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Research Article

In-Hospital Outcomes of Patients with Atrial Fibrillation and a Concurrent History of Radiotherapy

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ABSTRACT

Background: Atrial Fibrillation (AF) is the most common arrhythmia, with a prevalence of about 2.7 million to 6.1 million and is associated with a two-fold increase in mortality and major adverse cardiovascular events. Studies have shown relationships between AF, cancers and cancer therapies (radiotherapy, chemotherapy).

Objective: This study is focused on the in-hospital outcomes of patients with AF and a history of Radiotherapy (RT) for solid chest cancers.

Methods: This was a retrospective study done using the National In-patient Database (NIS). We identified patients who were admitted with atrial fibrillation and had a history of radiotherapy for a solid chest cancer (including breast and lung cancers), evaluated their associated socio-demographic and comorbid factors using ICD-10 codes. We utilized the chi-square test to compare baseline characteristics and multivariate logistic regression to identify outcomes.

Results: 2,294,144 with primary diagnoses of AF were identified, of which 5,465 also had concurrent history of radiotherapy for solid chest malignancies. We noted that the study population had significant smoking history and Charlson comorbidity index of ≥ 3. We observed significant mortality rates ((adjusted Odds Ratio) aOR 2.5, CI 1.7-3.57, p<0.001) and respiratory failure. We also noted CHF, dyslipidemia and history of RT as independent predictors of AF in patients with solid chest cancers. There were no significant differences in the mean length of stay but our studied population incurred lower hospital charges ($44,380 *vs.* $46,257).

Conclusion: A history of radiotherapy for solid chest malignancies is associated with worse outcomes in patients with AF.

Keywords: Radiotherapy; Atrial fibrillation; Outcomes; Cardiovascular disease; Mortality

Abbreviation: AF: Atrial Fibrillation; CCI: Charlson Comorbidity Index; CI: Confidence Interval; CKD: Chronic Kidney Disease; COPD: Chronic Obstructive Pulmonary Disease; LOS: Length of Stay; NSCLC: Non-Small Cell Lung Cancer; PCI: Percutaneous Coronary Intervention; RT: Radiotherapy; THC: Total Hospital Charge

INTRODUCTION

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia, it is an important contributor to patient morbidity and mortality [1]. The incidence and prevalence of atrial fibrillation are increasing globally. Based on data from the Framingham Heart Study (FHS), the prevalence of AF increased 3-fold over the last 50 years [2]. Atrial fibrillation is associated with increased mortality risk after adjusting for pre-existing cardiovascular conditions in which AF was related [3].

According to the national center for health statistics, cardiovascular disease and cancer are the first and second leading cause of death

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respectively in the United States in the year 2021.The incidence of cancer has increased globally, and radiotherapy demonstrates survival benefit in treatment of several malignancies including thoracic cancers. Radiation therapy destroys cancer by depositing high-energy radiation on the cancer tissues [4]. The cardiac effects of radiotherapy in the long term are heterogeneous and include coronary artery disease, valve disease; diseases of pericardium, myocardial diseases, with systolic and diastolic dysfunction in particular, and conduction system disturbances, including AF [5].

Although the exact prevalence of heart disease attributable to the effects of thoracic radiation is difficult to ascertain, studies have suggested that up to 10% patients may have significant valvular disease, whereas in 14%, stress-induced myocardial ischemia may occur [6]. Among the cardio-toxic effects of cancer and cancer therapy, cardiomyopathy and coronary artery disease have been well-studied, but the relationship between cancer and cardiac arrhythmias has been examined less [7]. Yet, due to the isolated nature of the above reports, and the lack of available comprehensive cardiac risk factor profiles in cancer survival focused RT clinical trials, the true risk or effects of AF events among thoracic RT treated patient's remains largely unknown.

We assessed the in-hospital outcomes of patients with atrial fibrillation and a history of radiotherapy for solid chest cancers and compared to AF patients without a history of radiotherapy. We also analyzed relationship between a history of radiation and advent AF.

MATERIALS AND METHODS

This retrospective study is reported after the Strengthening of the Reporting guidelines of Observational studies in Epidemiology (STROBE).

Study design and data source

This study examined the impact of chest radiotherapy on the in-hospital outcomes of patients admitted for Atrial Fibrillation (AF) from 2016-2020 using available discharge data from the National Inpatient Sample (NIS), Healthcare Cost and Utilization Project Database (HCUP) of the United States (US).

The NIS was created and maintained by the Agency for Healthcare Research and Quality and is the largest publicly available all-payer inpatient database in the United States of America (USA). It is designed as a stratified probability sample representing all community hospitals in the United States, excluding rehabilitation and long-term acute care hospitals. A systematic 20% probability sample of all hospitals within the hospital frame is collected. All discharges from these hospitals are recorded and then weighted to ensure they are nationally representative. Data from 47 state-wide data organizations (46 states plus the District of Columbia) encompassing more than 97% of the US population are included in the NIS 2020 sampling frame. As many as 40 discharge diagnoses for each hospitalization were recorded using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) in the NIS 2020 database. In the NIS, diagnoses are divided into principal and secondary. The principal/primary diagnosis was the main ICD-10 code for hospitalization. Secondary diagnoses were any ICD-10 code other than the principal diagnosis. Since all patient data in NIS are deidentified and publicly available, we waived the institutional review board approval.

Inclusion criteria and study variables

The study population consisted of all inpatient hospitalizations with a primary diagnosis of atrial fibrillation, recorded from 2016-2020. A discharge diagnosis of a history of radiotherapy for solid chest cancers (breast and lung cancer) was identified as a secondary diagnosis. Primary and secondary diagnoses were identified using ICD-10 codes recommended by the American Association of Cardiology and the American society of clinical oncology. The study population was further divided into 2 cohorts based on prior or no exposure to radiotherapy for solid chest cancers.

Demographic study variables that included age, gender, race, hospital characteristics, and medical comorbidities (computed from Charlson index comorbidities) were identified as variables already present in the data set (Table 1). Other covariates were identified using ICD 10 codes from previous published articles [5,7,8]. These ICD-10 codes were further confirmed from the American ICD10-CM (diagnosis) and ICD -10-PCS (procedure) medical billing website (Supplementary Table 1).

Table 1: Demographics of patients with AF and a history of RT for solid chest malignancies.

Variables	Patients with atrial fibrillation (%)		P-values
	Radiotherapy	No radiotherapy	
Patient characteristics	-	-	-
Age, years, mean ± SE	72.3 ± 0.29	70.5 ± 0.28	<0.0001
Sex	-	-	0.7414
Male	50.6	51.1	-
Female	49.45	48.95	-
Race	-	-	0.0008
White	83.66	81.71	-
Black	10.28	8.47	-
Hispanic	3.18	5.87	-
Asian	1.21	1.51	-
Native American	0.19	0.37	-
Comorbidities	-	-	-
Dyslipidemia	50.87	52.28	0.3522
History of MI	8.69	8.78	0.9197
CHF	31.11	40.06	<0.0001
CKD	15.74	19.2	0.0039
History of PCI	0.91	1.03	0.7054
History of CABG	6.5	7.47	0.2294
History of pacemaker placement	2.65	5.58	<0.0001
Carotid artery disease	2.01	1.36	0.0635
AKI	12.72	12.95	0.8159
History of stroke	0.55	0.57	0.9281
Hypertension	42.54	40.96	0.2819
Peripheral vascular disease	5.12	3.63	0.0082
Obesity	10.34	21.6	<0.0001
Smoking	53.61	29.11	<0.0001
Liver disease	2.84	3.42	0.2901
Electrolyte abnormalities	24.15	19.65	0.0002
Maintenance hemodialysis	0.64	2.22	0.0004
Oxygen dependence	12.44	3.53	<0.0001

Anemia	35.96	16.06	<0.0001
Diabetes	13.91	15.29	0.2095
Hospital teaching status	-	-	0.0448
Non-teaching	30.8	34.14	-
Teaching	69.2	65.86	-
Hospital location	-	-	0.0251
Rural	8.19	10.57	-
Urban	91.81	89.43	-
Charlson comorbidity index score	-	-	<0.0001
1	0.094	22.34	-
2	0.46	25.61	-
≥ 3	99.45	52.05	-

Outcomes

The primary outcome was to compare in-hospital mortality among AF patients with a history of heart radiotherapy exposure compared to patients without exposure. Secondary outcomes were rates of cardiac arrest, cardiogenic shock, cardioversion, ablation, respiratory failure, Length of Stay (LOS), and Total Hospital Cost (THC) among both subgroups of patients with AF. We also analyzed the independent predictors of AF in patients with prior history of solid chest cancer (Table 2).

Table 2: Independent predictors of atrial fibrillation in patients with solid chest malignancies.

Variables	Independent predictors of AF in patients with cancer	
	(aOR; CI)	P- values
CHF	2.64; 2.49-2.80	<0.001
Dyslipidemia	1.27; 1.21-1.34	<0.001
History of PCI	1.35; 1.05-1.72	<0.001
History of radiotherapy	1.13; 1.05-1.21	0.001

Statistical analysis

Data were analyzed using STATA, version 17 (Stata Corp, Texas, USA). Based on the descriptive analysis of our data, continuous variables were presented with mean standard deviation, and differences were tested using a T-test. Categorical variables were presented with numbers (percentages) and compared with the chi-square test.

Multivariate logistic and linear regression were used to analyze categorical and continuous outcomes (LOS and THC) respectively. A logistic regression model was built following a univariate screening of each outcome, with values less than 0.01 considered significant to be included as a covariate in our multivariate analysis. The final model had (age, gender, race, hospital location, Charlson comorbidity index, teaching status of admitting hospitals and cardiovascular comorbidities) as covariates for the multivariate analysis. The p-values considered significant in the multivariate analysis were two-sided, with <0.05 as the threshold for statistical significance.

RESULTS

Our study population comprised 2,294,144 with primary diagnoses of AF and of that, about 5,465 who also had concurrent history of radiotherapy for solid chest malignancies. The prevalence of AF in patients with a history of radiation for chest cancer was about 1.2%.

Our study population when compared to controls (population without history of radiotherapy for a solid chest malignancy) had a mean age of 72 years *vs.* 70 years (p<0.0001).

We noted that, in contrast to our controls, the study population had significant smoking history (53.6 *vs.* 29.1%, p<0.0001), Charlson comorbidity index of ≥ 3 (91% *vs.* 32.4%, p<0.0001), oxygen dependent (21% *vs.* 3.5%, p<0.0001), anemia (35.96% *vs.* 16.1%, p<0001) and electrolyte abnormalities (24.15% *vs.* 19.65%, p<0.001).

We observed CHF (aOR 2.64; 2.49-2.80, p<0.001), dyslipidemia (aOR 1.27; 1.21-1.34, p<0.001), history of PCI (aOR 1.35; 1.05-1.72, p<0.001) and a history of radiotherapy (aOR 1.13; 1.05-1.21, p=0.001) as independent predators of AF in patients with solid chest cancers.

We observed significant mortality rates (aOR 2.5, CI 1.7-3.57, p<0.001) and rates of respiratory failure (aOR 1.34, CI 1.08-1.66, p=0.007).

We also noted, as secondary outcomes; ablation (aOR 0.47, CI 0.31-0.71, p<0.001) and conversion to normal sinus rhythm (aOR 0.69, CI 0.56-0.85, p<0.001) in our population with AF and a history of radiotherapy for solid chest cancers. There were no significant differences in the mean length of stay (4.1 *vs.* 3.2, p=0.103) but our studied population incurred lower hospital charges (44,380 *vs.* 46,257, p<0.001).

DISCUSSION

This study analyzing the in-hospital outcomes of patients with AF and a history of RT showed higher rates of mortality, respiratory failure but a lower overall hospital cost incurred as compared to our controls. Our subanalysis observed CHF, dyslipidemia, history of PCI and Radiotherapy as independent predictors of AF in patients with solid chest cancers.

Atrial Fibrillation (AF) is the commonest arrhythmia seen among patients, and it is linked to an increased risk of death, stroke, and peripheral embolism. Studies put the global prevalence of AF at 33.5 million patients [8]. Cancer patients have been shown to have a higher risk of AF compared to the general population, with an estimated prevalence of about 20% [9].

This has been hinged on several common risk factors, such as smoking, obesity, and diabetes mellitus, consistent with our findings of a significant smoking history among the participants [10]. Smoking is known to propagate anatomical and physiologic changes of the heart resulting in susceptibility to atrial fibrillation [11]. Treatment of cancer remains a cardiovascular burden irrespective of what agents are used, be it chemotherapy or radiation therapy [12-14]. While the incidence of atrial fibrillation in patients undergoing chemotherapy remains more widely reported, by causing structural, electrical remodelling, inducing and maintaining inflammation and or causing cardiac damage and cellular apoptosis, studies have shown that radiation therapy especially to the left chest increases the risk of cardiac arrhythmia by causing myocardial fibrosis and autonomic dysfunction [15,16].

There are several postulates regarding the higher prevalence of AF in cancer patients with respect to the cancer or therapy received. These include inflammation during carcinogenesis, cardiotoxicity

caused by radiotherapy, and autonomic dysfunction in cancer patients that may lead to increased sympathetic nervous system function [7].

Literature addressing the link between radiation therapy and arrhythmias in cancer patients remains limited. A study done in China on 24,125 patients, 2.4% of patients had permanent, persistent AF at the time of cancer diagnosis and 1.8% developed new-onset AF during treatment for cancer. Of interest, cancer patients with AF had a two-times higher risk of thromboembolic events and six times higher risk of congestive heart failure, after adjusting for baseline cardiovascular risk factors [17]. Patients with cancer who received radiotherapy had a significantly higher prevalence of AF compared to patients who did not receive radiotherapy (5.9 *vs.* 4.2%; p= 0.046) [7]. Another study done on 3449 lung cancer patients receiving radiotherapy were identified from theSEER-Medicare linked data between 2010 and 2015, 830 were diagnosed with AF after radiotherapy (p=0.0014) [18]. A single center retrospective study of 7799 patients with cancer showed that radiotherapy was an independent risk factor for atrial fibrillation [7]. These risks increase in patients undergoing external beam radiation as compared to brachytherapy an effect attributable to lower chest wall doses with implanted radiation [19]. This was further discussed in a study by kyung Kim, which showed that in patient receiving radiotherapy to the thoracic region for Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), radiotherapy dose was associated with risk of new-onset AF with higher doses predisposing to an overall poor survival but no associated increase on non-AF cardiac events [20]. Studies have also shown increased major cardiovascular events which includes atrial fibrillation and heart failure within the early post radiation period which is regarded as a time window low in cardiovascular complications [21]. Our study demonstrated worse in-hospital outcomes, including a greater than three times increase in the mortality and higher rates of respiratory failure in our cohort and this might be explained by the underlying malignancies as well as the toxic effects of the chemo/radiotherapy on the cardiovascular system and this is in consortium with a study done by Grewal, showed that patients with atrial fibrillation undergoing radiotherapy for breast cancer were at risk of increased mortality (Table 3) [22]. Increased surveillances within the first decade post radiation therapy is recommended with Physicians having a high index of suspicion and maintaining a low threshold for detecting atrial fibrillation [23-27].

Table 3: In-hospital outcomes of patients with AF and a history of radiotherapy for solid chest malignancy.

Outcomes	AF and history of radiotherapy (%) (aOR, CI)	
	Radiotherapy	No Radiotherapy
Mortality	3.11 (2.48; 1.72-3.57 P<0.001)	0.86 (ref)
Cardiogenic Shock	0.73 (1.13; 0.52-2.48 P=0.759)	0.66 (ref)
Cardiac Arrest	0.36 (0.49; 0.13-1.92 P=0.307)	0.41 (ref)
Respiratory Failure	19.12 (1.34; 1.08-1.66 P=0.007)	7.0 (ref)
Ablation	2.84 (0.47; 0.31-0.71 P<0.001)	6.1 (ref)
Conversion to sinus rhythm	12.63 (0.69; 0.56-0.84 P<0.001)	19.83 (ref)
Length of Stay	4.1 (-0.19; -0.42- 0.039 P=0.103)	3.4(ref)
Total Hospital Charge ($)	44,380 (-9, 266; -12, 177 - -6, 356 P<0.001)	46,257 (ref)

CONCLUSION

There was a higher association between treatment of solid tumor in the thoracic area with radiotherapy and diagnosis of new onset of AF or worsening of existing AF as compared to the general population. These findings postulate that there may be myriads' underlying pathway to the cause and effects of radiotherapy and AF occurrence when we adjust for other cardiovascular factors and other comorbidities. Our study was the first to outline and report this finding for all thoracic solid tumor treated with both external beam and brachytherapy type of radiation. We need more multi-center study with collaboration among radiation oncologist, cardio-oncologist, electrophysiologist, medical oncologist and other multidisciplinary experts to further study the pathophysiology of the development of AF post-radiotherapy then come up with ways and guidelines to recommend the precise amount of radiation exposure during care, modalities to prevent AF occurrence and other cardiovascular diseases, evidence based management for AF diagnosed during and after radiation treatment, and ultimately improve the quality of life of the patients.

LIMITATIONS

This study is not without its limitations. The inherent properties of the NIS database are principally responsible for the study's limitations. Because the NIS is an administrative database, the accuracy of the analysis depends on how precisely the records were collected. In addition, because records were identified by ICD codes, there may have been inherent errors in estimating the studied diagnoses. The cohort is additionally constrained by the inadequacy of long-term follow-up due to the structure of the database. We could not establish a direct causality relationship between AF and RT and as well could not quantify the RT dose in our studied cohort.

CONFLICT OF INTEREST

All authors declare that they have no competing interests (financial and non-financial).

ETHICS DECLARATION

The study was not submitted for research ethics approval as the activities described were conducted as part of the Nationwide Inpatient Sample Database (NIS), which is part of the family of databases and software tools developed for the Healthcare Cost and Utilization Project (HCUP) and uses de-identified data collected from hospitalized patients. Consent was not obtained, given the use of a de-identified database. All the experiments in our study were under the guidelines and agreement regulations of the Agency Healthcare Research and Quality (AHRQ)

AUTHORS' CONTRIBUTION

Akanimo Antia contributed to the conception and design of the research; Favour Markson contributed to the design of the research; Daniel Ubokudom contributed to the acquisition and analysis of the data; Akanimo Antia contributed to the interpretation of the data; Ovie Okorare, Oladimeji Adabale and Emmanuel Daniel helped draft the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

CONSENT FOR PUBLICATION

Not applicable. All data using the National Readmission Database Sample is de-identified.

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None

DATA AND MATERIALS AVAILABILITY

The datasets generated and analyzed during the current study are available in the Healthcare Cost and Utilization Project National Data Registry (https://www.distributor.hcup-us.ahrq.gov/Databases.aspx). This Data Use Agreement ("Agreement") governs the disclosure and use of data in the HCUP Nationwide Databases from the Healthcare Cost and Utilization Project (HCUP), which the Agency maintains for Healthcare Research and Quality (AHRQ). Accordingly, HCUP Databases may only be released in "limited data set" form, as the Privacy Rule defines that term, 45 C.F.R. § 164.514(e). In addition, AHRQ classifies HCUP data as protected health information under the HIPAA Privacy Rule, 45 C.F.R. § 160.103. The datasets generated and analyzed during the current study are not publicly available except for the corresponding author who purchased the data and signed the HCUP Data Use agreement training. Researchers should readily be able to publicly purchase the same databases we did to conduct research. Contact information for further guidance on https://www.hcup-us.ahrq.gov/.

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