International Journal of COPD

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ORIGINAL RESEARCH

Incidence and outcomes of patients hospitalized with COPD exacerbation with and without pneumonia

This article was published in the following Dove Press journal:
International Journal of COPD
2 March 2016
Number of times this article has been viewed

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Background: Pneumonia may be a major contributor to hospitalizations for chronic obstructive pulmonary disease (COPD) exacerbation and influence their outcomes.

Methods: We examined hospitalization rates, health resource utilization, 30-day mortality, and risk of subsequent hospitalizations for COPD exacerbations with and without pneumonia in Denmark during 2006–2012.

Results: We identified 179,759 hospitalizations for COPD exacerbations, including 52,520 first-time hospitalizations (29.2%). Pneumonia was frequent in first-time exacerbations (36.1%), but declined in successive exacerbations to 25.6% by the seventh or greater exacerbation. Pneumonic COPD exacerbations increased 20% from 0.92 per 1,000 population in 2006 to 1.10 per 1,000 population in 2012. Nonpneumonic exacerbations decreased by 6% from 1.74 per 1,000 population to 1.63 per 1,000 population during the same period. A number of markers of health resource utilization were more prevalent in pneumonic exacerbations than in nonpneumonic exacerbations: length of stay (median 7 vs 4 days), intensive care unit admission (7.7% vs 12.5%), and several acute procedures. Thirty-day mortality was 12.1% in first-time pneumonic COPD exacerbations versus 8.3% in first-time nonpneumonic cases (adjusted HR [aHR] 1.20, 95% confidence interval [CI] 1.17–1.24). Pneumonia also predicted increased mortality associated with a second exacerbation (aHR 1.14, 95% CI 1.11–1.18), and up to a seventh or greater exacerbation (aHR 1.10, 95% CI 1.07–1.13). In contrast, the aHR of a subsequent exacerbation was 8%–13% lower for patients with pneumonic exacerbations.

Conclusions: Pneumonia is frequent among patients hospitalized for COPD exacerbations and is associated with increased health care utilization and higher mortality. Nonpneumonic COPD exacerbations predict increased risk of subsequent exacerbations.

Keywords: COPD, exacerbation, pneumonia, incidence, mortality

Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fifth leading cause of death worldwide, and is projected to be the fourth by 2030.[1] COPD affects 10%–20% of adults aged 40 years and older[2–4] and is one of the leading causes of hospitalization and high health care costs.[5–7] Acute exacerbations are responsible for up to 60% of the costs attributable to COPD,[5,8] and they reduce quality of life[9] and speed disease progression.[10]

Previous studies have shown that 50%–75% of exacerbations are associated with respiratory infections,[11] with an unknown proportion associated with pneumonia. Patients with COPD are at greater risk of developing pneumonia than the general population,[12–14] and COPD is an adverse prognostic factor for patients hospitalized with pneumonia.[15] However, little is known about the rate of COPD exacerbations with

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and without pneumonia, or about the impact of pneumonia on severity and outcomes of COPD exacerbations. The few previous studies reached conflicting conclusions, showing either no difference in 30-day mortality among patients with nonpneumonic and pneumonic COPD exacerbations[16,17] or up to 14% increased in-hospital mortality among patients with pneumonic exacerbations.[18,19] Pneumonia may worsen the course of COPD exacerbations due to thickening of the blood–gas barrier, leading to pulmonary dysfunction and increased hypoxemia, systemic inflammation, and risk of severe sepsis with hypotension and decreased perfusion of vital organs. Little is known about how pneumonic versus nonpneumonic exacerbations predict the risk of subsequent COPD exacerbations.[10]

The aim of our study was to examine incidence, health resource utilization, 30-day mortality, and risk of new hospitalizations for COPD exacerbation among patients with successive COPD exacerbations with and without pneumonia in Denmark during 2006–2012.

Material and methods

Setting

Denmark provides its entire population (5.6 million persons) with tax-supported health care and partial reimbursement for prescribed medications. A unique central personal registration number, assigned to all Danish residents at birth or upon immigration, is used to record health care services in various nationwide registries, allowing unambiguous linkage among registries.[20] The current nationwide cohort study is based on information from these registries.

Data sources

The Danish National Patient Registry (DNPR) provides information on all inpatient admissions to hospitals since 1977, and on all outpatient and emergency room visits since 1995.[21] For each hospitalization, DNPR files contain data on dates of admission and discharge, surgical procedures performed, if any, and up to 20 discharge diagnoses coded according to the International Classification of Diseases (ICD).

Information on all prescription drugs is maintained in the Danish National Health Service Prescription.[22] This database records patients' personal identifier, date of dispensing, and type and quantity of drug prescribed (according to the Anatomical Therapeutic Chemical classification system) each time a prescription is redeemed at any Danish pharmacy.

The Danish Civil Registration System (CRS) records information on date of birth, sex, change of address, date of immigration or emigration, and changes in vital status, with daily updates for all individuals legally residing in Denmark at any time since 1968.[20] The CRS allows for complete follow-up of all residents of Denmark.

All ICD and Anatomical Therapeutic Chemical codes used in this study are provided in the Table S1.

Identification of patients hospitalized for a COPD exacerbation with and without pneumonia

We used the DNPR to identify all first-time acute inpatient hospitalizations for COPD exacerbations in Denmark between 2006 and 2012.[6,23] COPD exacerbation was defined as acute admission with either a primary COPD discharge diagnosis or a primary diagnosis of respiratory tract infection, bronchitis, asthma, acute respiratory distress syndrome, or respiratory failure, combined with a secondary diagnosis of COPD listed during the same admission, or a previous primary diagnosis of COPD present within the preceding 10 years.[10] We used this expanded definition of COPD exacerbations because restriction to only hospitalizations coded with primary COPD discharge diagnoses results in a documented underreporting of hospitalized COPD exacerbations.[23] We excluded patients younger than age 40 years at the time of their first COPD hospitalization, given the low COPD prevalence in young people[6] and the potential risk of misclassification of asthma as COPD.

We categorized all COPD hospitalizations according to whether or not they included a primary or secondary diagnosis of pneumonia.

Data on confounding factors

We computed Charlson Comorbidity Index (CCI) scores for each patient based on all hospital diagnoses in DNPR records within 10 years preceding the date of the first hospitalization for COPD.[24] We categorized severity of comorbidity as none (CCI score =0), medium (CCI score =1−2), or high (CCI score ≥3).[25] Because alcoholism-related diseases, atrial fibrillation/flutter, asthma, hypertension, osteoporosis, depression, and venous thromboembolism may affect the prognosis of COPD patients and are not included in the CCI, we also identified previous hospitalizations for these conditions. As a marker of social support, we obtained information on marital status (married, never married, divorced, widowed, or unknown) from the CRS.[26] To assess the impact of COPD severity, we categorized patients according to their current use of short- and long-acting β-agonists, inhaled corticosteroids (beclomethasone, mometasone, fluticasone, and budesonide), combinations of inhaled corticosteroids

and long-acting β-agonists, and intermittent or continuous use of systemic corticosteroids (Table S1).

Health resource utilization, 30-day mortality, and new exacerbations

We estimated health resource utilization associated with each exacerbation by length of stay (defined as the difference between admission and discharge dates), admission to an intensive care unit, use of mechanical and noninvasive ventilation, inotropics and dialysis, and all-cause 30-day acute readmissions (defined as any readmission within 30 days following the index discharge). Information on these health resource utilization measures was obtained from the DNRP. Up-to-date information on mortality within 30 days of exacerbation was obtained from the CRS.[20] Data on new hospitalizations for COPD exacerbations were obtained from the DNRP.

Statistical analysis

We compared patient characteristics and associated health resource utilization among patients hospitalized for a COPD exacerbation, with and without pneumonia. Descriptive statistics were produced using frequencies, proportions, and prevalence proportion ratios (PPRs) for categorical data, and means, medians, and interquartile ranges (IQR) for continuous variables. We then computed overall rates of first COPD exacerbations, with and without pneumonia, as the number of first exacerbations per year divided by the corresponding midyear population above 40 years in Denmark (obtained from Statistics Denmark).

To examine the risk of 30-day mortality and of a new exacerbation, we followed patients from the date of their first hospitalization for a COPD exacerbation until death from any cause, emigration, or December 31, 2012, whichever came first. To assess the effect of each successive exacerbation on the risk of 30-day mortality, we used Cox regression analysis to compute the hazard ratio (HR) of 30-day mortality comparing COPD patients with and without pneumonic exacerbations. Thus, we assessed the risk of death from the admission date with first exacerbation among all patients with a first exacerbation, from the admission date with second exacerbation among all patients with a second exacerbation, and so forth. Age at first exacerbation, sex, CCI score, and respiratory medications as a marker of COPD severity were included as adjustment factors for the effect of pneumonia. The same Cox regression analysis approach was used to assess the effect of each successive COPD exacerbation on the risk of another hospitalization for an exacerbation during follow-up, considering death a competing risk.[27] To increase the likelihood of a correct diagnosis of COPD, we conducted a sensitivity analysis in which we excluded all patients with only a diagnosis of simple and mucopurulent chronic bronchitis or chronic bronchitis. Furthermore, because patients with pneumonic COPD exacerbations might be coded as having "COPD with acute lower respiratory infection" rather than pneumonia, we also conducted a sensitivity analysis in which we categorized these patients as having a pneumonic exacerbation.

All statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). The study was approved by the Danish Data Protection Agency (record no 2012-41-0793). According to Danish law, use of registry data for research purposes does not require informed consent.

Results

Hospitalization rates for COPD exacerbations with and without pneumonia

We identified 179,759 hospitalizations for COPD exacerbations in Denmark during 2006–2012. Of these, 119,877 (66.7%) were nonpneumonic and 59,882 (33.3%) were pneumonic. Among the 52,520 patients with a first-time hospitalization for a COPD exacerbation, 33,552 (63.9%) had a nonpneumonic exacerbation and 18,968 (36.1%) had a pneumonic exacerbation. The proportion of patients with pneumonic exacerbations decreased with an increasing number of exacerbations, reaching 25.6% for seven or more exacerbations (Figure 1). The annual rate of hospitalizations for nonpneumonic exacerbations decreased by 6% from 1.74 per 1,000 population aged 40 years or older in 2006 to 1.63 per 1,000 population aged 40 years or older in 2012. Concurrently, rates of pneumonic COPD exacerbations increased by 20%, reaching 1.10 per 1,000 population aged 40 years or older in 2012 (Figure 2).

Patient characteristics and health resource utilization

Characteristics of patients with a first-time hospitalization for a COPD exacerbation are listed in Table 1. Patients with a pneumonic exacerbation had a slightly lower probability than patients with a nonpneumonic exacerbation of receiving any respiratory medication within the 365 days preceding the index admission (72.0% vs 76.5%). As well, patients with nonpneumonic exacerbations were more likely than patients with pneumonic exacerbations to use oral corticosteroids

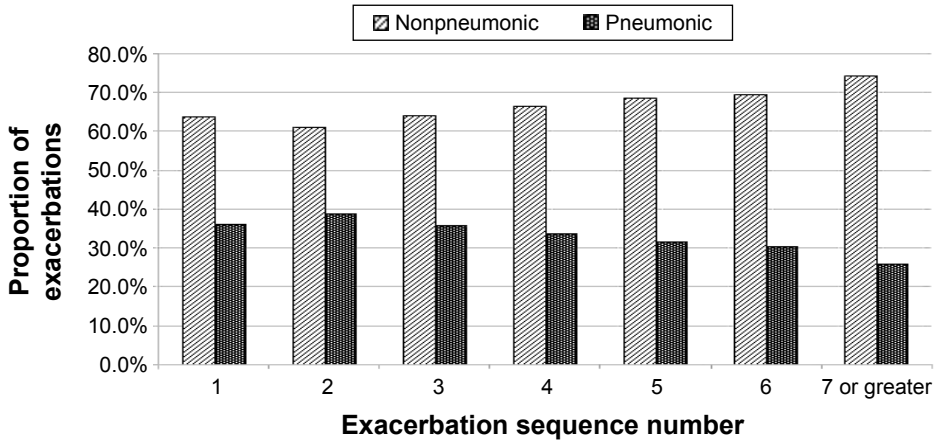

Figure 1 Proportion of pneumonic and nonpneumonic COPD exacerbations according to number of exacerbations, Denmark, 2006–2012.
Abbreviation: COPD, chronic obstructive pulmonary disease.

(26.8% vs 20.7%). Patients with a first-time pneumonic exacerbation were slightly older (median age 75 years, IQR 66–82 years) than patients with a nonpneumonic exacerbation (median age 73 years, IQR 64–80 years), and had a higher prevalence of virtually all comorbidities included in the analysis (57.4% had a CCI score ≥1 compared with 50.7% of patients with nonpneumonic exacerbations) (Figure 3).

Table 2 shows the health resource utilization associated with first-time COPD exacerbations. The median length of hospital stay was 4 days (IQR 2–8 days) for patients with a nonpneumonic exacerbation and 7 days (IQR 4–11 days) for patients with a pneumonic exacerbation. Mechanical or noninvasive ventilation was provided to 3.3% and 6.7% of patients with nonpneumonic exacerbations respectively, compared with 6.9% and 9.7% of patients with pneumonic exacerbations. Patients with pneumonic exacerbations were also more likely to receive inotropic therapy (PPR 2.15, 95% confidence interval [CI] 1.94–2.37) or dialysis (PPR 1.74, 95% CI 1.39–2.17), and were slightly more likely to be readmitted for any cause within 30 days following discharge (PPR 1.04, 95% CI 1.00–1.08) compared with patients with nonpneumonic exacerbations (Table 2).

Thirty-day mortality

Thirty-day mortality was 12.1% in patients with a first-time pneumonic exacerbation and 8.4% in those with a first-time

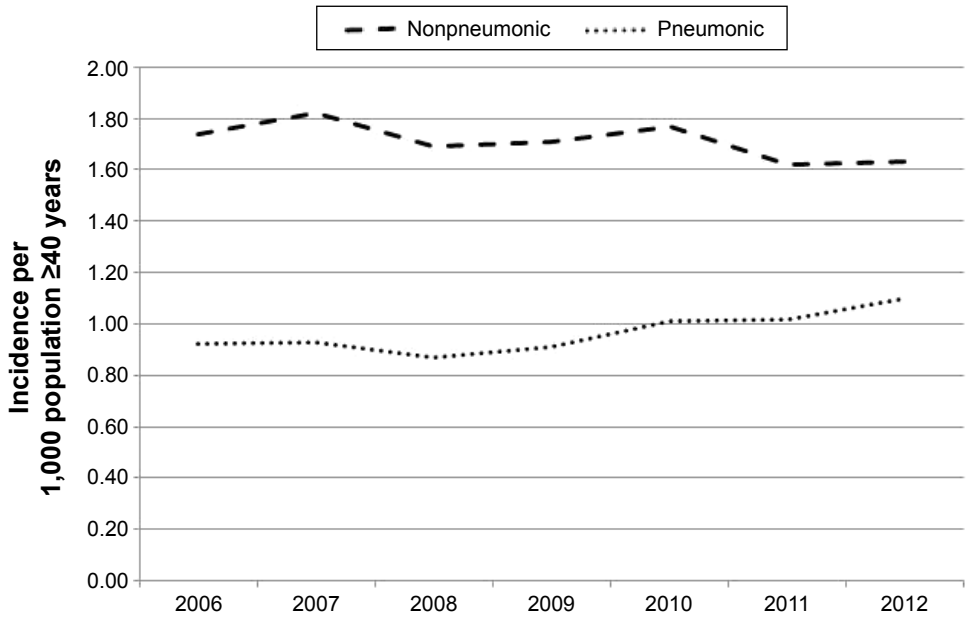

Figure 2 Incidence rates of pneumonic and nonpneumonic COPD exacerbations in individuals aged 40 years and older in Denmark, 2006–2012.
Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 1 Baseline characteristics of patients with a first-time hospitalization for a COPD exacerbation in Denmark, 2006–2012

Characteristic	Exacerbation type			
	Nonpneumonic exacerbation		Pneumonic exacerbation	
	No	%	No	%
Overall	33,552	100	18,968	100
Respiratory medications in the year prior to first hospitalization				
No respiratory medication use	7,897	23.5	5,309	28.0
Use of respiratory medications other than inhaled corticosteroids	11,030	32.9	6,592	34.8
Use of inhaled corticosteroids	3,388	10.1	1,788	9.4
Use of oral corticosteroids	8,979	26.8	3,917	20.7
Continuous use of oral corticosteroids	2,258	6.7	1,362	7.2
Sex				
Female	18,400	54.8	9,411	49.6
Male	15,152	45.2	9,557	50.4
Age, years				
40–49	1,538	4.6	552	2.9
50–59	4,036	12.0	1,792	9.4
60–69	7,954	23.7	4,125	21.7
70–79	11,247	33.5	6,421	33.9
80–89	7,789	23.2	5,291	27.9
90 and older	988	2.9	787	4.1
Marital status				
Married	13,281	42.3	7,336	42.6
Widowed	9,841	29.3	5,765	30.4
Divorced	6,472	19.3	3,338	17.6
Unmarried	1,779	5.3	857	4.5
Unknown	1,143	3.4	794	4.2
CCI score				
0	16,527	49.3	8,083	42.6
1	6,811	20.3	4,077	21.5
2	5,067	15.1	3,146	16.6
≥3	5,147	15.3	3,662	19.3

Abbreviations: CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease.

nonpneumonic exacerbation, equivalent to an adjusted HR (aHR) of 1.21 (95% CI 1.17–1.24) after adjusting for age, sex, comorbidity, and respiratory medications (Table 3). Presence of pneumonia also predicted increased mortality among patients hospitalized with a second exacerbation (aHR 1.14, 95% CI 1.11–1.18), and up to the seventh and subsequent exacerbation (aHR 1.10, 95% CI 1.07–1.13).

Among patients with a pneumonic COPD exacerbation, 37.3% had at least one subsequent severe exacerbation requiring hospitalization during median follow-up of 203 days, compared with 43.4% of patients with a nonpneumonic exacerbation during median follow-up of 213 days (Table 4). After taking into account death as a competing risk, the corresponding aHR of a subsequent hospitalization for an exacerbation associated with pneumonia was 0.93 (95% CI 0.91–0.96). The time span between successive exacerbations diminished with increasing number of exacerbations, both for pneumonic and nonpneumonic exacerbations. Nonetheless, the aHR of a subsequent exacerbation was 8%–13% lower for patients with pneumonic versus nonpneumonic exacerbations across numbers of exacerbations.

In the sensitivity analysis excluding patients with bronchitis, presence of pneumonia remained consistently associated with increased risk of death and lower risk of a subsequent exacerbation across numbers of exacerbations (data not shown). At their first-time hospitalization for a COPD exacerbation, 9.5% of patients had a diagnosis of "COPD with acute lower respiratory infection." Categorizing these patients as having pneumonic exacerbations attenuated the difference between pneumonic and nonpneumonic COPD exacerbations (Table S2).

Discussion

This nationwide population-based cohort study showed a large and apparently increasing burden of pneumonic COPD exacerbations. Approximately 36% of patients hospitalized for a first-time exacerbation also received a pneumonia diagnosis. During 2006–2012, the incidence of first-time

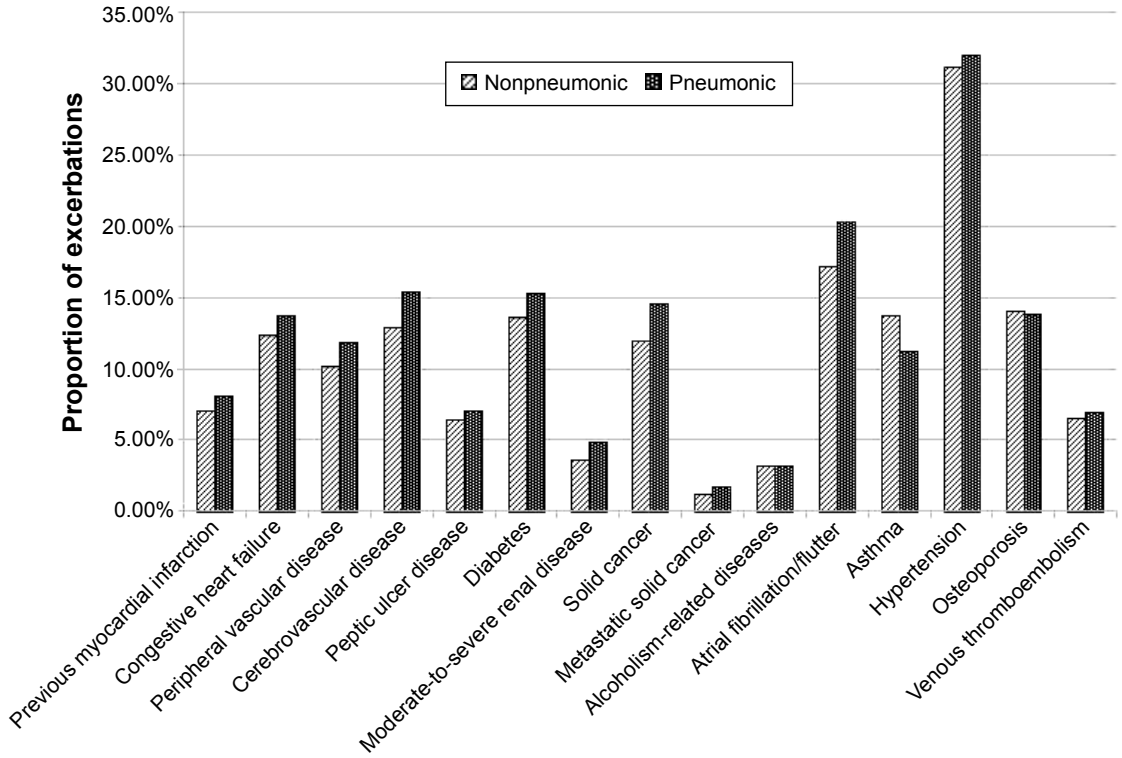

Figure 3 Proportion of comorbidities in patients with pneumonic and nonpneumonic COPD exacerbations, Denmark, 2006–2012.
Abbreviation: COPD, chronic obstructive pulmonary disease.

hospitalizations for pneumonic exacerbations increased by 20%. Over the same period, the rate of nonpneumonic exacerbations decreased by 6%. Patients with pneumonic exacerbations were older, had more comorbidity, and required more health resources in terms of a prolonged hospital stay, increased use of intensive care, assisted ventilation, inotropic therapy, dialysis, and readmission. Pneumonic exacerbations were also associated with higher 30-day mortality compared with nonpneumonic exacerbations, both in first-time and successive exacerbations, and after adjustment for age, sex, comorbidity, and COPD severity. At the same time, patients with nonpneumonic COPD exacerbations had a slightly higher risk of subsequent hospitalizations for exacerbations than patients with pneumonic exacerbations, regardless of number of exacerbations.

The paucity of data on pneumonic versus nonpneumonic exacerbations to some extent may stem from controversy as to whether or not a case of manifest pneumonia should be

Table 2 Health resource utilization among patients with a first-time nonpneumonic or pneumonic COPD exacerbation, Denmark 2006–2012

Health resource utilization	Exacerbation type		Prevalence proportion ratio pneumonic vs nonpneumonic (95% CI)
	Nonpneumonic	Pneumonic	
Median LOS (IQR), days	4 (2–8)	7 (4–11)	–
ICU stay			
N (%)	2,585 (7.7)	2,373 (12.5)	1.63 (1.54–1.71)
Mechanical ventilation			
N (%)	1,106 (3.3)	1,315 (6.9)	2.10 (1.95–2.27)
Noninvasive mechanical ventilation			
N (%)	2,240 (6.7)	1,841 (9.7)	1.45 (1.37–1.54)
Inotropic use			
N (%)	756 (2.3)	920 (4.9)	2.15 (1.94–2.37)
Dialysis			
N (%)	157 (0.5)	154 (0.8)	1.74 (1.39–2.17)
30-day acute readmission of any cause			
N (%)	5,886 (17.5)	3,453 (18.2)	1.04 (1.00–1.08)

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay.

Table 3 Crude and adjusted risk of 30-day mortality according to number of exacerbation[a]

Exacerbation number	Exacerbation type	Patients, N	30-day mortality (%)	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
First	Nonpneumonic	33,552	8.3	1 (reference)	1 (reference)
	Pneumonic	18,968	12.1	1.35 (1.31–1.39)	1.20 (1.17–1.24)
Second	Nonpneumonic	18,774	10.2	1 (reference)	1 (reference)
	Pneumonic	11,878	15.0	1.33 (1.29–1.38)	1.14 (1.11–1.18)
Third	Nonpneumonic	13,173	10.4	1 (reference)	1 (reference)
	Pneumonic	7,356	15.2	1.27 (1.22–1.32)	1.12 (1.08–1.17)
Fourth	Nonpneumonic	9,727	10.5	1 (reference)	1 (reference)
	Pneumonic	4,907	13.5	1.20 (1.15–1.26)	1.08 (1.03–1.14)
Fifth	Nonpneumonic	7,524	10.4	1 (reference)	1 (reference)
	Pneumonic	3,450	14.1	1.22 (1.16–1.29)	1.10 (1.04–1.16)
Sixth	Nonpneumonic	5,873	10.1	1 (reference)	1 (reference)
	Pneumonic	2,553	13.3	1.19 (1.12–1.27)	1.12 (1.06–1.19)
Seventh or greater	Nonpneumonic	31,254	8.9	1 (reference)	1 (reference)
	Pneumonic	10,770	11.3	1.17 (1.13–1.20)	1.10 (1.07–1.13)

Notes: [a]Risk of death is assessed from the admission date with first exacerbation among all patients with a first exacerbation, from the admission date with second exacerbation among all patients who have a second exacerbation, and so forth. [b]Adjusted for age, sex, CCI score, and respiratory medications as a marker of COPD severity.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

considered as part of a COPD exacerbation. Some consider pneumonia and acute exacerbations in COPD patients as separate acute events.[16,28] Still, the British Thoracic Society includes COPD patients with X-ray-confirmed pneumonia in their national audit of COPD exacerbations.[19] The Global Initiative for Chronic Obstructive Lung Disease defines an exacerbation as an event in the clinical course of COPD characterized by amplification of the state of chronic inflammation in the airways and acute onset of aggravation of baseline symptoms beyond normal day-to-day variations and leading to a change in medication.[29] This broad definition may include a wide range of manifestations, including those of pneumonia.[30] Accordingly, in this study, we considered hospitalization for pneumonia to be a COPD exacerbation.

Compared with the few previous studies,[17–19,31] we identified a relatively high proportion of patients with a first-time pneumonic COPD exacerbation. In a recent Norwegian study of 1,144 patients hospitalized with COPD exacerbations, 237 (20.7%) had pneumonia defined as a pneumonic infiltrate on X-ray and CRP equal to or above 40 mg/L.[17] In the 2008 National UK COPD audit, 16% of patients hospitalized with a COPD exacerbation presented with radiographic

Table 4 Crude and adjusted risk of a subsequent exacerbation according to number of exacerbation[a]

Exacerbation number	Exacerbation type	Patients with exacerbation, N	Proportion with a subsequent exacerbation (%)	Median time to subsequent exacerbation (days)	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
First	Pneumonic	14,560	43.4	213	1 (reference)	1 (reference)
	Nonpneumonic	7,073	37.3	206	0.94 (0.92–0.97)	0.93 (0.91–0.96)
Second	Pneumonic	10,949	58.3	142	1 (reference)	1 (reference)
	Nonpneumonic	5,786	48.7	146	0.87 (0.85–0.90)	0.88 (0.85–0.91)
Third	Pneumonic	8,581	65.1	106	1 (reference)	1 (reference)
	Nonpneumonic	4,131	56.2	120	0.90 (0.86–0.93)	0.92 (0.88–0.95)
Fourth	Pneumonic	6,838	70.3	83	1 (reference)	1 (reference)
	Nonpneumonic	3,016	61.5	97	0.86 (0.82–0.90)	0.87 (0.84–0.91)
Fifth	Pneumonic	5,433	72.2	75	1 (reference)	1 (reference)
	Nonpneumonic	2,223	64.4	86	0.90 (0.85–0.94)	0.91 (0.86–0.95)
Sixth	Pneumonic	4,405	75.0	66	1 (reference)	1 (reference)
	Nonpneumonic	1,739	68.1	74	0.93 (0.88–0.98)	0.94 (0.89–1.00)
Seventh or greater	Pneumonic	25,839	82.7	38	1 (reference)	1 (reference)
	Nonpneumonic	8,151	75.7	48	0.86 (0.84–0.89)	0.88 (0.86–0.90)

Notes: [a]Risk of new exacerbation is assessed from the admission date with first exacerbation among all patients with a first exacerbation, from the admission date with second exacerbation among all patients who have a second exacerbation, and so forth. [b]Adjusted for age, sex, CCI score, and respiratory medications as a marker of COPD severity.

Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.

consolidation.[19] In another study, 23 (9%) patients among 250 patients hospitalized for acute exacerbation had X-ray findings indicating pneumonia.[31] In contrast with our study, these studies focused on prevalent rather than incident episodes. We showed that the proportion of pneumonic exacerbations declined with the number of exacerbations, which explains part of the differences in findings. In their study, Steer et al[18] included patients with a first-time hospitalization for a COPD exacerbation and found that 299 (33%) of 920 patients were categorized with pneumonic exacerbations based on X-ray findings. This is in line with our finding that 36% of patients in our study who presented with a first-time COPD exacerbation had pneumonia. Also corroborating our findings, earlier studies reported that patients with pneumonic exacerbations tend to be older, have more comorbidity, a longer length of stay, and more assisted ventilation compared with patients with nonpneumonic exacerbations.[17–19]

In line with the findings of Suissa et al,[10] we observed that severe exacerbations appeared to recur progressively sooner after each subsequent severe exacerbation. The reason for the apparently higher risk of subsequent exacerbations among those with nonpneumonic exacerbations is not clear, but might be related to a phenotype associated with persistent and increased propensity for airway and systemic inflammation[32] without a propensity for manifest respiratory tract infection. Another explanation may be more intensive antibiotic therapy given to patients with manifest pneumonia, including possible prophylactic use of azithromycin in some patients, which may prevent or delay new COPD exacerbations.[33,34] Use of inhaled corticosteroids has been associated with decreased risk of subsequent exacerbations and increased risk for hospitalization with pneumonia.[35] However, prior use of inhaled corticosteroids differed little among nonpneumonic and pneumonic first-time admitted patients in our study, and therefore also was unlikely to explain any observed differences in mortality.[36] To some extent, the higher risk of subsequent exacerbation in patients following nonpneumonic exacerbations may have been related to the higher mortality during index admission in those with pneumonic exacerbation, leaving fewer frail patients at risk of subsequent exacerbations (depletion of susceptibles).

Our estimates of COPD exacerbation and mortality are based on a nationwide cohort study conducted in a setting in which a national health service provides unfettered access to health care, thus largely eliminating referral and diagnostic biases. Our study included the entire Danish population and had complete follow-up through the use of nationwide registries, so it also avoided the selection biases hampering clinic-based studies.

Our study also has limitations. It is important to note that our results focused only on COPD exacerbations requiring hospitalization. As well, the accuracy of diagnoses of pneumonic and nonpneumonic COPD exacerbation were dependent on proper ICD-10 coding. Previous DNRP validation studies have revealed positive predictive value 92%–100% of ICD codes for primary COPD[25] and COPD exacerbations.[23] Our data had similarly high accuracy for detecting pneumonia requiring hospitalization (ie, a predictive value of ~90%)[37,38] and for the comorbid conditions in the CCI.[25] The validity of pneumonia codes associated with COPD has not been well studied. The decline in the proportion of exacerbations with pneumonia over subsequent episodes may suggest that the likelihood of actually having COPD increases with each episode. However, any misclassification between pneumonic and nonpneumonic episodes would tend to diminish observed differences between the two conditions, not changing our conclusions. Another limitation is the lack of clinical data on the length of each exacerbation, making it difficult to differentiate between relapse and recurrence.[10,39,40] However, the majority of patients recover within 30 days after the onset of a COPD exacerbation.[40] In our data, the median time between hospitalizations ranged from 38 to 213 days, supporting the conclusion that they are in fact recurrent events. We also lacked clinical data on severity of symptoms, airflow limitations, and exercise intolerance, and lifestyle factors such as poor nutrition, alcohol consumption, and tobacco smoking that may influence prognosis.[41] However, we were able to control for hospital diagnoses of alcohol-related conditions and many other lifestyle-related diseases including diabetes, cardiovascular disease, and cancer.

We conclude that pneumonia is common in patients hospitalized with acute COPD exacerbations and is associated with increased health resource utilization and poor prognosis compared with patients with nonpneumonic exacerbations. Our results emphasize the need for increased attention to treatment and prevention of pneumonia in patients with COPD.

Acknowledgment

This study was partly supported by a research grant from Pfizer A/S to Aarhus University.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 ICD and ATC classification system codes used in the study

Codes used for identifying COPD exacerbation	
Simple and mucopurulent chronic bronchitis	ICD-10: J41
Chronic bronchitis	ICD-10: J42
Emphysema	ICD-10: J43
COPD	ICD-10: J44
Respiratory failure	ICD-10: J96
Acute respiratory infection	ICD-10: J00–J06, J09–J11, J13, J14–J18, J20–J22
Chronic lower respiratory disease	ICD-10: J40–J47
Acute respiratory distress	ICD-10: J80
Abscess of lung or pyothorax/empyema	ICD-10: J85–J86
Codes used for identifying pneumonia	ICD-10: J12–J18
Charlson Comorbidity Index	
Score 1	
Myocardial infarction	ICD-10: I21, I22, I23
Congestive heart failure	ICD-10: I50, I11.0, I13.0, I13.2
Peripheral vascular disease	ICD-10: I70, I71, I72, I73, I74, I77
Cerebrovascular disease	ICD-10: I60–I69, G45, G46
Dementia	ICD-10: F00–F03, F05.1, G30
Chronic pulmonary disease*	ICD-10: J40, J45–J47, J60–J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3
Connective tissue disease	ICD-10: M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86
Ulcer disease	ICD-10: K22.1, K25–K28
Mild liver disease	ICD-10: B18, K70.0–K70.3, K70.9, K71, K73, K74, K76.0
Diabetes types 1 and 2	ICD-10: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9
Score 2	
Hemiplegia	ICD-10: G81, G82
Moderate-to-severe renal disease	ICD-10: I2, I13, N00–N05, N07, N11, N14, N17–N19, Q61
Diabetes with end-organ damage	ICD-10: E10.2–E10.8, E11.2–E11.8
Any tumor	ICD-10: C00–C75
Leukemia	ICD-10: C91–C95
Lymphoma	ICD-10: C81–C85, C88, C90, C96
Score 3	
Moderate-to-severe liver disease	ICD-10: B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85
Score 6	
Metastatic solid tumor	ICD-10: C76–C80
AIDS	ICD-10: B21–B24
Additional comorbidities	
Alcoholism-related diseases	ICD-10: F10.7–F10.9, G31.2, G62.1, G72.1, I42.6, K.29.2, K70, K86.0
Atrial fibrillation/flutter	ICD-10: I48
Asthma	ICD-10: J45
Hypertension	ICD-10: I10–I13
Osteoporosis	ICD-10: M80, M81
Venous thromboembolism	ICD-10: I80.1–3; I26.0; I26.9
Additional codes	
Mechanical ventilation	Treatment code: BGDA0
Noninvasive mechanical ventilation	Treatment code: BGDA1
Dialysis	ICD-10: BJFD0
Treatment with inotropic agents	Treatment code: BFHC92; BFHC93; BFHC95

(*Continued*)

Table S1 (*Continued*)

Respiratory medications	
1) COPD with continuous oral glucocorticoid treatment	≥1 prescription for medications with ATC code H02AB group (except injections) 365 days before index date, with medication possession ratio >0.7, ie, total number of pills in package(s) covering more than 70% of the 365 days
2) COPD with oral glucocorticoid treatment	≥1 prescription for medications with ATC code H02AB group (except injections) 365 days before index date
3) COPD with inhaled corticosteroid treatment	≥1 prescription 365 days before index date of inhaled corticosteroids: beclomethasone, mometasone, fluticasone, budesonide (ATC codes R03BA01, R03BA02, R03BA03, R03BA05, R03BA07), or combinations of inhaled corticosteroids and long acting β-agonists: salmeterol + fluticasone and formoterol + budesonide (ATC codes R03AK06 and R03AK07, respectively)
4) COPD treated with other therapies than corticosteroids	≥1 prescriptions for medications with ATC code R03 group other than those in group 3 within 365 days before index date

Note: *Excluding COPD ICD-10: J41–J44.
Abbreviations: ATC, Anatomical Therapeutic Chemical; COPD, chronic obstructive pulmonary disease; ICD, International classification of diseases.

Table S2 Sensitivity analysis categorizing patients with a discharge diagnosis of "chronic obstructive pulmonary disease with acute lower respiratory infection" (ICD-10: J44.0) as having a pneumonic COPD exacerbation

Exacerbation number	Exacerbation type	Risk of 30-day mortality			Risk of a subsequent hospitalization for a COPD exacerbation		
		No of patients (%)	30-day mortality (%)	Adjusted HR[a] (95% CI)	Median time to subsequent exacerbation (days)	Proportion with a subsequent exacerbation (%)	Adjusted HR[a] (95% CI)
First	Nonpneumonic	28,582 (54.4)	8.4	1 (reference)	209	42.8	1 (reference)
	Pneumonic	23,938 (45.6)	11.3	1.15 (1.11–1.18)	214	39.2	0.97 (0.94–1.00)
Second	Nonpneumonic	15,928 (52.0)	10.5	1 (reference)	141	57.9	1 (reference)
	Pneumonic	14,724 (48.0)	13.7	1.10 (1.07–1.14)	146	51.0	0.91 (0.88–0.94)
Third	Nonpneumonic	11,046 (53.8)	10.6	1 (reference)	105	65.0	1 (reference)
	Pneumonic	9,483 (46.2)	14.0	1.12 (1.08–1.16)	117	58.4	0.94 (0.91–0.97)
Fourth	Nonpneumonic	8,164 (55.8)	10.8	1 (reference)	82	70.0	1 (reference)
	Pneumonic	6,470 (44.2)	12.3	1.07 (1.02–1.11)	94	64.0	0.90 (0.87–0.94)
Fifth	Nonpneumonic	6,308 (57.5)	10.7	1 (reference)	74	72.1	1 (reference)
	Pneumonic	4,666 (42.5)	12.8	1.10 (1.04–1.15)	84	66.7	0.92 (0.88–0.97)
Sixth	Nonpneumonic	4,923 (58.4)	10.2	1 (reference)	63	75.2	1 (reference)
	Pneumonic	3,503 (41.6)	12.4	1.11 (1.05–1.18)	74	69.7	0.92 (0.88–0.97)
Seventh or greater	Nonpneumonic	26,414 (62.9)	8.7	1 (reference)	38	82.8	1 (reference)
	Pneumonic	15,610 (31.7)	10.8	1.09 (0.07–1.12)	45	77.6	0.91 (0.89–0.93)

Note: [a]Adjusted for age, sex, CCI score, and respiratory medications as a marker of COPD severity.
Abbreviations: CI, confidence interval; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; HR, hazard ratio.