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Association of atrial fibrillation and various cancer subtypes

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Abstract

Background: Studies have shown that the incidence of atrial fibrillation (AF) in cancer is most likely due to the presence of inflammatory markers. The purpose of our study is to determine the association of AF with different cancer subtypes and its impact on in-hospital outcomes.

Methods: Data were obtained from the National Inpatient Sample database between 2005 and 2015. Patients with various cancers and AF were studied. ICD-9-CM codes were utilized to verify variables. Patients were divided into three age groups: Group 1 (age < 65 years), Group 2 (age 65-80 years), and Group 3 (age > 80 years). Statistical analysis was performed using Pearson chi-square and binary logistic regression analysis to determine the association of individual cancers with AF.

Results: The prevalence of AF was 14.6% among total study patients (n = 46 030 380). After adjusting for confounding variables through multivariate regression analysis, AF showed significant association in Group 1 with lung cancer (odds ratio, OR = 1.92), multiple myeloma (OR = 1.59), non-Hodgkin lymphoma (OR = 1.55), respiratory cancer (OR = 1.55), prostate cancer (OR = 1.20), leukemia (OR = 1.12), and Hodgkin's lymphoma (OR = 1.03). In Group 2, the association of AF with multiple myeloma (1.21), lung cancer (OR = 1.15), Hodgkin lymphoma (OR = 1.15), non-Hodgkin lymphoma (OR = 1.12), respiratory cancer (OR = 1.08), prostate cancer (OR = 1.06), leukemia (OR = 1.14), and colon cancer (OR = 1.01) were significant. In Group 3, AF showed significant association with non-Hodgkin lymphoma (OR = 1.06), prostate (OR = 1.03), leukemia (OR = 1.03), Hodgkin's lymphoma (OR = 1.02), multiple myeloma (OR = 1.01), colon cancer (OR = 1.01), and breast cancer (OR = 1.01). The highest mortality was found in lung cancer in age <80 and prostate cancer in age >80.

Conclusion: In patients age <80 years, AF has significant association with lung cancer and multiple myeloma, whereas in patients age >80 years, it has significant association with non-Hodgkin lymphoma and prostate cancer. In patients age <80 years, increased mortality was seen in AF with lung cancer and in patients age >80 years, increased mortality was seen in those with AF and prostate cancer.

Twitter Abstract: In age <80, lung cancer and multiple myeloma have a strong association with AF while thyroid and pancreatic cancers have no association with AF at any age. In age greater than 80, NHL and prostate cancer have a significant association with AF.

KEYWORDS
atrial fibrillation, cancers

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in the United States. Its prevalence and incidence increase every year.[1,2] AF has been associated with an increased risk of stroke, myocardial infarction, dementia, heart failure, CKD, venous thromboembolism, and mortality.[3,4]

Risk factors associated with an increased risk of atrial fibrillation include older age, obesity, diabetes, cardiomyopathy, myocarditis, pneumonia, COPD, pulmonary embolism (PE), hypertension, and cancer.[3,4] The bidirectional relation of AF and cancer is not well known and needs further research studies. Individual factors that influence the development of atrial fibrillation are genetics, aging, hypoxia, electrolyte abnormalities, systemic inflammation, and neurohormonal changes. Cancer treatment, including chemotherapy and radiation therapy, may lead to structural damage that increases the risk of atrial fibrillation. Chemotherapy is also strongly associated with inducing systemic inflammation.

Our study hypothesized that certain cancers (increase systemic inflammation, electrolyte abnormalities, and neurohormonal changes which) increase the development of AF compared with other cancers. The purpose of our study is to determine the association of AF with different cancers and its subsequent impact on in-hospital outcomes.

2 | METHODS

2.1 | Data source

The present study was conducted using the National Inpatient Sample (NIS) database, the largest inpatient database in the United States. The NIS is a part of the Healthcare Cost and Utilization Project developed by the Agency for Healthcare Research and Quality. The data were collected from 48 states. NIS represents more than 97% of the US population, and the data have an average of 7-8 million discharges each year. NIS data are obtained from more than 7 million hospital stays each year, and it estimates more than 35 million hospitalizations nationally. Each admission contains information on patient characteristics, including demographics, comorbidities, complications, as well as the primary and secondary discharge diagnoses. This has been explained in detail in previous studies.[5,6] The International Classification of Disease, 9th revision, Clinical Modification (ICD 9-CM) codes were used to identify diagnosis in the NIS database.[7] Data included in this study were obtained between January 2005 and October 2015, as data before October 2015 included the use of ICD-9-CM codes. NIS data include the charge-to-cost ratio. Charges showed the amount the hospital bills for services while cost represents how much the service costs including utilities cost, supplies, and wages. The study cohort was derived from a deidentified and publicly available database; hence, the study was considered exempt from the formal approval of the institutional review board.

2.2 | Diagnosis codes for AF and cancer

Clinical Classifications Software (CCS) codes from 11 to 43 which are for nonspecific and specific malignant cancers were used for extraction of specific cancers which were included in our study. The NIS data provide up to 30 CCS diagnoses for each inpatient visit.

We extracted cancer and AF hospitalizations using appropriate ICD-9-CM diagnosis codes in primary or secondary diagnosis (Table S1). Furthermore, we documented the following comorbidities: hypertension, diabetes, congestive heart failure, chronic obstructive pulmonary disease, deficiency anemia, hypothyroidism, coronary artery disease, smoking, obesity, and chronic kidney disease (CKD) in our study cohort. The present study included prostate cancer, lung cancer, colon cancer, other respiratory/intrathoracic cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma (NHL), leukemia, and multiple myeloma (MM).

2.3 | Subgroups

The data were separated into three groups based on age as follows: Group 1: 18-64, Group 2: 65-80, and Group 3: >80 years. Figure 1 illustrates the patient distribution into three groups.

2.4 | Figures

In figures, the individual cancers were merged to create four groups: gastrointestinal, respiratory, hematologic, and prostate cancers. The

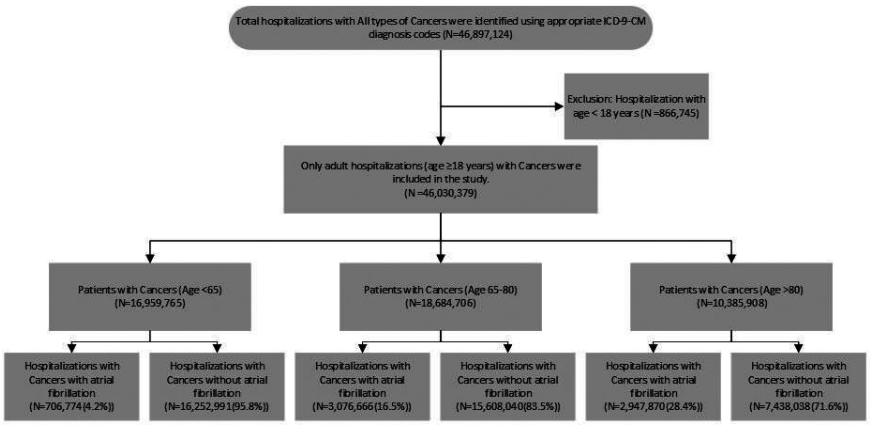

FIGURE 1 Flow chart of the study selection process

prevalence and mortality incidence of each group with AF is shown in the graphs.

2.5 | Statistical analysis

All the data extraction and analysis were done using SAS statistical software, version 9.4. All continuous variables were compared using Student's t test, and categorical variables were analyzed using the Pearson chi-square test. Categorical data were presented as weighted frequency in percentages. Continuous data were presented as mean ± standard deviation. A *P*-value of <.05 was considered statistically significant. Three models of multivariate regression analysis were made. After adjusting for age, hypertension, diabetes, congestive heart failure, chronic obstructive pulmonary disease, hypothyroidism, thyrotoxicosis, coronary artery disease, obesity, and collagen vascular disease, the association of AF with different cancers was analyzed. Logistic regression data were reported as odds ratios with a 95% confidence interval.

The primary outcome of our study was to determine which cancer had the highest association of AF. Secondary outcomes included in-hospital mortality, length of stay, and hospitalization costs.

3 | RESULT

Between the years 2005 and 2015, a total number of 46 897 124 adult hospitalizations were identified with a cancer diagnosis. After excluding 866 744 patients of <18 years, 40 030 380 were included in the study. The incidence of AF in these cancer patients was 14.6%.

3.1 | Comparison of cancer and AF baseline characteristics in subgroups

Cancer hospitalizations with AF were more likely to be male and Caucasian compared with those without AF in all groups. The prevalence of coronary artery disease, obstructive sleep apnea, congestive heart failure, valvular disease, chronic pulmonary disease, hypertension, diabetes mellitus, renal failure, obesity, collagen vascular disease, and hypothyroidism is higher in all groups of cancer hospitalizations with AF compared with those without AF (Tables 1-3).

3.2 | Comparison of cancer and AF coincidence/ odds ratio in subgroups

In Group 1, the prevalence of AF was highest in lung cancer (20.8% vs 10.9%) followed by prostate cancer (8.1% vs 6.5%), Hodgkin's lymphoma (1.9% vs 1.6%), NHL (7.5% vs 6.6%), leukemia (5.6% vs 6.6%), and multiple myeloma (3.2% vs 1.9%) (Table 1). In Group 2, the prevalence of AF was highest in lung cancer (18.8% vs 15.9%) followed by prostate cancer (17.5% vs 16.4%), NHL (6.2% vs 5.6%), leukemia (4.8% vs 4.3%), multiple myeloma (1.8% vs 1.5%) and Hodgkin's lymphoma (0.5% vs 0.4%) (Table 2). AF prevalence was lower in Group 2 compared with Group 1. In Group 3, the prevalence of AF was found to be elevated only in prostate cancer (21.3% vs 20.8%), NHL (5.3% vs 5.0%), and leukemia (4.8% vs 4.7%) (Table 3).

The study results showed AF prevalence with prostate, respiratory, hematologic, and GI cancers (Figure 2). The study showed that with increasing age, the difference between the prevalence of AF with cancer groups compared with those without AF is not statistically significant (Figure 2). In patients aged >80, the prevalence of AF with prostate, respiratory, hematologic, and GI cancers is not statistically significant to those without AF.

The association of AF with cancer was assessed using multivariate regression analysis (Table 4). Each independent predictor, including AF, was analyzed using multivariate regression analysis, and results were reported as an odds ratio with a 95% confidence interval. After multivariate regression analysis, in Group 1, a significantly higher odds of having AF was seen with lung cancer (1.92), multiple myeloma (1.59), NHL (1.55), respiratory cancer (1.55), prostate cancer (1.20), leukemia (1.12), and Hodgkins lymphoma (1.03) (Table 4). Pancreatic (0.79), colon (0.93), breast (0.70), and thyroid (0.6) cancers showed decreased association with AF. In Group 2, AF was significantly associated with multiple myeloma (1.21), lung cancer (1.15), Hodgkin's lymphoma (1.15), NHL (1.12), respiratory cancer (1.08), prostate cancer

TABLE 1 Patient-Level Characteristics of Cancers with atrial fibrillation versus Cancers without atrial fibrillation in 2005-2015 of Patients age < 65

Characteristics	Cancers with AF	Cancers without AF	
N = 16 959 765	N = 706 774 (4.2%)	N = 16 252 991 (95.8%)	*P*-value
Gender			
Male	428 695 (60.7%)	7 244 368 (44.6%)	<.0001
Female	278 047 (39.3%)	8 994 387 (55.4%)	
*Missing – 14 269			
Race			
Caucasians	492 390 (69.7%)	9 803 161 (60.3%)	<.0001
African-Americans	72 303 (10.2%)	2 027 905 (12.5%)	
Others	142 053 (20.1%)	4 421 087 (27.2%)	
*Missing – 866			
Cancers			
Colon	50 765 (7.2%)	1 268 542 (7.8%)	<.0001
Pancreas	11 079 (1.6%)	345 216 (2.1%)	<.0001
Lung	147 068 (20.8%)	1 773 532 (10.9%)	<.0001
Other respiratory	1721 (0.24%)	26 227 (0.21%)	<.0001
Breast	84 637 (11.9%)	2 634 046 (16.2%)	<.0001
Prostate	57 432 (8.1%)	1 064 019 (6.5%)	<.0001
Thyroid	14 863 (2.1%)	493 338 (3%)	<.0001
Hodgkins	13 294 (1.9%)	255 362 (1.6%)	<.0001
Non-Hodgkins	52 916 (7.5%)	1 067 287 (6.6%)	<.0001
Leukemia	39 712 (5.6%)	883 543 (5.4%)	<.0001
Multiple myeloma	22 646 (3.2%)	322 601 (1.9%)	<.0001
AHRQ Comorbidities			
Coronary arterial disease	166 073 (23.5%)	1 393 155 (8.6%)	<.0001
Obstructive Sleep Apnea	66 058 (9.3%)	509 589 (3.1%)	<.0001
CHRIST HOSPITAL PROGRAM	66 336 (9.4%)	262 607 (1.6%)	<.0001
Valvular disease	44 375 (6.3%)	284 196 (1.7%)	<.0001
Chronic pulmonary disease	203 525 (28.8%)	2 603 301 (16%)	<.0001
Hypertension	399 727 (56.6%)	6 230 063 (38.3%)	<.0001
Diabetes Mellitus	199 298 (28.2%)	2 792 885 (17.2%)	<.0001
Hypothyroidism	82 543 (11.7%)	1 417 091 (8.7%)	<.0001
Renal failure	97 422 (13.8%)	866 379 (5.3%)	<.0001
Obesity	113 339 (16%)	1 473 743 (9.1%)	<.0001
Alcohol abuse	34 075 (4.8%)	622 549 (3.8%)	<.0001
Drug abuse	16 590 (2.3%)	494 266 (3%)	<.0001
RA/Collagen vascular disease	17 815 (2.5%)	309 452 (1.9%)	<.0001
Outcomes			
In-hospital mortality	49 965 (7.1%)	553 337 (3.4%)	<.0001
*Missing – 7965	Adjusted odds ratio[a] 1.80 (1.78-1.82)		<.0001
Length of stay, days, (mean ± SD)	7.2 ± 8.8	5.5 ± 7.2	<.0001
Total hospitalization cost, $ (mean ± SD)	20 130 ± 30 396	14 574 ± 21 148	<.0001

[a]Adjusted for race, gender, AHRQ comorbidities

(1.06), leukemia (1.14), and colon cancer (1.01); however, AF showed decreased association with pancreatic cancer (0.76), breast cancer (0.91), and thyroid cancer (0.92). In Group 3, AF had an association with NHL (1.06), prostate cancer (1.03), leukemia (1.03), Hodgkins lymphoma (1.02), multiple myeloma (1.01), colon cancer (1.01), and breast cancer (1.01). In Group 3, the strongest association with AF was found with NHL followed by prostate cancer and leukemia. A decreased association of AF in Group 3 was found in Pancreatic (0.76), lung (0.95), respiratory (0.91), and thyroid cancers (0.95).

3.3 | Comparison of secondary outcomes (mortality, length of stay, cost) in subgroups

The secondary clinical outcomes of the study are shown in Tables 1-3. In all age groups, the mortality, hospitalization costs, and length of stay was higher in cancer patients with AF compared with those without AF. In Group 1, mortality was highest in lung cancer (36.9% vs 24.7%), followed by leukemia (9.9% vs 8%), MM (4.3% vs 2.5%),

TABLE 2 Patient-Level Characteristics of Cancers with atrial fibrillation versus Cancers without atrial fibrillation in 2005-2015 of Patients age 65-80

Characteristics	Cancers with AF	Cancers without AF	
N = 18 684 706	N = 3 076 666 (16.5%)	N = 15 608 040 (83.5%)	*P*-value
Gender			
Male	1 792 995 (58.3%)	7 924 758 (50.8%)	<.0001
Female	1 283 525 (41.7%)	7 679 425 (49.2%)	
*Missing – 4003			
Race			
Caucasians	2 353 070 (76.5%)	10 654 565 (68.3%)	<.0001
African-Americans	176 748 (5.7%)	1 445 919 (9.3%)	
Others	546 735 (17.8%)	3 506 546 (22.5%)	
*Missing – 1123			
BMI			<.0001
Cancers			
Colon	325 335 (10.65%)	1 659 302 (10.63%)	.003
Pancreas	49 049 (1.6%)	362 896 (2.3%)	<.0001
Lung	578 309 (18.8%)	2 477 666 (15.9%)	<.0001
Other respiratory	6469 (0.24%)	31 572 (0.21%)	.005
Breast	447 345 (14.5%)	2 483 820 (15.9%)	<.0001
Prostate	538 850 (17.5%)	2 564 687 (16.4%)	<.0001
Thyroid	36 886 (1.2%)	199 940 (1.3%)	<.0001
Hodgkins	14 896 (0.5%)	59 563 (0.4%)	<.0001
Non-Hodgkins	190 080 (6.2%)	874 527 (5.6%)	<.0001
Leukemia	147 709 (4.8%)	671 398 (4.3%)	<.0001
Multiple myeloma	84 372 (2.7%)	373 153 (2.4%)	<.0001
AHRQ comorbidities			
Coronary arterial disease	1 127 748 (36.6%)	3 714 817 (23.8%)	<.0001
Obstructive sleep apnea	213 675 (6.9%)	553 450 (3.5%)	<.0001
Congestive heart failure	223 895 (7.3%)	363 096 (2.3%)	<.0001
Valvular disease	274 048 (8.9%)	573 855 (3.7%)	<.0001
Chronic pulmonary disease	989 132 (32.1%)	3 745 872 (24%)	<.0001
Hypertension	2 051 799 (66.7%)	9 586 878 (61.4%)	<.0001
Diabetes mellitus	967 174 (31.4%)	4 251 791 (27.2%)	<.0001
Hypothyroidism	470 337 (15.3%)	2 017 313 (12.9%)	<.0001
Renal failure	569 866 (18.5%)	1 796 852 (11.5%)	<.0001
Obesity	312 301 (10.1%)	1 167 477 (7.5%)	<.0001
Alcohol abuse	70 535 (2.3%)	323 822 (2.1%)	<.0001
Drug abuse	12 832 (0.4%)	84 183 (0.5%)	<.0001
RA/Collagen Vascular Disease	93 517 (3%)	430 026 (2.8%)	<.0001
Outcomes			
In-hospital mortality	183 767 (5.9%)	637 237 (4.1%)	<.0001
*Missing – 8544	Adjusted odds ratio[a] 1.31 (1.30-1.32)		<.0001
Length of stay, days (mean ± SD)	6.5 ± 6.9	5.4 ± 6.2	<.0001
Total hospitalization cost, $ (mean ± SD)	15 994 ± 20 353	13 144 ± 16 108	<.0001

[a]Adjusted for race, gender, AHRQ comorbidities

TABLE 3 Patient-Level Characteristics of Cancers with atrial fibrillation versus Cancers without atrial fibrillation in 2005-2015 of Patients age > 80

Characteristics	Cancers with AF	Cancers without AF	
N = 10 385 908	N = 2 947 870 (28.4%)	N = 7 438 038 (71.6%)	*P*-value
Gender			
Male	1 478 166 (50.1%)	3 457 198 (46.5%)	<.0001
Female	1 469 620 (49.9%)	3 980 158 (53.5%)	
*Missing – 767			
Race			
Caucasians	2 379 865 (80.7%)	5 444 503 (73.2%)	<.0001
African-Americans	99 393 (3.4%)	495 031 (6.7%)	
Others	468 505 (15.9%)	1 497 883 (20.1%)	
*Missing – 729			
Cancers			
Colon	455 176 (15.4%)	1 146 301 (15.4%)	.23
Pancreas	34 103 (1.2%)	120 725 (1.6%)	<.0001
Lung	276 181 (9.48%)	699 986 (9.43%)	.03
Other respiratory	4187 (.1%)	11 659 (0.2%)	<.0001
Breast	590 118 (20%)	1 494 638 (20.1%)	<.0001
Prostate	628 403 (21.3%)	1 529 972 (20.6%)	<.0001
Thyroid	24 876 (0.8%)	62 965 (0.8%)	.67
Hodgkins	7187 (0.26%)	17 142 (0.24%)	<.0001
Non-Hodgkins	155 224 (5.3%)	372 270 (5%)	<.0001
Leukemia	142 707 (4.8%)	351 605 (4.7%)	<.0001
Multiple myeloma	52 551 (1.8%)	133 623 (1.8%)	.13
AHRQ Comorbidities			
Coronary arterial disease	1 148 642 (38.9%)	2 269 628 (30.5%)	<.0001
Obstructive sleep apnea	84 818 (2.9%)	116 202 (1.6%)	<.0001
Cardiomyopathy	182 271 (6.2%)	196 675 (2.6%)	<.0001
Valvular disease	372 294 (12.6%)	503 057 (6.8%)	<.0001
Chronic pulmonary disease	760 224 (25.8%)	1 560 519 (20.9%)	<.0001
Hypertension	2 029 505 (68.8%)	4 957 509 (66.6%)	<.0001
Diabetes mellitus	685 548 (23.3%)	1 684 862 (22.6%)	<.0001
Hypothyroidism	606 761 (20.6%)	1 325 029 (17.8%)	<.0001
Renal failure	689 878 (23.4%)	1 303 194 (17.5%)	<.0001
Obesity	102 487 (3.5%)	213 728 (2.9%)	<.0001
Alcohol abuse	21 989 (0.74%)	50 743 (0.72%)	<.0001
Drug abuse	4187 (0.1%)	11 639 (0.2%)	<.0001
RA/Collagen vascular disease	84 424 (2.9%)	201 790 (2.7%)	<.0001
Outcomes			
In-hospital mortality	190 809 (6.5%)	363 563 (4.9%)	<.0001
*Missing – 6380	Adjusted odds ratio[a] 1.23 (1.21-1.23)		<.0001
Length of stay, days (mean ± SD)	5.9 ± 5.8	5.3 ± 5.6	<.0001
Total hospitalization cost, $ (mean ± SD)	12 338 ± 14 079	10 678 ± 12 538	<.0001

[a]Adjusted for race, gender, AHRQ comorbidities

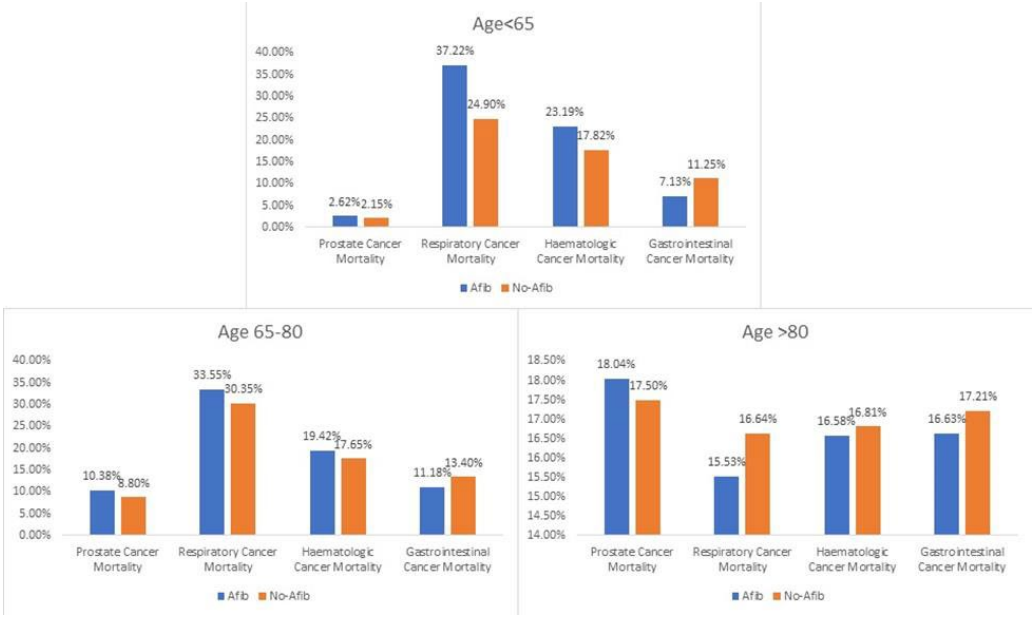

FIGURE 2 Prevalence of AF in prostate, respiratory, hematologic, and GI cancers

TABLE 4 Multiple regression analysis of Atrial fibrillation with different cancers after adjusting with diabetes mellitus, hypertension, coronary artery disease, obesity, congestive heart failure valve disorder, thyrotoxicosis, hypothyroidism, collagen vascular disease, and chronic pulmonary disease

	Age < 65	Age 65-80	Age > 80
	Odds ratio (95% CI, *P*-value)	Oddsratio (95% CI, *P*-value)	Odds ratio (95% CI, *P*-value)
Colon cancer	0.93 (0.92-0.94, <.0001)	1.01 (1.00-1.02, <.0001)	1.01 (1.00-1.02, <.0001)
Pancreas cancer	0.79 (0.77-0.80, <.0001)	0.76 (0.75-0.77, <.0001)	0.76 (0.75-0.77, <.0001)
Lung cancer	1.92 (1.90-1.93, <.0001)	1.15 (1.14-1.16, <.0001)	0.95 (0.94-0.96, <.0001)
Other respiratory cancer	1.55 (1.48-1.63, <.0001)	1.08 (1.05-1.11, <.0001)	0.91 (0.88-0.94, <.0001)
Breast cancer	0.70 (0.69-0.71, <.0001)	0.91 (0.90-0.92, <.0001)	1.01 (1.00-1.02, <.0001)
Prostate cancer	1.20 (1.19-1.21, <.0001)	1.06 (1.05-1.07, <.0001)	1.03 (1.02-1.04, <.0001)
Thyroid cancer	0.68 (0.67-0.70, <.0001)	0.92 (0.91-0.93, <.0001)	0.95 (0.93-0.96, <.0001)
Hodgkins	1.03 (1.01-1.05, .002)	1.15 (1.13-1.17, <.0001)	1.02 (0.99-1.05, .13)
Non-Hodgkins	1.15 (1.14-1.16, <.0001)	1.12 (1.11-1.13, <.0001)	1.06 (1.05-1.07, <.0001)
Leukemia	1.12 (1.10-1.13, <.0001)	1.14 (1.13-1.15, <.0001)	1.03 (1.02-1.05, <.0001)
Multiple myeloma	1.59 (1.57-1.61, <.0001)	1.21 (1.20-1.22, <.0001)	1.01 (1.00-1.02, .006)

prostate cancer (2.6% vs 2.1%), and Hodgkin's disease (1.8% vs 1.3%), (Table 5). In Group 2, the highest mortality was found in lung cancer (33.3% vs 30.2%), followed by prostate cancer (10.4% vs 8.8%), leukemia (8.4% vs 7.9%), NHL (7.4% vs 6.5%), MM (3.7% vs 3.3%), and Hodgkin's lymphoma (0.6% vs 0.5%) (Table 5). The mortality in Group 3 was highest in prostate cancer (18% vs 17.5%), followed by colon cancer (14.7% vs 13.9%), breast cancer (15.5% vs 13.9%), NHL (6.7% vs 6.3%), and thyroid cancer (0.7% vs 0.6%) (Table 5).

The figures further report the mortality incidence. Figure 3 shows AF mortality incidence in prostate, respiratory, hematologic, and GI cancers. In Figure 3, age <65 (Group 1), mortality was highest in the AF group with prostate, respiratory, and hematologic cancers. At age 65-80, the mortality incidence although elevated in the AF group with prostate, respiratory, and hematologic cancers. Group 3 (age > 80) shows that patients with AF and prostate cancer have higher mortality.

4 | DISCUSSION

This case–control study evaluates the risk of atrial fibrillation in 11 different cancer subtypes. Our study's core finding was that in patients younger than age 65, AF has the highest association with lung cancer followed by MM and NHL compared with other cancers. At age 65-80, AF's association was most significant in MM, followed by lung and Hodgkin's cancers. In the age group >80, the

TABLE 5 Mortality incidence rate of atrial fibrillation in individual cancer patients. The rates are shown for different age groups

	Age < 65			Age 65-80			Age > 80		
Mortality	AF	No AF		AF	No AF		AF	No AF	
Colon cancer	4.6%	6.4%	<.0001	8.4%	8.5%	.56	14.7%	13.9%	<.0001
Pancreas cancer	2.5%	4.9%	<.0001	2.8%	5%	<.0001	2%	3.3%	<.0001
Lung cancer	36.9%	24.7%	<.0001	33.3%	30.2%	<.0001	15.4%	16.5%	<.0001
Other respiratory cancer	0.3%	0.2%	<.0001	0.2%	0.2%	.06	0.2%	0.2%	.26
Breast cancer	7.3%	11.4%	<.0001	8.9%	9.1%	.001	15.5%	13.9%	<.0001
Prostate cancer	2.6%	2.1%	<.0001	10.4%	8.8%	<.0001	18%	17.5%	<.0001
Thyroid cancer	0.7%	0.6%	.01	0.6%	0.6%	.003	0.7%	0.6%	.004
Hodgkins	1.8%	1.3%	<.0001	0.6%	0.5%	<.0001	0.3%	0.3%	.59
Non-Hodgkins	8%	6.6%	<.0001	7.4%	6.5%	<.0001	6.7%	6.3%	<.0001
Leukemia	9.9%	8%	<.0001	8.4%	7.9%	<.0001	7.4%	7.9%	<.0001
Multiple myeloma	4.3%	2.5%	<.0001	3.7%	3.3%	<.0001	2.5%	2.7%	.0003

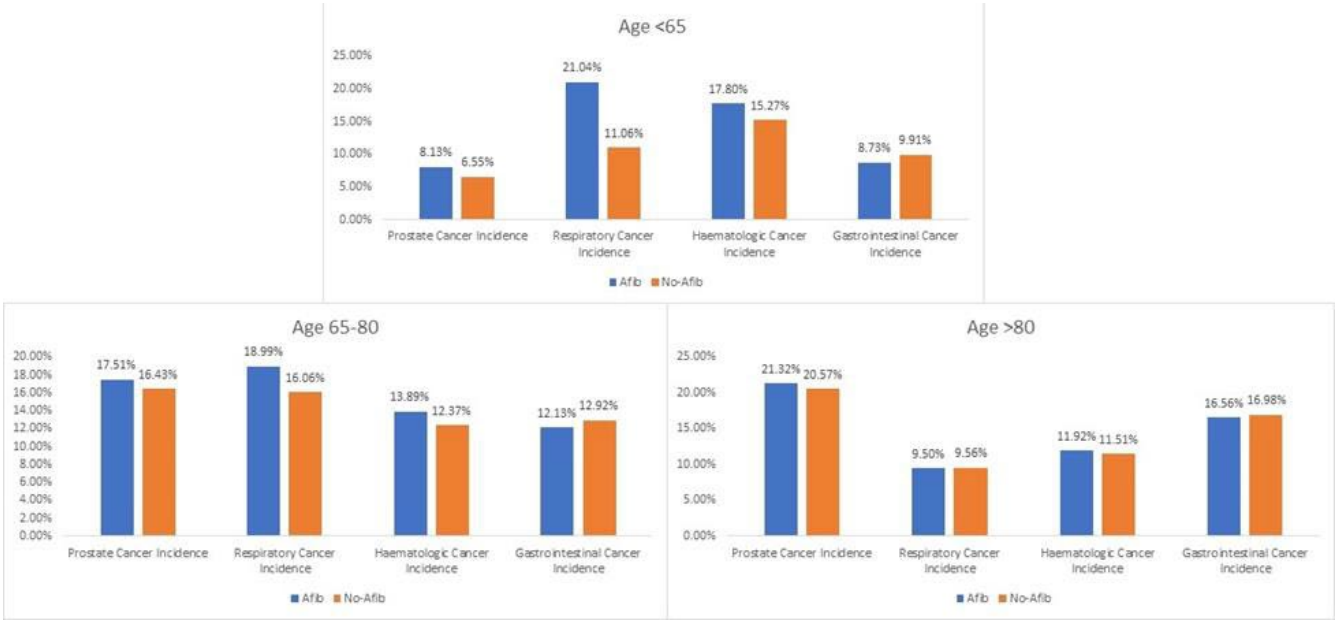

FIGURE 3 Mortality incidence in prostate, respiratory, hematologic, and GI cancers

strongest association of AF was seen with NHL, followed by prostate cancer and leukemia. The mortality, length of stay, and hospitalization costs were higher in all three age groups with AF and cancer compared with those without AF. The highest incidence of mortality with AF in age <65 years was seen with lung cancer followed by leukemia, whereas in age 65-80 years, lung cancer followed by prostate cancer, and in age >80 years, the highest mortality incidence of AF was found in prostate cancer followed by colon cancer.

The study of the association between cancers and cardiovascular diseases is referred to as oncocardiology.[9] Studies have shown a close association between cancers and new-onset atrial fibrillation. Among other pathophysiological mechanisms, systemic inflammation and autonomic dysfunction have been suggested to underlie this association.[10] Several clinical studies have demonstrated increased levels of pro-inflammatory markers in both AF and cancers.[11,12] A case–control study found higher levels of CRP in patients with AF than without AF.[13] Another population-based cohort study found elevated CRP associated with the presence of AF.[10] These findings imply that inflammation can induce the structural and electrophysiological remodeling responsible for arrhythmias [41-missing]. Similarly, cancer is associated with inflammation.[10] Studies have shown higher CRP levels in cancer patients compared with controls.[11,12] Autonomic dysfunction is another mechanism that may lead to the association of AF and cancer. An imbalance between the sympathetic and the parasympathetic system activities has been

associated with AF.[14] This autonomic dysfunction is also found to some degree in cancer patients.[14] The pain and emotional stress associated with cancer results in increased sympathetic activity predisposing to atrial fibrillation.[10] Emotional distress also explains the increased risk of AF within 90 days after a cancer diagnosis. A new cancer diagnosis can be anxiety-provoking resulting in increased emotional distress in this period. Studies have shown an increased risk of AF secondary to subclinical hyperthyroidism which alters the structure and function of the heart.[15] It has been hypothesized that tumors release thyroid hormones including thyroid-stimulating hormones (TSH) and triiodothyronine (T3).[8] Therefore, an abnormal release of thyroid hormone-like peptides could be a possible mechanism for AF in cancer.[15,16] Hypercoagulability associated with a neoplastic state leading to pulmonary microembolism is an additional mechanism leading to the development of AF.[17]

Our study showed the association of AF in all cancer subtypes. As discussed above, this increased risk of AF is possibly due to an inflammatory state and autonomic dysfunction in cancer patients. A meta-analysis by Yuan et al suggested an increased risk of AF in cancer patients.[18] Jacobson et al showed an increased incidence of AF in all cancer subtypes evaluated. A case–control study by Erichson et al concluded that colorectal cancer patients are at increased risk of AF compared with controls.[19] The same study also showed an increased risk for all types of cancers. In our study, we evaluated the association of AF with multivariate regression analysis. In multivariate regression analysis, we adjusted for hypertension, diabetes, congestive heart failure, chronic obstructive pulmonary disease, hypothyroidism, thyrotoxicosis, coronary artery disease, obesity, and collagen vascular disease. We divided the patients into three groups based on age as age has a significant effect on AF prevalence. Previous studies have shown that age is an independent risk factor for AF development. Our study showed that the association of AF in those <65 years was highest in lung cancer followed by MM, NHL, and other respiratory cancer/intrathoracic cancers. At age 65-80 years, the association of AF was highest in MM followed by lung cancer and Hodgkins lymphoma. The odds ratio of lung cancer and MM in age 65-80 years is lower compared with those <65, which shows that age has an impact on the development of AF. Our finding supports the study findings of Jacobson et al which showed lung cancer as the strongest risk for AF. In age >80 years, the association of AF was highest in NHL and prostate cancer. Colon cancer and breast cancer showed a significant association with the development of AF in age >80 years, although it showed a decreased risk of AF in age <80 years. Wassertheil-Smoller et al similarly showed an increased association of AF with breast and colorectal cancer.[20] In our study, lung cancer and MM had the strongest association with AF. Lung cancer increases the risk of AF due to its aggressive nature which may be responsible for the increased inflammatory effect. The anatomical location of lung cancer increases the risk of cardiotoxicity during radiation therapy as well as direct invasion. Similarly, paraneoplastic syndromes associated with lung cancer may be a possible mechanism for the increased risk of AF.[21]

Two cancer subtypes, pancreatic and thyroid cancer, had decreased association of AF after adjusting for the above variables. The prevalence of AF in thyroid and pancreatic cancer in our population was lower than the majority of other cancers. Our finding that pancreatic cancer does not significantly increase the risk of AF is contradicting to the previous study by Jacobson et al Jacobson et al also similarly noted nonsignificant association between endocrine cancer and risk of developing AF likely secondary to under power study.[21] The development of AF in pancreatic cancer may be low because of the higher mortality of pancreatic cancer. Due to high mortality, these patients often die prior to developing AF. Chemotherapy can induce AF through cardiotoxicity.[22] Our study lacked adjustment for treatment which may have resulted in confounding.

Our study also evaluated the effect of AF on mortality in cancer patients. We found higher mortality in cancer with AF group compared with those without AF group. In our study, the highest mortality of AF in those <65 years was seen with lung cancer followed by leukemia, in age >65-80 years, lung cancer followed by prostate cancer, and in age >80 years, prostate cancer followed by colon cancer.

The implications from these findings are that close surveillance and early management of atrial fibrillation may serve to reduce the burden of healthcare costs. Before application to clinical practice, further studies with better designs are necessary.

5 | LIMITATION

Our study has several limitations. The nature of the database limited can determine whether the patient developed AF before or after the development of their respective cancers. As our study sample is large and representative of US hospitals, after adjusting for other comorbidities, we were able to demonstrate that most of the cancers could be an independent risk factor of AF. We relied on diagnosis codes for cancer subtypes and AF, which could potentially lead to exposure and outcome misclassification, however, both ICD codes for AF and cancers are validated and used in several studies.[23,24] We did not investigate the severity and stages of cancers which could affect the development of AF. In addition, we did not study the effect of chemotherapy on the development of AF. Our study did not investigate the pathophysiology and mechanism behind the association of AF and cancer types and the higher mortality associated with cancer; however, possible hypothesis will be that certain cancer cause more systemic inflammation in different age groups and that is why they increase the development of AF. Finally, the patient population was limited to inpatient, and cancer patients without hospitalization were not be included in this study.

6 | CONCLUSION

In the age group <80, our study found that lung cancer and multiple myeloma have a strong association with AF, whereas thyroid and

pancreatic cancers have no association with AF at any age. In age >80, NHL and prostate cancer have a significant association with AF. The highest mortality incidence in age <80 was found in lung cancer and age >80 was seen in prostate cancer.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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