidence of CHF in patients older than 65 years of age with breast or lung cancer treated with adriamycin compared to those younger than 65 years of age (128). Age >65 years in patients with hematologic tumors treated with adriamycin may be a risk factor for the development of HF (129).	Pediatric patients-greater cardiovascular risk in women (124, 125, 130). Adults-greater reduction of LVEF in men (131). Adult-High incidence of cardiogenic adverse events in men (132).
Tyrosine kinase inhibitors (TKI)	AF and hypertension (133)	Patients receiving TKI are more likely to experience cardiotoxicity as they get older (134).	Sunitinib-more is likely to develop cardiotoxicity in women (135). Other drugs in TKI, such as imatinib and sorafenib-no gender difference in cardiotoxicity (136).
Paclitaxel	Bradycardia and coronary artery spasm	-	Women are more sensitive to paclitaxel treatment and are less likely to experience cardiotoxicity (137).

Anthracyclines are the most prominent antineoplastic agents for inducing cardiotoxicity. Cardiotoxicity is age and gender-related, as well as being dose-dependent (128, 138).

in cancer patients is at least 4 times higher, and a higher risk of VTE often indicates a poor prognosis of the cancer patients. A previous study showed that cancer of the pancreas, bile duct, and liver is associated with a higher risk of VTE (160).

Cancer patients release pro-inflammatory factors and pro-coagulation active substances, thereby promoting the adhesion between blood cells and blood vessels, resulting in a high coagulation state. The main factors of cancer patients that predispose to VTE include the type of cancer, central venous catheter chemotherapy, radiotherapy, surgical treatment, and related drug side effects (161).

Others: Hypertension, Valvular Heart Disease, Pericardial Disease

Hypertension is closely related to the occurrence of tumors. High blood pressure and cancer have some common risk factors (age, active or passive smoking, diabetes, dyslipidemia, overweight or obesity, low physical activity, unhealthy diet) (162). Vascular endothelial growth factor (VEGF) possibly plays an important role in the pathogenesis of hypertension and tumor by stimulating angiogenesis (163, 164). Forty-one years after Judah Folkman (165) proposed that tumor growth depends on the formation of new blood vessels by secreting factors, hyperactive angiogenesis is now becoming a therapeutic target for cancer (166). However, given the common biological characteristics of tumors and hypertension, some anti-tumor drugs can increase the incidence of hypertension. At present, it is believed that the anti-tumor drugs that can cause hypertension mainly refer to VEGF signal inhibitors, with a 19–47% incidence of hypertension (167). VEGF signal inhibitors may lead to an imbalance between vasodilators and vasoconstrictors, loss of capillary microcirculation, and altered glomerular function, all of which contribute to hypertension (168, 169). Some scholars believe that hypertension may be related to the effectiveness of anti-cancer treatment. Tanaka et al. (170) found that the development of hypertension in the early stage of treatment is related to the anti-tumor effect and maybe a predictor of treatment effect.

Anti-tumor therapy-related valvular heart disease is mainly caused by radiotherapy, especially involving the left heart valve. The pathological manifestations were valve tip and leaflet thickening, calcification, and retraction. Similarly, radiotherapy over 2 years can lead to pericarditis in up to 20% of tumor patients, so it is recommended that radiotherapy doses of <10 Gy should be limited to patients without prior cardiac disease during radiotherapy for thoracic tumors (171).

Cardiac metabolic syndrome is a condition caused by various metabolic disorders that affect about one in four adults. Saxena et al. (172) proposed that cardiac metabolic syndrome is associated with various cancers, especially pancreatic and rectal cancer in females and prostate cancer in males.

Cancer and Cardiovascular Disease Prevention

Poor lifestyle is a common risk factor for CVD and cancer, while a low-risk lifestyle reduces the incidence of cancer, CVD and diabetes, as well as the mortality due to related diseases, and prolongs the life expectancy of healthy people. A low-risk lifestyle includes non-smoking, a BMI of 18.5–24.9 kg/m^2, moderate daily exercise ($\geq$30 min/day), moderate alcohol consumption (5–15g/day for women, 5–30g/day for men), and a high-quality diet (173). Moderate drinking may prevent CVD, but cancer risk is relatively increasing, so non-alcoholic drinkers are not recommended to start drinking to prevent CVD (173). Dietary supplements of omega-3 fatty acids or vitamin D to prevent cancer and CVD are also not recommended for the general population, as they may cause problems with existing health conditions (174).

Prior to cancer treatment, especially before using treatment measures known to have cardiovascular toxicity, patients should be screened for the risk of underlying CVD, diabetes,

and other related diseases through Electrocardiogram (ECG), echocardiography, biomarkers, and other tests. Heart rate variability (HRV) may predict cardiovascular complications in breast cancer (175). More elaborate screening tests for underlying diseases and comorbid conditions should be undertaken for patients with pre-existing CVD. For patients with tumors at high cardiovascular risk, close monitoring of relevant indicators is recommended and antitumor therapies with clear cardiovascular toxicity should be avoided.

Recommended Diagnostic Methods

Blood Pressure Monitoring and Electrocardiogram

The diagnostic criteria for hypertension in cancer patients are the same as those in the general population.

The diagnosis of arrhythmia and acute ST-segment elevation myocardial infarction in cancer survivors can be confirmed by paying close attention to the dynamic changes of ECG. For paroxysmal arrhythmia, a dynamic ECG is feasible to make a clear diagnosis. Aggressive electrophysiological tests can be used to diagnose suspected arrhythmias, but the necessity of these tests depends on the patient's general state and life expectancy (176).

Imaging Examination

Echocardiography is the first choice for cancer patients to monitor cardiac function (i.e., LVEF) and diagnose valvular heart disease. 3D echocardiography is recommended as the first choice so that the endocardial boundary can be seen more clearly (177). Cardiac magnetic resonance imaging (CMR) has become the clinical gold standard for measuring left ventricular volume and ejection fraction, followed by radionuclide ventricular angiography (RVG)/ multigate cardiac pool imaging (multigate acquisition, MUGA). An endomyocardial biopsy can determine the extent of myocardial injury in cancer patients, but due to its invasive nature, the diagnosis is usually confirmed by the patient's symptoms and imaging examination (178, 179).

Arterial and venous ultrasound of bilateral lower extremities is preferred for VTE diagnosis. Computed tomography pulmonary angiography (CTPA) is recommended to confirm PE after DVT is diagnosed. CTPA is the preferred imaging modality for diagnosing PE. When patients have symptoms highly suspicion of PE, such as dyspnea, chest pain, hemoptysis, and cough, accompanied by hypoxemia, along with DVT, as suggested by arterial and venous ultrasound of lower limbs, the CTPA should be performed timely to make a confirmed diagnosis. CTPA is contraindicated in patients with contrast hypersensitivity, renal insufficiency, hypotension, advanced heart failure, or unable to perform CT scanning due to complex comorbid conditions or difficulty lying flat (159).

Biomarker

Biomarkers play an important role in the prevention and diagnosis of CVD (**Table 3**). However, a single biomarker has certain limitations, and many factors can lead to abnormal results, so a definite diagnosis generally requires imaging findings and lab tests.

TABLE 3 | The significance of monitoring biomarkers in cancer patients.

	Clinical significance
NPs[a]	NPs can be used as an early biomarker for cardiac insufficiency caused by conventional chemotherapy. However, there is no clear evidence for the diagnosis of cardiac insufficiency caused by other antitumor therapies.
D-D[b]	Although a definite diagnosis of VTE[d] cannot be made, higher serum D-dimer levels in cancer patients may predict an increased risk of mortality due to cancer and coronary heart disease (180). Oikawa (181) recently proposed that D-D can be used as an important parameter to predict cardiac dysfunction in cancer patients, with a cut-off value of 1.65μg/ ml.
cTn[c]	In patients receiving trastuzumab or high-dose chemotherapy, increased cTn indicates abnormal heart function and poor prognosis.

[a]NPs mainly refer to BNP and NT-proBNP in the monitoring indicators of cardiac insufficiency, where BNP > 100 pg/ml indicates cardiac insufficiency, and NT-proBNP < 125 ng/L can be used as an exclusion criterion; [b]D-D, D-dimer; [c]cTn, cardiac troponin; [d]VTE, Venous thromboembolism.

Natriuretic Peptide

Nearly half of the patients with cardiac dysfunction are not accompanied by reduced LVEF, so when patients have overt dyspnea, but no history of myocardial infarction and signs of pulmonary edema, it is recommended to measure natriuretic peptide (NP): B-type natriuretic peptide (BNP) or N-terminal precursor B-type brain natriuretic peptide (NT-proBNP) level (182).

D-Dimer

D-dimer (D-D) is the first choice for VTE diagnosis in a normal population. However, given the higher pathophysiological coagulation tendency in cancer patients, increased plasma D-D level is generally found in cancer patients. Therefore, arterial and venous color Doppler of the bilateral lower extremity is considered the first choice for VTE diagnosis in cancer patients (183).

Cardiac Troponin

The diagnostic approach of coronary heart disease in cancer patients is the same as that in normal people. Cardiac injury markers include creatine kinase MB (CK-MB), myoglobin, and cardiac troponin (cTn); among them, cTn is considered more important. For early reinfarction in patients with MI, CK-MB is relatively more significant (184).

Coronary Angiography

In addition to the patient's symptoms and vital signs, coronary angiography is the gold standard for diagnosing coronary artery disease (CAD) and evaluating vascular status. Diagnosis of CAD can be challenging in cancer patients, and some of the anti-tumor drugs mentioned earlier can cause transient coronary spasms that mimic the symptoms of a heart attack.

For patients at low risk for CAD, CCTA can be considered. Indications for coronary angiography are that the patient is suitable for coronary revascularization and that acute coronary

TABLE 4 | Prevention and treatment of cancer patients with cardiovascular disease.

	Prevention and evaluation before cardiovascular complications	Treatment of cardiovascular complications in cancer patients	Clinical advice
Cardiac dysfunction	During the anti-tumor treatment, assessment should be conducted at least every 3 months, and monitoring should be conducted at least every 6 months for 2 years after the completion of treatment. For patients with pre-existing cardiac insufficiency, it is recommended to monitor once a month.	Beta-blockers and ACEI/ARB should be used as early as possible, while other conventional therapies, such as diuretics and cardiac, should be used as appropriate in conjunction with the patient's symptoms. For most patients with cardiotoxicity, especially patients with left bundle branch block and heart failure, cardiac resynchronization therapy may relieve symptoms and reverse ventricular remodeling. However, ventricular assist devices are generally not recommended.	For advanced heart failure, heart resynchronization therapy and heart transplantation may produce higher returns in addition to drug treatment.
Coronary artery disease	Prevention of arterial disease should start with endothelial health, including statins, angiotensin-converting enzyme inhibitors and active exercise (187). Aspirin can be used as the main preventive drug to reduce the occurrence of arterial embolism and the progression of atherosclerotic plaque.	It is recommended to evaluate the severity of the patient's arterial toxicity and then determine whether to continue anti-tumor therapy. The first choice for treating patients with vasospasm is vasodilators, such as nitrates and calcium channel antagonists. When cancer patients are combined with atherosclerosis, drug therapy is the basis. The treatment measures mainly include adequate control of blood pressure and blood sugar, anti-platelet aggregation and lowering blood lipids, stabilizing plaque, slowing down disease progression, and eliminating the cause of myocardial infarction. Combining anticoagulation and interventional therapy may bring longer survival time to cancer patients with myocardial infarction. Drug-eluting stents (DES) are recommended for patients undergoing coronary stent implantation (143).	Patients who have received coronary revascularization and have a good prognosis can be given cancer treatment based on the benefit of the patient, but aspirin, calcium channel blockers and long-acting nitrate drugs should be given 3 days before the drug, and the ECG should be monitored continuously, and once symptoms such as angina pectoris appear again, treatment should be stopped immediately.
Arrhythmia	Re-check the patient's electrolytes, thyroid function and renal function within 7–15 days after treatment and after each treatment plan change, and should be monitored monthly for the first 3 months of treatment. People taking the chemical arsenic trioxide should monitor their ECG at least weekly.	Beta-blockers (atenolol and metoprolol) are the drugs of choice for controlling ventricular rate to treat atrial fibrillation. Non-dihydropyridine-calcium channel blockers are also optional but must be used appropriately according to the patient's heart condition. Cardioversion can be considered, when necessary, but patients who use ibrutinib are more likely to relapse after cardioversion. At the same time, amiodarone and digoxinine interact with certain cancer treatment drugs and should be used with caution. For patients with symptomatic or reduced ejection fraction heart failure and atrial fibrillation, radiofrequency ablation is also a necessary option (152). The anticoagulation strategy for cancers with atrial fibrillation is still based on the CHA2D2-VASC score. However, anticoagulant therapy may not be effective in the hypercoagulable state of cancer. Low molecular weight heparin (LMWH) is the first choice for anticoagulation therapy, followed by oral anticoagulants (DOAC).	-
Thrombotic disease and peripheral vascular disease	The use of anticoagulants for primary prevention of cancer patients is generally not recommended, but patients undergoing major cancer surgery should receive prophylaxis at least 7 days before surgery (188). Patients with a Khorana score $\geq$ 3 or Khorana score $\geq$ 2 and a high risk of thrombosis can start primary preventive anticoagulation therapy.	All cancer patients with new or recurrent VTE require anticoagulation therapy, and it is recommended to continue anticoagulation therapy for at least 3–6 months. LMWH or edoxaban is the first anticoagulant choice, but there may be technical limitations or patient intolerance. Now you can use LMWH or the oral anticoagulant edoxaban for 5–10 days, and then use DOAC other than warfarin or edoxaban. If active cancer or recurrent VTE occurs under active treatment, systemic treatment should be continued (143). The inferior vena cava filter (IVC) is used for VTE patients with contraindications to anticoagulation, and clinically, it is also used for patients with active anticoagulation therapy but still relapsed VTE[a].	Before using IVC, the patient's willingness and life expectancy should be evaluated, and it is generally not the first choice for VTE cancer patients.

(Continued)

TABLE 4 | Continued

	Prevention and evaluation before cardiovascular complications	Treatment of cardiovascular complications in cancer patients	Clinical advice
Others: hypertension, valvular heart disease, pericardium disease	The 2018 ESC/European Society of Hypertension (ESH) Arterial Hypertension Management Guidelines recommend that blood pressure be monitored once a week during the first cycle of cancer treatment, and at least once every 2–3 weeks thereafter (189). Antihypertensive therapy helps maintain the treatment plan and reduce the risk of serious complications, including malignant hypertension and reversible posterior leukoencephalopathy.	Patients with hypertension (≥140/90 mmHg) or elevated diastolic blood pressure (≥20 mmHg) should receive ACE inhibitors, ARBs, calcium channel blockers, or combination therapy. The calcium channel blockers diltiazem and verapamil should be avoided. Since VEGF inhibitors may cause diarrhea and dehydration, electrolyte disturbances caused by diuretics may aggravate, diuretics should be used with caution (190). For moderate hypertension (systolic blood pressure > 160 mmHg, diastolic blood pressure BBB > 0 mmHg), anti-tumor therapy should be suspended and antihypertensive therapy should be given until the blood pressure returns to the pre-treatment level or below 150/100 mmHg, and the treatment can be resumed. Catheter valve implantation is recommended for valvular heart disease related to tumor treatment.	If hypertension is poorly controlled or a hypertensive crisis occurs after 1 month of treatment, anti-tumor angiogenesis drugs should be permanently discontinued. The blood pressure goal of cancer patients is <140/90 mmHg, and patients with diabetes or proteinuria can be reduced to <130/80 mmHg as appropriate.

[a]*For patients with venous thrombosis, LMWH is the first choice for anticoagulant drugs. DOAC becomes a secondary option due to the relatively high risk of major bleeding (191). Edoxaban is the preferred oral anticoagulant, but recent studies have shown that rivaroxaban may be the best choice (192). Patients with renal insufficiency should avoid LMWH and DOAC. It is recommended to use warfarin and monitor the INR during use.*

syndrome or angina is not adequately controlled by optimal medication (185).

Early Detection and Treatment of Cardiovascular Diseases in Cancer Patients

When the detection time and treatment time for complications of cardiac insufficiency in cancer patients are doubled, the chance of LVEF returning to normal will be reduced by 25% (186). Therefore, cardiovascular complications in cancer patients should be strengthened (**Table 4**). First, it should be clear whether the patient is a patient with a high risk of CVD such as hypertension, diabetes, smoking, alcohol consumption, hyperlipidemia, obesity, poor lifestyle and presence of a family history of heart disease, and a 12-lead ECG should be routinely checked before anti-tumor treatment. Blood pressure and myocardial enzymes and other indicators should be recorded. Given that the electrolyte imbalance, abnormal thyroid function, or renal function may cause arrhythmia (193), patients should be routinely checked before cardiovascular toxicity occurs, and changes in the patient's ECG and myocardial enzymes should be monitored during anti-tumor treatment. Some drugs for treating tumor comorbidities, such as antiemetics and psychotropic drugs, can prolong the DT interval. It should be clear whether the arrhythmia caused by antitumor therapy or the treatment of comorbid drugs is caused. In high-risk situations, it is recommended to switch to other drugs to treat comorbidities (186).

CONCLUSION

Cancer survivors face several risks, including cancer recurrence and cardiovascular events. Cardio-Oncology provides a multidisciplinary approach to the entire treatment process and guides effective treatment of cancer patients with cardiovascular complications. However, the relevant studies are in their preliminary stages with several limitations. The positive results obtained from many studies may vary with age, gender, race, marital status, stage of cancer, time of diagnosis and surgical intervention. Therefore, large-scale study results are needed for further confirmation. Secondly, there is still much room to explore the interaction between cardiovascular drugs and anti-tumor drugs as well the effect of genes on the mechanism of these drugs. Clinical studies are required to decide the proper timing of discontinuation and restart of antitumor therapy due to cardiovascular complications and provide alternative therapies if needed.

When patients with both CVD and cancer are encountered clinically, the proper treatment strategies should be followed by clinicians. Moreover, oncologists should be informed of cardiovascular complications of antitumor therapy and their prevention, diagnosis and treatment. Furthermore, cardiologists should be alert to the high incidence of tumors caused by certain cardiovascular drugs in high-risk patients. Similarly, it calls on society to enhance the awareness and attention of cancer and CVD and hopes that doctors from all departments can cooperate to promote the continuous development of this discipline.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

YiW: reviewed the literature and drafted this review. YoW, XH, and CL: reviewed the literature, gave critical comments, and revised the manuscript. JS, BA, and JZ: gave critical comments and revised the manuscript. XM and ZC: reviewed the literature, gave critical comments, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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