



The burden and impact of arrhythmia in chronic obstructive pulmonary disease: Insights from the National Inpatient Sample

Rupak Desai^{a,*}, Upenkumar Patel^b, Sandeep Singh^c, Rushikkumar Bhuvu^d, Hee Kong Fong^e, Pratyusha Nunna^f, Dipen Zalavadia^g, Hitanshu Dave^h, Sejal Savaniⁱ, Rajkumar Doshi^j

^a Department of Cardiology, Atlanta VA Medical Center, Decatur, GA, USA

^b Department of Internal Medicine, Nassau University Medical Center, East Meadow, NY, USA

^c Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

^d Department of Internal Medicine, Canton Medical Education Foundation, Canton, OH, USA

^e Department of Internal Medicine, University of Missouri-Columbia, Columbia, MO, USA

^f Clinical Observer, Carle Foundation Hospital, Urbana, IL, USA

^g Department of Internal Medicine, The Wright Center for Graduate Medical Education, Scranton, PA, USA

^h Department of Internal Medicine, Jersey Shore University Medical Center, Neptune, NJ, USA

ⁱ Public Health, New York University, New York, NY, USA

^j Department of Internal Medicine, University of Nevada School of Medicine, Reno, NV, USA

ARTICLE INFO

Article history:

Received 8 September 2018

Received in revised form 22 December 2018

Accepted 18 January 2019

Available online 25 January 2019

Keywords:

Chronic obstructive pulmonary disease (COPD)

Arrhythmia

Atrial fibrillation

Prevalence

In-hospital mortality

Gender and racial disparities

ABSTRACT

Background: We aimed to analyze the burden and predictors of arrhythmias and in-hospital mortality in chronic obstructive pulmonary disease (COPD)-related hospitalizations using the nationwide cohort.

Methods: We queried the National Inpatient Sample (NIS) (2010–2014) databases to identify adult COPD hospitalizations with arrhythmia. Categorical and continuous variables were compared using Chi-square and Student's *t*-test/ANOVA. Predictors of any arrhythmia including AF and in-hospital mortality were evaluated by multivariable analyses.

Results: Out of 21,596,342 COPD hospitalizations, 6,480,799 (30%) revealed co-existent arrhythmias including 4,767,401 AF-arrhythmias (22.1%) and 1,713,398 non AF-arrhythmias (7.9%). The AF or non-AF arrhythmia cohort consisted mostly of older (mean age~ 75.8 & 69.1 vs. 67.5 years) white male (53.3% & 51.9% vs. 46.9%) patients compared to those without arrhythmias ($p < 0.001$). The all-cause mortality (5.7% & 5.2 vs. 2.9%), mean length of stay (LOS) (6.4 & 6.5 vs. 5.3 days), and hospital charges (\$52,699.49 & \$58,102.39 vs. \$41,208.02) were higher with AF and non AF-arrhythmia compared to the non-arrhythmia group ($p < 0.001$). Comorbidities such as cardiomyopathy (OR 2.11), cardiogenic shock (OR 1.88), valvular diseases (OR 1.60), congestive heart failure (OR 1.48) and pulmonary circulation disorders (OR 1.25) predicted in-hospital arrhythmias. Invasive mechanical ventilation (OR 6.41), cardiogenic shock (OR 5.95), cerebrovascular disease (OR 3.95), septicemia (OR 2.30) and acute myocardial infarction (OR 2.24) predicted higher mortality ($p < 0.001$) in the COPD-arrhythmia cohort.

Conclusions: About 30% of COPD hospitalizations revealed co-existent arrhythmias (AF 22.1%). All-cause mortality, LOS and hospital charges were significantly higher with arrhythmias. We observed racial and sex-based disparities for arrhythmias and related mortality.

© 2019 Elsevier B.V. All rights reserved.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the major chronic illnesses and the third leading killer in the United States (US) [1]. Cardiovascular disease has been linked to the cause of death in nearly one-fourth of COPD patients. COPD is known to pose a

higher risk of cardiovascular events such as conduction abnormality, arrhythmias, and ischemic heart diseases. The electrocardiographic (ECG) abnormalities in COPD patients have been investigated in recent past [2]. A study by Zaghla et al. demonstrated that over half of COPD patients developed fatal arrhythmias that amplified the mortality rate [3]. A study showed up to 1/3rd of COPD patients experiencing ≥ 30 premature ventricular beats per hour with the severity of COPD corresponding with the frequency of non-sustained and sustained ventricular tachycardia (VT) [4]. Atrial fibrillation (AF), multifocal atrial tachycardia, and ventricular arrhythmias are the common subtypes

* Corresponding author at: Division of Cardiology, Atlanta VA Medical Center, 1670 Clairmont Rd, Decatur, GA 30033, USA.

E-mail address: drrupakdesai@gmail.com (R. Desai).

discovered in COPD patients [5]. Inhaled bronchodilators, the main treatment modalities for COPD and COPD-associated risk factors such as age, smoking, hypoxemia and respiratory acidosis are also found to be contributing factors towards incident arrhythmias [6–8]. Few small sample studies have analyzed the frequency of different sub-types fatal and non-fatal arrhythmias in COPD patients; however, comprehensive nationwide data determining the burden and impact of arrhythmias and related outcomes in COPD-related hospitalizations remain indistinct in the US. Our study aimed to measure the burden of different arrhythmias, odds, and predictors of arrhythmias including AF and subsequent inpatient mortality in COPD patients.

2. Methods

2.1. Source of data

The National Inpatient Sample (NIS) databases (2010–2014) of the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ) were used. The NIS is the largest publicly accessible all-payer inpatient healthcare dataset in the US. It contains discharge data that represents approximately 20% of the US hospitals from >40 states, which comprise average 7 million un-weighted discharges per year that approximate >35 million weighted nationwide discharges. The NIS has one primary diagnosis and up to 24 secondary discharge diagnoses for each inpatient admission. The Institutional review board (IRB) approval was not mandatory since the NIS contains deidentified data. Further information about the database is available on the HCUP website [9].

2.2. Study population

We identified COPD and arrhythmia-related adult hospitalizations using the Clinical Classifications Software (CCS) code 127 and 106 respectively. The CCS is a scheme under which a large number of ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes are collapsed into a reduced number of clinically important categories that are more suitable for descriptive statistics than are individual ICD-9-CM codes [10]. The comorbidities and subtypes of arrhythmias were identified using the validated codes previously used for the NIS database studies [11–14].

2.3. Study outcomes

We assessed and compared the baseline demographics, hospital-level characteristics and associated comorbidities in COPD hospitalizations with AF & non-AF arrhythmia vs. no arrhythmia. The primary outcomes of interest were the burden (frequency) of arrhythmias including subtypes and gender differences, independent predictors of arrhythmia and related in-hospital mortality. Secondary outcomes were the mean length of hospital stay (days) and hospital charges (\$) due to arrhythmia in COPD hospitalizations. We performed a subgroup analysis to assess the impact of congestive heart failure (CHF), current or prior MI, history of revascularizations (percutaneous coronary intervention; PCI or coronary artery bypass grafting; CABG) on AF incidence and subsequent inpatient mortality during COPD hospitalizations.

2.4. Statistical analyses

We applied discharge weight (DISCWT) provided in the database to generate the national estimates. Pearson Chi-square test for categorical variables and Student's *t*-tests/one-way ANOVA for continuous variables were applied to compare the baseline demographics and hospital characteristics between the groups (with AF or non-AF arrhythmia vs. non-arrhythmia) among COPD hospitalizations. The categorical and continuous variables were expressed in percentages and mean \pm SD respectively. A two-tailed *p*-value of <0.05 was used to decide the statistical significance.

After regulating for age, sex, race, elective - nonelective admission type, median household income, length of stay, insurance payer, hospital bed size, ownership and location/teaching status of the hospital and all baseline comorbidities, a two-step hierarchical multivariate regression model was assessed the risk of arrhythmias including AF and subsequent inpatient mortality in COPD hospitalizations. We evaluated predictors of arrhythmias and related in-hospital mortality by univariate analysis and then clinically relevant variables were integrated into the multivariable analysis. Adjusted odds ratio (OR), 95% confidence interval (CI), and *p*-values were considered to account logistic regression results. We utilized IBM SPSS Statistics 22.0 (IBM Corp, Armonk, New York) software for all the statistical analyses.

3. Results

3.1. Baseline characteristics of study population

Out of 21,596,342 COPD hospitalizations, 6,480,799 (30%) revealed arrhythmias including 4,767,401 AF-arrhythmias (22.1%) and 1,713,398

non AF-arrhythmia (7.9%). The COPD hospitalizations with AF or non AF arrhythmia consisted mostly older (mean age years 75.8 ± 10.3 & 69.1 ± 12.8 vs. 67.5 ± 13.2) male (53.3% & 51.9% vs. 46.9%) patients who were Medicare beneficiaries (84.8% & 71.4% vs. 68.9%) as compared to those without arrhythmia ($p < 0.001$). Whites dominated the study cohorts (Table 1).

3.2. Baseline comorbidities

Co-morbid conditions such as hypertension (70.3% & 66.9% vs. 64.4%), congestive heart failure (CHF) (33.5% & 19.4% vs. 17.1%), valvular heart diseases (10.6% & 6.2% vs. 4.2%), pulmonary circulation disorders (7.9% & 5.5% vs. 3.8%), cardiomyopathy (10.6% & 9.0% vs. 4.3%), previous history of coronary artery bypass grafting (CABG) (12.0% & 8.3% vs. 7.1%) were more prevalent in the AF and non-AF arrhythmia group as compared non-arrhythmia group ($p < 0.001$) (Table 1).

3.3. Burden of arrhythmias

Total of 6,480,799 (30%) COPD patients experienced in-hospital arrhythmias. The frequency of subtypes of arrhythmias in the descending order were: AF 22.1%, other unspecified causes 6.8%, atrial flutter (AFL) 2.1%, ventricular tachycardia (VT) 2.0%, sinoatrial (SA) node dysfunction 1.0%, ventricular premature beats 0.6%, paroxysmal supraventricular tachycardia (PSVT) 0.5%, premature atrial/ventricular complex (PAC/PVC) 0.2%.

3.4. Gender comparison of sub-types of arrhythmias in COPD hospitalizations

Male patients with COPD were affected by arrhythmia more frequently as compared to females (32.6% vs. 27.6%, $p < 0.001$). Furthermore, the burden of major subtypes of arrhythmias (AF; 24.1% vs. 20.1%, VT; 2.7% vs. 1.3% and AFL; 2.7% vs. 1.6%) were significantly higher among male COPD patients (Supplementary Fig. 1).

3.5. Impact of arrhythmias on in-hospital outcomes of COPD hospitalizations

In-hospital mortality rate was found higher in COPD-AF and arrhythmia groups (5.7% & 5.2% vs. 2.9%, $p < 0.001$). The mean length of stay (days) (6.4 ± 6.6 & 6.5 ± 7.3 vs. 5.3 ± 6.1 , $p < 0.001$) and total hospital charges (\$52,699.49 & \$58,102.39 vs. \$41,208.02, $p < 0.001$) were considerably higher in the arrhythmia group. The transfers to other facilities were also higher in arrhythmia cohort (Table 1).

3.6. Predictors of arrhythmias in COPD

As displayed in Fig. 1, an advanced age (≥ 65 years: OR 3.30, CI 3.23–3.63, $p < 0.001$), male sex (OR = 1.28, CI = 1.28–1.30, $p < 0.001$) and white (OR = 1.17, CI = 1.15–1.19, $p < 0.001$) race demonstrated higher odds of arrhythmia.

The odds of arrhythmias in COPD were substantially higher with comorbid conditions/complications such cardiomyopathy (OR 2.11, CI 2.09–2.13, $p < 0.001$), cardiogenic shock (OR 1.88, CI 1.82–1.94, $p < 0.001$), valvular heart disease (OR 1.60, CI 1.58–1.61, $p < 0.001$), history of sudden cardiac arrest (OR 1.51, CI 1.44–1.59, $p < 0.001$), CHF (OR 1.48, CI 1.47–1.49, $p < 0.001$) and family history of CAD (OR 1.28, CI 1.26–1.30, $p < 0.001$). Pulmonary circulation disorders (OR 1.25, CI 1.24–1.27, $p < 0.001$), respiratory failure (OR 1.13, CI 1.12–1.14, $p < 0.001$) and invasive mechanical ventilation (IMV) (OR 1.16, CI 1.15–1.18, $p < 0.001$) also independently increased the risk of arrhythmia in COPD.

Table 1

Baseline characteristics and outcomes of chronic obstructive pulmonary disease hospitalizations without arrhythmia vs. with arrhythmia vs. with AF.

Variable	No arrhythmia (N = 15,112,843)	Non AF arrhythmia (N = 1,713,398)	AF arrhythmia (N = 4,767,401)	P
Age (years) at admission				<0.001
Mean age \pm SD	67.5 \pm 13.2	69.1 \pm 12.8	75.8 \pm 10.3	
18–44	4.0%	3.1%	0.4%	
45–64	36.2%	31.4%	14.2%	
\geq 65	59.8%	65.4%	85.4%	
Sex				<0.001
Male	46.9%	51.9%	53.3%	
Female	53.1%	48.1%	46.7%	
Race				<0.001
White	79.8%	78.5%	86.2%	
African American	11.7%	13.1%	6.9%	
Hispanic	5.0%	4.8%	3.8%	
Asian or Pacific Islander	1.0%	1.2%	1.0%	
Native American	0.6%	0.5%	0.4%	
Other	1.9%	1.9%	1.6%	
Primary expected payer				<0.001
Medicare	68.9%	71.4%	84.8%	
Medicaid	11.4%	9.5%	4.0%	
Private including HMO	14.0%	13.5%	8.7%	
Self – Pay/No charge/Other	5.9%	5.5%	2.5%	
Type of admission				<0.001
Non-elective	83.8%	87.8%	87.9%	
Elective	16.2%	12.2%	12.1%	
Location/teaching status of hospital				<0.001
Rural	17.8%	15.0%	15.1%	
Urban - non teaching	41.0%	41.3%	42.1%	
Urban - teaching	41.2%	43.7%	42.8%	
Comorbidities				
Cardiovascular				
Hypertension	64.4%	66.9%	70.3%	<0.001
Congestive heart failure	17.1%	19.4%	33.5%	<0.001
Acute myocardial infarction	3.8%	6.9%	5.0%	<0.001
Peripheral vascular disorders	11.2%	13.2%	15.3%	<0.001
Valvular disease	4.2%	6.2%	10.6%	<0.001
Cardiomyopathy	4.3%	9.0%	10.6%	<0.001
Thromboembolism	7.1%	7.3%	8.4%	<0.001
Previous myocardial infarction	8.2%	10.6%	10.8%	<0.001
Family history of CAD	1.9%	2.7%	1.8%	<0.001
Previous PCI	7.5%	8.6%	9.1%	<0.001
Previous CABG	7.1%	8.3%	12.0%	<0.001
Respiratory				
Pulmonary circulation disorders	3.8%	5.5%	7.9%	<0.001
Neurological				
Cerebrovascular disease	1.8%	2.1%	2.6%	<0.001
Substance abuse				
Alcohol abuse	6.1%	6.4%	3.7%	<0.001
Smoking	51.7%	53.2%	40.0%	<0.001
Drug abuse	4.5%	4.0%	1.4%	<0.001
Hemato-oncological				
Deficiency anemia	21.6%	24.9%	27.4%	<0.001
Chronic blood loss anemia	1.1%	1.2%	1.5%	<0.001
Coagulopathy	5.0%	6.7%	7.3%	<0.001
Solid tumor without metastasis	3.5%	3.7%	3.6%	<0.001
Lymphoma	0.8%	0.9%	1.0%	<0.001
Endocrinological				
Diabetes with chronic complications	5.8%	5.4%	6.5%	<0.001
Hypothyroidism	13.9%	13.4%	18.3%	<0.001
Obesity	14.1%	14.0%	14.9%	<0.001
Renal				
Renal failure	16.2%	18.5%	27.6%	<0.001
Fluid and electrolyte disorders	29.9%	38.0%	35.1%	<0.001
Gastrointestinal				
Liver disease	3.7%	3.3%	2.5%	<0.001
Outcomes				
All-cause In-hospital mortality	2.9%	5.2%	5.7%	<0.001
Disposition of Patient				<0.001
Routine	54.6%	49.5%	38.9%	
Transfer to short-term Hospital	2.6%	3.4%	2.8%	
Other Transfers (SNF, ICF, Another facility)	21.5%	23.1%	30.7%	
Home Health Care	17.1%	17.7%	21.2%	
Against Medical Advice	1.3%	1.1%	0.6%	
Length of stay (days) Mean \pm SD	5.3 \pm 6.1	6.5 \pm 7.3	6.4 \pm 6.6	<0.001
Total hospital charges (Mean)	\$41,208.02	\$58,102.39	\$52,699.49	<0.001

P-values <0.05 indicates clinical significance. HMO=Health Maintenance Organization, SNF=Skilled Nursing Facility, ICF = Intermediate Care Facility, AF = Atrial Fibrillation, CAD – Coronary Artery Disease, PCI – Percutaneous Coronary Intervention, CABG – Coronary Artery Bypass Grafting.

Multivariable Predictors of Arrhythmias in COPD Hospitalizations

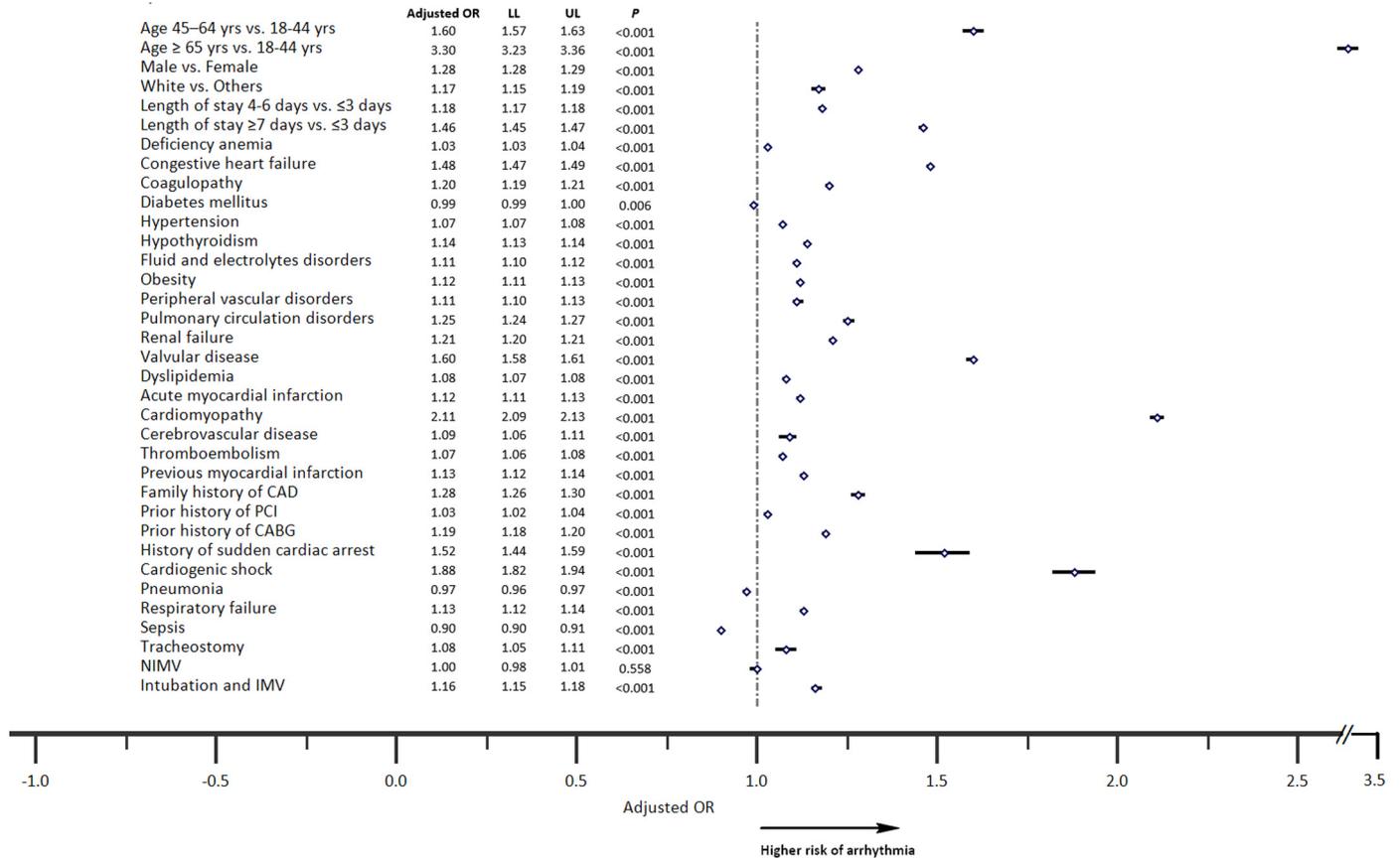


Fig. 1. Multivariable predictors of arrhythmia in chronic obstructive pulmonary disease. Note: Multivariate regression model was adjusted for baseline demographics including age, sex and race, median household income, payer status, admission type (non-elective or elective), hospital bed size, location/teaching status and region, all baseline comorbidities. OR = adjusted odds ratio, LL = lower level, UL = upper level, $p < 0.05$ indicates clinical significance. An advanced age (≥ 45 years), male sex and white race demonstrated higher odds of arrhythmia. The odds of arrhythmias in COPD were substantially higher with co-morbid conditions/complications such cardiomyopathy, cardiogenic shock, valvular heart disease, history of sudden cardiac arrest, congestive heart failure and family history of coronary artery disease. Pulmonary circulation disorders, respiratory failure and invasive mechanical ventilation also independently increased the risk of arrhythmia in COPD.

3.7. Predictors of in-hospital mortality in COPD with arrhythmia

As displayed in Table 2, age group >45 yrs., male sex and Asian or Pacific Islander showed higher risk of inpatient mortality in the COPD-arrhythmia cohort.

Comorbidities such as pulmonary circulation disorders (OR 1.41, CI 1.39–1.42, $p < 0.001$), coagulopathy (OR 1.79, CI 1.77–1.81, $p < 0.001$), CHF (OR 1.55, CI 1.53–1.56, $p < 0.001$), and liver disease (OR 1.24, CI 1.21–1.26, $p < 0.001$) were independent predictors of in-hospital mortality in the arrhythmia group.

The complications such as cardiogenic shock (OR 5.95, CI 5.84–6.07, $p < 0.001$), respiratory failure (OR 2.16, CI 2.12–2.21, $p < 0.001$), respiratory acidosis (OR 1.40, CI 1.37–1.44, $p < 0.001$), pneumonia (OR 1.15, CI 1.13–1.17, $p < 0.001$), and septicemia (OR 2.30, CI 2.25–2.35, $p < 0.001$) also raised the odds of inpatient mortality. The need for invasive mechanical ventilation (OR 6.41, CI 6.26–6.58, $p < 0.001$) independently predicted in-hospital mortality in COPD patients with arrhythmias.

3.8. Impact of co-existing CHF, MI and a prior history of MI/PCI/CABG on AF incidence and in-hospital mortality among COPD hospitalizations

The odds of AF among COPD patients were considerably higher with co-existing CHF (OR 1.72, CI 1.71–1.73, $p < 0.001$) and a prior history of MI/PCI/CABG (OR 1.15, CI 1.14–1.15, $p < 0.001$),

respectively (Table 3A). In addition, the odds of mortality was significantly higher in the COPD-AF cohort with coexisting CHF (OR 1.22, CI 1.10–1.25, $p < 0.001$) and current AMI (OR 1.76, CI 1.70–1.82, $p < 0.001$) (Table 3B).

4. Discussion

To our knowledge, this is the largest population-based analysis to date reporting the burden and impact of in-hospital arrhythmias including AF on COPD hospitalizations using the nationwide cohorts in the US. The remarkable findings of this study are as follows. We determined that 30% of COPD hospitalizations demonstrated in-hospital arrhythmias with AF (22.1%) being the most common subtype. Male patients with COPD more often suffered arrhythmia and related inpatient mortality, whereas on racial analysis, whites were found to have arrhythmias more often and Asians showed the highest odds of in-hospital mortality. The arrhythmias posed a significant impact on the outcomes of patients with COPD in terms of higher in-hospital mortality, LOS and hospitalization charges.

We analyzed the frequency, and racial and sex distinctions in the incidence of arrhythmias to stratify the risk of arrhythmias in COPD. AF was the most common subtype followed by unspecified arrhythmia, VT and AFL, consistent with the other studies [15]. However, there are studies reporting ventricular arrhythmias as the most common subtype [16,17]. The incidence and risk of arrhythmia, explicitly AF, was significantly high among the older white male population consistent with the

Table 2
Multivariate predictors of In-hospital mortality in COPD patients with arrhythmias.

Predictors	Adjusted Odds Ratio ^b	95% CI	P-value ^a
		Lower-Upper	
Age (years) at admission			
45–64 vs. 18–44	1.69	1.60–1.78	<0.001
≥65 vs. 18–44	2.53	2.39–2.66	<0.001
Sex			
Male vs. Female	1.08	1.07–1.09	<0.001
Race			
African American vs. white	0.87	0.86–0.88	<0.001
Hispanic vs. white	1.00	0.98–1.02	0.838
Asian or Pacific Islander vs. white	1.14	1.11–1.18	<0.001
Native American vs. white	0.94	0.88–0.99	0.042
Other vs. white	1.08	1.05–1.11	<0.001
Length of stay			
4–6 days vs. ≤3 days	0.52	0.52–0.53	<0.001
≥7 days vs. ≤3 days	0.74	0.74–0.75	<0.001
Bed Size of Hospital			
Medium vs. Small	1.01	1.00–1.04	0.022
Large vs. Small	1.06	1.06–1.09	<0.001
Co-morbidities			
Intubation and IMV	6.41	6.26–6.58	<0.001
Cardiogenic shock	5.95	5.84–6.07	<0.001
Cerebrovascular disease	3.95	3.87–4.04	<0.001
Sepsis	2.30	2.25–2.35	<0.001
Acute myocardial infarction	2.24	2.21–2.27	<0.001
Respiratory failure	2.16	2.12–2.21	<0.001
Fluid and electrolytes disorders	2.14	2.12–2.15	<0.001
Coagulopathy	1.79	1.77–1.81	<0.001
History of sudden cardiac arrest	1.72	1.62–1.81	<0.001
Congestive heart failure	1.55	1.53–1.56	<0.001
Pulmonary circulation disorders	1.41	1.39–1.42	<0.001
Acidosis	1.40	1.37–1.44	<0.001
Atherosclerosis	1.29	1.27–1.32	<0.001
Liver disease	1.24	1.21–1.26	<0.001
Renal failure	1.23	1.22–1.24	<0.001
Pneumonia	1.15	1.13–1.17	<0.001
Diabetes, uncomplicated	0.94	0.93–0.94	<0.001
Peripheral vascular disorders	0.91	0.89–0.94	<0.001
Alcohol abuse	0.88	0.86–0.89	<0.001
Hypothyroidism	0.88	0.87–0.88	<0.001
Chronic blood loss anemia	0.84	0.82–0.87	<0.001
Hypertension	0.82	0.81–0.83	<0.001
Diabetes with chronic complications	0.80	0.78–0.81	<0.001
Obesity	0.76	0.75–0.76	<0.001
Dyslipidemia	0.69	0.69–0.70	<0.001
NIMV	0.48	0.47–0.50	<0.001
Tracheostomy	0.36	0.34–0.39	<0.001

^a Significant P-value ≤0.05 (bold values) at 95% Confidence Interval, CI - Confidence Interval, LL-lower level, UL-upper level.

^b Multivariate model was adjusted for baseline demographics, hospital-level characteristics, payer status, median household income, type of admission, and all baseline comorbidities. IMV = Invasive Mechanical Ventilation, NIMV = Noninvasive Mechanical Ventilation.

findings of previous studies [18,19]. Similarly, odds of inpatient mortality were higher among males as compared to females. Chug et al. in their study reporting the global burden of AF suggested higher mortality among females; however, in developed nations, AF-related mortality has been found to be higher among males [20]. The racial disparity regarding a predisposition of arrhythmia remains multifactorial. In Caucasians compared to African American, large atrial diameter, chamber volume, atrial tissue composition, and genetic makeup are described as potential culprits for higher AF prevalence [21–25]. Resource utilization in terms of LOS and total hospital charges were significantly higher among the arrhythmia group. Although odds of arrhythmia increased with an extended LOS with COPD, there was an inverse association with the odds of mortality, suggesting that arrhythmia occurrence during COPD hospitalizations contributed towards early inpatient mortality.

This study determined that coexisting cardiac comorbidities played a significant role in predicting in-hospital arrhythmia and ensuing

Table 3
Odds of atrial fibrillation and inpatient mortality in COPD hospitalizations.

A. Odds of atrial fibrillation in COPD hospitalizations				
Comorbidity		Odds Ratio	95% CI (LL-UL)	P-value ^a
COPD with CHF	Unadjusted	2.39	2.38–2.41	<0.001
	Adjusted	1.72	1.71–1.73	<0.001
COPD with current MI	Unadjusted	1.23	1.22–1.24	<0.001
	Adjusted	0.93	0.92–0.94	<0.001
COPD with prior history of MI, PCI OR CABG	Unadjusted	1.47	1.46–1.48	<0.001
	Adjusted	1.15	1.14–1.15	<0.001
B. Odds of in-hospital mortality in COPD hospitalizations with atrial fibrillation				
Comorbidity		Odds Ratio	95% CI (LL-UL)	P-value ^a
COPD with CHF	Unadjusted	1.62	1.59–1.65	<0.001
	Adjusted	1.22	1.20–1.25	<0.001
COPD with current MI	Unadjusted	2.91	2.83–2.99	<0.001
	Adjusted	1.76	1.70–1.82	<0.001
COPD with prior history of MI, PCI OR CABG	Unadjusted	0.72	0.70–0.73	<0.001
	Adjusted	0.83	0.81–0.85	<0.001

^a Significant P-value ≤0.05 at 95% Confidence Interval, CI - Confidence Interval, LL-lower level, UL-upper level, COPD = chronic obstructive pulmonary disease, CHF = congestive heart failure, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting.

in-hospital mortality in COPD patients. Obesity, peripheral vascular disease, and dyslipidemia were found to be independent predictors of arrhythmia but not the inpatient mortality among COPD patients [26,27]. Atherosclerosis, by promoting atrial tissue fibrosis and microscopic scarring, increases the likelihood of reentry mechanisms, shortened refractory period and a decrease in the conduction velocity ultimately leading to AF, which may increase inpatient mortality among COPD [28–31]. COPD patients with a current MI and prior cardiovascular comorbidities such as a history of cardiac arrest, MI, PCI or CABG, a family history of CAD showed a higher risk of AF and in-hospital mortality. However, a high prevalence of CAD and the odds of CAD-induced generation of arrhythmogenic substrates including reactive oxygen species and revascularization-induced MI may possibly make COPD population with cardiovascular disorders more prone to arrhythmias [4,32]. Furthermore, the occurrence of reentry in the infarcted zone and increased ratio of cyclic AMP/cyclic GMP have also been proposed as potential mechanisms for ischemia-related dysrhythmias [33,34]. COPD patients with valvular heart disease had a significantly increased likelihood of arrhythmia. Atrial enlargement owing to a valvular abnormality increases the risk of re-entrant arrhythmias by reducing the maximum diastolic potential and slow response action potential [35]. Nonetheless, in the ENGAGE AF-TIMI 48 study, Gupta et al. reported 19% of AF subjects with an impaired left atrial (LA) emptying function despite normal LA size [36]. Furthermore, valvular heart disease can lead to atrial fibrosis-related inhomogeneity of electrical conduction resulting in dysrhythmias [34]. COPD and CHF often times ensue concurrently with a high burden of COPD reported in HF patients. The burden of cardiogenic shock has been reported in around 30% of chronic HF patients and bears a mortality rate of up to 25%–30% [37]. Long-term CHF leads to cardiomyopathy which highly increases the likelihood of non-sustained VT and the risk of sudden cardiac death [38].

Circulatory compromise and respiratory acidosis among mechanically ventilated patients could be a potential culprit for the increased risk of arrhythmia among these patients [23]. Studies have reported an increased risk of arrhythmia and increased mortality among the respiratory failure patients and those who require invasive mechanical ventilation [16,24]. Pulmonary circulation disorder, pneumonia, and respiratory failure were some of the non-cardiac comorbidities, which increased the chance of arrhythmia among the COPD patients. Rusinowicz et al. also reported significantly increased the frequency of paroxysmal atrial fibrillation and supraventricular premature beats among the respiratory failure patients as compared to the nonrespiratory failure ones [16].

Pulmonary circulation disorder, pneumonia, and respiratory failure were prevalent noncardiac comorbidities increasing the odds of arrhythmia among COPD patients. COPD leads to pulmonary artery remodeling due to pulmonary endothelial dysfunction and coagulopathy, leading to a state of pulmonary artery hypertension (PAH) [39]. Modulation in autonomic activity, delayed cardiac repolarization and right ventricular remodeling predispose PAH patients to arrhythmias [40]. Consistently, prior studies suggest an increased risk of arrhythmia and related worse outcomes due to PAH [41–44]. Rusinowicz et al. also reported a significantly increased frequency of paroxysmal AF and supraventricular premature beats among patients with respiratory failure as compared to those without [17]. Circulatory compromise and respiratory acidosis among mechanically ventilated patients could be potential culprits for the increased risk of arrhythmia among COPD patients [45]. Studies have reported worse outcomes in arrhythmia and respiratory failure requiring invasive mechanical ventilation [17,46].

COPD patients are at the risk of developing renal failure (RF) [47,48]. We observed a 21% higher risk of arrhythmia among COPD hospitalizations and 23% higher risk inpatient mortality among the COPD-arrhythmia cohort. AF prevalence in pre-dialysis and on long-term dialysis patients has been reported to be 9–21% and 13–27%, respectively [49]. Furthermore, long-term CKD leads to vascular calcification leading to an increased risk of sudden cardiac death [49].

Although sepsis has been known as an independent predictor of arrhythmia, it was not an independent predictor of arrhythmia among COPD patients in our study; however, it was a predictor of mortality in COPD-arrhythmia cohort. Conversely, numerous studies suggest an increased risk of arrhythmia and subsequent mortality in sepsis patients owing to its ability to create procoagulant state and subsequent risk of coronary thrombi [39,50].

5. Limitations

The NIS, being an administrative dataset, increases the possibility of administrative coding errors and selection bias. New-onset arrhythmia vs. previous history of arrhythmia could not be differentiated based on the available ICD-9 codes. The data on the duration of illness and follow-up outcomes were not available. Furthermore, we cannot measure the severity of COPD and arrhythmia and therefore, the findings may not be generalizable to whole COPD population as the risk of arrhythmia and subsequent outcomes vary depending on the hospital bed size, location, and availability of health care resources. Although LOS, total hospital charges, and identified complications can indirectly reflect the prognosis of disease; we could not report the specific cause of death. Given the large sample size, these limitations minimally influence the study results.

6. Conclusion

This study concludes nearly one-third of (30%) COPD patients, with certain comorbidities, are at high risk of developing an arrhythmia including AF, which further increases the risk of mortality and healthcare resource utilization with evident racial and gender disparities. Since COPD itself is a major healthcare concern, further strides are warranted to lower the incident arrhythmias and ensuing worse outcomes and positively influence the US healthcare system.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.01.074>.

Disclosure

None.

Funding source

None.

References

- [1] C.J. Murray, C. Atkinson, K. Bhalla, et al., The state of US health, 1990–2010: burden of diseases, injuries, and risk factors, *JAMA* 310 (2013) 591–608.
- [2] S.P. Bhatt, M.T. Dransfield, Chronic obstructive pulmonary disease and cardiovascular disease, *Transl. Res.* 162 (2013) 237–251.
- [3] A.H. Zaghla, A. Samir, M. Kamal, Arrhythmias in patients with chronic obstructive pulmonary disease, *Egypt. J. Chest Dis. Tuberc.* 62 (2013) 377–385.
- [4] T. Konecny, J.Y. Park, K.R. Somers, et al., Relation of chronic obstructive pulmonary disease to atrial and ventricular arrhythmias, *Am. J. Cardiol.* 114 (2014) 272–277.
- [5] B.F. Sode, M. Dahl, B.G. Nordestgaard, Myocardial infarction and other comorbidities in patients with chronic obstructive pulmonary disease: a Danish nationwide study of 7.4 million individuals, *Eur. Heart J.* 32 (2011) 2365–2375.
- [6] D. Gorecka, Cardiac arrhythmias in chronic obstructive pulmonary disease, *Monaldi Arch. Chest Dis.* 52 (1997) 278–281.
- [7] H.T. Shih, C.R. Webb, W.A. Conway, E. Peterson, B. Tilley, S. Goldstein, Frequency and significance of cardiac arrhythmias in chronic obstructive lung disease, *Chest* 94 (1988) 44–48.
- [8] M. Wilchesky, P. Ernst, J.M. Brophy, R.W. Platt, S. Suissa, Bronchodilator use and the risk of arrhythmia in COPD: part 2: reassessment in the larger Quebec cohort, *Chest* 142 (2012) 305–311.
- [9] HCUP Databases, Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality, Rockville, MD, August 2018, www.hcupus.ahrq.gov/nisoverview.jsp, Accessed date: December 2018.
- [10] HCUP CCS, Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality, Rockville, MD, March 2017, www.hcupus.ahrq.gov/toolsoftware/ccs/ccs.jsp, Accessed date: December 2018.
- [11] R. Desai, C. Rupareliya, U. Patel, et al., Burden of arrhythmias in epilepsy patients: a nationwide inpatient analysis of 1.4 million hospitalizations in the United States, *Cureus* 9 (2017) e1550.
- [12] J. Menzin, L. Boulanger, J. Marton, et al., The economic burden of chronic obstructive pulmonary disease (COPD) in a U.S. Medicare population, *Respir. Med.* 102 (2008) 1248–1256.
- [13] R. Desai, U. Patel, A. Deshmukh, R. Sachdeva, G. Kumar, Burden of arrhythmia in recreational marijuana users, *Int. J. Cardiol.* 264 (2018) 91–92.
- [14] R. Desai, K. Kakumani, H.K. Fong, et al., The burden of cardiac arrhythmias in sarcoidosis: a population-based inpatient analysis, *Ann. Transl. Med.* 6 (2018) 330.
- [15] P. Buch, J. Friberg, H. Scharling, P. Lange, E. Prescott, Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study, *Eur. Respir. J.* 21 (2003) 1012–1016.
- [16] C.R. Laratta, S. van Eeden, Acute exacerbation of chronic obstructive pulmonary disease: cardiovascular links, *Biomed. Res. Int.* 2014 (2014) 528789.
- [17] T. Rusinowicz, T.M. Zielonka, K. Zycinska, Cardiac arrhythmias in patients with exacerbation of COPD, *Adv. Exp. Med. Biol.* (2017), https://doi.org/10.1007/5584_2017_41.
- [18] C.-Y. Chen, K.-M. Liao, The impact of atrial fibrillation in patients with COPD during hospitalization, *Int. J. Chron. Obstruct. Pulmon. Dis.* 13 (2018) 2105–2112.
- [19] J. Li, S.K. Agarwal, A. Alonso, et al., Airflow obstruction, lung function, and incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study, *Circulation* 129 (2014) 971–980.
- [20] S.S. Chugh, G.A. Roth, R.F. Gillum, G.A. Mensah, Global burden of atrial fibrillation in developed and developing nations, *Glob. Heart* 9 (2014) 113–119.
- [21] T.S. Tsang, M.E. Barnes, K.R. Bailey, et al., Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women, *Mayo Clin. Proc.* 76 (2001) 467–475.
- [22] T.J. Wang, H. Parise, D. Levy, et al., Obesity and the risk of new-onset atrial fibrillation, *JAMA* 292 (2004) 2471–2477.
- [23] T. Nakai, R.J. Lee, N.B. Schiller, et al., The relative importance of left atrial function versus dimension in predicting atrial fibrillation after coronary artery bypass graft surgery, *Am. Heart J.* 143 (2002) 181–186.
- [24] G.M. Marcus, A. Alonso, C.A. Peralta, et al., European ancestry as a risk factor for atrial fibrillation in African Americans, *Circulation* 122 (2010) 2009–2015.
- [25] G.M. Marcus, J.E. Olgin, M. Whooley, et al., Racial differences in atrial fibrillation prevalence and left atrial size, *Am. J. Med.* 123 (2010) 375.e371–375.e3757.
- [26] J.W. Olin, B.A. Sealove, Peripheral artery disease: current insight into the disease and its diagnosis and management, *Mayo Clin. Proc.* 85 (2010) 678–692.
- [27] A.M. Gotto, Evolving concepts of dyslipidemia, atherosclerosis, and cardiovascular disease, *The Louis F. Bishop Lecture*, 46, 2005, pp. 1219–1224.
- [28] K.R. Anderson, M.G. Sutton, J.T. Lie, Histopathological types of cardiac fibrosis in myocardial disease, *J. Pathol.* 128 (1979) 79–85.
- [29] J.L. Cox, T.E. Canavan, R.B. Schuessler, et al., The surgical treatment of atrial fibrillation. II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and atrial fibrillation, *J. Thorac. Cardiovasc. Surg.* 101 (1991) 406–426.
- [30] P.F. Cranefield, A.L. Wit, B.F. Hoffman, Genesis of cardiac arrhythmias, *Circulation* 47 (1973) 190–204.
- [31] J. Heeringa, D.M. van der Kuip, A. Hofman, et al., Subclinical atherosclerosis and risk of atrial fibrillation: the Rotterdam study, *Arch. Intern. Med.* 167 (2007) 382–387.
- [32] J.D. MacLay, W. MacNee, Cardiovascular disease in COPD: mechanisms, *Chest* 143 (2013) 798–807.

- [33] N. el-Sherif, W.B. Gough, M. Restivo, Reentrant ventricular arrhythmias in the late myocardial infarction period: mechanism by which a short-long-short cardiac sequence facilitates the induction of reentry, *Circulation* 83 (1991) 268–278.
- [34] D.V. Unverferth, R.H. Fertel, B.J. Unverferth, C.V. Leier, Atrial fibrillation in mitral stenosis: histologic, hemodynamic and metabolic factors, *Int. J. Cardiol.* 5 (1984) 143–152.
- [35] A.J. Hordof, R. Edie, J.R. Malm, B.F. Hoffman, M.R. Rosen, Electrophysiologic properties and response to pharmacologic agents of fibers from diseased human atria, *Circulation* 54 (1976) 774–779.
- [36] D.K. Gupta, A.M. Shah, R.P. Giugliano, et al., Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48, *Eur. Heart J.* 35 (2014) 1457–1465.
- [37] F. Zannad, A. Mebazaa, Y. Juilliere, et al., Clinical profile, contemporary management and one-year mortality in patients with severe acute heart failure syndromes: the EFICA study, *Eur. J. Heart Fail.* 8 (2006) 697–705.
- [38] P.J. Podrid, R.I. Fogel, T.T. Fuchs, Ventricular arrhythmia in congestive heart failure, *Am. J. Cardiol.* 69 (1992) 82G–95G (discussion 95G–96G).
- [39] A. Cavaillès, G. Brinchault-Rabin, A. Dixmier, et al., Comorbidities of COPD, *Eur. Respir. Rev.* 22 (2013) 454.
- [40] A. Rajdev, H. Garan, A. Biviano, Arrhythmias in pulmonary arterial hypertension, *Prog. Cardiovasc. Dis.* 55 (2012) 180–186.
- [41] E.A. Demerouti, A.N. Manginas, G.D. Athanassopoulos, G.T. Karatasakis, Complications leading to sudden cardiac death in pulmonary arterial hypertension, *Respir. Care* 58 (2013) 1246.
- [42] D. Rottlaender, L.J. Motloch, D. Schmidt, et al., Clinical impact of atrial fibrillation in patients with pulmonary hypertension, *PLoS One* 7 (2012), e33902.
- [43] B. Smith, M.V. Genuardi, A. Koczo, et al., Atrial arrhythmias are associated with increased mortality in pulmonary arterial hypertension, *Pulm. Circ.* 8 (2018), <https://doi.org/10.1177/2045894018790316> (2045894018790316).
- [44] L. Wen, M.-L. Sun, P. An, et al., Frequency of supraventricular arrhythmias in patients with idiopathic pulmonary arterial hypertension, *Am. J. Cardiol.* 114 (2014) 1420–1425.
- [45] T.J. Williams, D.V. Tuxen, C.D. Scheinkestel, D. Czarny, G. Bowes, Risk factors for morbidity in mechanically ventilated patients with acute severe asthma, *Am. Rev. Respir. Dis.* 146 (1992) 607–615.
- [46] P.K. Lindenauer, M.S. Stefan, M.S. Shieh, P.S. Pekow, M.B. Rothberg, N.S. Hill, Outcomes associated with invasive and noninvasive ventilation among patients hospitalized with exacerbations of chronic obstructive pulmonary disease, *JAMA Intern. Med.* 174 (2014) 1982–1993.
- [47] R. Antonelli Incalzi, A. Corsonello, C. Pedone, S. Battaglia, G. Paglino, V. Bellia, Chronic renal failure: a neglected comorbidity of COPD, *Chest* 137 (2010) 831–837.
- [48] B. Gjerde, P.S. Bakke, T. Ueland, J.A. Hardie, T.M.L. Eagan, The prevalence of undiagnosed renal failure in a cohort of COPD patients in western Norway, *Respir. Med.* 106 (2012) 361–366.
- [49] P.R. Roberts, D. Green, Arrhythmias in chronic kidney disease, *Heart* 97 (2011) 766.
- [50] K. Ueda, M. Sugiura, S. Ohkawa, et al., Disseminated intravascular coagulation in the aged complicated by acute myocardial infarction, *Jpn. J. Med.* 20 (1981) 202–210.