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ORIGINAL RESEARCH

The Presence of COPD Does Not Influence Clinical Outcomes in Hospitalized Patients with Community-Acquired Pneumonia

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Abstract

Introduction: Community acquired pneumonia (CAP) is a leading cause of death worldwide. Chronic obstructive pulmonary disease (COPD) is a well-established risk factor for development of CAP. What is not as clear is the impact of COPD on the outcomes of patients with CAP. In this study, we compared the outcomes of CAP in COPD and non-COPD patients.

Methods: This was a retrospective cohort study. We conducted an analysis of the Community-Acquired Pneumonia Organization (CAPO) international cohort study database, which includes patients with CAP admitted to several hospitals throughout the world. Patients were categorized into two groups based on the status of COPD: COPD positive or negative. Outcomes were time to clinical stability, length of hospital stay, and in-hospital mortality. Regression models were used to assess the independent effect of COPD on the outcomes.

Results: This study included 7,325 patients. Of these, 1,869 (25.5%) had COPD. Patients with COPD had higher severity of illness (pneumonia severity index class V: 15% vs 9%; $P < 0.001$). Accelerated failure time models with adjustment for co-variables showed no significant difference in the probability of clinical stability ($P = 0.451$) and of discharge ($P = 0.232$) in COPD vs. non-COPD patients. There was no difference in the crude in-hospital mortality between COPD and non-COPD patients (9% vs 9%; $P = 0.37$).

Conclusion: Our study results show that COPD should not be considered a risk factor for poor outcomes in hospitalized patients with CAP.

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1 Introduction

Community acquired pneumonia (CAP) is a major cause of death. In 2015, lower respiratory infections were estimated to be the third leading cause of death globally.¹ The outcomes of this condition are directly related to factors associated with host, causal agent, and conditions of diagnosis and treatment. The presence of comorbidities is the most important factor linked to poorer outcomes.²

Chronic obstructive pulmonary disease (COPD) is a condition characterized by persistent airflow limitation and inflammation. It is generally progressive and associated with chronically increased inflammatory response in the airways and lungs as a consequence of exposure to noxious particles or gases.³ Worldwide,

approximately 210 million people have COPD, which is considered the fourth leading cause of mortality resulting in approximately 7.8% of all deaths.⁴ The incidence of CAP in subjects with COPD is estimated to be 22.4 cases per 1,000 people with COPD per year.⁵

The presence of COPD as a comorbidity that affects mortality in CAP is controversial. Some studies have found an association with increased mortality, whereas others show no relationship with COPD and poorer outcomes.⁶ Luna *et al.* observed a mortality rate of 4.6% for CAP in individuals with no comorbidities and 4% when associated with COPD. In this case, COPD was not an independent factor associated with mortality.² A case-control study from Switzerland observed lower in-hospital mortality and a lower rate of complications when COPD was present.⁷ Nonetheless, Torres *et al.* reported that asthma, smoking, chronic cardiovascular disease, diabetes and COPD increase the risk for pneumococcal disease (CAP and invasive pneumococcal disease), and have a detrimental effect on outcomes.⁸ In a study on elderly

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patients with CAP, COPD and dementia were considered independent risk factors for admission.⁹ In a different study, the most important factors contributing to higher mortality in patients with COPD and CAP admitted to the intensive care unit (ICU) were the presence of bilateral lung infiltrates and prolonged mechanical ventilation, while systemic corticosteroid use and shorter length of ICU stay seemed to be protective against a fatal outcome.¹⁰ Disease severity is also independently associated with worse outcomes, increasing mortality and complication rates.¹¹ In the long term follow-up, taking into account a 5-year period after the acute event, COPD, cardiovascular disease and malignancy were the leading causes of death.¹²

Due to controversy in the literature, we conducted a study to test the hypothesis that COPD is a risk factor for worse outcomes in patients with CAP.

2 Methods

2.1 Study Design

This was a retrospective cohort study. We conducted an analysis of the Community-Acquired Pneumonia Organization (CAPO) international cohort study database, which is formed by a collaboration of investigators throughout the world. Investigators fill out a case report form for each case. Subsequently the data is transferred online to a HIPAA-compliant database hosted by the CAPO study-coordinating center located at the University of Louisville in Louisville, KY, USA. Research associates at the coordinating center validate the cases by ensuring data quality and integrity.

Our study included adult patients who required hospitalization for CAP from April 27, 2000 to March 13, 2016. Hospitalizations were from Europe, Latin American, USA, and Canada. Enrollment criteria included age ≥ 18 years-old and the diagnosis of CAP.

2.2 Study Definitions

CAP was defined as a new pulmonary infiltrate plus at least one of the following: new or worsening cough, fever ($T > 37.8^{\circ}\text{C}$ or $> 100^{\circ}\text{F}$) or hypothermia ($< 35.6^{\circ}\text{C}$ or $< 96^{\circ}\text{F}$), increased white cell count, left shift, or decreased white cell count. For the purpose of this study, "community-acquired" means the patient must not have been hospitalized within the 2 weeks prior to the current hospitalization. Patient was defined as having COPD if the presence of COPD was documented in the medical record. The availability of pulmonary function test was not a requirement for the diagnosis of COPD.

Time to clinical stability was defined as the first day the patient fulfilled all four criteria: cough improving, afebrile for at least 8 hours, white blood cell improving or normal, and adequate oral intake and absorption.

2.3 Measurements

Outcomes were time to clinical stability, length of hospital stay, and in-hospital mortality. We obtained the following variables: demographics, physiological variables (e.g. temperature), need for mechanical ventilation, need for ICU admission,

co-morbidities, smoking status, pneumonia severity index (PSI) class,¹³ receipt of home infusion therapy, receipt of home wound care, receipt of chronic dialysis within past 30 days, whether the patient was hospitalized > 2 days in the past 90 days, receipt of intravenous antibiotics therapy in the past 90 days, and whether the patient is a nursing home resident.

2.4 Statistical Methods

Descriptive statistics were performed on these hospitalizations. Categorical variables were reported using frequency and percent. Chi-Square tests were performed to compare patients with COPD and patients without COPD for each categorical variable of interest. Continuous variables were reported using median and interquartile range (IQR). Wilcoxon Rank Sum tests were performed to compare patients with COPD and patients without COPD for each continuous variable of interest.

Kaplan Meier charts were used to compare time-to-event outcomes between patients with COPD and patients without COPD. Log-rank tests were performed. Logistic regression was performed to find a model of best-fit predicting in-hospital mortality. Variables used as predictors in the regression model were presence of COPD controlled by direct admission to the ICU, hospital region, and PSI risk class.

Accelerated failure time (AFT) models were created using the log-normal distribution for time to clinical stability and length of stay among patients with and without COPD. Variables that were controlled for each model were PSI risk class, hospital region, and direct admission to the ICU. These models were made under the assumption that "risk" for clinical stability and hospital discharge change over time. Statistical significance was determined by a P-value of less than 0.05. We used R software version 3.2.3. for statistical analysis.¹⁴

3 Results

3.1 Patient Characteristics

A total of 7,325 patients were included in the analysis. Of these, 1,869 (25.5%) had COPD. Patients with COPD were older (median age in years [IQR]: 75 [17] vs 65 [33]; $P < 0.001$), had more direct admissions to the ICU (12% vs 10%; $P = 0.004$), required more ventilator support (22% vs 12%; $P < 0.001$), and had higher severity of illness (PSI class V: 15% vs 9%; $P < 0.001$) (see **Table 1**). Patients with COPD who required mechanical ventilation (168 [22%]) were supported predominantly through noninvasive ventilation (123 out of 168 [73%]). Conversely, of non-COPD patients who required mechanical ventilation (296 [12%]), half (149 [50%]) were supported through noninvasive ventilation.

3.2 Outcomes

The median length of stay was 8 (interquartile range [IR]: 5.13) days for patients with COPD vs 7 (IR: 5,12) days for patients without COPD. Log-rank test showed patients with COPD had lower probability of discharge over time ($P < 0.001$) (see **Figure 1**). Time to clinical stability was similar in patients with COPD (4 days; IR: 3,8) vs patients without COPD (4 days; IR: 3,8). Log-

Table 1 Characteristics of the patients.

	COPD	Non-COPD	P-value
Age, median (IQR)	75 (17)	65 (33)	<0.001
Gender (male), n (%)	1328 (71)	3073 (56)	<0.001
Altered mental status at admission, n (%)	248 (14)	754 (14)	0.639
Oxygen saturation (%), median (IQR)	92 (7)	94 (7)	<0.001
SBP (mmHg), median (IQR)	130 (35)	123 (30)	<0.001
Temperature (Celsius), median (IQR)	37.2 (1.6)	37.8 (1.6)	<0.001
Directly admitted to ICU, n (%)	230 (12)	540 (10)	0.004
Transferred to ICU, n (%)	49 (4)	140 (4)	0.38
Need for ventilator support day 0, n (%)	168 (22)	296 (12)	<0.001
Invasive mechanical ventilation, n (%)	45 (27)	147 (50)	<0.001
Non-invasive mechanical ventilation, n (%)	123 (73)	149 (50)	<0.001
Alcoholic, n (%)	31 (4)	106 (4)	0.918
Cerebrovascular disease, n (%)	290 (16)	762 (14)	0.1
Diabetes, n (%)	377 (20)	980 (18)	0.035
HIV, n (%)	40 (2)	349 (6)	<0.001
Liver disease, n (%)	95 (5)	322 (6)	0.203
Neoplastic Disease within the past year, n (%)	226 (12)	551 (10)	0.017
Renal disease, n (%)	225 (12)	548 (10)	0.016
Chronic renal failure, n (%)	241 (13)	480 (9)	<0.001
BUN in mg/dL, Median (IQR)	35.5 (35)	31 (32)	<0.001
Serum glucose mg/dl, Median (IQR)	125 (57)	119 (47)	<0.001
Hematocrit (%), Median (IQR)	39 (8)	38 (7.1)	<0.001
Serum sodium (mEq/L), Median (IQR)	137 (6)	136 (5)	<0.001
Mortality at Discharge, n (%)	175 (9)	472 (9)	0.37
Smoking status			
Current Smoker, n (%)	272 (24)	733 (20)	0.001
History of smoking, n (%)	569 (51)	909 (25)	<0.001
Non-smoking history, n (%)	279 (25)	2061 (56)	<0.001
Chronic dialysis within past 30 days, n (%)	6 (1)	11 (0)	0.252
Risk Class I*, n (%)	50 (3)	995 (18)	<0.001
Risk Class II*, n (%)	319 (17)	1180 (22)	<0.001
Risk Class III*, n (%)	533 (29)	1124 (21)	<0.001
Risk Class IV*, n (%)	685 (37)	1646 (30)	<0.001
Risk Class V*, n (%)	281 (15)	508 (9)	<0.001
Home infusion therapy, n (%)	7 (1)	27 (1)	0.84
Home wound care, n (%)	6 (1)	24 (1)	0.829
Hospitalized >2 days in the past 90 days, n (%)	75 (10)	164 (6)	0.003
IV antibiotics therapy in the past 90 days, n (%)	60 (8)	110 (4)	<0.001
Nursing home resident, n (%)	118 (6)	295 (5)	0.147

*Risk class of pneumonia severity index.¹³

rank test showed that time to clinical stability curves were not significantly different ($P = 0.105$) (see **Figure 2**). There was no difference in the crude in-hospital mortality between COPD and non-COPD patients (9% vs 9%; $P = 0.37$). Additionally, there was no significant difference in the adjusted risk of in-hospital mortality in COPD patients (RR: 0.849; 95% CI: 0.698 - 1.032; $P = 0.1$) (see **Table 2**).

Accelerated failure time models with adjustment for co-variables showed no significant difference in the probability of clinical stability ($P = 0.451$) and of discharge ($P = 0.232$) (see **Figures 3 and 4**).

3.3 Outcomes

4 Discussion

In patients with CAP, those with COPD were older, presented with higher severity of illness, had more direct admissions to the ICU, and required more mechanical ventilator support. Despite these findings, they had similar unadjusted and adjusted in-hospital mortality and time to clinical stability. COPD patients had higher length of hospital stay. However, the difference was no longer significant after adjustment for co-variables. The literature is consistent in showing that COPD is a risk factor for CAP,^{5,9} and that this risk increases with the severity of the COPD.⁸ What is not as clear is the impact of COPD on the outcomes of patients with CAP.

Jiang *et al.* observed more frequent ICU admissions and need for mechanical ventilation in the COPD group; however, COPD was not associated with a higher mortality rate.⁶ Similar results were found by Liapikou *et al.* and Dusemund *et al.* where in-hospital mortality was similar for both groups.^{7,15} On the other hand, in an observational study of 710 in which all patients underwent spirometry, COPD was independently associated with an increased risk of 30-day mortality (odds ratio = 2.62 [95% CI: 1.08-6.39]).¹⁶

In our study, patients with COPD were older and had more comorbidities such as decompensated heart failure, renal disease, and diabetes. Despite that, mortality rates did not differ between groups. The finding of patients with more comorbidities not having worse outcomes is counterintuitive. We have four hypothetical reasons that may explain our findings. First, patients with COPD often receive systemic corticosteroids prior to and during hospitalization with respiratory failure. Systemic corticosteroids have been shown to be beneficial in CAP.¹⁷ The benefit of systemic corticosteroids is particularly pronounced in patients with severe CAP where a reduction in mortality by 61% was found in a meta-analysis.¹⁸ It can be speculated that the outpatient or inpatient use of corticosteroids for the management of COPD may unintentionally improve CAP outcomes in these patients. Second, the chronic lung inflammation in COPD could paradoxically have a protective effect in these patients. In this light, our group

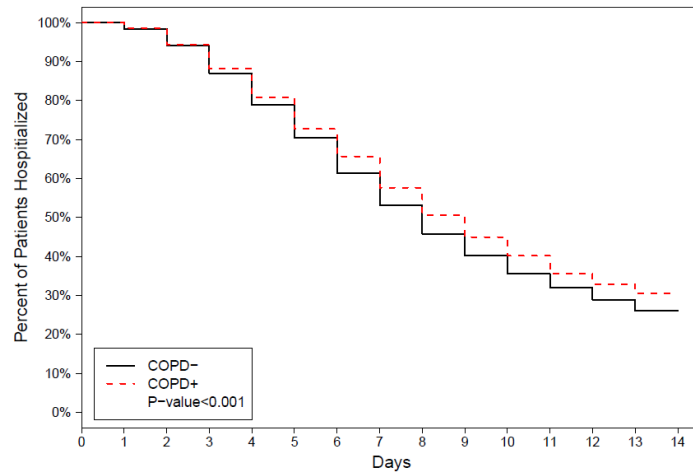


Fig. 1 Kaplan-Meier curves and log-rank test comparing probability of hospital discharge between COPD and non-COPD patients.

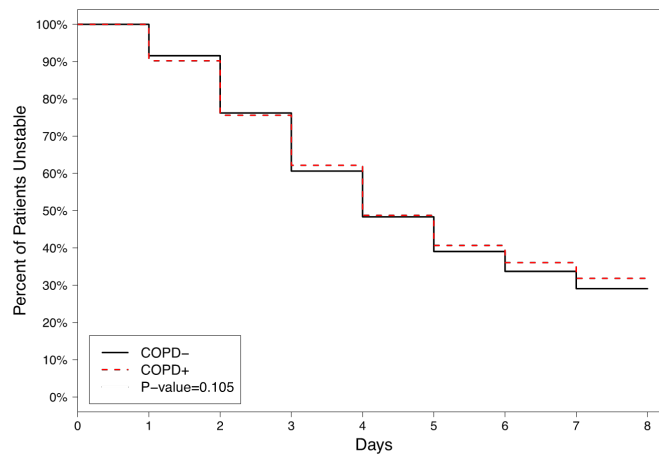


Fig. 2 Kaplan-Meier curves and log-rank test comparing time to clinical stability between COPD and non-COPD patients.

performed a prospective observational study in 40 hospitalized patients with CAP with the goal of characterizing their inflammatory response. Patients with severe CAP had higher levels of inflammatory cytokines in the blood but lower levels of inflammatory cytokines in the sputum as compared with patients with non-severe CAP.¹⁹ The presence of chronic local inflammation could have a protective effect against pathogen growth in the lung although this is hypothetical and one could also argue that chronic lung inflammation may lead to immune-senescence with detrimental effects. Third, perhaps the diagnosis of COPD prompts physicians to take a more proactive approach in this group of patients with CAP. This proactive approach could include measures such as closer monitoring of the respiratory status, earlier ICU admission, earlier use of non-invasive ventilation for those with hypercapnic respiratory failure, and a more thoughtful selection of the antimicrobial regimen. Our study showed that patients with COPD were more often directly admitted to the ICU, which could reflect their higher severity of illness but also that physicians were more cautious with this group of patients. Fourth, it is possible that COPD patients were misdiagnosed with CAP when they ac-

tually had COPD exacerbations. The diagnosis of CAP in COPD patients can be challenging, especially with a high frequency of previously existing radiographic abnormalities, which could be misleading to the clinician. As an example, a study showed that the agreement among radiologists for the diagnosis of pneumonia on the chest radiograph is only moderate ($\kappa = 0.53$). In the presence of COPD, the agreement is even lower ($\kappa = 0.20$).²⁰ Additionally, most COPD exacerbations are triggered by an upper respiratory tract infection,²¹ the symptoms of which can be similar to those of a pneumonia.

We recognize a number of limitations in our study. The main limitation is that the diagnosis of COPD was based on a history of COPD as outlined in the medical record. These diagnoses therefore could have self-reported by patients (which was most common), based on clinical suspicion, or based on spirometry. It should be noted that a self-reported diagnosis of COPD is highly predictive of spirometry-confirmed COPD but the absence of a self-reported diagnosis of COPD does not substantially decrease the likelihood of spirometry-confirmed COPD. For example, in an accuracy study of 309 patients, a self-reported history of chronic

Table 2 Multiple logistic regression assessing the effect of variables on in-patient mortality.

	Risk Ratio (95% CI)	P value
History of COPD	0.849 (0.698-1.032)	0.1
Direct ICU admission	3.047 (2.442-3.801)	<0.001
Region		
Europe	0.92 (0.735-1.153)	0.471
Latin America	1.788 (1.41-2.266)	<0.001
Risk Class*		
II	1.823 (1.093-3.042)	0.021
III	3.26 (2.013-5.279)	<0.001
IV	7.555 (4.793-11.908)	<0.001
V	19.15 (11.945-30.699)	<0.001

*Risk class of pneumonia severity index.¹³

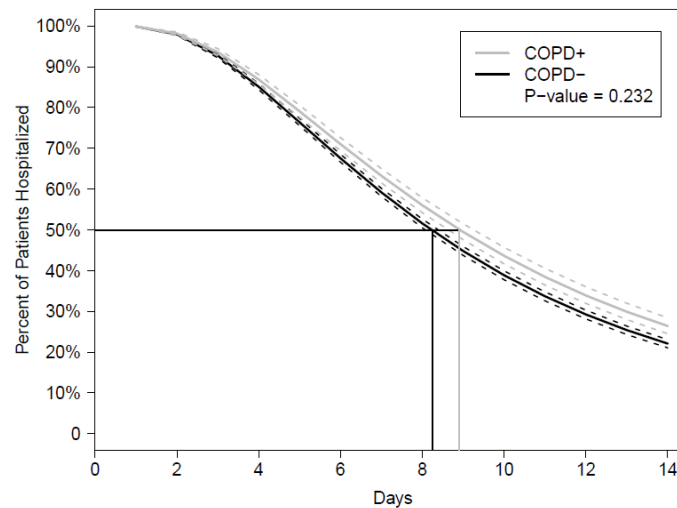


Fig. 3 Accelerated failure time model comparing adjusted probability of discharge between COPD and non-COPD patients (dotted lines represent 95% confidence interval).

obstructive airway disease had an adjusted positive likelihood ratio of 7.3 for the diagnosis of spirometry-confirmed COPD. On the other hand, the absence of self-reported history of chronic obstructive airway disease had an adjusted negative likelihood ratio of 0.5 for spirometry-confirmed COPD.²² Our study is thus susceptible to misclassification bias, which would be non-differential and bias the effect of COPD on outcomes towards the null. Additionally, the severity of COPD is directly related to worse outcomes including mortality.¹¹ Severity of COPD could not be assessed in the present study because data related to pulmonary function tests and COPD staging were not available for the majority of the patients. Another limitation is that we do not have information on systemic and inhaled corticosteroid use, or prior outpatient antibiotic use. Finally, we do not provide information on long-term outcomes. Our study also has a number of strengths including a large sample size, a worldwide patient population, which increases the external validity of the study, and the collection of several clinical and physiological variables, which allowed for a comprehensive description of our patient population and the ability to adjust for severity of illness in the regression analyses. Future research could include studies with a cohort design in which COPD is established by pulmonary function tests and the impact of COPD on both short-term and long-term outcomes are assessed. Additionally, the impact of the severity of COPD on the outcomes of CAP should be evaluated. A better characterization

of the effect of pharmacological therapies for COPD on outcomes of CAP is needed. For instance, what is the impact of COPD on the outcomes of CAP after adjustment for the use of systemic corticosteroid? Is the use of inhaled corticosteroid during treatment of CAP detrimental? Interestingly, a systematic review that included 43 randomized clinical trials (over 30,000 patients) found that inhaled corticosteroids increase the risk of pneumonia and hospitalizations in patients with COPD but do not increase the all-cause mortality in these patients.²³ In summary, our study results show that in patients with CAP, those with COPD are sicker as assessed by severity of illness and co-morbidities. Yet these patients do not have worse short-term outcomes. Our findings are in line with the PSI, a clinical prediction rule to risk stratify patients with CAP that was initially prospectively validated in a cohort of over 2,000 patients with CAP. COPD is not one of the co-existing conditions that are part of this risk score.¹³ We conclude that COPD should not be considered a risk factor for poor outcomes in hospitalized patients with CAP.

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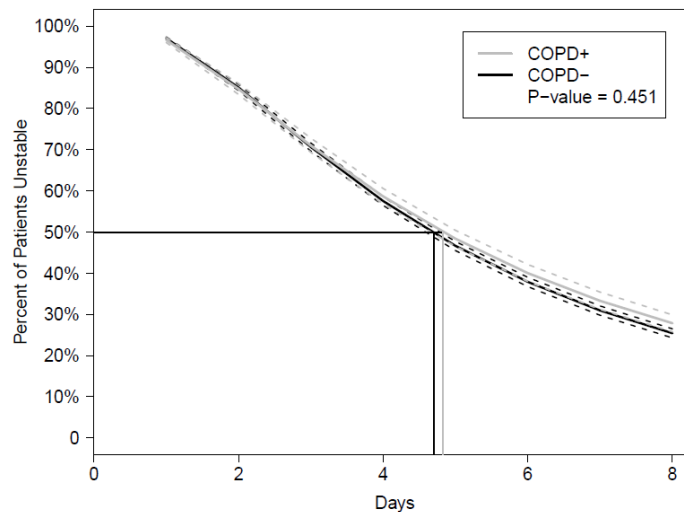


Fig. 4 Accelerated failure time model comparing adjusted probability of clinical stability between COPD and non-COPD patients (dotted lines represent 95% confidence interval).

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