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COPD is associated with increased mortality in patients with community-acquired pneumonia

M.I. Restrepo*,¶, E.M. Mortensen*,#, J.A. Pugh*,# and A. Anzueto¶

ABSTRACT: Patients with chronic obstructive pulmonary disease (COPD) who develop community-acquired pneumonia (CAP) may experience worse clinical outcomes. However, COPD is not included as a distinct diagnosis in validated instruments that predict mortality in patients with CAP. The aim of the present study was to evaluate the impact of COPD as a comorbid condition on 30- and 90-day mortality in CAP patients. A retrospective observational study was conducted at two hospitals. Eligible patients had a discharge diagnosis and radiological confirmation of CAP.

Among 744 patients with CAP, 215 had a comorbid diagnosis of COPD and 529 did not have COPD. The COPD group had a higher mean pneumonia severity index score (105±32 *versus* 87±34) and were admitted to the intensive care unit more frequently (25 *versus* 18%). After adjusting for severity of disease and processes of care, CAP patients with COPD showed significantly higher 30- and 90-day mortality than non-COPD patients.

Chronic obstructive pulmonary disease patients hospitalised with community-acquired pneumonia exhibited higher 30- and 90-day mortality than patients without chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease should be evaluated for inclusion in community-acquired pneumonia prediction instruments.

KEYWORDS: Chronic obstructive pulmonary disease, community-acquired pneumonia, mortality

Chronic obstructive pulmonary disease (COPD) is currently the fifth leading cause of death, whereas community-acquired pneumonia (CAP) is the seventh leading cause of overall death and first leading cause of infectious death in the USA [1, 2]. COPD alone affects ~20 million Americans, and is one of the most frequently reported comorbid conditions in CAP patients [3–6]. Despite COPD being one of the most frequent comorbid conditions and a risk factor for developing pneumonia, it has not been shown to be a risk factor for mortality in CAP patients [6–9]. The well-validated prediction rule developed as part of the pneumonia Patient Outcomes Research Team (PORT) cohort study, that evaluated 30-day mortality in patients with CAP, excluded chronic pulmonary disease as a risk factor [10]. The prediction rule was based on 20 variables that included five comorbid illnesses (cardiovascular, history of malignancy, cerebrovascular, renal and liver diseases) [10, 11]. In addition, FINE *et al*. [6] published a meta-analysis related to prognosis and outcomes in CAP patients, and found that patients with pulmonary diseases, including COPD, asthma and interstitial lung disease, did not show higher mortality. However, in previous research (PORT studies and the meta-analysis), the diagnosis of COPD was combined with asthma and interstitial lung diseases, which might be inaccurate given that these conditions exhibit different natural histories, and may bias the overall impact of COPD on CAP morbidity and mortality [6]. Therefore, the present authors are unaware of any studies that have specifically evaluated the association of mortality in hospitalised CAP patients with COPD only as chronic pulmonary disease and excluding asthma and interstitial lung disease.

The purpose of the current study was to examine whether the comorbid condition of COPD is a predictor for increased mortality in patients hospitalised for CAP. It was hypothesised that COPD patients with CAP would have a higher mortality than CAP patients without COPD.

METHODS

The present study was a retrospective cohort study of hospitalised CAP patients at two

For editorial comments see page 262.

AFFILIATIONS
*The Veterans Evidence-based Research, Dissemination, and Implementation Center, Audie L Murphy Veterans Hospital, and, Divisions of #General Medicine, and ¶Pulmonary and Critical Care Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA.

CORRESPONDENCE
M.I. Restrepo
VERDICT (11C6) at the South Texas Veterans Health Care System
Audie L. Murphy Division at San Antonio
7400 Merton Minter Boulevard
San Antonio TX
78284
USA
Fax: 1 2105674423
E-mail: restrepom@uthscsa.edu

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academic teaching tertiary care hospitals (University Hospital and South Texas Veterans Health Care System Audie L. Murphy Division, San Antonio, TX, USA). The Institutional Review Board of the University of Texas Health Science Center at San Antonio approved the research protocol with exempt status.

Study sites and inclusion and exclusion criteria

All patients admitted to the study hospitals between January 1, 1999 and December 1, 2002 with a primary discharge diagnosis of pneumonia (International Classification of Diseases, ninth revision (ICD-9) codes 480.0–483.99 or 485–487.0) or secondary discharge diagnosis of pneumonia with a primary diagnosis of respiratory failure (518.81) or sepsis (038.xx) were identified. Patients were included in the present study if they were: 1) aged $\geqslant$18 yrs; 2) had an admission diagnosis of CAP; and 3) underwent chest radiography or chest computerised tomography within 24 h of admission with findings that were consistent with CAP.

Exclusion criteria included: 1) discharge from an acute care facility within 14 days of admission; 2) transfer after being admitted to another acute care hospital; 3) HIV/AIDS; and 4) having ''comfort measures only'' status during the admission. If a subject was admitted more than once during the study period, only the first hospitalisation was abstracted.

Definition of COPD

The definition of COPD was based on baseline clinical data obtained by chart review. Owing to the absence of pulmonary function test results, terms including ''chronic obstructive pulmonary disease'', ''emphysema'' and ''chronic bronchitis'' were used as proxy measures for COPD. Missing values or data were assumed to be normal and not show COPD. This strategy is widely used in the application of prognostic prediction rules and reflects the methods used in the original pneumonia severity index (PSI) score studies [10, 12].

The primary outcomes were 30- and 90-day mortality, and secondary outcomes were length of hospital stay, need for intensive care unit (ICU) admission and need for mechanical ventilation. Both 30- and 90-day mortality were included to differentiate between the proportion of deaths attributable to pneumonia and other causes, respectively [13].

Mortality was assessed using information from the Texas Department of Health and Department of Veterans Affairs clinical database (Austin, TX, USA). Mortality status was assessed during December 2002.

Data abstraction

Chart review data included: demographics, comorbid conditions, physical examination findings, laboratory data, and chest radiographic reports. Comorbid conditions were identified from either the admission note or the chart problem list. In addition, data on important processes of care measures for patients hospitalised with CAP were also abstracted: 1) timing of first dose of antibiotics; 2) collection of blood cultures prior to antibiotic administration; and 3) obtention of blood cultures and oxygen saturation measurements within 24 h of presentation [14, 15]. Antimicrobial therapy was considered guideline-concordant if it agreed with either the 2003 Infectious Diseases Society of America (IDSA) or 2001 American Thoracic Society (ATS) guidelines [14, 15]. Information on outpatient corticosteroid use was recorded from either the admission note or the electronic medical record.

Diagnostic criteria

Microbiological data were reviewed, and a microbiological cause assigned independently by two of the principal investigators (M.I. Restrepo and E.M. Mortensen). The cause of pneumonia was stratified as definitive or presumptive. A definitive diagnosis was considered to be present if one of the following conditions were met: 1) positive blood cultures for bacterial or fungal pathogens (in the absence of an extrapulmonary source of infection); 2) pleural fluid cultures yielding a bacterial pathogen; 3) endotracheal aspirates with moderate or heavy growth of bacterial pathogens; and 4) significant quantitative culture growth from bronchoscopic respiratory samples ($\geqslant 1 \times 10^3$ colony-forming units (cfu) per mL in protected specimen brush cultures, and $\geqslant 1 \times 10^4$ cfu·mL^{-1} in bronchoalveolar lavage fluid). In addition, a presumptive diagnosis was made if qualitative valid sputum samples yielded one or more predominant bacterial pathogen. Definitive and presumptive causes were combined for reporting purposes. When two or more microbiological causes were present, the cause was classified as polymicrobial pathogens. A patient was considered to have CAP of unknown cause if no diagnostic tests were performed, or tests were performed but test results did not meet criteria for assigning a microbiological cause (including a contaminant pathogen).

Risk adjustment

The PSI was used to assess severity of illness on presentation. The PSI is a validated prediction rule for 30-day mortality in patients with CAP [10]. This rule was based on three demographic characteristics, five comorbid illnesses, five physical examination findings, and seven laboratory and radiographic findings from the time of presentation. Patients were classified into five risk classes, with 30-day mortality ranging from 0.1% for Class I to 27% for Class V for patients enrolled in the PORT cohort study [10].

Statistical analyses

Univariate statistics were used to test the association of demographic and clinical characteristics with all-cause 30- and 90-day mortality. Categorical variables were analysed using the Chi-squared test and continuous variables using an unpaired t-test.

Two Cox's proportional-hazards models were used to estimate, and plot, baseline survivor functions with either 30- or 90-day mortality as the dependent variable [16]. Variables were included in the survival analysis if they had either been previously demonstrated to be associated with CAP-related outcomes (*e.g.* PSI and processes of care) [10] or a p-value of <0.10 in the univariate analyses. History of COPD was entered into the model as an independent dichotomised variable, and PSI score was used as the risk adjustment tool [10]. In addition, processes of care measures (initial antibiotics within 4 h, obtention of blood cultures prior to initial dose of antibiotics, and whether antimicrobial therapy was guideline-concordant) were used as potential confounding variables.

RESULTS

Of the 744 patients identified with an admission diagnosis of CAP, 215 had a concomitant clinical diagnosis of COPD, compared with 529 patients who did not have COPD.

Patient characteristics

The cohort consisted of 582 (78%) males and 162 (22%) females. Their mean±SD age was 61±16 yrs (range 18–105 yrs). Of the patients, 83% were admitted *via* the emergency department from their own home and 7% from a nursing home; 128 (17%) had received outpatient antibiotic therapy prior to admission (table 1).

One or more concomitant comorbid medical conditions were present in 635 (85%) patients. The most frequently associated conditions were congestive heart failure (123 patients) and a prior history of stroke (105 patients). No known prior significant medical disorders existed in 109 (15%) patients. CAP patients with COPD were significantly more likely to be older males, admitted from a nursing home and placed in the ICU within 24 h of admission (table 1). In addition, COPD patients with CAP showed higher rates of congestive heart failure and a history of neoplastic disease. Physical examination and laboratory/radiological data demonstrated that CAP patients with COPD were significantly more likely to be tachypnoeic, acidotic and hypoxaemic, but less likely to exhibit hyperglycaemia than non-COPD patients. COPD patients used inhaled corticosteroids more frequently; however, they used similar amounts of systemic steroids to patients without COPD (table 1).

TABLE 1 Subject demographic and clinical characteristics by chronic obstructive pulmonary disease (COPD) diagnosis

	Non-COPD	COPD	p-value
Subjects n	529	215	
Age yrs	58.2±16.5	69.4±12.2	<0.001
Males	385 (73)	197 (92)	<0.001
Nursing home residents	31 (6)	22 (10)	0.04
Admitted *via* emergency department	483 (83)	180 (84)	NS
Admitted to ICU	95 (18)	53 (25)	0.04
Mechanical ventilation needed	56 (10)	28 (13)	NS
Pre-existing comorbid conditions			
Congestive heart failure	69 (13)	54 (25)	<0.001
History of stroke	72 (14)	33 (15)	NS
Chronic liver disease	62 (12)	21 (10)	NS
History of malignancy	43 (8)	35 (16)	0.002
Renal insufficiency	59 (11)	23 (11)	NS
Bronchiectasis	3 (0.6)	3 (1.4)	NS
History and clinical data			
Altered mental status	54 (10)	25 (12)	NS
f_R >30 breaths·min^{-1}	49 (10)	30 (14)	0.06
Systolic blood pressure <90 mmHg	10 (2)	8 (4)	NS
Cardiac frequency >125 beats·min^{-1}	71 (13)	28 (13)	NS
Temperature <95°F or >104°F	13 (3)	6 (3)	NS
Arterial pH <7.35	27 (5)	20 (9)	0.03
Arterial oxygenation saturation <90%	104 (20)	66 (31)	0.001
Haematocrit <30%	50 (10)	13 (6)	NS
Serum BUN >30 mg·dL^{-1}	118 (22)	41 (19)	NS
Serum glucose >250 mg·dL^{-1}	61 (11)	14 (6)	0.04
Serum sodium <130 mEq·L^{-1}	81 (15)	27 (13)	NS
Pleural effusion on chest radiograph	132 (25)	49 (23)	NS
PSI score	87±34	105±32	0.05
Corticosteroid use	77 (15)	83 (39)	<0.001
Oral steroids	48 (9)	26 (12)	NS
Inhaled steroids	32 (6)	70 (33)	<0.001

Data are presented as mean±SD or n (%) unless otherwise stated. ICU: intensive care unit; f_R: respiratory frequency; BUN: blood urea nitrogen; PSI: pneumonia severity index; NS: nonsignificant. 1 mmHg=0.133 kPa; 1°F=1.8°C+32.

Administration of antibiotics within 4 h occurred more commonly in COPD patients (35 *versus* 26%; p=0.02). However, COPD patients received other processes of care less commonly, including collection of appropriate blood cultures prior to antibiotics and within the first 24 h (70 *versus* 77%; p=0.04), and tended to have received antimicrobial therapy not concordant with the recommendation from national guidelines (74 *versus* 80%; p=0.05). There were no significant differences in the rate of oxygenation status assessment.

Pneumonia aetiology

An aetiological diagnosis could not be obtained in 77% of the cohort. A microbiological diagnosis was assigned in 172 (23%) patients with microorganisms identified from cultures of blood and/or sputum. Diagnosis was established by a positive blood culture in 63 (8.5%) patients. Bacteraemia was present in 53 (10%) hospitalised CAP patients without COPD and 10 (4.6%) patients with COPD. The organisms most frequently involved were *Streptococcus pneumoniae* (56 cases) and *Staphylococcus aureus* (39 cases). Hospitalised CAP patients with COPD showed more infections attributable to *Pseudomonas aeruginosa*, a trend of higher rates of *Haemophilus influenzae*, but less *S. aureus* than patients without COPD (table 2). However, there were no other significant differences between other pathogens in either group.

Clinical outcomes

For this study cohort, the median length of stay was longer by 2 days in COPD *versus* non-COPD patients (7±8 *versus* 9±25 days; p=0.05). The overall 30- and 90-day mortality were 10 and 14%, respectively. The unadjusted mortality was lower for non-COPD patients than COPD patients: 30 day, 8.7 *versus* 10.6% (p=0.4); 90 day, 11.7 *versus* 18.6% (p=0.013). The mean PSI score was significantly higher for COPD patients than for CAP patients without COPD (105±32 *versus* 87±34; p=0.05). Of the patients, 148 (20%) were admitted to the ICU and 83 (14%) required mechanical ventilation. When comparing COPD and non-COPD patients, the proportion of patients that required hospitalisation in the ICU was higher among COPD patients, but the percentage needing mechanical ventilation was not (table 3). There were no differences in mortality within 30 or 90 days for CAP patients with COPD who needed ICU admission, received mechanical ventilation or were bacteraemic (table 3). In addition, CAP patients with COPD receiving any form of corticosteroids, whether inhaled or systemic, did not show any significant differences in 30- or 90-day mortality compared with non-COPD patients (table 3).

TABLE 2 Aetiological definition used for diagnosis of pneumonia in patients by chronic obstructive pulmonary disease (COPD) diagnosis

	Non-COPD	COPD
Subjects n	529	215
Streptococcus pneumoniae	42 (7.3)	14 (6.5)
Staphylococcus aureus	32 (6.0)	7 (3.2)
Pseudomonas aeruginosa [#]	7 (1.3)	12 (5.6) [f]
Haemophilus influenzae	10 (1.9)	8 (3.7) [##]
Enterobacteriaceae [¶]	13 (2.5)	4 (1.9)
Miscellaneous [+]	5 (0.9)	2 (0.9)
Other Gram-positive cocci [§]	4 (0.7)	0 (0)
Polymicrobial	6 (1.1)	6 (2.8)
All identified pathogens	119 (22.5)	53 (24.6)
Test performed	469 (88.6)	182 (84.6)
No test performed	60 (11.3)	33 (15.3)

Data are presented as n (%) unless otherwise stated. Statistical comparisons were not performed for Enterobacteriaceae, miscellaneous or other Gram-positive cocci due to the small sample size. [#]: all isolates occurred in non-bronchiectatic patients; [¶]: including *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca* and *Proteus mirabilis*, [+]: comprising *Acinetobacter* spp., *Aspergillus* spp. and *H. parainfluenzae*; [§]: including *Enterococcus* spp. and *Streptococcus* spp. [f]: p=0.001; [##]: p=0.07.

In the Cox's proportional-hazards model, after adjusting for potential confounders, including processes of care and severity of illness, patients with a history of COPD exhibited significantly increased 30- (hazard ratio (HR) 1.32; 95% confidence interval (CI) 1.01–1.74) and 90-day mortality (HR 1.34; 95% CI 1.02–1.76). The Cox survival curve shows the variation in mortality from the initiation of the hospitalisation to 30 and 90 days for patients with and without COPD (fig. 1).

Discussion

In the present study, it was found that COPD patients hospitalised with CAP, compared to patients without COPD, show significantly higher 30- and 90-day mortality. In addition, hospitalised CAP patients with COPD exhibit significantly higher rates of ICU admission and a longer length of hospital stay compared with those without COPD. These data confirm that COPD should be considered for inclusion as a comorbid condition for pneumonia severity of illness measures.

COPD is considered a risk factor for the development of CAP, and previous studies of CAP including outpatient, inpatient and ICU cohorts have shown that COPD is a frequently reported comorbid condition [3, 4, 9, 17–22]. However, COPD has not been previously identified as being a risk factor for mortality in CAP patients [6–9]. The present study showed that hospitalised CAP patients with COPD show higher mortality at 30- and 90-days compared to patients without CAP. The present authors believe that this difference was found by examining only patients with COPD, and excluding other pulmonary conditions, including asthma, bronchiectasis and interstitial lung disease. Therefore, it was possible to examine the impact of COPD without dealing with other potential confounding pulmonary conditions. TORRES *et al.* [23] showed, in a large Spanish multicentric study, an in-hospital mortality rate of 8% in a cohort of 124 CAP patients with COPD. However, the main difference, compared with the present study, was the lack of a comparison group of CAP patients without COPD, which limited their ability to compare clinical outcomes.

There were important differences in COPD *versus* non-COPD patients, which included being older males, more admissions from nursing homes and requiring ICU treatment within 24 h of admission. In addition, COPD patients with CAP were more tachypnoeic, acidotic and hypoxaemic. All of these variables are also included in the PSI score, the severity of illness predictor used in the present study [10]. The PSI score assesses five comorbid conditions (cardiovascular, history of malignancy, cerebrovascular, renal and liver diseases), but does not include COPD as one of them [10].

It was expected that COPD patients hospitalised with CAP, who had higher PSI scores, rates of ICU admission and a longer length of stay in the hospital, would also show a higher mortality. One of the possible explanations for not finding a higher mortality in these specific groups is that the PSI score does not completely adjust for all of the abnormalities that are

TABLE 3 Mortality at 30 and 90 days in hospitalised patients with community-acquired pneumonia by chronic obstructive pulmonary disease (COPD) diagnosis

	Subjects	30 days			90 days		
		Non-COPD	COPD	p-value	Non-COPD	COPD	p-value
Subjects		529	215		529	215	
ICU admission	148	23/95 (24)	12/53 (23)	0.8	25/95 (26)	17/53 (32)	0.5
Mechanical ventilation	83	4/55 (7)	2/28 (7)	1.0	6/55 (11)	5/28 (18)	0.4
Bacteraemic pneumonia	63	9/53 (17)	2/10 (20)	0.8	10/53 (19)	3/10 (30)	0.4
Any corticosteroids	160	5/77 (6)	7/83 (6)	0.6	8/77 (10)	16/83 (19)	0.3
Inhaled corticosteroids	102	2/32 (6)	6/70 (9)	0.7	4/32 (12)	13/70 (19)	0.4
Systemic corticosteroids	74	3/48 (6)	2/26 (8)	0.8	5/48 (10)	4/26 (15)	0.5

Data are presented as n or n (%). ICU: intensive care unit.

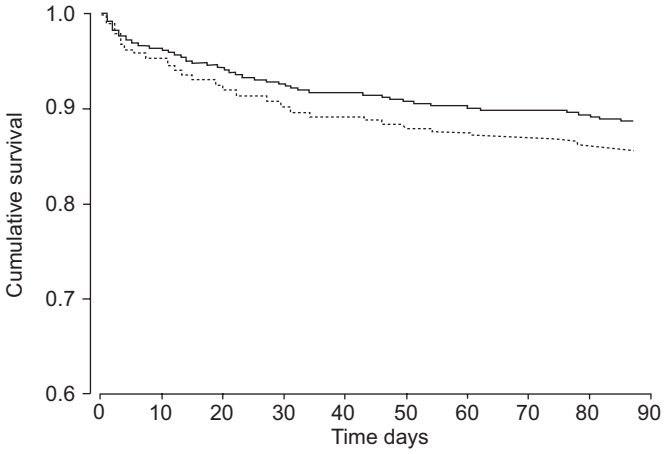

FIGURE 1. Cox survival curve showing proportion of surviving hospitalised community-acquired pneumonia patients by the presence (-----; n=215) or absence (——; n=529) of chronic obstructive pulmonary disease after adjusting for other potential confounders.

common in COPD patients. In addition, the ability to accurately predict medical outcomes in CAP influences patient management decisions made by physicians. These include the decision to hospitalise the patient, the length of inpatient care if the patient is hospitalised, and the choice of antimicrobial or other types of immediate therapy. The choice of appropriate empirical antibiotic regimens depends on several factors, including the aetiology of CAP.

The present results show that hospitalised CAP patients with COPD had more infections attributable to *P. aeruginosa*. Other studies have found that *P. aeruginosa* is an important pathogen in patients with pulmonary comorbid conditions, especially those with bronchiectasis [3, 23, 24]. The present data show that *P. aeruginosa* was the second-most-common organism in patients with COPD; therefore, appropriate anti-pseudomonal coverage should be considered in patients with COPD, whether or not bronchiectasis is present. The present data support the IDSA [14] and ATS [15] clinical practice treatment guidelines, which recommend stratifying patients based on the presence of coexisting cardiopulmonary disease (COPD and congestive heart failure) in order to select an appropriate antimicrobial agent. Therefore, it is important to recognise COPD in patients with CAP so that they may receive appropriate antimicrobial therapy.

The present study has several limitations that are important to acknowledge. First, it was a retrospective cohort study, and inherent problems related to this design include ascertainment and selection bias. However, the present authors do not feel that this study has significant problems with either of these biases, due to the methods involving admission and discharge diagnosis ICD-9 codes to identify patients and the fact that only a small amount of missing data was encountered. Furthermore, it was possible to verify that all of the patients had a radiological diagnosis of CAP. Secondly, the present sample was predominantly male since one of the sites was a Veterans Administration hospital and so it was not possible to examine whether or not females with COPD and CAP may exhibit a different clinical course, or outcomes, compared with males. Thirdly, unfortunately, no serological information was available, including *Legionella* urinary antigen. Fourthly, patients were identified as having COPD by medical history, which has been demonstrated in past studies to be the same method as that used to identify other comorbid conditions included to create the PSI score [6, 10, 23, 25, 26]. However, it was not possible to collect data regarding pulmonary function tests or COPD disease severity. Pulmonary function data could be helpful in predicting which patients with COPD might show the highest morbidity and mortality when they develop CAP.

In conclusion, the present study demonstrates significantly higher 30- and 90-day mortality, and increased length of stay and intensive care unit admission in chronic obstructive pulmonary disease patients hospitalised for community-acquired pneumonia compared with patients without chronic obstructive pulmonary disease. These findings have implications regarding how to evaluate patients with community-acquired pneumonia and chronic obstructive pulmonary disease, and how to decide which antimicrobial agents should be used for initial empirical therapy. Further prospective cohort studies are warranted to determine the impact of chronic obstructive pulmonary disease severity (confirmed by pulmonary function tests) and the use of anti-pseudomonal antibiotics on clinical outcomes for chronic obstructive pulmonary disease patients with community-acquired pneumonia.

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