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Impact of timing of atrial fibrillation, CHA_2DS_2-VASc score and cancer therapeutics on mortality in oncology patients

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ABSTRACT

Objectives To investigate timing and age distribution of atrial fibrillation (AF) in selected oncology patients, and the impact of AF timing, CHA_2DS_2-VASc score and cancer therapeutics on mortality.

Methods This is a retrospective cohort study of oncology patients referred to the cardio-oncology service from 2011 to 2018 for echocardiographic cardiosurveillance and/or pre-existing cardiovascular risk factor/disease management. Rates of first AF diagnosis was assessed using a parametric multiphase hazard model (predictive modelling) and non-parametrically by Kaplan-Meier with transformations tested using a bootstrap methodology.

Results Among 6754 patients identified, 174 patients had their first AF diagnosis *before* cancer while 609 patients had their first diagnosis of AF *after* cancer. Most first AF diagnosis occurred at/early after cancer diagnosis. Increasing AF prevalence at time of cancer diagnosis was seen across older age groups ranges. Diagnosis of cancer at an older age and exposure to cardiotoxic treatment (anthracyclines, HER2-neu inhibitors, tyrosine kinase inhibitors including ibrutinib and radiation) were associated with an increased risk of AF.

Modelling of the hazard function of AF identified a high left-skewed peak within 3 years after cancer diagnosis ('early phase'), followed by a gradual late slight rise 3 years after cancer diagnosis ('late phase'). AF diagnosis was only associated with death in the early phase ($p<0.001$), while CHA_2DS_2-VASc score was only associated with death in the late phase ($p<0.001$).

Conclusions This study reports a nuanced/complex relationship between AF and cancer. First diagnosis of AF in patients with cancer was more common at/early after cancer diagnosis, especially in older patients and those exposed to cardiotoxic treatment. Pre-existing AF or a diagnosis of AF within 3 years after cancer diagnosis carried a negative prognosis. CHA_2DS_2-VASc score did not relate to mortality in those that developed AF within 3 years of cancer diagnosis.

Key questions

What is already known about this subject?

- Atrial fibrillation (AF) is the most common arrhythmia in the world and is a major cause of morbidity and mortality.
- AF has been reported to be more common in patients with cancer compared with patients without cancer.

What does this study add?

- First diagnosis of AF was more common at/early after cancer diagnosis.
- Those at an older age and those with exposure to cardiotoxic treatment had a higher risk of AF.
- Pre-existing AF or a diagnosis of AF within 3 years of cancer diagnosis negatively impacted prognosis.
- CHA_2DS_2-VASc score was not associated with mortality in those that developed AF within 3 years of cancer diagnosis.

How might this impact on clinical practice?

- The increasing awareness of association of cancer and the complex relationship with cardiovascular disease, specifically AF, has led to the increased need for cardiovascular input in the oncological setting.
- Our results give more insight into the timing and age distribution of AF in oncology patients and the impact of AF timing, CHA_2DS_2-VASc score and cancer therapeutics on mortality.

INTRODUCTION

Cardio-oncology is an important and emerging field[1 2] and the association between various cardiac pathologies especially atrial fibrillation (AF) and cancer has been increasingly studied.[3–7]

In the general population, AF is a very common arrhythmia with a reported prevalence of 2% and a lifetime risk of

development of AF of one in four in those over the age of 40 years.[8 9] However, AF has been reported to be even more common in patients with cancer compared with patients with cancer.[10 11]

AF is a growing problem known to adversely affect mortality and to be associated with an increased risk of cardiac comorbidities.[12–14] An increase in the overall burden of AF in the general population in recent years has been reported (in terms of higher AF incidence and prevalence as well as mortality directly related to AF),[15 16] which may in part relate to our ageing population, and rising prevalence rates of cardiovascular risk factors. But such risk factors for AF and cardiovascular disease are also associated with an increased risk of cancer.[17] Unfortunately, to date, there are limited published data regarding the triumvirate of AF, cardiovascular disease and cancer.

This study investigated first diagnosis of AF relative to cancer diagnosis according to age and the associations between AF timing, CHA_2DS_2-VASc score, cancer therapeutics and mortality in selected oncology patients.

METHODS

Study design and population

All adult patients with cancer that attend the cardio-oncology service at our institution from January 2011 up to June 2018 were included. The study protocol was reviewed and approved by the Institutional Review Board with waiver of individual informed consent. Longitudinal clinical information was retrospectively collected using electronic medical health record database by use of International Classification of Diseases (ICD)-9/ICD-10 codes. AF, CHA_2DS_2-VASc score and all-cause mortality were extracted based on ICD-9/ICD-10 coding and verified manually in the clinical notes.

The reasons for referral to the cardio-oncology service were for echocardiographic cardiosurveillance ('baseline and serial evaluation for patients on therapy with cardiotoxic agents'), and/or for pre-existing cardiovascular risk factor/disease management.[18] All patients had baseline ECG and echocardiography performed. Follow-up cardiology studies were performed at the discretion of the cardio-oncology team. As per standard treatment protocols, patient's vitals were checked and history and physical were obtained at every chemotherapy visit.

AF was defined as first clinical diagnosis of AF, diagnosed clinically using electrocardiography or other heart rhythm monitoring formally reported by a staff cardiologist. AF screening method was determined in a number of ways including patient history, baseline ECG, history and physical at every chemotherapy visit; AF detection postchemotherapy relied on patient-reported symptoms together with history and physical during subsequent follow-up visits.

CHA_2DS_2-VASc score was calculated for each patient and was defined as one point for congestive heart failure, hypertension, age 65–74 years, diabetes mellitus, vascular disease and female sex, and two points for age >75 years and history of stroke, transient ischaemic attack or arterial thromboembolism.[19]

Details of cancer were collected and this included cancer diagnosis date, cancer type and stage of cancer. Cancer diagnosis date was considered as time zero. Stage of cancer at initial diagnosis was extracted from this registry which categorises stage based on the Facility Oncology Registry Data Standards 2016.[20] Mortality information was cross-checked with online obituary records where available.[21] Data were also cross-checked with the prospective institutional tumour registry which includes chemotherapy treatment details and mortality information. This registry has dedicated coordinators who follow-up patients via phone call as per state regulation and is updated annually.[20]

Statistical analyses

Descriptive statistics were computed to summarise the data. Continuous non-normal variables were presented by medians with IQR, and categorical or ordinal variables were presented as number (percentage). Pearson's χ^2 tests were used for categorical variable comparisons and the Wilcoxon rank-sum test were used for continuous and ordinal variable comparisons.

First diagnosis of AF for the entire cohort was assessed using a parametric multiphase hazard model[22] and non-parametrically by the Kaplan-Meier method. Patients who had AF diagnosed prior to cancer diagnosis were excluded from hazard analysis. To determine the relationship between age at cancer diagnosis and the risk for AF diagnosis following cancer diagnosis, age at cancer diagnosis was forced into the model. Various transformations were tested using a bootstrap methodology to find the most appropriate transformation.[10 23] Patients who had AF diagnosis the same day were flagged as having the diagnosis the day after cancer diagnosis. A parametric hazard function was modelled for death after cancer diagnosis and time-varying covariate adjustment was made for CHA_2DS_2-VASc score.

RESULTS

Study participants

A total of 6754 oncology patients referred to the cardio-oncology service from January 2011 up to June 2018 were analysed. Total cohort follow-up after cancer diagnosis was a median of 40 months (IQR, 17–75 months). One hundred seventy-four patients had their first AF diagnosis *before* cancer, while 609 patients had their first diagnosis of AF *after* cancer.

Table 1 details baseline patient characteristics for the total cohort (n=6754) relative to cancer diagnosis (time zero). Briefly, mean age was 56±14, 3898 (58%) were female, 5762 (85%) were white and mean body mass index was 28.3±7. Breast cancer, lymphoma and leukaemia comprised 60% of all cancer types in the total cohort. Stage at cancer diagnosis was available for

Table 1 Patient characteristics at baseline (at cancer diagnosis)

Characteristic	Total cohort N=**6754**
Age of cancer diagnosis (years)	
Mean (SD)	56 (14)
Gender (%)	
Female	3898 (58%)
Male	2856 (42%)
Race (%)	
White	5762 (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%)
Mean body mass index (kg/m^2) (SD)	28.3 (6.84)
Cancer type (%)	
Breast	1999 (30%)
Lymphoma	1246 (18%)
Leukaemia	841 (12%)
Gastrointestinal	614 (9%)
Multiple myeloma	605 (9%)
Genitourinary	541 (8%)
Lung	280 (4%)
Myelodysplastic syndrome	190 (3%)
Sarcoma	168 (2%)
Other	149 (2%)
Head and neck	121 (2%)
Stage at cancer diagnosis*	
In situ	50 (1%)*
1	808 (23%)*
2	1086 (31%)*
3	797 (22%)*
4	802 (23%)*
CHA_2DS_2-VASc (%)	
0	1726 (26%)
1	3161 (47%)
2	1119 (17%)
3+	748 (11%)

*Percentages represent percentage of patients that had stage at cancer diagnosis information available (3543 (52%) of the total cohort).
†Due to the predictive modelling described in this study, atrial fibrillation versus non-atrial fibrillation groups cannot be characterised due to the time-varying covariate nature of this variable.

3543 (52%). CHA_2DS_2-VASc scores were 0 in 1726 (26%) patients, 1 in 3161 (47%) patients, 2 in 1119 (17%) patients, 3 in 495 (7%) patients, 4 in 177 (3%) patients, 5 in 58 (1%) patients, 6 in 14 (<1%) patients, 7 in 3 (<1%) patients and 8 in 1 (<1%) patient. Due to the predictive modelling described in this study, AF versus non-AF groups cannot be characterised numerically due to the time-varying covariate nature of this variable.

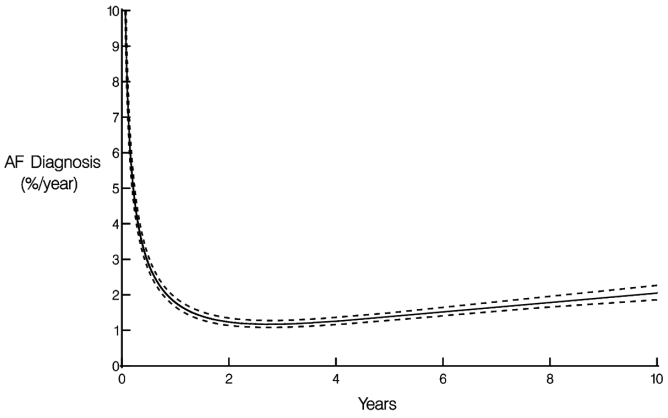


Figure 1 Rate of atrial fibrillation (AF) diagnosed per year after cancer diagnosis. Solid line represents parametric estimates within a CI band (equivalent to 1 SD).

Primary and key secondary outcomes

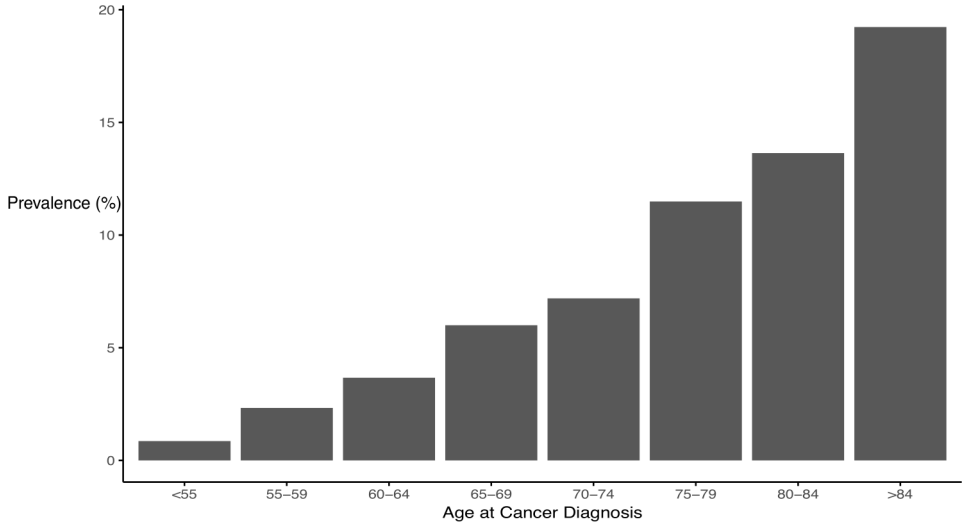
The instantaneous risk of new AF after cancer diagnosis is demonstrated in figure 1, which shows that most first AF diagnosis occurred at/early after cancer diagnosis. Figure 2 shows increasing prevalence of AF at time of cancer diagnosis across older age groups ranges. Patients diagnosed with cancer at an older age had a higher risk of AF compared with those diagnosed with cancer at a younger age as shown in figure 3.

The parametric hazard function modelled for death after cancer diagnosis with adjustment for AF as a time-varying covariate was plotted and broken down into phases (figure 4A). The final model combined an early phase (within 3 years after cancer diagnosis) and a late phase (3 years after cancer diagnosis) (figure 4B).

Modelling revealed that a diagnosis of AF at or within 3 years after cancer diagnosis was associated with death (p<0.001), but no association with death in those diagnosed with AF after 3 years (table 2).

After adjusting for CHA_2DS_2-VASc score, the model showed no association of CHA_2DS_2-VASc with death when AF was diagnosed at or within 3 years after cancer diagnosis; however, CHA_2DS_2-VASc score was associated with death in those diagnosed with AF after 3 years (0.19±0.053, p<0.001) (table 3).

We also analysed our data on treatment type in relation to incidence of AF. Because cancer therapeutics start date varied from time zero (date of cancer diagnosis), we analysed cardiotoxic cancer therapeutics (anthracyclines, HER2-neu inhibitors, tyrosine kinase inhibitors including ibrutinib and radiation) versus 'non-cardiotoxic' cancer therapeutics (all others) as a time-varying covariate using parametric hazard function modelling. Results are outlined in table 4. The model revealed that in the early phase (within 3 years after cancer diagnosis), timing of first cardiotoxic cancer therapeutics was associated with a



Age Group	<55	55-59	60-64	65-69	70-74	75-79	80-84	>84
Number of patients	2916	1074	1063	867	459	235	88	52

Figure 2 Prevalence of atrial fibrillation at cancer diagnosis, stratified by age at cancer diagnosis.

significant increase in AF diagnosis. The time component and yes/no component are parent-child variable (patients only have a time if they experienced the relevant class of cancer therapeutics although the effect alone of the cancer therapeutic is not significant when you consider the timing of it as well). Within the early phase, the later the time of the cardiotoxic cancer therapeutic, the higher the risk of AF. In contrast, in the late phase (at least 3 years after cancer diagnosis), commencement of either cardiotoxic versus non-cardiotoxic cancer therapeutics were not associated with incidence of AF diagnosis.

In summary, exposure to cardiotoxic cancer therapeutics was associated with an increased risk of AF within 3 years after cancer diagnosis, especially when time to that exposure was delayed.

Having shown that pre-existing AF or AF occurring within 3 years of cancer diagnosis negatively impacted mortality, figure 5 was derived to illustrate the modelled association of predicted survival following cancer diagnosis for the following arbitrary groups of patients: (A) those with no AF, (B) those diagnosed with AF 3 years after cancer diagnosis, (C) those diagnosed with AF 1.5 years after cancer diagnosis and (D) those with pre-existing AF. Patient numbers are not included in this figure as this is a derived model of predicted survival rather than actual survival.

DISCUSSION

In this study, first diagnosis of AF in oncology patients was more common at/early after cancer diagnosis similar to a previous report of increased incidence of AF following cancer diagnosis.[10 24] For oncology patients, early after diagnosis is a time of increased physician visits, investigations and hospitalisations and for a susceptible, high-risk population with a high burden of pre-existing cardiovascular risk factors in the face of extensive testing and therapeutics (not limited to biopsy, staging, chemotherapy,

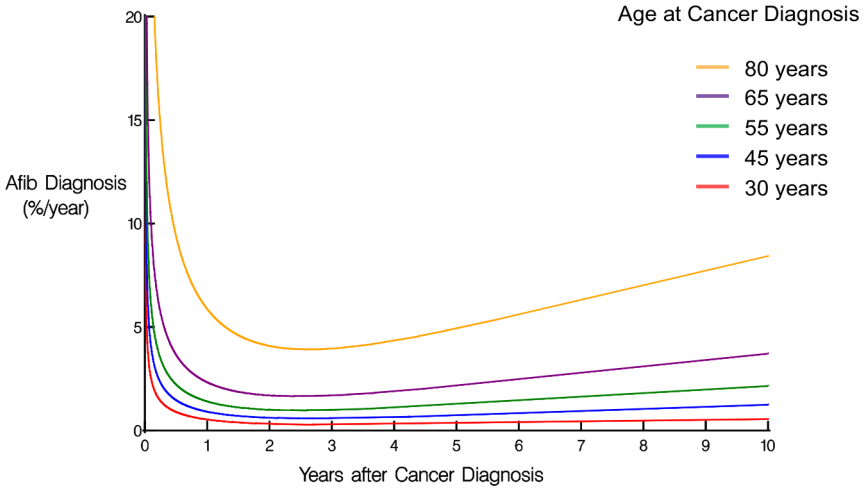


Figure 3 Rate of atrial fibrillation diagnosed per year after cancer diagnosis across age groups.

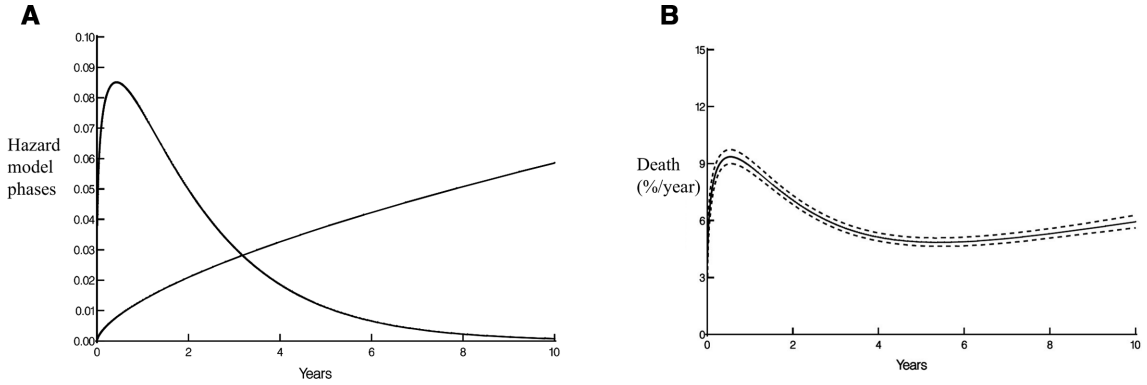


Figure 4 Predictive modelling: risk of death after atrial fibrillation (AF) diagnosis. (A) Hazard model breakdown into phases. An early peaking phase (<3 years) and a late rising phase (>3 years) can be seen. (B). Final hazard model after combining models in part A.

radiotherapy, surgery, subsequent restaging and so on), it is not surprising to see a high burden of manifest concomitant AF peaking around the time of cancer treatment especially in older patients.

This study also found that those with exposure to cardiotoxic cancer therapeutics was associated with an increased risk of early phase AF (within 3 years after cancer diagnosis), especially when time to that exposure was delayed. Cancer treatment has been shown to be associated with higher rates of AF, especially with the use of alkylating agents, tyrosine kinase inhibitors and HER2-neu receptor blockers.[25] Why those patients who had later exposure to cardiotoxic treatment had higher risk of AF may reflect selection bias (eg, they may be sicker patients, or those that had a treatment delay for adverse reasons, or those that had second-line cardiotoxic treatment after upfront non-cardiotoxic treatment, while it is possible that some treatments given later like radiation may be associated with higher AF risk).

AF has consistently been shown to carry a strong negative prognosis in the general population[26] and in multiple selected subpopulations such as those with heart failure[27] and in patients with cancer postoncological surgery.[28 29] This study found that pre-existing AF or AF occurring within 3 years of cancer diagnosis negatively impacted mortality (table 2, figure 4). Those that never developed AF had the best survival outcome (figure 5). Why AF development occurring after >3 years postcancer diagnosis was not associated with adverse prognosis may also reflect selection bias (such patients survived their cancer and did not develop early phase AF despite going through extensive testing and therapeutics as discussed above).

CHA_2DS_2-VASc score has previously been reported to be associated with mortality in oncology patients.[30] However, that study did not subanalyse timing of AF, an important finding of the current study, namely that CHA_2DS_2-VASc score was not associated with death in those diagnosed with AF within 3 years after cancer diagnosis. Given that neither the $CHADS_2$ nor the CHA_2DS_2-VASc score was specifically developed for patients with cancer, many authors have raised concerns that these risk stratification models may be inadequate in patients with cancer.[31] Our data would reflect this more nuanced view that there are other factors such as cancer type, stage, prognosis and bleeding risk that may confound such scores in patients with cancer in the early phase.

Table 2 Incremental risk factor for death after cancer diagnosis

Factor	Coefficient±SE	P value
Early phase/within 3 years after cancer diagnosis		
AF diagnosis	1.05±0.091	<0.001*
Time of AF diagnosis	0.59±0.024	<0.001*
Late phase/(at least) 3 years after cancer diagnosis		
AF diagnosis	0.08±0.260	0.76
Time of AF diagnosis	0.00±0.081	0.93

Time-varying covariate of AF diagnosis and time of AF diagnosis was forced into the model.
*p<0.05.
AF, atrial fibrillation.

Table 3 Incremental risk factor for death after cancer diagnosis: with adjustment for CHA_2DS_2-VASc score*

Factor	Coefficient±SE	P value
Early phase/within 3 years after cancer diagnosis		
AF diagnosis	1.10±0.095	<0.001*
Time of AF diagnosis	0.54±0.027	<0.001*
CHA_2DS_2-VASc score	−0.05±0.038	0.17
Late phase/(at least) 3 years after cancer diagnosis		
AF diagnosis	−0.07±0.256	0.79
Time of AF diagnosis	−0.05±0.071	0.51
CHA_2DS_2-VASc score	0.19±0.053	<0.001*

Time-varying covariate of AF diagnosis and time of AF diagnosis was forced into the model and adjusted for CHA_2DS_2-VASc score.
*Due to the predictive modelling described in this study, AF versus non-AF groups cannot be characterised numerically due to the time-varying covariate nature of this variable.
*p<0.05.
AF, atrial fibrillation.

Table 4 Incremental risk factor for AF diagnosis: cardiotoxic versus non-cardiotoxic cancer therapeutics

Factor	Coefficient±SE	P value
Early phase/within 3 years after cancer diagnosis		
Cardiotoxic cancer therapeutics	0.10±0.220	0.66
Time of first cardiotoxic cancer therapeutic	0.94±0.039	<0.001*
Non-cardiotoxic cancer therapeutics	0.14±0.220	0.51
Time of first non-cardiotoxic cancer therapeutic	0.03±0.051	0.59
Late phase/(at least) 3 years after cancer diagnosis		
Cardiotoxic cancer therapeutics	−0.21±0.250	0.40
Time of first cardiotoxic cancer therapeutic	−0.06±0.069	0.36
Non-cardiotoxic cancer therapeutics	0.44±0.340	0.19
Time of first non-cardiotoxic cancer therapeutic	0.06±0.049	0.27

Time-varying covariate of AF diagnosis and time of AF diagnosis was forced into the model and adjusted for cardiotoxic versus non-cardiotoxic cancer therapeutics. Because cancer therapeutics timing varies from time zero (date of cancer diagnosis), we analysed cardiotoxic versus non-cardiotoxic cancer therapeutics as a time-varying covariate using parametric hazard function modelling. Cardiotoxic cancer therapeutics included anthracyclines, HER2-neu inhibitors, tyrosine kinase inhibitors, targeted chemotherapy and radiation. Non-cardiotoxic chemotherapy included all other chemotherapy such as alkylating agents, antimetabolites and antimicrotubule inhibitors.
*p<0.05.
AF, atrial fibrillation.

In oncology patients, improved screening techniques and treatments have led to improved survivorship.[32] This paper adds weight to the importance of identifying AF in patients with cancer particularly for those who can tolerate anticoagulation therapy given their higher thrombotic risk. For symptomatic patients, the choice of duration of AF monitoring is generally determined by the frequency of symptoms (ie, for patients with active symptoms, an ECG may suffice; for those with daily symptoms, a 24-hour Holter monitor may suffice and so on). For asymptomatic patients, detection can be more difficult as sensitivity will likely vary according to the duration of monitoring (although this is a highly evolving field with the advent of devices/phone apps that allow patient self-monitoring).[33]

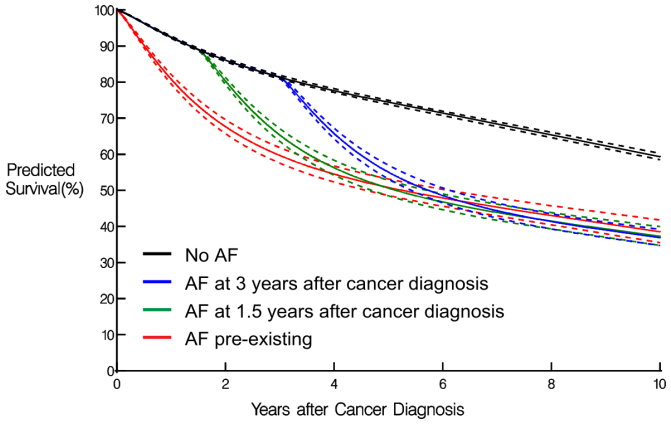


Figure 5 Association of survival following cancer diagnosis based on timing of atrial fibrillation (AF) diagnosis relative to cancer*. Solid line represents parametric estimates within a CI band (equivalent to 1 SD). *Due to the predictive modelling described in this study, AF versus non-AF groups cannot be characterised numerically due to the time-varying covariate nature of this variable.

Limitations

This is an observational study involving oncology patients referred to cardiology. While this methodology introduces selection or 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. Given that most first AF diagnosis was noted at/early after cancer diagnosis, this may partly relate to detection bias. This retrospective study used electronic health records and ICD-9/ICD-10 coding to collect patient information. In order to try and minimise reporting bias, cardiac outcomes data collected manually were crosschecked with clinical events to extract the most accurate, clinical information. Cancer stage, which may compete with AF with regard to risk of death, was not studied as stage of cancer at diagnosis data was only available for just over half of patients. Out-of-hospital cause of death was not attainable (in any case, such death certificates have high reported inaccuracy).[34] To limit reporting error, mortality information was cross-referenced with the institutional tumour registry and obituary data (which has been shown to be an established, reliable and valid method to collect mortality data).[21]

Conclusions

This study reports a nuanced/complex relationship between AF and cancer. First diagnosis of AF in patients with cancer was more common at/early after cancer diagnosis, especially in older patients and those exposed to cardiotoxic treatment. Pre-existing AF or a diagnosis of AF within 3 years after cancer diagnosis carried a negative prognosis. CHA_2DS_2-VASc score did not relate to mortality in those that developed AF within 3 years of cancer diagnosis.

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