Temporal Trends of Cardiac Outcomes and Impact on Survival in Patients With Cancer

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To evaluate the temporal relations of cardiovascular disease in oncology patients referred to cardio-oncology and describe the impact of cardiovascular disease and cardiovascular risk factors on outcomes. All adult oncology patients referred to the cardio-oncology service at the Cleveland Clinic from January 2011 to June 2018 were included in the study. Comprehensive clinical information were collected. The impact on survival of temporal trends of cardiovascular disease in oncology patients were assessed with a Cox proportional hazards model and time-varying covariate adjustment for confounders. In total, 6,754 patients were included in the study (median age, 57 years; [interquartile range, 47 to 65 years]; 3,898 women [58%]; oncology history [60% - breast cancer, lymphoma, and leukemia]). Mortality and diagnosis of clinical cardiac disease peaked around the time of chemotherapy. 2,293 patients (34%) were diagnosed with a new cardiovascular risk factor after chemotherapy, over half of which were identified in the first year after cancer diagnosis. Patients with preexisting and post-chemotherapy cardiovascular disease had significantly worse outcomes than patients that did not develop any cardiovascular disease ($p < 0.0001$). The highest 1-year hazard ratios (HR) of post-chemotherapy cardiovascular disease were significantly associated with male (HR 1.81; 95% confidence interval 1.55 to 2.11; $p < 0.001$] and diabetes [HR 1.51; 95% confidence interval 1.26 to 1.81; $p < 0.001$]. In conclusion, patients referred to cardio-oncology, first diagnosis of cardiac events peaked around the time of chemotherapy. Those with preexisting or post-chemotherapy cardiovascular disease had worse survival. In addition to a high rate of cardiovascular risk factors at baseline, risk factor profile worsened over course of follow-up. **(Am J Cardiol 2020;137:118−124)**

The association between (CVD) and cancer is increasingly recognized.[1−8] Cardiovascular (CV) risk factors are more common in cancer survivors as compared with the general population.[9] In general, co-morbidity has been associated with worse survival in oncology patients.[10,11] Similarly, the nature and number of CV risk factors is adversely related with survival.[12,13] To date, there is limited published data regarding the frequency and temporal relations of clinical CV risk factors and cardiac outcomes to chemotherapy start date. A previous study that examined the impact on survival of new-onset CVD in oncology patients reported significantly worse longer−term (at 8years) mortality, but excluded those with preexisting CVD and those that died within 2 years of their cancer diagnosis [14]. This study aims to define the frequency and temporal relations of CVD with regard to chemotherapy start date in a large contemporaneous cohort of oncology patients referred to cardio-oncology and to describe the impact of preexisting CVD and CV risk factors on such outcomes.

Methods

All adult patients with cancer referred to the cardio-oncology service at the Cleveland Clinic from January 2011 to June 2018 were included. The study protocol was

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reviewed and approved by the Cleveland Clinic Institutional Review Board with waiver of patient informed consent. Patients or public were not directly involved in the design, conduct, reporting, or dissemination plans of our research.

The patient pool in this study represents oncology patients seen by oncology specialists at our institution underwent cancer therapeutics and referred for cardiology evaluation/testing based upon cardiac risk factor profile or cardiac co-morbidity. Patients at any point on the cancer continuum were indeed considered. Cancer types are detailed in Table 1. Patients with recurrent cancers or second cancers were not excluded but likely represent a small minority of patients. We are not aware of any patients lost to follow up due to insurance reasons. Our institution accepts Medicare and Medicaid patients in addition to those with private insurance and financial counselors are available to all patients to assist with coverage requirements. Comprehensive clinical information was collected using Cleveland Clinic electronic medical health record database (EPIC) by use of International Classification of Diseases (ICD 9/10) codes. Data was also cross-checked with the prospective Cleveland Clinic Tumor Registry which includes chemotherapy treatment details and mortality information. This registry has coordinators following up patients via phone call as per Ohio regulation and is updated annually.[15] Presence of traditional risk factors such as diabetes, hypertension, history of smoking, elevated body mass index (BMI), family history of heart disease, and hyperlipidemia were also collected also by use of ICD 9/10 codes. All ICD 9/10 codes were manually checked by looking at patient charts on EPIC for accuracy.

Table 1
Baseline patient characteristics

Characteristic	Total Cohort n = 6,754
Age of cancer diagnosis (years)	
Median (IQR)	57 (47−65)
Female	3,898 (58%)
Male	2,856 (42%)
White	5,762 (85%)
Black	703 (10%)
Unknown	109 (2%)
Multiracial/Multicultural	93 (1%)
Asian	75 (1%)
American Indian/Alaska Native	8 (<1%)
Native Hawaiian/Pacific Islander	4 (<1%)
Median body mass index (kg/m^2)	27
≥30	2,314 (34%)
25−29.9	2,091 (31%)
<25	2,349 (35%)
Hypertension	1,898 (28%)
Current/ previous smoker	3,380 (50%)
Hyperlipidemia	1,555 (23%)
Diabetes mellitus	698 (10%)
Cancer type	
Breast	1,999 (30%)
Lymphoma	1,246 (18%)
Leukemia	842 (12%)
Gastro-Intestinal	614 (9%)
Multiple myeloma	606 (9%)
Genito-Urinary	541 (8%)
Lung	280 (4%)
Myelodysplastic syndrome	190 (3%)
Sarcoma	168 (2%)
Other	144 (2%)
Head and Neck	124 (2%)
Chemotherapy type	
Anthracycline	2,768 (41%)
HER2 Neu inhibitor	914 (14%)
Kinase inhibitor	794 (12%)
Other	2,278 (34%)
Radiation	2,908 (43%)
Medications	
Aspirin	1,650 (24%)
ACE inhibitor/ ARB	1,729 (26%)
Beta blocker	3,272 (48%)
Statin	1,480 (22%)

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; IQR, inter-quartile range.

CVD end points (including diagnosis of heart failure [HF], HF admissions, myocardial infarction [MI], stroke, atrial fibrillation, coronary artery disease, all-cause mortality and in-patient cardiac death) were extracted based upon ICD 9/10 coding and verified manually in the clinical notes. HF with preserved ejection fraction was defined clinically as symptoms and signs of HF, a left ventricular ejection fraction ≥50 percent. Mortality information was also cross-checked with online obituary records where available. In-hospital deaths were adjudicated into cardiac versus non-cardiac death. "All CVD" includes first diagnosis of coronary artery disease, atrial fibrillation, HF, stroke and MI. Survival outcomes were analyzed at 1-year, 5-year, and long term follow up after starting chemotherapy.

Descriptive statistics were computed to summarize the data. Continuous non-normal variables were presented by medians with interquartile range, and categorical or ordinal variables were presented as number. Pearson chi − square tests were used for categorical variable comparisons and the Wilcoxon rank sum test were used for continuous and ordinal variable comparisons.

Unadjusted Kaplan-Meier survival curves were built to describe all-cause mortality after chemotherapy initiation 1-year, 5-year, and long-term separately in 3 different CVD associated subgroups, no CVD, pre-CVD, and post-CVD. The date of the last known follow-up was identified as the last date of observation for censored patients. The final date to adjudicate overall mortality follow-up was February 1, 2019. The log-rank test with the Benjamini & Hochberg adjustment was used for survival comparisons among 3 CVD associated subgroups.[16] Comparator age- and gender-matched survival curves for the general population were added to the survival graphs.[17]

Cox proportional hazards models were used to test associations between with multiple covariates and all-cause mortality after chemotherapy initiation 1-year, 5-year, and long-term respectively. Fixed covariates included age, gender, BMI, smoking, and family history. Time varying covariates included hypertension, hyperlipidemia, and diabetes. The adjusted effects of covariates with all-cause mortality were estimated with hazard ratios (and 95% confidence interval) and the Wald chi − square test was used to evaluate the covariates with statistically significant coefficients. Cox models were used to determine covariate-adjusted

survival probabilities. After this adjusted analysis, patients were stratified into 3 subgroups no CVD, pre-CVD, and post-CVD to compare each as a predictor of survival. The covariates dataset creation for time-varying regression were generated by "lifelines" packages on python 3.7 platform. All survival analyses were performed using the survival (v2.44-1.1) and survminer (v0.4.6) packages on R version 3.5.2 (R Foundation for Statistical Computing). The code written for and used in this study is available from the corresponding author upon reasonable request.

Results

Total 6,754 oncology patients referred to the cardio-oncology service at the Cleveland Clinic from January 2011 to June 2018 were analyzed. Table 1 details baseline patient characteristics for the total cohort relative to start of chemotherapy (time zero). Despite a relatively young cohort (median age was 57 (SD, 47 to 65 years), 5,144 patients (76%) had 1 or more of these risk factors at baseline; 2,767 patients (41%) had 2 or more, whereas 908 patients (13%) had preexisting CVD. Breast cancer, lymphoma, and leukemia consisted of 60% of cancers in the total cohort. Total cohort follow-up after chemotherapy start date was a median of 40 months (interquartile range, 19 to 83 months).

Temporal trends of CVD relative to start of chemotherapy are illustrated in Figure 1 and detailed in Table 2. Temporal trends of all CVD within 1 year of chemotherapy is shown in Supplemental Figure 1. 1,929 (29%) patients from the total cohort (n = 6,754) were diagnosed with CVD. 1,021 patients (15%) had first CVD diagnosis made post-chemotherapy, of which 425 patients (6%) within the first year. Six hundred and seventy eight patients (10%) had a diagnosis of HF at any time-point, mainly associated with HF with reduced ejection fraction, occurring post-chemotherapy, and treated in the outpatient setting. Of these 678 patients, only 87 (1%) had a hospital admission due to HF. 2,293 patients (34%) were diagnosed with a new CV risk factor after chemotherapy, over half of which were identified in the first year (see **Table 2**). CVD across cancer subtypes is included in Supplemental Table 1.

Post-chemotherapy mortality rates in the total cohort (all-cause death, in-hospital death and in-hospital cardiac death respectively) are illustrated in Figure 1b and detailed in Table 2. All mortality rates peaked around the time of starting chemotherapy. 2,391 patients (35%) died during the follow-up period, of which 731 patients (11%) died within the first year of starting chemotherapy.

Survival curves are illustrated in Figure 2 at 1-year, 5-years and long-term. Supplemental Figure 2 details breakdown of CVD groupings. The presence of CVD (either pre- or post-chemotherapy) was associated with significantly worse mortality at 1-year and 5-year after commencing chemotherapy compared with patients that never developed CVD, independent of CV risk factor adjustment ($p < 0.0001$). In general, post-chemotherapy CVD was associated with the worst adjusted survival at 1-year even when compared with those with preexisting CVD; this difference was not evident beyond 5-year.

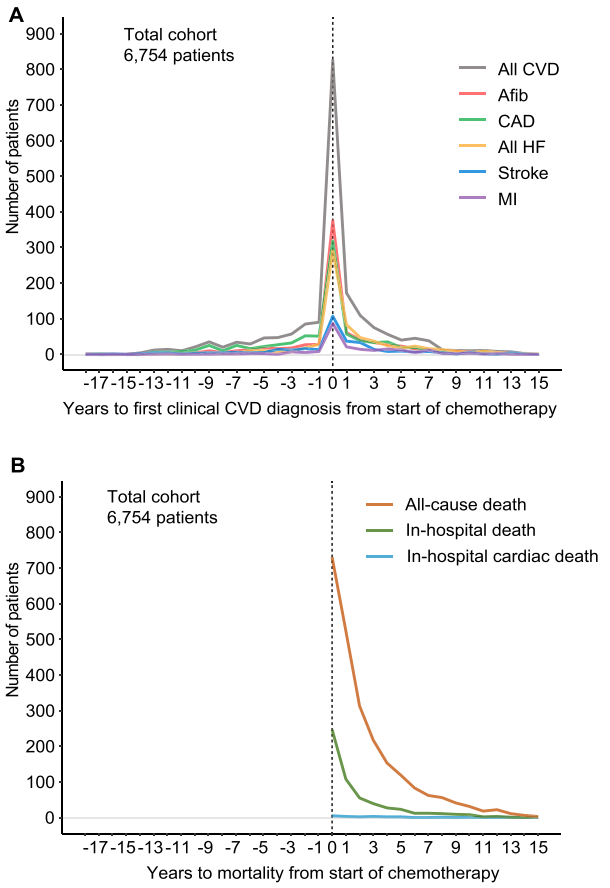

Figure 1. (***A***) **Title:** Temporal trends of clinical cardiovascular disease diagnoses from time of starting chemotherapy.
Caption: Graph illustrates time to first diagnosed clinical cardiovascular disease (CVD) relative to time of starting chemotherapy. Clinical CVD includes atrial fibrillation (Afib), coronary artery disease (CAD), all heart failure (HF), stroke and myocardial infarction (MI). All CVD includes Afib, CAD, all HF, stroke and MI.
Figure 1. (*B*) Title: Temporal trends of all-cause mortality from time of starting chemotherapy.
Caption: Mortality is sub-classified as all-cause death, in-hospital death and in-hospital cardiac death.

Hazard ratios (HR) of traditional CV risk factors all-cause mortality at 1-year, 5-year, and long-term post-chemotherapy are demonstrated in Figure 3. Amongst standard CV risk factors, the highest 1-year risk-adjusted hazard ratios (HR) of post-chemotherapy CVD were associated with male sex (HR 1.81; 95% confidence interval [CI] 1.55 to 2.11; $p < 0.001$), diabetes (HR 1.51; 95% CI 1.26 to 1.81; $p < 0.001$) and hypertension (HR 1.43; 95% CI 1.21 to 1.69; $p < 0.001$). The hazard ratio for post-chemotherapy CVD compared with those with preexisting CVD was significant at 1 year (HR 1.37; 95% CI 1.07 to 1.77; p=0.014); this difference was not evident beyond 5-year. Hazard ratio for post-chemotherapy CVD risk is illustrated in Supplemental Figure 3.

Around 1 in 8 patients had preexisting CVD (before chemotherapy) and these patients had a higher rate of another subsequent post-chemotherapy CVD and higher all-cause mortality ($p < 0.001$) compared with those without preexisting CVD as shown in Supplemental Table 2. Amongst

Table 2a
Rates of clinical cardiovascular disease (CVD) diagnoses and risk factors preexisting chemotherapy, post-chemotherapy and in the first year before and after chemotherapy

Total Cohort (n = 6,754 (%))	Total Number of Patients	Preexisting Comorbidity (Any)	Preexisting Comorbidity (in 1 Year Prior to Chemotx)	Post chemotx Comorbidity (in 1 Year Post Chemotx)	Post chemotx Comorbidity (Any)
All CVD	1,929 (29%)	908 (13%)	401 (6%)	425 (6%)	1,021 (15%)
CAD	848 (13%)	461 (7%)	168 (2%)	157 (2%)	387 (6%)
Atrial fibrillation	783 (12%)	318 (5%)	156 (2%)	221 (3%)	465 (7%)
All HF	678 (10%)	189 (3%)	94 (1%)	204 (3%)	489 (7%)
HFrEF	462 (7%)	130 (2%)	65 (1%)	140 (2%)	332 (5%)
HF Admission	87 (1%)	16 (0.2%)	7 (0.1%)	27 (0.4%)	71 (1%)
Stroke	331 (5%)	134 (2%)	41 (1%)	67 (1%)	197 (3%)
MI	214 (3%)	62 (1%)	35 (1%)	54 (1%)	152 (2%)
Hypertension	3,403 (50%)	1,898 (28%)	805 (12%)	821 (12%)	1,505 (22%)
Hyperlipidemia	2,570 (38%)	1,555 (23%)	429 (6%)	370 (5%)	1,015 (15%)
Diabetes mellitus	1,333 (20%)	698 (10%)	341 (5%)	308 (5%)	635 (9%)

Caption: All CVD includes coronary artery disease (CAD), atrial fibrillation, all heart failure (HF), HF with reduced ejection fraction (HFrEF), HF admission, stroke and myocardial infarction (MI). Cardiovascular risk factors include hypertension, hyperlipidemia and diabetes mellitus. Abbreviations: Chemotx, chemotherapy.

post-chemotherapy CVD, atrial fibrillation, and MI carry the worst outcomes in terms of both all-cause mortality as shown in Supplemental Figure 4.

Discussion

First diagnosis of CVD events in patients referred to cardio-oncology peaked around the time of chemotherapy. In Figure 1, it appears that vast majority of events occurred at time zero - that is, at start of chemotherapy, but when time on the x-axis is spread out over months (Supplemental Figure 1), it can be seen that this increased event rate is normally distributed. The number of echocardiograms performed also dramatically peaked around this time which would account for some new diagnoses (Supplemental Figure 5). How much of this peak in CVD diagnosis reflected preexisting disease / latent disease discovered at the time of increased physician visits, investigations, and hospitalizations versus de novo disease in a susceptible, high risk population with a high burden of preexisting CV risk factors in the face of extensive testing and therapeutics (not limited to biopsy, staging, chemotherapy, radiotherapy, surgery, subsequent re-staging etc.) is unclear. Regardless, it does not take away from the central finding of this paper that there was high burden of manifest concomitant CVD peaking around the time of cancer treatment. We believe these data offer further justification for the burgeoning subspecialist discipline of cardio-oncology to support multidisciplinary management of oncology patients. The rapid rise in cardio-oncology clinics across the world may reflect a practical recognition of these trends.[18-21] Our data would suggest that the highest risk period was the first year post-chemotherapy where arguably focused optimal CV preventative and treatment strategies may provide the highest yield. Survival analyses demonstrated the precise extent to which concomitant CVD (either preexisting or post-chemotherapy) compounded the already reduced survival of oncology patients compared with age, gender-matched population. Similar previous work to our study also reported reduced overall survival in cancer survivors who develop CVD but included only those that had survived cancer by 1 to 2 years).[14,22] Our data supports and expands on the findings of that data especially given the early peak in CV event rate as seen in our study. How did type of post-chemotherapy CVD diagnosis affect survival? MI and AF carried the worst outcomes in terms of all-cause mortality, even worse than (any stage) HF. There is limited data regarding survival post MI in cancer patients, although it is recognized oncology patients that experience acute coronary syndrome were less likely to undergo percutaneous coronary intervention than those without.[23] AF in most cohorts is strongly prognostic echoing what we saw in our data.[24] How did timing of CVD diagnosis relative to chemotherapy start time affect survival? Those with preexisting CVD clearly had the worst initial outcomes but shortly after 6 months, the survival of those who suffered a post-chemotherapy CVD diagnosis (without preexisting CVD) became relatively worse. There may have been many underlying reasons as to why this happened. We hypothesize that the ability to cope with a new CVD diagnosis may be lower in patients with established cancer due to lack of pre-conditioning effect, increased frailty and a deficiency of "clinical reserve".[25-28] Male sex, diabetes and hypertension were the standard CV risk factors associated with the highest 1-year risk-adjusted HR of post-chemotherapy CVD. In contrast, as adjusted risk factors, family history, and hyperlipidemia were more favorable which we speculate may relate to better primary prevention and an apparent high rate of statin

Table 2b
Rates of mortality in the total cohort

Variable	Total Number of Patients (N = 6,754)	Within First Year Post Chemotx
All-cause mortality	2,391 (35%)	731 (11%)
In-hospital mortality	559 (8%)	247 (4%)
In-hospital cardiac mortality	19 (0.3%)	5 (0.07%)

Caption: Mortality is sub-classified as all-cause death, in-hospital death and in-hospital death.

Abbreviations: Chemotx, chemotherapy.

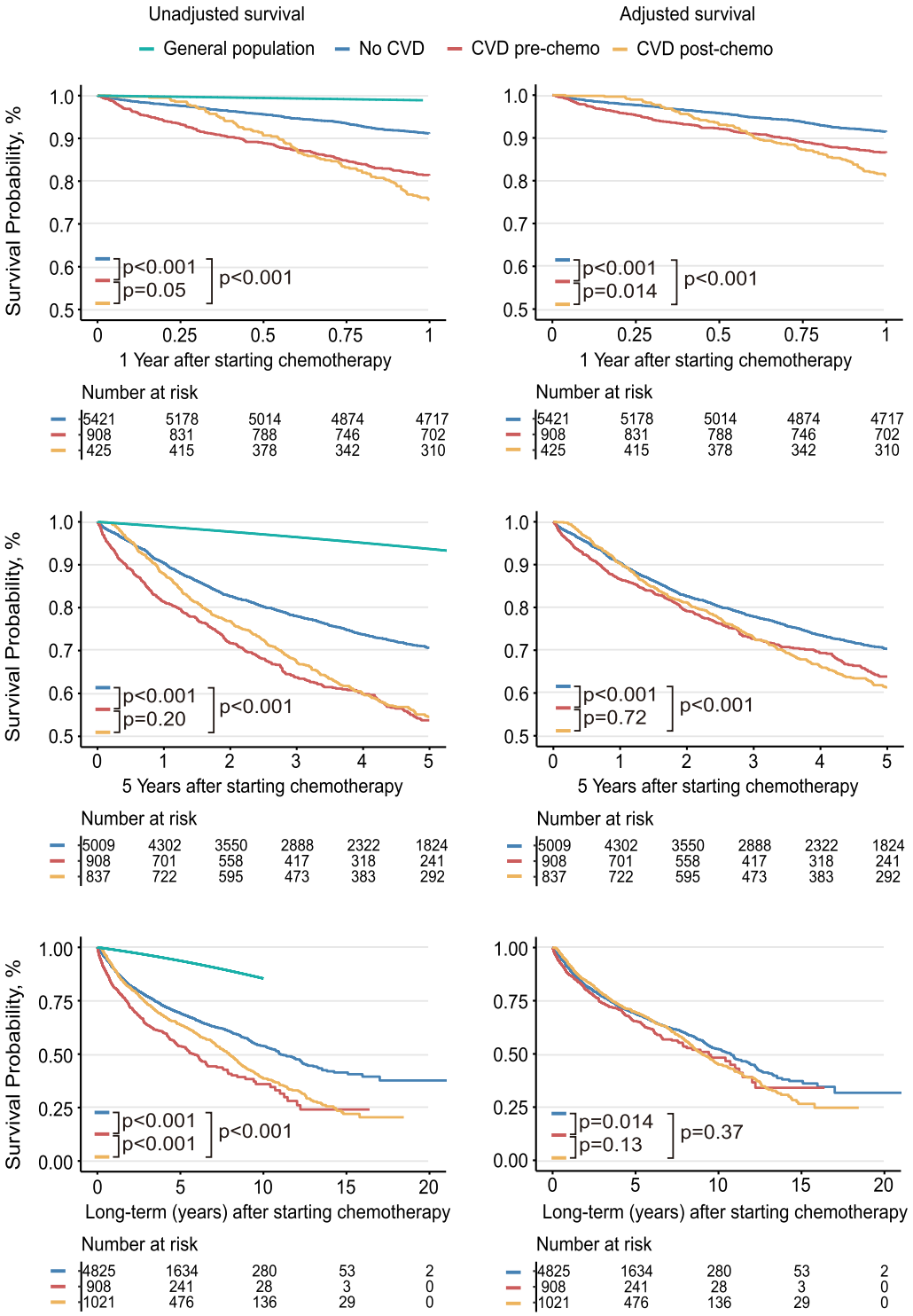

Figure 2. **Title:** 1-year, 5-years and long-term survival in patients without cardiovascular disease (CVD) "no-CVD"; patients with pre-existing "CVD pre-chemo"; and those that develop CVD post-chemotherapy "CVD post-chemo."
Caption: Time zero is chemotherapy start date. Unadjusted and adjusted survival graphs shown at 1-year, 5-year and long-term mortality. Adjustment made for CVD confounders include age, gender, hypertension, hyperlipidemia, diabetes mellitus, smoking status, body mass index and family history of heart disease. Age-matched and sex-matched survival of the general population is also shown.

use in these subgroups. Risk factor profile worsened over time. Over a third of the total cohort were subsequently diagnosed with a new CV risk factor. Rates of diabetes and hypertension nearly doubled. One might expect a population with cancer to experience a drop in average BMI during follow-up; however, over the course of this study, the BMI was relatively unchanged and actually rose slightly. These findings expose an unmet need for better

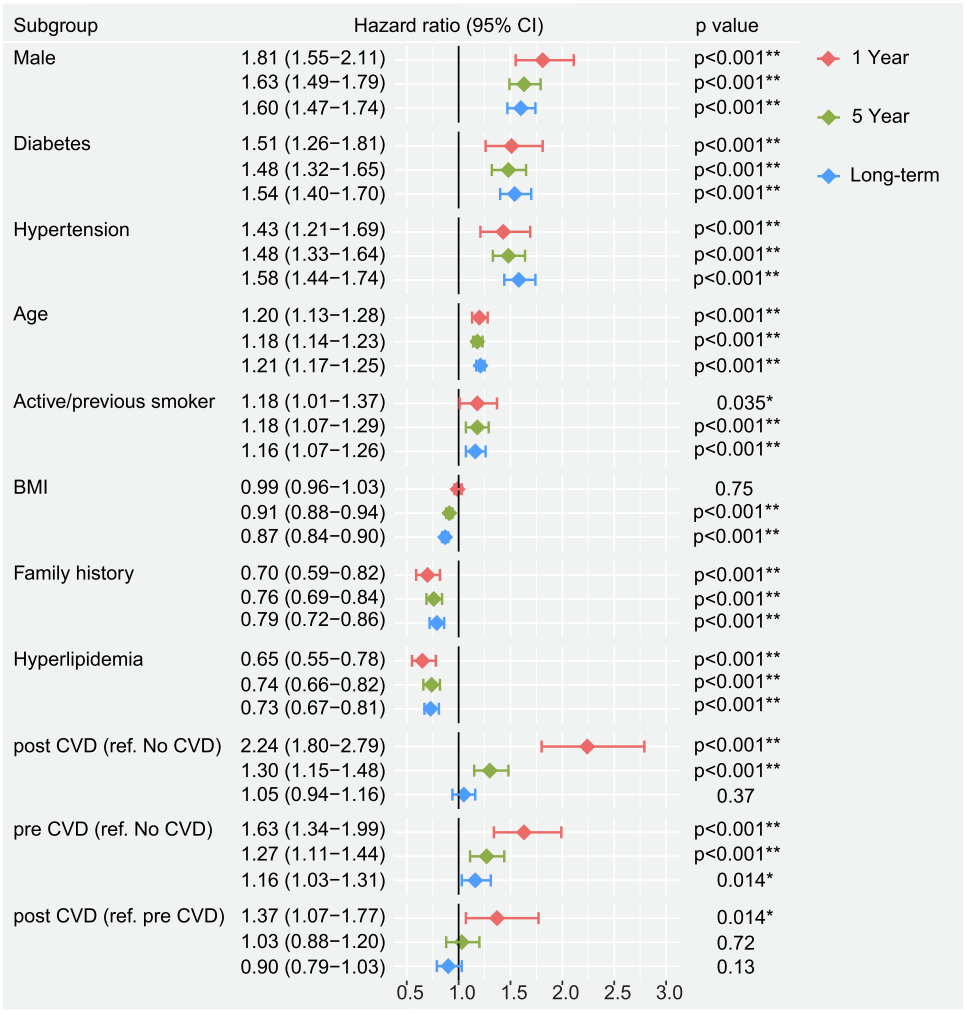

Figure 3. **Title:** 1-year, 5-years and long-term hazard ratios of all-cause mortality.
Caption: Time zero is chemotherapy start date. Forest plot of hazard ratios for all-cause mortality at 1-year, 5-years and long-term post-chemotherapy. CI - Confidence interval, BMI − body mass index, CVD − cardiovascular disease. *Denotes significant association ($p < 0.05$).

prevention in this population. It is likely that some of this exacerbation of risk factor profile was related to cancer treatment itself as many cancer chemotherapeutics have been shown to have adverse effects on both lipid metabolism and rates of hypertension.[29-31]

This is an observational study involving oncology patients referred to cardiology. Although this methodology introduces referral bias, the study population is reflective of practical real-world patients with a wide variety of cancers and treatment types seen by cardio-oncology. Data collection involved using electronic health records and ICD 9/10 coding; each event was verified by a physician via retrospective chart review. In order to try and minimize screening bias, definition of CVD was limited to clinically overt disease and the dates of all events were reviewed for accuracy. Change in CV risk factor profile during follow-up was mitigated for using time-varying covariate adjustment (smoking status change was not available). To minimize reporting bias, outcome data was manually crosschecked with clinical events. Mortality data was cross-referenced with an Intuitional Tumor Registry and obituary data. Socio-economic status, diet, exercise, impact of either chemotherapy, or medical therapy were not examined in this study. All-cause mortality was examined in this study which we felt was the least biased metric given the universal difficulty in acquiring accurate cause of death.[32] Despite competing risk of cancer-related death as a cause for death, there was no difference in rates of advanced staged disease (stage 4) between those with pre-existing CVD versus those without (staging data available in 52% of the cohort).

Amongst patients referred to cardio-oncology, first diagnosis of cardiac events peaked around the time of chemotherapy. Those with pre-existing or post-chemotherapy CV events had worse survival. In addition to a high rate of CV risk factors at baseline, this risk factor profile worsened over the course of follow-up. Focused preventative cardiology input is likely warranted for patients with cancer particularly around the time of and in the first year after chemotherapy.

Declarations

Conflicts of interest/ Competing interests: None

Ethics approval: Reviewed and approved by the Institutional Review Board with waiver of individual informed consent

Consent to participate: Yes

Consent for publication: Yes

Availability of data and material: Upon request

Code availability: Upon request

Authors contribution

1. Conception or design of the work- MH, YH, BH, SN, BG, FC, PC.

2. Data collection- MH, YH, BH, FC, PC.

3. Data analysis and interpretation- MH, YH, BH, FC, PC.

4. Drafting the article- MH, YH, BH, FC, PC.

5. Critical revision of the article- MH, YH, CW, RM, CS, JA, TB, WT, EF, KJ, JE, BX, BH, PCr, CJ, RG, NG, ZP, LC, MD, SN, SK, LS, BG, FC, PC.

6. Final approval of the version to be published- MH, YH, CW, RM, CS, JA, TB, WT, EF, KJ, JE, BX, BH, PCr, CJ, RG, NG, ZP, LC, MD, SN, SK, LS, BG, FC, PC.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.09.030.

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