Role of Comorbidities in Treatment and Outcomes after Chronic Obstructive Pulmonary Disease Exacerbations

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Abstract

Rationale: Hospital readmissions are an important cause of morbidity and mortality among patients with chronic obstructive pulmonary disease (COPD). Although comorbidities are associated with outcomes in COPD, it is unknown how they affect treatment choices.

Objectives: We sought to examine whether comorbidity was associated with readmission, mortality, and delivery of in-hospital treatment for COPD exacerbations.

Methods: We performed a cohort study of veterans hospitalized with a COPD exacerbation to six Veterans Affairs hospitals between 2005 and 2011. We collected comorbidities in the year before hospitalization. We defined our primary outcome as readmission and/or mortality within 30 days of discharge, and treatment quality as receipt of systemic corticosteroids and respiratory antibiotics during the index hospitalization.

Results: A total of 2,391 patients were included. Each one-point increase in Charlson index was associated with greater odds of readmission or death (adjusted odds ratio [aOR], 1.24; 95% confidence interval [CI], 1.18–1.30) and reduced odds of receiving treatment with steroids and antibiotics (aOR, 0.90; 95% CI, 0.85–0.95), in adjusted analyses. Patients with comorbid congestive heart failure (aOR, 0.64; 95% CI, 0.52–0.79), coronary artery disease (aOR, 0.73; 95% CI, 0.60–0.89), and chronic kidney disease (aOR, 0.74; 95% CI, 0.55–0.99) were less likely to receive corticosteroids and antibiotic treatment than patients without those comorbidities. We did not identify any comorbidity that was associated with increased odds of receiving appropriate therapies.

Conclusions: Comorbidity was associated with 30-day readmission and mortality, and with delivery of fewer treatments known to be beneficial among patients with COPD exacerbation.

Keywords: chronic obstructive pulmonary disease; comorbidity; treatment quality

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Chronic obstructive pulmonary disease (COPD) exacerbations are a major source of early hospital readmissions (1), resulting in patient morbidity and health care costs for COPD-related care (2, 3). The Center for Medicare and Medicaid Services (CMS) implemented a penalty for hospital systems

with excess hospital readmission rates for COPD exacerbations in 2014 that has generated substantial interest in reducing readmission among patients with COPD (4). Although comorbid conditions have been previously identified as risk factors for hospitalization (5, 6), readmission (7, 8),

and mortality (9–11) in patients with COPD, the mechanism as to how comorbidity leads to higher risk is unclear.

It is often assumed that adults with a greater number of comorbid conditions are sicker, and therefore are at greater risk of readmission or death from COPD and other

disease processes. This has formed the basis of adjustment for comorbidities when measuring performance, and when developing models and indices to predict mortality and health care resource utilization (12–14). However, another possible explanation is that patients with multiple comorbid conditions may also experience diminished effectiveness of appropriate therapies, or may receive effective treatments by physicians at a lower rate because of diagnostic uncertainty in the face of multimorbidity. We sought to examine comorbidities associated with 30-day readmission and/or mortality, and the association with delivery of treatments during hospital admission for a COPD exacerbation.

Methods

Design, Setting, and Participants

We conducted a cohort study of veterans discharged from hospital for a COPD exacerbation within the Veterans Affairs (VA) Veterans Integrated Service Network (VISN)-20. VISN-20 encompasses six hospitals in the Pacific Northwest, which represent both academic and nonacademic systems. We utilized information from the VISN-20 data warehouse that collects data from the electronic medical record and is commonly used for research purposes (15–18).

We identified all patients at least 40 years of age, hospitalized between 2005 and 2011 with a primary discharge diagnosis of COPD by *International Classification of Diseases, Ninth Revision* (ICD-9) codes (491.xx [chronic bronchitis], 492.xx [emphysema], and 496.xx [chronic airway obstruction]) (19–22). The CMS penalty includes these patients, and also those with a primary diagnosis of acute respiratory failure and an additional diagnosis of COPD at the exact second position (23). We did not include this second group of patients to reduce the possibility of misclassification of COPD with other conditions. We defined an index date as the date of discharge from the first COPD-related hospitalization. Patient time accrued for 30 days. We excluded patients who died during the index hospitalization.

Measuring Readmission, Mortality, and Treatment Delivery

We defined the primary outcome as all-cause mortality or readmission within 30 days of discharge from index hospitalization

(24). We also sought to examine whether comorbidity would be associated with delivery of systemic corticosteroids and antibiotics during the index hospital admission, two therapies that are generally recommended for the treatment of COPD exacerbations among hospitalized patients (25–28). We included corticosteroid treatments at 20-mg equivalents or greater of prednisone and assumed their use was intended for COPD exacerbation treatment (28). We included antibiotics that provided respiratory pathogen coverage.

Measuring Comorbidity

We defined a comorbid condition as present if it was coded in either the inpatient or outpatient setting in the preceding 12 months of index admission. The burden of comorbidity was examined using the Deyo-Charlson index, a standard scale of 13 individual comorbidities weighted for severity (13).

Collection of Covariates

We examined a range of individual characteristics, including demographics, body mass index (BMI), and smoking status. We assessed COPD severity through the use of inhaled controller medications and prescription of systemic steroids in the previous year (29). Spirometry results were not available for this cohort. Current smoking status was collected using the VA's clinical reminder system and was assessed at least annually.

Statistical Analysis

We built a logistic regression model to assess for comorbidity as a predictor of our outcomes. We examined the Charlson index in a model with adjustment for known risk factors for COPD exacerbations, including age, smoking status (30), and BMI (31). We also adjusted for the receipt of systemic corticosteroids for an exacerbation in the year before admission as a surrogate marker of COPD severity. We then examined several individual comorbidities with overlapping symptoms of dyspnea, or that were likely to affect medication treatment choices, for associations with the delivery of corticosteroids and antibiotics during the inpatient stay. We performed sensitivity analyses to exclude those with a concomitant discharge diagnosis of pneumonia by ICD-9 code, given the possibility of misclassification with COPD exacerbations. We used Stata 14 software (StataCorp) for all analyses. This study was approved by the VA Institutional Review Board (#00461).

Results

We identified 2,454 patients who were eligible for entry into our cohort (Figure 1). Sixty-three (3%) died during the index hospitalization and were excluded, leaving 2,391 patients for analysis. Overall, the mean age of the cohort was 68 years and patients were mostly male, consistent with a prior study of patients in the VA system (Table 1).

Figure 1. Derivation of the study cohort. COPD = chronic obstructive pulmonary disease; ICD-9 = *International Classification of Diseases, Ninth Revision*.

Table 1. Characteristics of cohort

	Cohort (n = 2,391)
Demographics	
Age, mean (SD), yr	68.0 (10.4)
Male	2,319 (97)
Race, n (%)	
Black	89 (4)
White	1,980 (83)
Body mass index, n (%)	
Underweight	201 (8)
Normal	738 (31)
Overweight	610 (26)
Obese	842 (35)
Comorbid conditions, n (%)	
Coronary artery disease	728 (30)
Arrhythmia	608 (25)
Congestive heart failure	548 (23)
Diabetes	643 (27)
Chronic kidney disease	216 (9)
Cerebral vascular accident	192 (8)
Pulmonary hypertension	136 (6)
Metastatic cancer	51 (2)
Charlson index, mean (SD)	2.5 (2.1)
Smoking status, n (%)	
Current smoker	1,173 (49)
Former or never smoker	1,218 (51)
COPD severity, n (%)	
LAMA	356 (15)
LABA	872 (36)
ICS	1,154 (48)
Systemic steroid use in year prior	1,030 (43)

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β -agonist; LAMA = long-acting muscarinic antagonist.

Nearly one-half of the cohort had experienced a COPD exacerbation requiring corticosteroid treatment within the prior year (48%, $n = 1,030$) and were also active smokers (49%, $n = 1,173$). Few patients required invasive mechanical ventilation during hospitalization (2%, $n = 57$) or noninvasive positive pressure ventilation (10%, $n = 247$). About one-half of the cohort was treated with long-acting bronchodilators (51%, $n = 1,228$) for maintenance therapy, and 48% received inhaled corticosteroid therapy ($n = 1,154$). Comorbid conditions were common in this cohort (Table 1), and patients often had multiple comorbidities with a mean Charlson index of 2.5.

Sixteen percent ($n = 388$) of the cohort was readmitted or died during the 30 days after discharge from index hospitalization. Of these, 100 (4%) died within 30 days, with a median length of survival of 14.7 days

(interquartile range, 6.9–22.9). Twenty-seven patients experienced both readmission and death within 30 days. Around one-third of the 30-day readmissions were attributed to COPD (36%, $n = 112$). Cardiac diseases including heart failure were the second most common reason for readmission (12%, $n = 38$).

Patients who were readmitted or died had a higher mean Charlson index (3.0 vs. 2.3; $P < 0.01$). Among patients with a lower Charlson index of 1–2 ($n = 1,509$), 14% ($n = 211$) were readmitted or died, which increased to 19% ($n = 130$) of those with a Charlson index of 3–4 ($n = 691$). Patients with the greatest comorbidity (Charlson ≥ 5 , $n = 191$) were readmitted or died with the greatest frequency (25%, $n = 47$, test of trend, $P < 0.01$). In multivariable logistic regression, each one-point increase in Charlson index was associated with readmission and death (adjusted odds ratio [aOR], 1.24; 95% confidence interval [CI], 1.18–1.30) when adjusted for age, BMI, smoking status, and exacerbation history.

Overall, 85% ($n = 2,038$) of the cohort received corticosteroid therapy for a COPD exacerbation, and 74% ($n = 1,775$) received respiratory antibiotics. The delivery of corticosteroids and antibiotics varied by comorbidity and by Charlson index (Figure 2). Fewer patients with congestive heart failure (CHF) received dual steroid and antibiotic therapy ($n = 369$, 59%), as did those with coronary artery disease (CAD) ($n = 446$, 61%) and arrhythmias ($n = 414$, 68%), when compared with those without the comorbidity. Among those who were treated with steroids and antibiotics, 17% ($n = 54$) of patients with CHF, 20% ($n = 91$) with CAD, and 20% ($n = 83$) with arrhythmias were readmitted or died. Among those who did not receive either treatment, 15% ($n = 8$) with CHF, 18% ($n = 13$) with CAD, and 28% ($n = 8$) with arrhythmias were readmitted or died.

For each one-point increase in Charlson index, there were reduced odds of receipt of corticosteroids and antibiotics (aOR, 0.90; 95% CI, 0.85–0.95) in adjusted analysis. Patients with a Charlson index equal to or exceeding 4 were 34% less likely to receive treatment with steroids and antibiotics (aOR, 0.66; 95% CI, 0.54–0.81). When examining individual comorbidities, patients with comorbid CHF (aOR, 0.64; 95% CI, 0.52–0.79), CAD (aOR, 0.73; 95% CI, 0.60–0.89), and chronic kidney disease

(aOR, 0.74; 95% CI, 0.55–0.99) were less likely to receive corticosteroids and antibiotic treatment than patients without those comorbidities in adjusted analyses (Figure 3).

Discussion

We found that veterans who were admitted to hospital for a COPD exacerbation frequently had multiple comorbidities, and that comorbidity was associated with delivery of fewer COPD exacerbation treatments, greater readmission, and increased mortality. We also found that a higher Charlson index was associated with a greater risk of 30-day readmission and death in a “dose-dependent” fashion. Although this relationship has been demonstrated in a prior study, there was no additional exploration into the reason behind this association. We found that comorbidity was associated with the delivery of fewer treatments for COPD exacerbations, which is a novel finding. The relationship between comorbidity and readmission risk has been thought of as a nonmodifiable issue of overall increased severity of illness. However, our study suggests that one potential explanation may be that comorbidity may also be a driver of care quality, as patients with increased comorbidity receive fewer treatments with oral corticosteroids and antibiotics.

The underuse of treatments for COPD exacerbations may have a number of explanations. First, increased comorbidity is associated with increased overall treatment complexity and may lead to overall poor quality of COPD care. This complexity could also lead to poor care quality for other diseases, as has been shown with β -blocker underuse in CHF (32). Second, clinicians may have wanted to avoid, or patients may have previously experienced, unwanted side effects of COPD treatments; such as hyperglycemia or fluid retention from steroids (33–35). Despite these potential reasons, current COPD treatment guidelines recommend the use of corticosteroids and antibiotics in severe exacerbations without modification for comorbidities (36, 37).

An additional explanation is that patients with multiple comorbidities and etiologies for dyspnea and respiratory symptoms will understandably lead to diagnostic uncertainty or misclassification

Figure 2. Patients with comorbidities receive fewer corticosteroids and antibiotics for chronic obstructive pulmonary disease exacerbations. y-axis, percent (%). Error bars represent 95% confidence intervals. An asterisk denotes a *P* value less than 0.05 in test of difference of proportions compared with patients without the comorbidity. CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease.

of disease (38). Uncertainty about COPD as the primary contributor to the hospitalization and misclassification may lead to appropriate nonprovision of steroids or antibiotics. Ideally, COPD would be confirmed by diagnostic pulmonary function tests. However, spirometry use in the community is notoriously low (39, 40), especially among those patients with mild COPD, and restricting to only those with pulmonary function tests would have introduced bias into our population-based sample despite the chance that some of these patients may not have COPD by

spirometry (21, 41). Nonetheless, the inclusion criteria we used to capture patients hospitalized for COPD are reasonable when examining patterns of care quality in COPD exacerbations. Understanding why a physician might diagnose a COPD exacerbation in a patient with multiple comorbidities, yet elect to defer evidence-based treatments, is an area in need of additional investigation.

Our study showed that overall delivery of antibiotics and corticosteroids varied significantly by comorbidities, and that corticosteroids were consistently provided

more commonly among patients than were antibiotics. The guideline recommendations surrounding the use of antibiotics for COPD exacerbations are not always clear and could contribute to lower utilization of this therapy. The current *Global Strategy for the Diagnosis, Management, and Prevention of COPD* statement (Global Initiative for Chronic Obstructive Lung Disease [GOLD]) recommends use “when indicated” in the summary table, but does go on to state that there is evidence to treat moderately or severely ill patients with COPD exacerbations when reading the detailed text (36). Patients with severe exacerbations of COPD include those who are hospitalized, and therefore would include the patients in this cohort. The use of antibiotics in severe cases of COPD exacerbations is additionally supported in guidelines published by the European Respiratory Society and the American Thoracic Society, which also mention the less clear benefit in ambulatory patients (37). Understandably, this might lead to confusion when selecting antibiotics as treatment. Finally, none of the comorbidities, as well as a prior history of a COPD exacerbation/systemic steroid use, increased the odds of receiving either steroids or antibiotics.

The CMS currently adjusts for comorbidities in their readmission measure (23). The results described in our article suggest that adjusting for comorbidity could potentially mask quality of care issues at

Figure 3. Delivery of corticosteroids and antibiotics varies by comorbidities in adjusted analysis. Adjusted odds ratios (ORs) from multivariable logistic regression with 95% confidence interval (CI). OR adjusted for age, body mass index, smoking status, and prior history of exacerbation.

the heart of the CMS policy. A similar recommendation was made by the National Quality Forum when deciding not to adjust the CMS measure for socioeconomic status or race out of concern that such adjustment could hide differences in care or reduce motivation to improve outcomes in this population. A similar argument could be made for patients with a high burden of comorbidity based on our results.

Our study has a number of potential limitations. Our population is reflective of those from the Department of Veterans Affairs, limiting the population to those of lower socioeconomic means and largely men. In addition, this cohort was derived by ICD codes and did not include spirometry, which may lead to misclassification of acute exacerbations of COPD in this cohort. However, a prior study has shown that one or more inpatient ICD-9 codes carries a 99% specificity for COPD (19, 32), as we have performed in this analysis. Our cohort preceded the imposition of the CMS penalty

for COPD readmissions, and given the efforts to reduce readmission, these findings may not apply to current practice. For those limitations, we had a number of potential strengths. First, this cohort is reflective of all patients receiving care within the Pacific Northwest region and allows for the assessment of other important markers of disease severity, including outpatient inhaler use, comorbidities, and history of prior exacerbations. Second, the VA is an integrated health system and we were able to capture not only hospital readmission that occurred within the VA system, but also those readmissions for which the VA was financially responsible. Third, using a large number of patients and facilities, we limit selection biases that can be seen in examining readmissions from less comprehensive health systems. VISN-20 also provides a broad service area of rural and urban locations, with six sites for study that encompass both academic and nonacademic facilities, enhancing

generalizability. Finally, previous data suggest that care within the VA is similar to that of other academic facilities (42).

Conclusion

Comorbidities were common among patients admitted to hospital with COPD, and a greater burden of comorbidities was associated with readmission and death after hospitalization for a COPD exacerbation. One potential explanation is that comorbidity may lead to lower quality of COPD-related care, suggesting a target for additional studies. Our findings could also provide insight into future quality improvement strategies to better understand this disparity among the patients with COPD, as well as to encourage reassessment of the adjustments performed in the CMS COPD penalty for comorbidities. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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