Relationship of Atrial Fibrillation to Outcomes in Patients Hospitalized for Chronic Obstructive Pulmonary Disease Exacerbation

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Abstract

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of hospitalization and is associated with an increased incidence of atrial fibrillation (AF). The impact of AF on in-hospital outcomes, including mortality, in patients hospitalized for COPD exacerbation is not well elucidated.

Methods

We used the National Inpatient Sample database to examine discharges with the primary diagnosis of COPD exacerbation and compared mortality, length of stay and costs in patients with AF compared to those without AF. The study adjusted the outcomes for known cardiovascular risk factors and confounders using logistic regression and propensity score matching analysis.

Results

Among 1,377,795 discharges with COPD exacerbation, 16.6% had AF. Patients with AF were older and had more comorbidities. Mortality was higher (2.4%) in the AF group than in the no AF group (1%), p <0.001. After adjustment to age, sex and confounders, AF remained an independent predictor for mortality, OR:1.44 (95% CI 133 – 1.56, p <0.001), prolonged length of stay, OR:1.63 (95% CI 1.57 – 1.69, p <0.001) and increased cost, OR: 1.45 (95% CI: 1.40 – 1.49, p <0.001).

Conclusions

Among patients with COPD exacerbation, AF was associated with increased mortality and higher resource utilization.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of resource utilization and hospitalization worldwide. Patients with COPD also have increased risk of cardiovascular mortality and development of arrhythmias, including atrial fibrillation (AF) [1-6]. Studies showed worse outcomes and symptom burden in patients with AF when associated with COPD, compared to those without COPD, beyond what was explained by the classical cardiovascular risk factors [7]. Although the relationship is bidirectional, little is known about the impact of atrial fibrillation on patients hospitalized for COPD exacerbation. The aim of this study was to examine the mortality and costs associated with AF in a cohort of patients hospitalized for COPD exacerbation.

Key Words

Atrial fibrillation, Chronic Obstructive Lung Disease, COPD, Arrhythmia, In-hospital mortality, National Inpatient Sample, ICD code.

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Methods

The study used discharge records from the National Inpatient Sample (NIS) database. The NIS is the largest all-payer hospitalization database in the United States and is available to the public. It is part of the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality (AHRQ). Data was analyzed for the years 2012 to 2014 due to similarities in the sampling design. For these years the NIS provided a 20% stratified sample from all hospital discharges nationwide excluding rehabilitation and long-term care units. It contains approximately 7 million discharge records per year and contains a weight variable

(DISCWT) that allows calculation of national estimates amounting to 35 million records or 97% of all discharges nationwide. The NIS is a discharge level database and does not provide longitudinal information about readmissions and multiple hospitalizations for the same patient. Information provided includes demographic data, principal diagnosis and up to 29 associated secondary diagnoses addressed during the hospitalization, procedures performed, payer data and total charges [8].

We included records of those patients ≥ 18 years of age hospitalized for COPD exacerbation as the primary diagnosis identified by the International Classification of Diseases, 9th Revision- Clinical Modification (ICD-9-CM) code 491.21 [9]. The study divided the records into two groups - the AF group and no AF group - based on the presence of AF (identified by the ICD-9 code 427.31) as a secondary diagnosis. We excluded patients with missing data on sex, age, mortality and length of stay (LOS). Patient with an indicator for transfer to another acute hospital were excluded to reduce the risk of record duplication.

The primary outcome was in-hospital mortality. Secondary outcomes included prolonged LOS defined arbitrarily as LOS > 90th percentile (8 days) and high total charges defined as charges >90th percentile (54,785 $) for patients with COPD exacerbation.

The analysis compared the baseline characteristics and outcomes between between the two groups. To adjust for known confounders, we incorporated covariables with significant differences in univariate analysis into a logistic regression model to calculate the adjusted Odds Ratio (AOR). The final model included age, sex and cardiovascular risk factors such as hypertension, obesity, hyperlipidemia, history of coronary artery disease obstructive sleep apnea (OSA), and the presence of myocardial infarction. We also adjusted for the need for mechanical ventilation, acute kidney injury, and the presence of pneumonia or sepsis. Furthermore, the analysis added the numerical Charlson Index to the model. The Charlson Index is often used to predict mortality in studies based on administrative databases [10]. The score is based on 17 indicators for comorbidities that affect the in-hospital mortality such as myocardial infarction, heart failure, diabetes mellitus with or without complications, chronic kidney disease, rheumatic disease, cerebrovascular disease, hemiplegia, cancer, COPD and AIDS. Higher score indicates more comorbidities and correlates with an increased risk of death [11]. All covariables were identified using the relevant ICD-9 codes illustrated in supplementary file 1. We created a secondary logistic model adjusting for all above variables included in the Charlson index excluding COPD. Continuous variables were compared using student t-test. Categorical variables were compared using Chi-square test. Data analysis used Stata software version 14 (StataCorp LP, College Station, TX).

The study used propensity score matching analysis to generate matched control group for the AF group. Using weighted results, we matched patients with AF in a "nearest neighbor" algorithm with 1:1 ratio to matched controls. Matching was based on a single propensity score which was derived from multiple variables and comorbid conditions that can affect the development of AF and influence the outcomes [12]. Covariables used in the propensity score analysis include age, sex, Charlson score, AKI, HTN, history of chronic coronary artery disease, obesity, use of mechanical ventilation, OSA, the presence of sepsis or pneumonia. To ensure adequate matching, a balance of >10% of the standardized difference between the AF and the control groups was deemed as significant [13]. The analysis subsequently compared the outcomes using Mc Nemar test for correlated binary proportions [12] .

The Rochester Regional Health Institution Review Board exempted the study as no identifying personal information was included in the database.

Results

The study included a total of 1,377,795 "weighted" discharges with a primary diagnosis of COPD exacerbation. AF was present in 45,769 16.6%. Mean age was 68.56, women 55.5 %. The overall in-hospital mortality rate was 1.25 %.

Those with atrial fibrillation were older and had more comorbidities [Table 1]. Mortality rate was higher in the AF group compared to the no-AF group; 2.4% versus 1%, p <0.001. On multivariable regression analysis, AF was associated with AOR: 1.46 (95% CI 134 – 1.59, p <0.001) for in-hospital mortality. Other independent predictors of mortality are demonstrated in [Table 2]. After propensity score matching, AF was associated with relative risk 1.48 (1.35 - 1.62) for in-hospital mortality. Table 3 illustrates the baseline characteristics post propensity score matching. AF was also associated with prolonged LOS, AOR: 1.631.63 (95% CI 1.57 – 1.69, p <0.001), and high costs, AOR: 1.45 (95% CI: 1.40 – 1.49, p <0.001) (supplementary file1).

Discussion

Most of the studies that examined the relationship between AF, COPD and outcomes focused on AF population. In this study, we found a high prevalence of AF (16.6%) in patients hospitalized for COPD exacerbation regardless of onset. This is similar to prior studies with an estimated prevalence of 15%. [14] In a retrospective study of COPD patients referred for Holter monitoring, AF was found in 23% of patients. The prevalence increases with COPD severity [2,5]. Several mechanisms have been postulated to explain the high prevalence such as the presence of common cardiovascular risk factors including smoking, underlying atherosclerosis, heart failure, inflammation, and OSA. Furthermore, the effect of beta-agonists, hypoxia, inducing higher sympathetic drive and altering automaticity, and hypercapnia, by increasing atrial refractoriness, have been postulated [15]. Reports from the Malmo project have adjusted for several of these mechanisms highlighting the possibility of reduced lung volumes as an independent predictor for the development of AF [5].

In our study, AF was associated with 1.46 times the odds of in-hospital mortality. Several prospective studies have elucidated the higher mortality associated with AF in the general population and in a selected subgroup of patients [16,17]. Limited data is available on the impact of AF on outcomes of COPD specifically [18]. As in our study, the effect on mortality remained significant after the

Table 1: Baseline characteristics

Variable	Atrial fibrillation (N=228,845)	No Atrial fibrillation (N= 1,148,940)	Overall (N= 1,377,785)	p-value
Age (mean, 95% CI)	74.9 (74.77 - 74.95)	67.3 (67.27 - 67.36)	68.57 (68.52 - 68.61)	<0.001
Female sex	110,915 (48.5%)	654,015 (56.9%)	764,925 ()	<0.001
Essential hypertension	117,945 (51.5%)	614,600 (53.5%)	732,545 53.2% ()	<0.001
Coronary artery disease	103,935 (45.4%)	331,380 (28.8%)	435,315 (31.6%)	<0.001
Acute kidney injury	28,425 (12.4%)	82,815 (7.2%)	111,240 (8.1%)	<0.001
Mechanical ventilation	7,240 (3.2%)	23,780 (2.1%)	31,020 (2.3%)	<0.001
Sepsis	3,415 (1.5%)	10,895 (0.9%)	14,310 (1.0%)	<0.001
Myocardial infarction	25,835 (11.3%)	91,875 (8.0%)	117,710 (8.5%)	<0.001
Congestive heart failure	122,650 (53.6%)	270,360 (23.5%)	393,010 (28.5%)	<0.001
Diabetes mellitus	72,500 (31.7%)	301,375 (26.2%)	373,875 (27.1%)	<0.001
Diabetes with Complications	8,380 (3.7%)	33,880 (2.9%)	42,260 (3.1%)	<0.001
Obstructive sleep apnea	31,895 (13.9%)	118,935 (10.4%)	150,830 (10.9%)	<0.001
Morbid obesity	18,485 (8.1%)	82,540 (7.2%)	101,025 (7.3%)	<0.001
Chronic renal disease	52,890 (23.1%)	139,345 (12.1%)	192,235 (14.0%)	<0.001
Pneumonia	52,710 (23.0%)	239,315 (20.8%)	292,025 (21.2%)	<0.001
Cerebrovascular accident	9,370 (4.1%)	32,230 (2.8%)	41,600 (3.0%)	<0.001
Ventricular tachycardia	5,540 (2.4%)	9,465 (0.8%)	15,005 (1.1%)	<0.001
Ventricular fibrillation	155 (0.07%)	370 (0.03%)	525 (0.04%)	<0.001
Charlson Index (mean)	2.96 (2.94 - 2.97)	2.27 (2.27 - 2.28)	2.39 (2.38 - 2.39)	<0.001
In-hospital mortality	5,440 (2.4%)	11,805 (1.0%)	17,245 (1.3%)	<0.001

Table 2: In-hospital mortality and independent predictors of mortality

Variable	OR	p-value	95% CI	
Atrial fibrillation	1.45	<0.001	1.33	1.58
Age (per year)	1.05	<0.001	1.05	1.05
Female sex	0.96	0.268	0.89	1.03
Acute kidney injury	2.04	<0.001	1.86	2.23
Charlson Index	1.12	<0.001	1.10	1.15
Pneumonia	1.23	<0.001	1.14	1.34
Hypertension	0.93	0.082	0.86	1.01
Sepsis	4.06	<0.001	3.50	4.70
Coronary artery disease	0.87	0.001	0.80	0.94
Hyperlipidemia	0.78	<0.001	0.72	0.84
Obstructive sleep apnea	0.66	<0.001	0.57	0.76
Morbid obesity	0.77	0.004	0.65	0.92
Mechanical ventilation	24.37	<0.001	22.24	26.72

Table 3: Post-propensity score characteristics and outcomes.

Variable	AF (N= 45,769)	No AF (N= 45,769)	SD
Age (mean)	74.86	75.01	-1.4
Female sex	48.5%	48.4%	0.1
Charlson Index (mean)	2.96	2.99	-1.8
Acute kidney injury	12.4%	12.3%	0.5
Pneumonia	23.0%	22.2%	2.1
Hypertension	51.5%	51.6%	-0.1
Sepsis	1.5%	0.9%	5.5
Obstructive sleep apnea	13.9%	12.9%	3.3
Morbid obesity	8.1%	7.1%	3.5
Mechanical ventilation	3.2%	2.0%	7
Coronary artery disease	45.4%	45.6%	-0.4
Hyperlipidemia	43.3%	43.7%	-0.9
In-hospital mortality	2.4%	1.6%	6
Ventricular tachycardia	2.4%	1.1%	10.8
Ventricular fibrillation	0.07%	0.04%	1.5
Prolonged length of stay (> 8 days)	12.2%	8.1%	14.2
High charges (> 54785 dollars)	16.3%	11.1%	15.4

adjustment for known cardiovascular risks and comorbidities. In this report, patients with AF were less likely to be females and had more comorbidities; notably heart failure, coronary artery disease and OSA. Work is ongoing to reflect the progress in our understanding of the multidirectional influence these risk factors [10,19,20]. AF may constitute a surrogate for worse cardiovascular risks, via coronary artery disease or heart failure. For example, in a multinational prospective study, heart failure was the main causes of death in patients with AF [21]. Our analysis adjusted for these variables, but the impact remained significant. A study of post myocardial infarction patients found increased risk of ventricular fibrillation in patients presenting with chronic AF [22]. In our study, there was increased ventricular fibrillation in the AF group, but the rates were low to explain the increased mortality. Furthermore, the presence of history of prior history of coronary artery disease was not associated with increased mortality during the short in-hospital stay. Patients with known coronary artery disease are often on medical therapy including statin, beta-blockers and aspirin which provide protective effect. Interestingly, ventricular tachycardia was increased in the AF group up to 2.4% versus 1.1 after propensity matching. It was not possible to differentiate between sustained and non-sustained ventricular tachycardia in this database, and therefore would not explain the

excess mortality. It leaves the possibility of AF as an independent predictor of mortality in COPD as seen in the general population.

In addition to worse mortality, our analysis showed increased resource utilization. The presence of AF was associated with higher rates of prolonged LOS even after adjustment for confounders. COPD exacerbation constitutes one of the major causes for hospitalization in the US. Further study is needed to examine the impact of AF control, rhythm or rate, and use of beta-blockers on resource utilization.

Limitations of this study include the lack of characterization of AF subtypes in our cohort as new onset, paroxysmal or permanent. The analysis also did not account for continuous variables such as heart rate, blood pressure, ejection fraction, lipid profile, and the use of medications including beta-blockers and anticoagulants. Despite the use of logistic regression and propensity score matching, retrospective studies carry the risk of missing unaccounted confounding variables. Administrative databases rely on ICD-9-CM codes to identify covariables and study subjects. Coding practices may be inconsistent among participating hospitals and may be influenced by reimbursement value and the condition of interest [23,24]. Data entries included in the NIS are discharge level rather than patient level and do not account for readmission and so allows for duplication [25]. We aimed to reduce the duplication risk by the exclusion of patients with an indicator for transfer to another acute care facility. The database doesn't provide longitudidal follow-up for patient. Nevertheless, the NIS databases representation has been validated against the center for Medicare and Medicaid Services. We included patients with a principal diagnosis of COPD exacerbation to generate the most representative cohort of patients hospitalized primarily for COPD exacerbation.

The study used the strength of the NIS database with it's large sample size. It used 2 approaches to adjust for multiple confounding variables, logistic regression and propensity matching analysis, with consistent results. This is one of the few reports that examined the impact of AF specifically on in-hospital mortality in COPD exacerbation. Our findings may suggest that there is an opportunity to look at AF as a detrimental event in COPD exacerbation. Whether a tailored management approach is of prognostic value remains to be studied.

Conclusion

The presence of AF in patients hospitalized for COPD exacerbation was associated with increased risk of inpatient mortality, prolonged LOS and higher costs.

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