IJC Heart & Vasculature 42 (2022) 101106

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Effects of atrial fibrillation on outcomes of influenza hospitalization

Alexander Bolton [a,*,2], Harshith Thyagaturu [b,2], Muddasir Ashraf [a,2], Ryan Carnahan [a,1,2], Denice Hodgson-Zingman [c,1,2]

[a] College of Public Health, University of Iowa, Iowa City, IA, USA
[b] Bassett Medical Center, Cooperstown, NY, USA
[c] Division of Cardiovascular Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

ARTICLE INFO

Keywords:
Atrial Fibrillation
Influenza
Hospitalization
Hospital Mortality

ABSTRACT

Background: There is little information available on AF and its association with outcomes in adult influenza hospitalizations.
Methods: The National Inpatient Sample was queried from years 2009–2018 to create a cohort of discharges containing an influenza diagnosis. AF was the primary exposure. Univariate and multivariate regression analysis was used to describe the association of AF with clinical and healthcare-resource outcomes. Finally, a doubly-robust analysis using average treatment effect on the treated (ATT) propensity score weighting was performed to verify the results of traditional regression analysis.
Results: After adjustment, the presence of AF during influenza hospitalization was associated with higher odds of in-hospital mortality (aOR 1.56, 95 % CI 1.49 – 1.65), acute respiratory failure (aOR 1.22, 95 % CI 1.19 – 1.25), acute respiratory failure with mechanical ventilation (aOR 1.37, 95 % CI 1.32 – 1.41), acute kidney injury (aOR 1.09, 95 % CI 1.06 – 1.12), acute kidney injury requiring dialysis (aOR 1.61, 95 % CI 1.46 – 1.78) and cardiogenic shock (aOR 1.90, 95 % CI 1.65 – 2.20, all p-values < 0.0001). These findings were validated in our propensity score analysis using ATT weights. The presence of AF was also associated with higher total charges and costs of hospitalization, as well as a significantly longer length of stay (all p-values < 0.0001).
Conclusion: AF is a cardiovascular comorbidity associated with worse clinical and healthcare resource outcomes in influenza requiring hospitalization. Its presence should be used to identify patients with influenza at risk of worse prognosis.

1. Introduction

Cardiovascular disease is a risk factor for hospitalization in patients with respiratory viral infection, and is a contributor to cardiovascular complications and worsened in-hospital outcomes in this population [1–3]. These findings were replicated in studies with patients admitted to the hospital with SARS-CoV-2 infection during the current COVID-19 pandemic [4–6]. Before SARS-CoV-2, the strongest link between cardiovascular disease and worsened in-hospital outcomes for respiratory viral infections was found for influenza, an illness that affected 37.4 to 42.9 million individuals in the United States in the 2018–2019 season [7]. Multiple studies have found that patients with heart failure (HF) have worse outcomes if hospitalized with influenza, [8–10] and other studies have had similar findings for patients with coronary artery disease (CAD) and myocardial infarction (MI) [11,12]. Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia in clinical practice and is increasingly recognized as a chronic cardiovascular disease as it becomes more prevalent around the world [13,14]. AF is similar to other chronic cardiovascular conditions in that it confers worse in-hospital outcomes for acute conditions such as exacerbation of chronic obstructive pulmonary disease (COPD) [15,16] sepsis [17], and pancreatitis [18]. However, the effect of AF on in-hospital outcomes for respiratory viral illnesses, including influenza, is not well studied. Therefore, we conducted an observational cross-sectional study using a nationally representative inpatient database to determine if AF confers worse clinical and healthcare-resource outcomes to patients hospitalized with influenza.

* Corresponding author at: c/o Department of Epidemiology, University of Iowa College of Public Health, 145 N Riverside Dr, Iowa City, IA 52242, USA.
E-mail address: abolton@uiowa.edu (A. Bolton).
[1] Co-senior authors.
[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcha.2022.101106
Received 5 May 2022; Received in revised form 23 July 2022; Accepted 9 August 2022

2. Methods

The study examined differences in clinical and healthcare resource outcomes for influenza hospitalizations based on AF status using discharge data from the National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest, all-payer inpatient care database in the United States, containing publicly available, de-identified data on approximately 7 million inpatient discharges per year [19]. Prior to 2012, each year of the NIS (then known as the Nationwide Inpatient Sample) contained all discharge data from a 20 % sample of hospitals within the frame. In 2012, the NIS was redesigned so that each year contains a 20 % sample of discharges across all hospitals in the sampling frame. As our dataset contains years using both NIS designs, we used trend weights designed by AHRQ for years prior to 2012 so that all years in our dataset had equivalent discharge weights. As the study was performed using publicly available, de-identified data, the University of Iowa Institutional Review Board exempted the study from formal review (study ID #202108629).

To identify our cohort of influenza hospitalizations, we used International Classification of Disease (ICD) codes (International Classification of Disease, 9th edition, Clinical Modification [ICD-9-CM] from January 2009 to September 2015, and International Classification of Disease, 10th edition, Clinical Modification [ICD-10-CM] from October 2015 to December 2018) to identify records with an ICD code for influenza, and then divided this cohort into groups based on presence or absence of an ICD code for AF (see **Supplementary Table 1** for a list of all ICD codes used in this study). For our primary analysis, a record was determined to have either influenza or AF if an ICD code for the respective disease was present in any diagnosis code field. Additionally, we performed a pre-specified sensitivity analysis using only records with a primary ICD code for influenza, with outcomes analyzed based on the presence or absence of a secondary ICD code for AF.

Demographic characteristics that were collected include age (categorized as 18–49, 50–64, 65–79, and 80 + years), sex, race (categorized as White, Black, Hispanic/Latino or Other), primary payer (categorized as Medicare, Medicaid, private pay, or Other), median income by associated ZIP code (in quartiles), hospital type/location (rural, urban/non-teaching and urban/teaching), tobacco use status (yes/no), and a group of chronic conditions as defined by Elixhauser comorbidity software (congestive heart failure, chronic pulmonary disease, diabetes [both uncomplicated and with chronic complications], hypertension, obesity, peripheral vascular disorders, pulmonary circulation disorders, renal failure and valvular disease). Outcomes studied include in-hospital mortality, acute respiratory failure (ARF, both in general and requiring mechanical ventilation), acute kidney injury (AKI, both in general and requiring hemodialysis), and cardiogenic shock as clinical outcomes, and total hospitalization charges (amount billed to insurance for the hospitalization) and costs (actual expenses incurred in providing services during the hospitalization, minus physician fees) as well as length of stay as healthcare resource outcomes. In-hospital mortality as well as the total charges of hospitalization and length of stay were provided as data elements within the NIS. ICD codes were used to define ARF, ARF requiring mechanical ventilation, AKI, AKI requiring hemodialysis and cardiogenic shock. Supplemental cost-to-charge ratio files were provided by AHRQ for each year of the NIS, and were merged into the dataset to calculate the total costs of hospitalization by multiplying the total charge by the cost-to-charge ratio.

2.1. Statistical methods

Demographic variables for the with and without AF groups were expressed as total number and percentage for categorical variables, and as mean ± standard deviation for continuous variables. The Chi-square test was used to compare categorical variables, and Student's *t*-test was used for continuous variables. Univariate analysis was first performed to evaluate if AF alone was significantly associated with each of the specified outcomes as defined by ICD coding. Next, multivariate analysis was performed using all demographic characteristics as covariates. Finally, a propensity score model was created using all demographic characteristics as well as the discharge weights as independent variables. With this model, we generated average treatment effect on the treated (ATT) weights, which were then multiplied by the discharge weights within the NIS to create final weights. After the groups with and without AF were compared using the final weights to ensure balance across all variables in the model (defined as a standardized mean difference between − 0.1 and 0.1 for each variable, see **Supplementary Tables 2 and 3**), the final weights were then used in the multivariate adjusted models to conduct propensity score weighted analyses for all the aforementioned outcomes using doubly robust models. All outcome analyses were performed on the entire dataset, and then repeated in the subset of records with primary influenza diagnoses and secondary AF diagnoses for the sensitivity analysis. Records with ages < 18, as well as records with missing data were excluded from this analysis. In the interests of promoting quality research and reporting using the NIS, the "Checklist for Working with the NIS" from AHRQ was followed while designing and interpreting the study results [20].

Logistic regression was used for the evaluation of dichotomous outcomes and the generation of odds ratios, and linear regression was used for evaluation of continuous outcomes, as well as for generation of parameter estimates. The type 1 error rate was set at 0.05 for the purposes of determining statistical significance. All analyses were performed using PROC SURVEY procedures using SAS version 9.4 (Cary, NC). As the analysis was performed using multiple years of the NIS, both the hospital variable ("HOSP_NIS") and the year ("YEAR") were used as strata.

Our dataset had missing data across several variables, the most significant being race at 5.3 %. The frequency of missing data is outlined in **Supplementary Table 4**. As the missing data was not monotone in structure and was found across binary, categorical, and continuous variables, multiple imputation using fully conditional specification was performed using PROC MI in SAS version 9.4. Ten imputed datasets were created using the same variables present in the adjusted multivariate analyses. Both the primary and sensitivity analyses were then repeated using the imputed datasets to generate ten parameter estimates for each outcome, which were then pooled using PROC MIANALYZE in SAS version 9.4. The pooled parameter estimates using imputed data were then compared to the original parameter estimates from complete case analysis (see **Supplementary Table 5)**. As there is no significant difference between the original and imputed parameter estimates, we have determined that the missing data in our dataset had no significant impact on the results of our study. Therefore, we present the results from the original complete case analysis.

3. Results

Between the years 2009 and 2018 of the NIS, a total of 1,381,293 weighted records with influenza diagnoses were obtained for the primary analysis, of which 265,678 (19 %) had AF. The demographics of the primary analysis are described in Table 1**.** Records with influenza and AF were older than those without AF, with over 50 % of the group aged greater than 80 years, and correspondingly those with influenza and AF overwhelmingly had Medicare as their primary payer. Records with influenza and AF were more likely to be male (49 % vs 43 % without AF) and White (77 % vs 62 %), and have a higher comorbidity burden, especially in regard to heart failure (39 % vs 14 %), chronic pulmonary disease (40 % vs 35 %), hypertension (73 % vs 58 %), renal failure (29 % vs 16 %) and valvular disease (14 % vs 4 %, all p-values < 0.0001). Median income level, obesity and tobacco use were similar between the two groups.

In both univariate and multivariate primary analyses using traditional regression techniques, records with influenza and AF were

Table 1
Demographics of Influenza Hospitalizations Based on Association with Atrial Fibrillation, National Inpatient Sample 2009–2018.

Characteristics	Without Atrial Fibrillation (N = 1,115,615)	With Atrial Fibrillation (N = 265,678)	p-value
Age			< 0.0001
18–49	269,663 (24)	5,936 (2)	
50–64	291,721 (26)	31,602 (12)	
65–79	309,858 (28)	93,613 (35)	
80+	244,374 (22)	134,527 (51)	
Female	638,436 (57)	135,145 (51)	< 0.0001
Race			< 0.0001
White	696,680 (62)	205,838 (77)	
Black	166,765 (15)	18,390 (7)	
Hispanic/Latino	120,638 (11)	16,132 (6)	
Other	70,678 (6)	13.310 (5)	
Primary payer			< 0.0001
Medicare	621,888 (56)	222,333 (84)	
Medicaid	160,460 (14)	9,993 (4)	
Private (including HMO)	247,157 (22)	26,497 (10)	
Other	84,392 (8)	6,621 (2)	
Hospital type/location			< 0.0001
Rural	142,791 (13)	31,104 (12)	
Urban, non-teaching	315,155 (28)	73,879 (28)	
Urban, teaching	655,724 (59)	160,532 (60)	
Median Income (by ZIP code, in quartiles)			< 0.0001
First (lowest income)	342,077 (31)	64,222 (24)	
Second	286,442 (26)	67,439 (25)	
Third	254,841 (22)	67,633 (25)	
Fourth (highest income)	208,373 (19)	62,210 (23)	
Tobacco use	403,638 (36)	89,319 (34)	< 0.0001
Elixhauser Comorbidity Measures			
Congestive heart failure	154,677 (14)	104,532 (39)	<. 0001
Chronic pulmonary disease	387,562 (35)	105,828 (40)	< 0.0001
Diabetes, uncomplicated	205,908 (18)	51,382 (19)	< 0.0001
Diabetes with chronic complications	131,040 (12)	42,019 (16)	< 0.0001
Hypertension	644,033 (58)	194,877 (73)	< 0.0001
Obesity	170,889 (15)	40,153 (15)	0.2407
Peripheral vascular disorders	52,897 (5)	25,185 (9)	< 0.0001
Pulmonary circulation disorders	21,980 (2)	10,679 (4)	< 0.0001
Renal failure	180,077 (16)	77,284 (29)	< 0.0001
Valvular disease	46,776 (4)	37,074 (14)	< 0.0001

HMO = health maintenance organization.
Values expressed as N (%). Because of missing values, percentages do not always add to 100% for each variable.

associated with worse clinical outcomes compared to those without AF, including higher odds of in-hospital mortality (adjusted odds ratio (aOR) 1.56, 95 % confidence interval (CI) 1.49 – 1.65), more ARF (aOR 1.22, 95 % CI 1.19 – 1.25), including ARF requiring mechanical ventilation (aOR 1.37, 95 % CI 1.32 – 1.41), AKI (aOR 1.09, 95 % CI 1.06 – 1.12), including AKI requiring dialysis (aOR 1.61, 95 % CI 1.46 – 1.78) and more cardiogenic shock (aOR 1.90, 95 % CI 1.65 – 2.20, all p-values < 0.0001, see Table 2 as well as **Supplementary Table 6** for a description of the adjusted clinical outcomes models for the primary analysis). In addition, records with influenza and AF were associated with worse healthcare resource outcomes, including higher total hospitalization charges (mean $61,348 vs $49,157 without AF), higher total hospitalization costs (mean $15,628 vs $12,737) and longer length of stay (mean 6.6 vs 5.5 days, all p-values < 0.0001, see Table 3).

For the primary propensity score weighted analysis, the final weights produced good covariate balance between the groups of influenza records with and without AF, as demonstrated by the standardized mean differences (SMDs) between groups ranging between − 0.1 and 0.1 (see **Supplementary Table 2**). As seen in Tables 2 and 3, the propensity score analysis using ATT weighting validated the results of the primary regression analysis.

A total of 628,644 weighted records with a primary ICD code for influenza were obtained from years 2009–2018 of the NIS, of which 114,660 (18 %) had a secondary ICD code for AF. The results of the unadjusted sensitivity analysis were the same as for the primary analysis, showing significantly elevated odds across all measured outcomes (see Tables 4 and 5). For the adjusted sensitivity analysis, while records with influenza and AF had significantly elevated odds of in-hospital mortality (aOR 1.55, 95 % CI 1.38 – 1.74, p-value < 0.0001), ARF (aOR 1.17, 95 % CI 1.12 – 1.22, p-value < 0.0001), ARF requiring mechanical ventilation (aOR 1.44, 95 % CI 1.33 – 1.55, p-value < 0.0001) and AKI requiring dialysis (aOR 1.59, 95 % CI 1.23 – 2.04, p-value = 0.0003), they did not have significantly increased odds of AKI in general (aOR 0.99, 95 % CI 0.95 – 1.04, p-value = 0.6951) or for cardiogenic shock (aOR 1.52, 95 % CI 0.96 – 2.41, p-value = 0.0776, see Table 4 as well as **Supplementary Table 7** for a description of the adjusted clinical outcomes models for the sensitivity analysis). For healthcare resource outcomes, univariate and multivariate sensitivity analysis demonstrated that records with influenza and AF were associated with significantly increased total hospitalization charges (mean $41,470 vs $32,012 without AF), increased total hospitalization costs (mean $10,875 vs $8,551) and increased length of stay (mean 5.3 vs 4.2 days, all p-values < 0.0001, see Table 5) compared to influenza records without AF.

For the propensity score sensitivity analysis, the propensity model again yielded final weights that balanced the groups with and without AF well based on SMDs ranging between − 0.1 and 0.1 (see **Supplementary Table 3**). Again, the propensity score analysis yielded the same results as the multivariate logistic regression analysis, showing that influenza hospitalizations with AF were associated with increased odds of in-hospital mortality, ARF, ARF requiring mechanical ventilation, and AKI requiring dialysis, but not significantly increased odds for AKI in general or cardiogenic shock (see Table 4). For healthcare resource outcomes, the results of the propensity score analysis again matched the multivariate linear regression analysis, showing increased total hospitalization charges, costs, and length of stay for influenza records associated with AF compared to records without AF (see Table 5).

4. Discussion

In this cross-sectional study across 10 years of nationwide discharge data, the presence of AF was associated with worse clinical and healthcare resource outcomes for those hospitalized with influenza, including increased odds of in-hospital mortality. This was validated using propensity score methods to verify the findings observed through traditional regression analysis, and through the use of a sensitivity analysis in those with a primary diagnosis of influenza. This mirrors similar adverse effects seen when influenza occurs alongside other comorbid cardiovascular disorders, such as HF [8,9] or acute MI [11,12].

Our findings that the presence of AF is associated with worse outcomes on influenza hospitalization is concerning, especially in light of the increasing prevalence of AF. In the United States alone, the projected prevalence of AF is expected to rise to 12.1 million cases by the year 2030. [21] In our study, our cohort with AF has a higher mean age as well as an increased frequency of comorbidities compared to our cohort without AF, such as HF, hypertension, valvular disease and diabetes. Therefore, the demographic profile of our study cohort with AF mirrors the characteristics of patients found to have worse outcomes with influenza infection [8,22–24], which coincidentally mirrors the known

Table 2
Primary Analysis of Clinical Outcomes for Influenza Hospitalizations Based on Association with Atrial Fibrillation, National Inpatient Sample, 2009–2018.

	Without AF (N = 1,115,615)	With AF (N = 265,678)	Odds Ratio, unadjusted (±95 % CI)	p-value	Odds Ratio, adjusted* (±95 % CI)	p-value	Odds Ratio, PS analysis† (±95 % CI)	p-value
Outcome								
In-hospital mortality	33,631 (3)	16,760 (6)	2.17 (2.08–2.26)	< 0.0001	1.56 (1.49–1.65)	< 0.0001	1.45 (1.37–1.53)	< 0.0001
Acute respiratory failure	305,159 (27)	98,309 (37)	1.56 (1.53–1.59)	< 0.0001	1.22 (1.19–1.25)	< 0.0001	1.22 (1.08–1.24)	< 0.0001
Acute respiratory failure requiring mechanical ventilation	112,569 (10)	37,179 (14)	1.45 (1.41–1.49)	< 0.0001	1.37 (1.32–1.41)	< 0.0001	1.36 (1.31–1.41)	< 0.0001
Acute kidney injury	216,474 (19)	73,360 (28)	1.59 (1.55–1.62)	< 0.0001	1.09 (1.06–1.12)	< 0.0001	1.07 (1.04–1.10)	< 0.0001
Acute kidney injury requiring dialysis	12,314 (1)	4,346 (2)	1.49 (1.38–1.61)	< 0.0001	1.61 (1.46–1.78)	< 0.0001	1.54 (1.39–1.70)	< 0.0001
Cardiogenic shock	4,764 (<1)	2,539 (1)	2.25 (2.02–2.51)	< 0.0001	1.90 (1.65–2.20)	< 0.0001	1.81 (1.57–2.10)	< 0.0001

AF = atrial fibrillation, CI = confidence interval, PS = propensity score.
Values expressed as N (%) unless otherwise indicated.
* Logistic regression model adjusted for age, sex, race, primary payer, hospital type/location, median income by ZIP code, tobacco use, and 10 comorbidities as defined by Elixhauser software criteria (congestive heart failure, chronic pulmonary disease, diabetes, both uncomplicated and with chronic complications, hypertension, obesity, peripheral vascular disorders, pulmonary circulation disorders, renal failure and valvular disease).
† Propensity score analysis using ATT (average effect of treatment on the treated) weights.

Table 3
Primary Analysis of Healthcare Resource Outcomes for Influenza Hospitalizations Based on Association with Atrial Fibrillation, National Inpatient Sample, 2009–2018.

Outcomes	Without AF (N = 1,115,615)	With AF (N = 265,678)	Parameter Estimate, unadjusted (±SE)	p-value	Parameter Estimate, adjusted† (±SE)	p-value	Parameter Estimate, PS analysis‡ (±SE)	p-value
Total Charges, US dollars ($)	49,157 (±399)	61,348 (±650)	12,192 (±583)	< 0.0001	11,873 (±646)	< 0.0001	12,334 (±603)	< 0.0001
Total Costs, US dollars ($)	12,737 (±86)	15,628 (±135)	2,891 (±134)	< 0.0001	2,787 (±148)	< 0.0001	2,931 (±138)	< 0.0001
Length of Stay, days	5.5 (±0.02)	6.6 (±0.03)	1.2 (±0.04)	< 0.0001	0.8 (±0.04)	< 0.0001	0.8 (±0.04)	< 0.0001

AF = atrial fibrillation, PS = propensity score, SE = standard error.
Values described as mean (±SE) unless otherwise indicated.
† Linear regression model adjusted for age, sex, race, primary payer, hospital type/location, median income by ZIP code, tobacco use, and 10 comorbidities as defined by Elixhauser software criteria (congestive heart failure, chronic pulmonary disease, diabetes, both uncomplicated and with chronic complications, hypertension, obesity, peripheral vascular disorders, pulmonary circulation disorders, renal failure and valvular disease).
‡ Propensity score analysis using ATT (average effect of treatment on the treated) weights.

Table 4
Sensitivity Analysis of Clinical Outcomes for Influenza Hospitalizations Based on Association with Atrial Fibrillation, National Inpatient Sample, 2009–2018.

	Without AF (N = 513,984)	With AF (N = 114,660)	Odds Ratio, unadjusted (±95 % CI)	p-value	Odds Ratio, adjusted† (±95 % CI)	p-value	Odds Ratio, PS analysis‡ (±95 % CI)	p-value
Outcomes								
In-hospital mortality	6,728 (1)	3,618 (3)	2.46 (2.24–2.70)	< 0.0001	1.55 (1.38–1.74)	< 0.0001	1.37 (1.22–1.54)	< 0.0001
Acute respiratory failure	102,621 (20)	31,020 (27)	1.49 (1.44–1.54)	< 0.0001	1.17 (1.12–1.22)	< 0.0001	1.16 (1.11–1.21)	< 0.0001
Acute respiratory failure requiring mechanical ventilation	22,907 (4)	7,616 (7)	1.53 (1.44–1.62)	< 0.0001	1.44 (1.33–1.55)	< 0.0001	1.39 (1.28–1.51)	< 0.0001
Acute kidney injury	73,866 (14)	23,294 (20)	1.52 (1.46–1.58)	< 0.0001	0.99 (0.95–1.04)	0.6951	0.98 (0.94–1.03)	0.3638
Acute kidney injury requiring dialysis	2,188 (<1)	678 (1)	1.39 (1.15–1.68)	< 0.0001	1.59 (1.23–2.04)	0.0003	1.45 (1.13–1.86)	0.0039
Cardiogenic shock	437 (<1)	230 (<1)	2.36 (1.65–3.38)	< 0.0001	1.52 (0.96–2.41)	0.0776	1.47 (0.93–2.32)	0.1027

AF = atrial fibrillation, CI = confidence interval, PS = propensity score.
Values expressed as N (%) unless otherwise indicated.
† Logistic regression model adjusted for age, sex, race, primary payer, hospital type/location, median income by ZIP code, tobacco use, and 10 comorbidities as defined by Elixhauser software criteria (congestive heart failure, chronic pulmonary disease, diabetes, both uncomplicated and with chronic complications, hypertension, obesity, peripheral vascular disorders, pulmonary circulation disorders, renal failure and valvular disease).
‡ Propensity score analysis using ATT (average effect of treatment on the treated) weights.

Table 5
Sensitivity Analysis of Healthcare Resource Outcomes for Influenza Hospitalizations Based on Association with Atrial Fibrillation, National Inpatient Sample, 2009–2018.

Outcomes	Without AF (N = 513,984)	With AF (N = 114,660)	Parameter Estimate, unadjusted (±SE)	p-value	Parameter Estimate, adjusted* (±SE)	p-value	Parameter Estimate, PS analysis† (±SE)	p-value
Total Charges, US dollars ($)	32,012 (±274)	41,470 (±624)	9,459 (±604)	< 0.0001	7,753 (±676)	< 0.0001	7,715 (±653)	< 0.0001
Total Costs, US dollars ($)	8,551 (±62)	10,875 (±134)	2,324 (±141)	< 0.0001	1,845 (±153)	< 0.0001	1,837 (154)	< 0.0001
Length of Stay, days	4.2 (±0.02)	5.3 (±0.04)	1.1 (±0.04)	< 0.0001	0.6 (±0.04)	< 0.0001	0.6 (±0.04)	< 0.0001

AF = atrial fibrillation, PS = propensity score, SE = standard error.
Values described as mean (±SE) unless otherwise indicated.
* Linear regression model adjusted for age, sex, race, primary payer, hospital type/location, median income by ZIP code, tobacco use, and 10 comorbidities as defined by Elixhauser software criteria (congestive heart failure, chronic pulmonary disease, diabetes, both uncomplicated and with chronic complications, hypertension, obesity, peripheral vascular disorders, pulmonary circulation disorders, renal failure and valvular disease).
† Propensity score analysis using ATT (average effect of treatment on the treated) weights.

risk profile for AF. [14,25] It is notable, however, that even after adjustment for these confounders by using traditional regression as well as propensity score weighting, AF was still significantly associated with worse outcomes in our study.

Of the 19 % of our influenza hospitalization cohort who had AF, the percentage of pre-existing versus new-onset AF cannot be determined due to the lack of "present on admission" indicators for diagnoses within the NIS. Interestingly, the frequency of AF in our cohort is larger than the prevalence seen in the general United States population within similar age groups. In the ATRIA study [26], which used records from a large, integrated health maintenance organization in California, the prevalence of AF ranged from 3.8 % in adults aged 60 or higher, to 9.0 % in adults aged 80 or higher. Given the demographics of our AF cohort, it would be reasonable to suggest that a significant portion of our cohort represents patients with pre-existing AF. Patients with pre-existing AF have chronic atrial fibrosis and resultant remodeling of the electric pathways, down to the cellular level. [27] When infected by influenza, the resulting pro-inflammatory state can act as a catalyst, stimulating the development and maintenance of AF in influenza patients [28]. Therefore, increased inflammation leading to exacerbation of AF could be one explanation for how patients with pre-existing AF may require hospital admission due to influenza infection.

However, given that the AF prevalence of 19 % is much higher in our study cohort than in the general population, it would also be reasonable that patients with new-onset AF comprise a significant portion of our AF cohort as well. Influenza infection is hypothesized to lead to the development of new-onset AF through multiple pathways. A study utilizing a mouse model demonstrated that the influenza virus can directly infect cardiomyocytes and cause direct effects on electrical conduction through the myocardium [29,30]. Influenza also promotes a systemic inflammatory response, including an increased production of pro-inflammatory IL-6 and IL-8, which have been found to promote the development of AF [31,32], as well as increased sympathetic tone that is also arrhythmogenic [33–35]. Additionally, influenza can promote other cardiac complications through similar inflammatory mechanisms that can lead to cardiac injury and secondary AF, such as atherosclerosis and acute MI [31,36] as well as myocarditis and heart failure [29,30,37].

Indeed, most of the available research examining the relationship between influenza and AF focuses on how influenza infection may lead to the development of new-onset AF. A study by Chang et al [35] used a national health insurance database to enroll patients with newly diagnosed AF across 10 years, along with age and sex-matched controls without AF. After dividing the patients into groups based on influenza infection and influenza vaccination status one year prior to their enrollment, Chang et al found that those with influenza and were unvaccinated had a higher odds of developing new-onset AF (aOR 1.18, 95 % CI 1.01–1.38, p-value 0.032) than those who did not have influenza. If the participants both developed influenza and received the influenza vaccine within the past year, the risk of new-onset AF was insignificant (aOR 1.14, 95 % CI 0.93–1.39, p-value 0.214). More recently, in a retrospective cohort study across a nationwide discharge database in France, Piroth et al [38] noted that compared to COVID-19 infection, AF was more likely to complicate influenza infection during the 2018–19 seasonal influenza pandemic (15.8 % vs 12.4 % of those with COVID-19, p-value < 0.0001).

To our knowledge, only one other study examined the clinical outcomes of influenza hospitalization based on AF status. In a retrospective cohort study using an electronic records database across a network of 5 hospitals in New York City, Musikantow et al compared the outcomes of two overlapping cohorts of COVID-19 patients against a cohort of patients with laboratory-confirmed influenza infection. Patients who had both influenza and AF were found to have a higher risk of in-hospital mortality compared to those with influenza and without AF (16 % vs 9 % without AF, risk ratio (RR) 1.78, p-value < 0.01), as well as a higher risk of intubation (14 % vs 7 %, RR 2.00, p-value < 0.01) and longer length of stay (median 7 vs 5 days, p-value < 0.01) [39]. Our study validates these findings, and adds further evidence that patients with AF constitute a high-risk group of those infected with influenza. As the Center for Disease Control and Prevention lists patients with cardiovascular conditions as a priority for influenza vaccination due to increased risk of severe influenza, [40] future studies are indicated to see if influenza vaccination can prevent the worse outcomes seen in patients with influenza and AF.

In recognition of the differences in diagnosis coding strategies seen within administrative databases, we produced a sensitivity analysis using a subset of records with a primary diagnosis code for influenza as the reason for admission, complicated by secondary AF. Within this subset of the data, both the standard regression and propensity score-weighted analyses yielded results similar to the main analysis. However, while all forms of AKI and cardiogenic shock were found to be significantly associated with the presence of AF in the main analysis, the association was not present in the sensitivity analysis. Interestingly, the presence of AF remained significantly associated with more serious forms of AKI requiring dialysis in the sensitivity analysis, even after accounting for pre-existing renal disease in both regression and propensity score models. Both AF and renal disease share multiple risk factors, and as renal disease becomes more severe and advances towards later stages, AF becomes more common [41]. Therefore, a potential explanation for our findings is that AKI is more severe when it occurs during influenza hospitalization and when AF is also present; therefore, if AKI were to occur, it would be more likely to require hemodialysis.

5. Limitations

Our study contained several limitations that are commonly found in

secondary analysis of administrative datasets. While the intent of our analysis was to study the effects of comorbid AF complicating influenza hospitalizations, as stated previously the NIS does not contain prior to admission indicators for any diagnosis codes. Therefore, while it is reasonable to assume that influenza and not AF was the primary reason for hospitalization for the sensitivity analysis, it is impossible to determine if the AF is new-onset as a result of influenza infection or a pre-existing condition. In addition, there is a possibility that patients with AF would be excluded from the analysis if the AF was stable during hospitalization and not the focus of the hospital stay, in which case the corresponding AF diagnosis code may not be on the discharge record.

As the NIS is an administrative database, no clinical data is available to make inferences regarding outcomes based on the type and severity of either AF or influenza. Also, because of the lack of clinical data available, misattribution bias could be present due to inaccurate coding and the inability to use clinical information to validate ICD codes used within the database. As only acute hospitalizations are recorded within the NIS, we were not able to study long-term outcomes in patients with influenza who have AF and were able to discharge from the hospital. Finally, it is important to note that our study includes data before, during and after the year 2015, when the transition from ICD to 9-CM to ICD-10-CM took place. To account for this, we crosswalked all codes used in the study to ensure equality as much as possible between both ICD versions of our study definitions. However, inevitable variation exists between the two versions, and so it is possible that the discrepancy could have affected our results.

6. Conclusion

In conclusion, in a cross-sectional analysis across 10 years of a nationwide, all-payer discharge dataset, the presence of AF is associated with worse clinical and healthcare resource outcomes for patients with influenza requiring hospitalization, including higher odds of in-hospital mortality.

Declaration of Competing Interest

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

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.101106.

References

[1] B. Chuaychoo, S. Ngamwongwan, B. Kaewnaphan, et al., Clinical manifestations and outcomes of respiratory syncytial virus infection in adult hospitalized patients, J. Clin. Virol. 117 (2019) 103–108.

[2] E. Walker, M.G. Ison, Respiratory viral infections among hospitalized adults: experience of a single tertiary healthcare hospital, Influenza Other Respir. Viruses 8 (3) (2014) 282–292.

[3] K. Widmer, Y. Zhu, J.V. Williams, M.R. Griffin, K.M. Edwards, H.K. Talbot, Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults, J. Infect. Dis. 206 (1) (2012) 56–62.

[4] A. Hessami, A. Shamshirian, K. Heydari, et al., Cardiovascular diseases burden in COVID-19: Systematic review and meta-analysis, Am. J. Emerg. Med. 46 (2021) 382–391.

[5] L. Kim, S. Garg, A. O'Halloran, et al., Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified through the US Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET), Clin. Infect. Dis. 72 (9) (2021) e206–e214.

[6] G. Cabezón Villalba, I.J. Amat-Santos, C. Dueñas, et al., Impact of the presence of heart disease, cardiovascular medications and cardiac events on outcome in COVID-19, Cardiol J 28 (3) (2021) 360–368.

[7] X. Xu, L. Blanton, A.I.A. Elal, et al., Update: Influenza Activity in the United States During the 2018–19 Season and Composition of the 2019–20 Influenza Vaccine, MMWR Morb. Mortal. Wkly Rep. 68 (24) (2019) 544–551.

[8] M.S. Panhwar, A. Kalra, T. Gupta, et al., Effect of Influenza on Outcomes in Patients With Heart Failure, JACC Heart Fail 7 (2) (2019) 112–117.

[9] M.S. Panhwar, A. Kalra, T. Gupta, et al., Relation of Concomitant Heart Failure to Outcomes in Patients Hospitalized With Influenza, Am. J. Cardiol. 123 (9) (2019) 1478–1480.

[10] C. Sandoval, S.D. Walter, P. Krueger, M. Smieja, A. Smith, S. Yusuf, M.B. Loeb, Risk of hospitalization during influenza season among a cohort of patients with congestive heart failure, Epidemiol. Infect. 135 (4) (2007) 574–582.

[11] P. Vejpongsa, D. Kitkungvan, M. Madjid, et al., Outcomes of Acute Myocardial Infarction in Patients with Influenza and Other Viral Respiratory Infections, Am. J. Med. 132 (10) (2019) 1173–1181.

[12] R. Cardoso, M. Rivera, M.J. Czarny, et al., In-Hospital Management and Outcomes of Patients With Acute Myocardial Infarction and Influenza, Am. J. Cardiol. 125 (6) (2020) 840–844.

[13] S.S. Chugh, R. Havmoeller, K. Narayanan, et al., Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study, Circulation 129 (8) (2014) 837–847.

[14] G. Lippi, F. Sanchis-Gomar, G. Cervellin, Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge, Int J Stroke 16 (2) (2021) 217–221.

[15] J. Steer, J. Gibson, S.C. Bourke, The DECAF Score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease, Thorax 67 (11) (2012) 970–976.

[16] A.S. Abdullah, G. Eigbire, M. Ali, et al., Relationship of Atrial Fibrillation to Outcomes in Patients Hospitalized for Chronic Obstructive Pulmonary Disease Exacerbation, J Atr Fibrillation 12 (2) (2019) 2117.

[17] R. Desai, B. Hanna, S. Singh, et al., Trends and Outcomes in Sepsis Hospitalizations With and Without Atrial Fibrillation: A Nationwide *Inpatient* Analysis, Crit. Care Med. 47 (8) (2019) e630–e638.

[18] S. Jamal, M.Z. Khan, A. Kichloo, et al., The Effect of Atrial Fibrillation on Inpatient Outcomes of Patients with Acute Pancreatitis: A Two-year National Inpatient Sample Database Study, J Innov Card Rhythm Manag 11 (12) (2020) 4338–4344.

[19] Overview of the National (Nationwide) Inpatient Sample (NIS). www.hcup-us.ahrq.gov/nisoverview.jsp. (Accessed August 15, 2021.).

[20] Checklist for Working with the NIS. https://www.hcup-us.ahrq.gov/db/nation/nis/nischecklist.jsp. (Accessed August 30, 2021.).

[21] S. Colilla, A. Crow, W. Petkun, D.E. Singer, T. Simon, X. Liu, Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population, Am. J. Cardiol. 112 (8) (2013) 1142–1147.

[22] W.W. Thompson, D.K. Shay, E. Weintraub, et al., Mortality associated with influenza and respiratory syncytial virus in the United States, JAMA 289 (2) (2003) 179–186.

[23] J. Mauskopf, M. Klesse, S. Lee, G. Herrera-Taracena, The burden of influenza complications in different high-risk groups: a targeted literature review, J Med Econ 16 (2) (2013) 264–277.

[24] D. Mertz, T.H. Kim, J. Johnstone, et al., Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis, BMJ 347 (2013), f5061.

[25] R.R. Huxley, F.L. Lopez, A.R. Folsom, et al., Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study, Circulation 123 (14) (2011) 1501–1508.

[26] A.S. Go, E.M. Hylek, K.A. Phillips, et al., Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study, JAMA 285 (18) (2001) 2370–2375.

[27] S. Nattel, M. Harada, Atrial remodeling and atrial fibrillation: recent advances and translational perspectives, J. Am. Coll. Cardiol. 63 (22) (2014) 2335–2345.

[28] M.D. Engelmann, J.H. Svendsen, Inflammation in the genesis and perpetuation of atrial fibrillation, Eur. Heart J. 26 (20) (2005) 2083–2092.

[29] D. Filgueiras-Rama, J. Vasilijevic, J. Jalife, et al., Human influenza A virus causes myocardial and cardiac-specific conduction system infections associated with early inflammation and premature death, Cardiovasc. Res. 117 (3) (2021) 876–889.

[30] H.Y. Pan, H. Yamada, J. Chida, et al., Up-regulation of ectopic trypsins in the myocardium by influenza A virus infection triggers acute myocarditis, Cardiovasc. Res. 89 (3) (2011) 595–603.

[31] J.J. Bouwman, F.L. Visseren, M.C. Bosch, K.P. Bouter, R.J. Diepersloot, Procoagulant and inflammatory response of virus-infected monocytes, Eur. J. Clin. Invest. 32 (10) (2002) 759–766.

[32] Y. Guo, G.Y. Lip, S. Apostolakis, Inflammation in atrial fibrillation, J. Am. Coll. Cardiol. 60 (22) (2012) 2263–2270.

[33] P.S. Chen, L.S. Chen, M.C. Fishbein, S.F. Lin, S. Nattel, Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy, Circ. Res. 114 (9) (2014) 1500–1515.

[34] K.M. Grebe, K. Takeda, H.D. Hickman, et al., Cutting edge: Sympathetic nervous system increases proinflammatory cytokines and exacerbates influenza A virus pathogenesis, J. Immunol. 184 (2) (2010) 540–544.

[35] T.Y. Chang, T.F. Chao, C.J. Liu, et al., The association between influenza infection, vaccination, and atrial fibrillation: A nationwide case-control study, Heart Rhythm 13 (6) (2016) 1189–1194.

[36] M. Madjid, M. Naghavi, S. Litovsky, S.W. Casscells, Influenza and cardiovascular disease: a new opportunity for prevention and the need for further studies, Circulation 108 (22) (2003) 2730–2736.

[37] S. Kytömaa, S. Hegde, B. Claggett, et al., Association of Influenza-like Illness Activity With Hospitalizations for Heart Failure: The Atherosclerosis Risk in Communities Study, JAMA Cardiol 4 (4) (2019) 363–369.

[38] L. Piroth, J. Cottenet, A.S. Mariet, et al., Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study, Lancet Respir Med 9 (3) (2021) 251–259.
[39] D.R. Musikantow, M.K. Turagam, S. Sartori, et al., Atrial Fibrillation in Patients Hospitalized With COVID-19: Incidence, Predictors, Outcomes, and Comparison to Influenza, JACC Clin Electrophysiol 7 (9) (2021) 1120–1130.
[40] Who Should and Who Should NOT get a Flu Vaccine. https://www.cdc.gov/flu/prevent/whoshouldvax.htm. (Accessed November 15, 2021.).
[41] K.P. Ng, N.C. Edwards, G.Y. Lip, J.N. Townend, C.J. Ferro, Atrial fibrillation in CKD: balancing the risks and benefits of anticoagulation, Am. J. Kidney Dis. 62 (3) (2013) 615–632.