COPD: Journal of Chronic Obstructive Pulmonary Disease

ISSN: 1541-2555 (Print) 1541-2563 (Online) Journal homepage: informahealthcare.com/journals/icop20

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To cite this article: Prasadini N. Perera, Edward P. Armstrong, Duane L. Sherrill & Grant H. Skrepnek (2012) Acute Exacerbations of COPD in the United States: Inpatient Burden and Predictors of Costs and Mortality, COPD: Journal of Chronic Obstructive Pulmonary Disease, 9:2, 131-141, DOI: 10.3109/15412555.2011.650239

To link to this article: https://doi.org/10.3109/15412555.2011.650239

Published online: 12 Mar 2012.

COPD JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

informa healthcare

COPD, 9:131–141, 2012
ISSN: 1541-2555 print / 1541-2563 online

DOI: 10.3109/15412555.2011.650239

ORIGINAL RESEARCH

Acute Exacerbations of COPD in the United States: Inpatient Burden and Predictors of Costs and Mortality

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Abstract

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are a leading cause of hospitalizations in the United States and the major cost driver of COPD. This study determined the national inpatient burden of AECOPD and assessed the association of co-morbidities and hospital characteristics with inpatient costs and mortality. Discharge records from the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample for 2006 was utilized. Outcomes of costs and mortality were assessed for AECOPD hospitalizations in cases ≥40 years of age. Multivariate regression analyses using a generalized linear model framework were conducted to determine predictors of inpatient costs and mortality controlling for patient demographics, primary payer, co-morbidity index, length of stay, hospital region, mechanical ventilation, and admission period. Overall, 1,254,703 hospitalizations for AECOPD were observed with mean costs of \$9545(±12,700) and total costs of \$11.9 billion. In-hospital mortality was 4.3% (N = 53,748). Discharges averaged 70.6 (±11.9) years of age. The majority were female (52.8%) and of white race (83.6% of reported race). Several co-morbidities were significantly associated with both costs and mortality ($p < 0.001$): acute myocardial infarction; congestive heart failure; cerebrovascular disease; lung cancer; cardiac arrhythmias; pulmonary circulation disorders; and weight loss. Significantly higher costs ($p < 0.001$) were associated with large and urban hospitals. The importance of co-morbidities in AECOPD is indicated in their association with prognosis and inpatient costs. Future research should determine if better management of these conditions can favorably impact the COPD disease burden.

Keywords: Chronic obstructive pulmonary disease, Hospitalization, Co-morbidities, Economic burden

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Introduction

The mortality, morbidity, economic, and social burden of chronic obstructive pulmonary disease (COPD) in the United States is substantial (1–4). Prevalence of the disease (diagnosed and undiagnosed COPD) was estimated at 24 million and, in 2006, COPD and allied conditions were ranked as the fourth-leading cause of death (3). As one of the most costly conditions in the United States (5), COPD was projected to have an economic burden of \$49.9 billion in 2010 (inclusive of morbidity, mortality and direct costs), with more than one quarter of these costs attributed to hospital care alone (US\$13.2 billion) (3). As a first-listed diagnosis, COPD accounted for 672,000 hospitalizations in 2006 (6), with hospitalizations representing 52–70% of direct per patient costs of the disease (7).

Of notable relevance is an acute exacerbation of COPD (AECOPD), an important clinical feature that can alter the natural course of the disease (8).

Among hospitalizations for AECOPD, both in-hospital mortality and mortality following discharge is considerable. In the United States, in-hospital mortality ranged from 2.5% for a generalizable national estimate for all hospital admissions for AECOPD, to 28% for patients requiring mechanical ventilation (9–12).

AECOPD are the principal reason for unscheduled visits and, consequently, for increased healthcare resource utilization in COPD patients (13, 14). As a result, acute exacerbations are the major cost driver of COPD and can contribute to 50–75% of total direct disease costs (15). From 1997–2008, excluding 2003, hospitalizations with a principal diagnosis of AECOPD was one of the 10 leading causes of hospitalization in the United States (16). Therein, hospitalizations account for the largest proportion of costs related to AECOPD (17, 18), ranging from 38–93% (17).

Although numerous studies have quantified the costs of COPD in the United States (7), studies focusing on acute exacerbations of the disease are few in number (11, 19–21), limited in scope, and have used data sources that are now more than a decade old. Niederman et al. (1999) conducted the most comprehensive study on national treatment costs in AECOPD; and direct inpatient and outpatient burden in 1995 was estimated at US$1.59 billion and US$47 million, respectively (19). One important impetus for our study was to provide a more recent estimate of the inpatient burden of AECOPD.

A number of studies have investigated risk factors of in-hospital mortality in AECOPD (9, 10, 22, 23). Physiologic characteristics indicative of exacerbation severity (e.g., abnormal blood gas values) and case severity (i.e., complication during hospital stay, organ system dysfunction, severe COPD, exacerbation severity) (10, 22, 23), co-morbid conditions (more co-morbidities and specific conditions such as arrhythmias) (9, 23), and older age (9, 10, 22, 23), have been identified to increase the risk of in-hospital mortality.

However, literature evaluating predictors of inpatient costs is limited; one study identified increasing age, use of home oxygen, and chronic heart failure as predictors of acute care costs (24). However, for either outcome, previous studies have not evaluated the role of a number of co-morbidities, and hospital characteristics within a single study (while adjusting for a number of other confounders), as possible predictors of costs and mortality in AECOPD in an inpatient setting. This study attempts to address this limitation by quantifying the relationship between these predictors and outcomes employing a nationally representative sample of inpatient hospital discharges of AECOPD.

We particularly focused on co-morbidities due to the recent recognition of COPD as a systemic disease (25), along with increased susceptibility of COPD patients to suffer from multiple co-existing diseases (26, 27). Identification of co-morbidities associated with worse outcomes can direct treatment and disease management priorities in COPD. Additionally, hospital characteristics were evaluated as these have previously been suggested to be associated with patient outcomes (e.g., mortality) in other conditions (28, 29).

The specific objectives of this study were to: 1) determine the direct inpatient burden (costs and mortality); 2) characterize hospitalizations in terms of patient, hospital, and clinical characteristics; 3) determine the top ten diagnoses for all AECOPD discharges and mortality cases; and 4) determine the association of co-morbidities and hospital characteristics on inpatient costs and mortality in hospitalizations for AECOPD.

Methods

This study was a retrospective, attributable, inpatient burden of illness investigation of a nationally-representative sample of hospital discharges for AECOPD in the United States.

Database

Inpatient discharge records from the Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) for 2006 were used (30). This database is the largest publicly available, all-payer inpatient care database in the United States and includes information on patient demographics, diagnoses, procedures, admission and discharge characteristics, payer, total charges, length of stay (LoS), and hospital characteristics. Hospitals within the NIS are sampled from participating states (38 in 2006) to approximate a 20% stratified sample of U.S. community hospitals. In 2006, the NIS represented 39,450,216 national discharges from a sample of 1,045 hospitals (30). Human subjects' approval for the study was granted by the institutional review board of the University of Arizona.

Study population

HCUP allows up to 15 diagnoses, and the first three were considered for the identification of AECOPD discharges. Inclusion criteria were defined as cases ≥40 years (25), and: 1) presence of International Classification of Diseases, Ninth Revision (ICD-9) code for obstructive chronic bronchitis (491.2x); or 2) presence of any other ICD-9 code for COPD (490-492, 494-496) with a concurrent diagnosis for pneumonia (481-486), or a procedure code for mechanical ventilation (93.90, 96.70, 96.71, 96.72). The rationale for the broader inclusion criteria was based upon the possible misclassifications and resultant exclusions of AECOPD that can occur if inclusion criteria were restricted to the principal ICD-9 code of 491.2x (11). Because patient identifiers were not available in the HCUP NIS, the unit of analysis is the hospital discharge record.

Table 1. Hospitalization costs due to AECOPD

		Aggregate costs		Mean (±SD) costs		Median costs	
	N (weighted)	2006	2010[e]	2006	2010[e]	2006	2010[e]
AECOPD (overall)[a]	1,254,703	$11.98 billion	$14.05 billion	$9545 (±12 700)	$11,195 (±14895)	$6062	$7110
Principal diagnosis for AECOPD[b]	421,251	$2.96 billion	$3.47 billion	$7015 (±8289)	$8228 (±9722)	$4983	$5844
AECOPD excluding mechanical ventilation[c]	1,107,220	$8.38 billion	$9.83 billion	$7569 (±7434)	$8877 (±8719)	$5583	$6548
AECOPD with mechanical ventilation[d]	147,473	$3.59 billion	$4.22 billion	24,374 (±26 608)	28,588 (±31 208)	$16,098	$18,881

[a]Inclusion criteria: 1) ICD-9 code for obstructive chronic bronchitis (491.2x); or 2) presence of any other ICD-9 code for COPD (490-492, 494-496) with a concurrent diagnosis for pneumonia (481-486) or, a procedure code for mechanical ventilation (93.90, 96.70, 96.71, 96.72).
[b]Inclusion criteria: ICD-9 code 491.21 indicating an AECOPD in the principal diagnosis position.
[c]Same as a) above excluding procedure codes for mechanical ventilation (93.90, 96.70, 96.71, 96.72).
[d]Hospitalizations with a procedure codes for mechanical ventilation (93.90, 96.70, 96.71, 96.72) from overall sample initially identified as described in a) above.
[e]Inflation adjusted to 2010 US$.

Outcome and independent variables

Two key outcomes were assessed in this study: 1) hospitalization costs; and 2) in-hospital mortality. Hospitalization costs were derived by linking the AHRQ hospital-specific cost-to-charge ratio file to total charges within HCUP (31). Independent variables for the study included: patient demographics (age, sex, race, median household income by patients' ZIP code area); hospital characteristics (bed size, location and teaching status); hospital region; primary payer; mechanical ventilation; LoS; Deyo-modified Charlson co-morbidity index (D-CCI) (32); and relevant co-morbidities for COPD identified from previous literature (26, 33). These co-morbidities included: acute myocardial infarction (MI); congestive heart failure (CHF); cerebrovascular disease; cardiac arrhythmias; pulmonary circulation disorders; diabetes; weight loss, ischemic heart disease (IHD) excluding acute MI; lung cancer; and other cancers excluding lung cancer. As the occurrence of AECOPDs may be more frequent during colder months (34, 35), the admission month was dichotomized (December-March and April-November) and included as another independent variable.

Statistical analysis

All analyses used weighting to obtain national estimates (30). Descriptive statistics were employed to report means, standard deviations (SD±), medians, and proportions, as appropriate. Two Generalized Linear Models (GLM) were fitted independently with the following outcomes: 1) hospitalization costs; and 2) in-hospital mortality. All analyses included the predetermined independent variables addressed here (i.e., patient demographics, D-CCI, hospital region, mechanical ventilation, primary payer, admission month, and LoS were included as control variables). The optimal model for each outcome was selected based upon the evaluation of residual analyses and goodness of fit statistics.

Hospitalization costs were log transformed and assessed using a GLM with Gaussian family distribution and identity link function (results presented as $exp\ \widehat{\beta}$), and in-hospital mortality was assessed using a binomial family distribution and logit link function in the GLM (results presented as odds ratio, OR). Statistical significance was assessed at alpha 0.01 due to the study's large sample size, and robust standard errors were used to adjust for any within hospital correlation. All analyses were conducted using the statistical software package Stata/IC, version 10.1 (Stata Corp., College Station, TX).

Results

Overall, 1,254,703 hospitalizations were reported for AECOPD in 2006. Aggregate, mean, and median costs for 2006, and costs inflation adjusted to 2010 US$ are reported in Table 1. The average LoS was 5.9(±6.1) days (median: 4 days), and in-hospital mortality was 4.3% (N = 53,748).

Descriptive statistics

Demographics of the inpatient cases appear in Table 2. On average, cases were aged 70.6(±11.9) years and had 2.3(±1.6) co-morbidities. The majority were of white race (83.6% of reported race) and female (52.8%). One-third belonged to the lowest national income quartile (33.7%), and the primary payer for the majority of discharges was Medicare or Medicaid (82.7%).

The top 10 diagnoses for all cases and mortality cases appear in Table 3. Beyond COPD or AECOPD, the most commonly occurring diagnoses across all cases were essential hypertension, heart failure, and chronic IHD. In mortality cases, these were: other diseases of lung, disorders of electrolyte and acid-base balance, and cardiac dysrhythmias. The prevalence of co-morbidities of particular relevance to COPD as identified from the literature is presented in Table 4. Approximately one-fifth or more had a diagnosis for CHF (32.8%), cardiac arrhythmias (25.2%), diabetes (26.3%), IHD excluding acute MI (29.6%), and anxiety and/or depression (18.7%). The proportion of cases with a diagnosis for pneumonia and a procedure code for mechanical ventilation was 36.3% and 11.8%, respectively, noting these were also potentially used as selection criteria.

Table 2. Patient characteristics and primary payer of acute exacerbations of chronic obstructive pulmonary disease discharges in 2006[a]

Patient characteristic	Hospital discharges N = 1,254,703 (weighted)
Mean age (±SD) (years)	70.6 (±11.9)
Age	
≤61	22.6
>61–71	26.8
>71–79	25.3
≥80	25.3
Missing	–
Sex	
Female	52.8
Male	47.2
Missing	<0.1
Median household income by ZIP code	
$0–24,999	33.7
$25,000-34,999	27.2
$35,000-44,999	21.5
$45,000+	15.1
Missing	2.4
Race[b]	
White	59.4
Black	5.9
Hispanic	3.7
Asian/Pacific islander	0.6
Native American	0.5
Other	1.0
Missing	28.9
Primary payer	
Medicare	74.8
Medicaid	7.9
Private insurance	12.6
Self-pay	2.3
No charge	0.3
Other	1.9
Missing	0.2
Mean Deyo-modified Charlson co-morbidity index (±SD)	2.3 (±1.6)
Missing	–

[a]All values are given as % of all hospital discharges, unless otherwise indicated.
[b]When missing values are excluded the percentage in each race category are as follows: White (83.6%), Black (8.3%), Hispanic (5.2%), Asian/Pacific Islander (0.9%), Native American (0.7%), and other (1.5%).

Hospital and admission characteristics appear in Table 5. The majority of discharges were in larger hospitals (54.6%), in the South (44.9%), and in urban hospitals (74.8% urban teaching and nonteaching hospitals). Admission during the four months from December to March represented 40% of all discharges.

Table 3. Top 10 diagnoses for all discharges and mortality cases of acute exacerbations of chronic obstructive pulmonary disease in 2006

Diagnosis	%
All discharges (Weighted N = 1,254,703)	
Essential hypertension	46.2
Heart failure	33.4
Chronic ischemic heart disease	30.6
Disorders of fluid, electrolyte, and acid-base balance	29.7
Diabetes mellitus	26.9
Cardiac dysrhythmias	25.1
Disorders of lipid metabolism	21.8
Other diseases of lung	20.2
Esophageal reflux	14.9
History of tobacco use	14.5
Mortality cases (Weighted N = 53,748)	
Other diseases of lung (e.g., respiratory failure, pulmonary collapse, pulmonary insufficiency, acute edema of lung)	63.6
Disorders of fluid, electrolyte, and acid-base balance	56.3
Cardiac dysrhythmias	52.7
Heart failure	46.5
Septicemia, sepsis, and septic shock	35.7
Essential hypertension	32.4
Chronic ischemic heart disease	26.4
Diabetes mellitus	21.8
Hypertensive chronic kidney disease/chronic kidney disease	20.6
Acute renal failure	19.4

Table 4. Co-morbidities of acute exacerbations of chronic obstructive pulmonary disease discharges in 2006[a]

Co-morbidities	Hospital discharges N = 1,254,703 (weighted)
Pre-identified co-morbidities	
Acute MI	8.3
Other ischemic heart disease	29.6
Congestive heart failure	32.8
Cerebrovascular disease	4.0
Diabetes with complications	26.3
Lung cancer	3.4
Other cancers	4.3
Cardiac arrhythmias	25.2
Pulmonary circulation disorders	6.9
Weight loss	4.2
Anxiety and/or depression	18.7

[a]Values are given as % of all hospital discharges.

Table 5. Hospital characteristics, hospital region, admission time, mechanical ventilation, and length of stay for discharges of acute exacerbations of chronic obstructive pulmonary disease in 2006[a]

Characteristic	Hospital discharges N = 1,254,703 (weighted)
Hospital bed size	
Small	18.5
Medium	26.5
Large	54.6
Missing	0.3
Hospital location and teaching status	
Rural	24.8
Urban nonteaching	42.8
Urban teaching	32.0
Missing	0.3
Hospital Region	
Northeast	18.8
Midwest	25.1
South	44.9
West	11.2
Missing	–
Mechanical ventilation	
Non-invasive mechanical ventilation	3.9
Invasive mechanical ventilation	7.9
No ventilation	88.2
Admission period[b]	
Dec-Mar	36.4
Apr-Nov	54.0
Missing	9.6
Mean length of stay (±SD) (days)	5.9 (±6.1)
Missing (n)	24[c]

[a]Values are given as % of all hospital discharges, unless otherwise indicated.
[b]When missing values are excluded percentage in each admission period category are as follows: Dec–Mar (40.3%), Apr–Nov(59.7%).
[c]Number of missing values.

Multivariate analyses

The results of the multivariate analyses are presented in Table 6.

Hospitalization costs

Several co-morbidities investigated were associated with significantly higher hospitalization costs ($p < 0.001$). These were: acute MI ($exp\ \widehat{\beta} = 1.055$), other IHD excluding acute MI ($exp\ \widehat{\beta} = 1.033$), CHF ($exp\ \widehat{\beta} = 1.056$), cerebrovascular disease ($exp\ \widehat{\beta} = 1.046$), lung cancer ($exp\ \widehat{\beta} = 1.029$), cardiac arrhythmias ($exp\ \widehat{\beta} = 1.092$), pulmonary circulation disorders ($exp\ \widehat{\beta} = 1.095$), and weight loss ($exp\ \widehat{\beta} = 1.076$). Anxiety and/or depression ($exp\ \widehat{\beta} = 0.981$) were associated with significantly ($p < 0.001$) lower costs.

Concerning hospital characteristics, higher costs were significantly associated ($p < 0.001$) with hospitals with both medium ($exp\ \widehat{\beta} = 1.052$) and large bed sizes ($exp\ \widehat{\beta} = 1.031$) relative to hospitals with small bed sizes; and both teaching ($exp\ \widehat{\beta} = 1.042$) and nonteaching ($exp\ \widehat{\beta} = 1.038$) urban hospitals compared to rural hospitals.

In-hospital mortality

Co-morbidities that were associated with significantly higher ($p < 0.001$) in-hospital mortality were: acute MI (OR = 1.143), CHF (OR = 1.078), cerebrovascular disease (OR = 1.361), lung cancer (OR = 1.755), cardiac arrhythmias (OR = 1.418), pulmonary circulation disorders (OR = 1.168), and weight loss (OR = 1.970). Several co-morbidities were associated with significantly ($p < 0.001$) lower inpatient mortality. These were other IHD excluding acute MI (OR = 0.711), diabetes (OR = 0.667), and anxiety and/or depression (OR = 0.768).

Hospital characteristics in terms of size (bed size: small, medium, large) and location and teaching status (rural, urban nonteaching, urban teaching) were not statistically significantly associated ($p > 0.01$) with in-hospital mortality.

Sensitivity analysis

Because this study utilized a broad definition to classify acute exacerbations, a sensitivity analysis was conducted in a subgroup of hospitalizations that had a principal diagnosis for AECOPD (ICD-9 code: 491.21). Cost results are included in Table 1. Cost comparisons (Table 1) and results of the primary cost regression (Table 6) identified mechanical ventilation as a cost driver. Therefore, costs were additionally calculated for overall AECOPD hospitalizations without and with mechanical ventilation (Table 1). Results indicate that the difference in mean and median costs was substantially less for hospitalizations with a principal diagnosis for AECOPD and all AECOPD hospitalizations without mechanical ventilation, compared to all hospitalizations with mechanical ventilation.

In-hospital mortality and LoS was also determined. For hospitalizations with a principal diagnosis for AECOPD, and overall AECOPD hospitalizations without and with mechanical ventilation inpatient mortality was 2.1%, 2.2%, and 20.0%, respectively, and mean LoS was 4.8 (±4.6) days (median: 4 days), 5.2(±4.5) days (median: 4 days), and 11.0(±11) days (median: 8 days), respectively.

Regression analyses with AECOPD as a principal diagnosis yielded similar results to that of the primary analysis. However, for the cost regression, acute MI, cerebrovascular disease, and anxiety and/or depression were no longer statistically significant. Lung cancer ($\widehat{\beta} = 0.961$) and other cancers ($\widehat{\beta} = 0.962$) were associated with significantly lower costs ($p < 0.01$). With consideration to associations between hospital characteristics and costs, only the association indicating higher costs in hospitals with medium bed size (compared to hospitals with small bed size) remained statistically significant ($p < 0.001$).

Table 6. Predictors of hospitalization costs and in-hospital mortality for all discharges of acute exacerbations of chronic obstructive pulmonary disease in 2006

	Hospitalization costs (log transformed)[a]		In-hospital mortality[b]	
Predictors	exp $\widehat{\beta}$ (99% CI)	p-value	OR (99% CI)	p-value
Patient demographics				
Age (Referent ≤ 61 yrs)				
>61-71 yrs	1.003 (0.994, 1.011)	0.454	1.753 (1.577, 1.950)	<0.001
>71-79 yrs	0.985 (0.976, 0.995)	<0.001	2.517 (2.251, 2.815)	<0.001
≥80 yrs	0.953 (0.944, 0.962)	<0.001	3.894 (3.481, 4.356)	<0.001
Female	1.007 (1.001, 1.012)	0.002	0.918 (0.867, 0.971)	<0.001
Race (Referent: white)				
Black	1.030 (1.017, 1.042)	<0.001	0.744 (0.655, 0.846)	<0.001
Hispanic	1.071 (1.056, 1.088)	<0.001	1.001 (0.868, 1.155)	0.981
Asian/Pacific Islander	1.041 (1.004, 1.080)	0.004	0.844 (0.602, 1.182)	0.194
Native American	0.948 (0.897, 1.000)	0.011	1.132 (0.722, 1.775)	0.478
Other	1.024 (0.994, 1.055)	0.041	1.050 (0.806, 1.368)	0.633
Missing Race	1.036 (1.030, 1.043)	<0.001	0.923 (0.858, 0.992)	0.004
Income (Referent <$25,000)				
$25,000-34,999	1.044 (1.036, 1.051)	<0.001	1.041 (0.965, 1.123)	0.168
$35,000-44,999	1.057 (1.048, 1.066)	<0.001	1.005 (0.926, 1.092)	0.865
≥$45,000	1.128 (1.117, 1.139)	<0.001	1.038 (0.946, 1.138)	0.303
Primary payer (Referent: Medicare)				
Medicaid	0.977 (0.963, 0.988)	<0.001	0.914 (0.791, 1.056)	0.108
Private Insurance	0.993 (0.984, 1.003)	0.073	1.024 (0.926, 1.132)	0.542
Combined category[c]	0.984 (0.969, 0.998)	0.004	1.119 (0.951, 1.316)	0.075
Mechanical ventilation (Referent: no ventilation)				
Non-invasive mechanical ventilation	1.364 (1.343, 1.386)	<0.001	5.101 (4.601, 5.655)	<0.001
Invasive mechanical ventilation	1.843 (1.785, 1.903)	<0.001	15.305 (14.248, 16.442)	<0.001
Admission period (Referent:Apr-Nov)				
Dec-Mar	0.987 (0.981, 0.993)	<0.001	1.103 (1.039, 1.171)	<0.001
Missing admission month	1.074 (1.063, 1.084)	<0.001	0.922 (0.828, 1.027)	0.052
Length of stay[d]	1.083 (1.078, 1.089)	<0.001	0.997 (0.993, 1.001)	0.070
Hospital region (Referent: Northeast)				
Midwest	0.907 (0.898, 0.916)	<0.001	0.819 (0.742, 0.900)	<0.001
South	0.836 (0.829, 0.844)	<0.001	0.906 (0.833, 0.986)	0.003
West	1.042 (1.027, 1.058)	<0.001	0.853 (0.768, 0.948)	<0.001
Co-morbidities				
Deyo-modified Charlson co-morbidity Index[d]	1.030 (1.026, 1.033)	0.001	1.168 (1.139, 1.197)	<0.001
Acute Myocardial infarction (MI)	1.055 (1.043, 1.067)	<0.001	1.143 (1.039, 1.257)	<0.001
Other ischemic heart disease (excluding acute MI)	1.033 (1.027, 1.040)	<0.001	0.711 (0.663, 0.761)	<0.001
Congestive heart failure	1.056 (1.048, 1.064)	<0.001	1.078 (1.006, 1.155)	0.005
Cerebrovascular disease	1.046 (1.030, 1.062)	<0.001	1.361 (1.214, 1.526)	<0.001
Diabetes	0.994 (0.986, 1.001)	0.029	0.667 (0.618, 0.719)	<0.001
Lung cancer	1.029 (1.011, 1.046)	<0.001	1.755 (1.532, 2.0117)	<0.001
Cancers excluding lung cancer	0.999 (0.982, 1.017)	0.915	1.120 (0.962, 1.304)	0.055
Cardiac arrhythmias	1.092 (1.084, 1.100)	<0.001	1.418 (1.334, 1.507)	<0.001
Pulmonary circulation disorders	1.095 (1.084, 1.107)	<0.001	1.168 (1.055, 1.293)	<0.001
Weight loss	1.076 (1.052, 1.100)	<0.001	1.970 (1.777, 2.183)	<0.001
Anxiety and /or depression	0.981 (0.974, 0.988)	<0.001	0.768 (0.704, 0.838)	<0.001

(Continued)

Table 6. Continued.

Predictors	Hospitalization costs (log transformed)[a]		In-hospital mortality[b]	
	exp $\hat{\beta}$ (99% CI)	p-value	OR (99% CI)	p-value
Hospital characteristics				
Hospital bed size (Referent: small)				
Medium	1.052 (1.043, 1.061)	<0.001	0.951 (0.872, 1.038)	0.143
Large	1.031 (1.023, 1.039)	<0.001	0.951 (0.878, 1.029)	0.100
Hospital location and teaching status (Referent: Rural)				
Urban nonteaching	1.038 (1.028, 1.048)	<0.001	0.952 (0.874, 1.036)	0.133
Urban teaching	1.042 (1.032, 1.052)	<0.001	0.942 (0.863, 1.028)	0.079

[a] Multivariate GLM regression of log transformed costs with Gaussian family and identify link, Log pseudolikelihood = –1,417,313.738, AIC = 11.488.
[b] Multivariate GLM regression of in-hospital mortality with binomial family and logit link, Log pseudolikelihood = –170,225.282, AIC = 1.373.
[c] Combined category includes self-pay, no charge and other.
[d] Included as continuous variables.

For the in-hospital mortality regression, the only change from the primary analysis were among several co-morbidities (i.e., acute MI, cerebrovascular disease, pulmonary circulation disorders, and anxiety and/or depression) that were no longer significant.

Discussion

Using a nationally representative sample of hospital discharges, this investigation estimated the inpatient burden of AECOPD in the Unites States. For 1,254,703 hospitalizations in 2006, total inpatient cost was US$11.9 billion, average hospitalization costs were US $9545 (SD = 12,700) per case, and mortality was 4.3% (53,748 deaths), indicating the substantial inpatient burden due to COPD exacerbations. Furthermore, given the recognition of COPD as a disease with systemic manifestations and the increased occurrence of certain co-morbidities in COPD patients (26, 27), the current study quantified the independent associations between a number of these co-morbidities and the clinical and economic outcomes of mortality and costs in the inpatient setting. After controlling for patient demographics, primary payer, co-morbidity index, LoS, admission period, hospital characteristics, hospital region, and mechanical ventilation, several co-morbidities were significantly ($p < 0.01$) associated with both higher costs and higher mortality including acute MI, CHF, cerebrovascular disease, lung cancer, cardiac arrhythmias, pulmonary circulation disorders, and weight loss.

The current investigation improves on previous research in several important ways. First, determining the inpatient burden of AECOPD is important, as exacerbations related hospitalizations have been identified as the major cost driver in COPD (15, 17, 18). This investigation provided a more recent nationally representative and generalizable estimate of the inpatient burden of AECOPD in the United States. In contrast, the inpatient burden reported in previous studies used data sources which are now more than a decade old (19, 20). Second, this investigation defines AECOPD using broader inclusion criteria than previous work to capture a more accurate representation of the disease.

These inclusion criteria were based upon findings from an analysis of severe COPD patients hospitalized for acute exacerbations which illustrated that restricting cases to a principal diagnosis code alone fails to capture a large proportion of acute exacerbations (11). Third, although several studies have previously evaluated the role of co-morbidities and mortality (11, 23, 36–41), and to a lesser extent between co-morbidities and costs (42–44), this study quantified the independent associations between these outcomes and a number of important co-morbidities while controlling for several possible confounding variables in the inpatient setting. The findings add to the understanding of co-morbidities and COPD by identifying co-existing diseases that pose a greater disease burden specifically in hospitalized patients.

Using somewhat different criteria, the National Heart, Lung, and Blood Institute (NHLBI) estimated the national cost of hospital care across all cases of COPD in 2007 at US$11.3 billion (45). Our study of AECOPD alone reported US$11.9 billion in 1,254,703 cases within an inpatient setting using broader inclusion criteria to best capture the prevalence of AECOPD. Of several studies that have reported average hospitalization costs in COPD (19–21, 46), two have focused specifically on acute exacerbations (19, 20). Niederman et al. (1999) reported costs of $5516 in 1995 [inflation adjusted to $8626 US, 2006] for hospitalizations with a principal diagnosis of acute exacerbations of chronic bronchitis using both HCUP NIS and Medicare data (19).

Saint et al. (2001) reported $6285 and $6625 in 1998/1999 [inflation adjusted to $8783 and $8895, US, 2006 respectively] using two data sources of U.S. academic hospitals (20). When compared to the inflation adjusted costs of these studies, the average costs reported in our study are higher. Cost differences are likely a combination of varying inclusion criteria, and importantly

due to the use of a procedure code for mechanical ventilation for case identification in our study. Mechanical ventilation used as a control variable in the multivariate analysis indicated that costs were higher by a factor of 1.36 and 1.84 for non-invasive and invasive mechanical ventilation, respectively, than cases without.

The impact of using mechanical ventilation as a criterion for study inclusion on costs was evident in the sensitivity analysis that was conducted, as cases with mechanical ventilation averaged $24,374(±26 608) versus $7569(±7434) without. Furthermore, costs for hospitalizations with a principal diagnosis of AECOPD alone was $7015(±8289), and was lower than inflation adjusted (2006 US$) mean costs (reported above) from studies that used similar inclusion criteria.(19, 20) One reason for this difference maybe shorter LoS for AECOPD hospitalizations in 2006, compared to LoS a decade earlier (19, 20).

In-hospital mortality in the current study was 4.3%. The most prevalent diagnoses in these cases were: diseases of the lung (e.g., respiratory failure, pulmonary collapse, pulmonary insufficiency, acute edema of lung); disorders of fluid, electrolyte, and acid-base balance; cardiac dysrhythmias; heart failure; and septicemia, sepsis, and septic shock. Mortality following hospital admission has previously been reported to range from 2.5% for a generalizable national estimate (9), to 24% among patients admitted to intensive care units (10). Our study is most comparable to the study by Patil et al. (2003), which obtained the estimate for mortality using the 1996 HCUP NIS for hospitalizations with a principal diagnosis for AECOPD (9).

Again, the impact of including mechanical ventilation as an inclusion criterion in the current study was evident from the results of the sensitivity analysis of the two subgroups. Mortality among hospitalizations with a principal diagnosis for AECOPD and all hospitalizations without mechanical ventilation was 2.1% and 2.2%, respectively, compared to 20.0% for hospitalizations with mechanical ventilation.

The multivariate analysis examined the presence of independent associations for a number of co-morbidities found to commonly occur in patients with COPD, controlling for several other potential confounding variables. Two reasons have been suggested for the frequent occurrence of certain cormobidities in COPD: 1) as a direct consequence of the disease which can lead to systemic manifestations and development of other co-morbidities; and 2) by sharing common risk factors that contribute to both COPD and other diseases (27). Several of the co-morbidities investigated were associated with significantly ($p < 0.01$) higher hospitalization costs including acute MI, other IHD, CHF, cerebrovascular disease, lung cancer, cardiac arrhythmias, pulmonary circulation disorders, and weight loss.

The increases in costs ranged from a factor of 1.029 for lung cancer to 1.095 for pulmonary circulation disorders. Anxiety and/or depression was associated with significantly ($p < 0.01$) lower costs. Although the costs associated with most co-morbidities were statistically significant, for some conditions (e.g., other IHD, lung cancer, diabetes, and anxiety and/or depression), these differences may not be clinically relevant despite their statistical significance. Nevertheless, consistent with the general trend in the results of our investigation, several studies have previously reported associations between individual co-morbidities and increased costs in COPD (42–44). To illustrate, Lin et al. (2010) conducted a comprehensive analysis by investigating a number of different co-morbidities. (43) Of the co-morbidities evaluated in our study, with the exception of acute MI, COPD patients with CHF, cerebrovascular disease, diabetes, or depression had significantly higher ($p < 0.001$) incremental medical costs compared to patients with the co-morbidity but without COPD (43).

In a second multivariate analysis, independent associations between mortality and co-morbidities were investigated. Several co-morbidities were significantly ($p < 0.001$) associated with increased mortality. These were acute MI, CHF, cerebrovascular disease, lung cancer, cardiac arrhythmias, pulmonary circulation disorders, and weight loss, with odds ratios ranging from 1.078 (CHF) to 1.970 (weight loss). Likely due to the less acute nature of the conditions in an inpatient setting, several co-morbidities was significantly ($p < 0.001$) associated with lower risk of inpatient mortality.

These included other IHD, diabetes, and anxiety and/or depression, with odds ratios ranging from 0.667 (diabetes) to 0.768 (anxiety and/or depression). The co-morbidities associated with a decreased risk of mortality are prevalent chronic conditions in the general population, as well and among hospitalizations for AECOPD; a diagnosis for other IHD, diabetes, and anxiety and/or depression were present among 29.6%, 26.3%, and 18.7% of AECOPD hospitalizations, respectively.

Although IHD and diabetes are diseases with high mortality rates, this may not be reflected in hospitalizations for AECOPD. Instead, the reason for hospital admission and thus death may be more likely associated with conditions such as pulmonary circulation disorders (e.g., cor pulmonale, pulmonary embolism), lung cancer, and cardiac arrhythmias that are more closely linked with, and can aggravate, or even mimic AECOPD (25). Importantly, other studies that evaluated co-morbidities beyond the inpatient setting have reported associations with increased risk of mortality with diseases such as IHD, and depression (36, 37).

This suggests that these diseases can be associated with worse outcomes in COPD patients and observed associations may differ for certain co-morbidities dependent on the study setting and follow-up. A number of studies have previously assessed the role of co-morbidities in predicting mortality in COPD and AECOPD (11, 23, 36-41). However, few studies specifically evaluated co-existing conditions in an inpatient setting in AECOPD (23, 41). Instead, several assessed their role over a period

of follow-up after discharge from hospitalization due to AECOPD (11, 37, 39).

Of the co-morbidities evaluated in our study, an increased risk of mortality in COPD patients was found with CHF (36, 38), acute MI (38), arrhythmias (23, 38, 41), IHD (36), thoracic malignancies (36), pulmonary embolism (15), depression (37), and low body mass index (BMI) (40). However, some varying findings have also been reported including no association of mortality with acute MI (23, 39), or low BMI (23), and lower risk of mortality with cor pulmonale, and CHF (11).

In terms of hospital characteristics, hospitals with medium and large bed size compared to small bed size, and both teaching and nonteaching urban hospitals compared to rural hospitals were associated with significantly ($p < 0.001$) higher costs. No associations with hospital characteristics and in-hospital mortality were observed. Overall, the association with hospital characteristics and costs has been known to exist (47). Larger hospitals may more likely be located in urban areas which, in turn, make treatment at these hospitals more costly due to reasons such as: 1) greater size; 2) increased labor costs; and, 3) provision of more sophisticated services (47).

Teaching hospitals differ from nonteaching hospitals due to several reasons that can translate to higher costs, and include their role in medical education, provision of a more complex range of services, having more sophisticated equipment, and a disproportionately severe case-mix (47). However, the current study did attempt to adjust for disease severity by using the Deyo-modified Charlson co-morbidity index and by separately controlling for a number of co-morbidities and mechanical ventilation.

There are several potential limitations to consider in this study. First, retrospective database analyses have inherent limitations that can apply to this study and include coding errors, omissions, and unmeasured confounding factors. An example of the latter includes other measures of COPD disease severity such as medications, staging of COPD, clinical measurements, spirometry readings, and smoking status. Second, noting the large sample size of the study, some multivariate estimates may have reached statistical significance without reaching clinical relevance. Third, the current study used broader inclusion criteria to define an AECOPD compared to previous studies (9, 19), and was an attempt to address the possible diagnosis misclassifications that can occur in COPD, as reported by Connors et al. (1996) (11).

Although both our study and the investigation by Connors et al. (1996) was conducted among hospitalized patients, the latter was specifically conducted among a cohort of patients with severe COPD (11), whereas the current investigation made no distinction by disease severity and included a broader sample. As a result of the diverse patient populations, use of broader criteria to identify AECOPDs in our study may have included some hospitalizations erroneously identified as AECOPD.

Given this, and to allow for comparisons with other studies, a sensitivity analysis was conducted limiting cases to a principal AECOPD diagnosis alone. A fourth limitation is that the method of cost estimation used in this study gives overall inpatient costs, and does not seek to separate out costs explicitly associated with AECOPD versus other conditions. Future investigations may address the burden of AECOPD using an excess cost approach that allows for the quantification of costs attributed as a consequence of the disease alone (48). Finally, although this study provided national estimates, caution should be exercised in generalizing the results to specific care settings.

This investigation provided a recent nationally representative estimate of the inpatient disease burden of AECOPD in terms of both costs and mortality. After controlling for a number of possible confounders, several co-morbidities were identified to be risk factors of higher costs and mortality. Given that the findings may differ in specific care settings, future research may assess the role of co-morbidities in specific settings while controlling for measures of disease severity that were not available for control in our study. Furthermore, COPD disease management programs that also comprehensively address the management of co-morbidities may be evaluated to determine if they can impact and improve outcomes in COPD patients.

Conclusions

The findings of the current study indicate that the national inpatient burden of AECOPD is substantial. Furthermore, a number of co-morbidities were associated with increased inpatient costs and mortality, suggesting the relevance of co-morbidities in COPD. The presence of co-existing diseases can be used to identify patients prone to increased resource utilization and poor outcomes. More targeted management of these co-morbidities in COPD may help to reduce some of the disease burden in COPD. Future research should be conducted to explore the outcomes of comprehensive COPD management programs that concurrently emphasize the management of co-morbidities prevalent with the disease.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of this paper.

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