Depression Is Associated with Readmission for Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract

Rationale: Hospitalization for acute exacerbation of chronic obstructive pulmonary disease (COPD) is associated with significant morbidity and health care costs, and hospitals in the United States are now penalized by the Centers for Medicare and Medicaid Services for excessive readmissions. Identifying patients at risk of readmission is important, but modifiable risk factors have not been clearly established, and the potential contributing role of psychological disease has not been examined adequately. We hypothesized that depression and anxiety would increase the risk of both short- and long-term readmissions for acute exacerbation of COPD.

Objectives: To characterize the associations between depression and anxiety and COPD readmission risk.

Methods: We examined the medical records for all patients with a primary diagnosis of acute exacerbation of COPD by *International Classification of Diseases, Ninth Revision* codes admitted to the University of Alabama at Birmingham Hospital between November 2010 and October 2012. Those who did not meet the standardized study criteria for acute exacerbation of COPD and those with other respiratory illnesses as the primary diagnosis were excluded. Comorbidities were recorded on the basis of physician documentation of the diagnosis and/or the use of medications in the electronic medical record. Multivariable regression analyses identified factors associated with readmission for acute exacerbation of COPD at 1 year and within 30 and 90 days.

Measurements and Main Results: Four hundred twenty-two patients were included, with 132 readmitted in 1 year. Mean age was 64.8 ± 11.7 years, and mean percent predicted FEV_1 was 48.1 ± 18.7%. On univariate analysis, readmitted patients had lower percent predicted FEV_1 (44.9 ± 17.3% vs. 50.2 ± 19.4%; $P = 0.05$) and a higher frequency of depression (47.7% vs. 23.4%; $P < 0.001$). On multivariable analysis, 1-year readmission was independently associated with depression (adjusted odds ratio [OR], 2.67; 95% confidence interval [CI], 1.59–4.47) and in-hospital tobacco cessation counseling (adjusted OR, 0.34; 95% CI, 0.18–0.66). Depression also predicted readmission at 30 days (adjusted OR, 3.83; 95% CI, 1.84–7.96) and 90 days (adjusted OR, 2.47; 95% CI, 1.34–4.55).

Conclusions: Depression is an independent risk factor for both short- and long-term readmissions for acute exacerbation of COPD and may represent a modifiable risk factor. In-hospital tobacco cessation counseling was also associated with reduced 1-year readmission.

Keywords: chronic obstructive pulmonary disease; exacerbations; risk; depression

(Received in original form July 16, 2015; accepted in final form November 2, 2015)

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Author Contributions: S.P.B. is the guarantor of the manuscript and is responsible for the work as a whole; A.S.I., S.P.B., and M.T.D. contributed to the study design; A.S.I., S.P.B., J.J.G., N.M.P., and J.C.W. contributed to the data collection; S.P.B., J.J.G., and M.T.D. contributed to the data analysis; A.S.I., S.P.B., and M.T.D. contributed to the writing of the manuscript; J.J.G., J.M.W., J.L.T., N.M.P., d.K., J.C.W., and M.T.D. contributed to the review of the manuscript for important intellectual content.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Ann Am Thorac Soc Vol 13, No 2, pp 197–203, Feb 2016

DOI: 10.1513/AnnalsATS.201507-439OC
Internet address: www.atsjournals.org

Chronic obstructive pulmonary disease (COPD) accounts for significant morbidity and health care costs and is the third leading cause of death in the United States (1, 2). Acute exacerbations of COPD represent critical events in the course of this disease and are associated with decline in lung function, worse quality of life, and increased mortality (3–6). The majority of health care costs associated with COPD result from hospitalization (7, 8), and approximately one-half of patients hospitalized are readmitted for acute exacerbation within 1 year and up to 22% of patients within 30 days (9–11). Reducing 30-day readmissions for acute exacerbation of COPD has been recognized recently by the United States Centers for Medicare and Medicaid Services as an important target for both physicians and health care systems (12, 13).

COPD is a complex multisystem disease with numerous physical and psychological processes causing acute exacerbations and influencing hospitalization (14–16). Previously described risk factors for readmission include age, FEV_1, hypercarbia, functional status, and prior hospitalizations (11, 17–20), although most of these factors are not modifiable. Numerous medical comorbidities have also been associated with increased risk of readmission (17, 21), and recent literature suggests that a large proportion of COPD readmissions are not for acute exacerbations (12).

Although many medical comorbidities play a role in respiratory decompensation and rehospitalization (22, 23), the impact on readmissions of psychological comorbidities such as depression and anxiety, which are highly prevalent in patients with COPD and affect quality of life, remains largely unexplored (24, 25). In small cohorts, data showed that depressive symptoms in patients with COPD predicted exacerbation risk over 1 year (26, 27). We hypothesized that depression and anxiety would increase the risk of both short- and long-term readmissions because of acute exacerbation of COPD.

Methods

Study Design and Patient Selection

The medical records for patients admitted to the University of Alabama at Birmingham Hospital with a primary diagnosis of acute exacerbation of COPD by *International Classification of Diseases, Ninth Revision* codes 491.21, 491.22, and 496 from November 2010 to October 2012 were reviewed. Three physicians (A.I., J.G., and J.W.) reviewed individual electronic medical records and excluded those patients who did not meet the standardized study criteria for acute exacerbation of COPD defined by increased dyspnea, increased cough, or purulent sputum present for at least 48 hours on admission in a patient with known COPD (28). Those with respiratory illnesses other than COPD as a primary diagnosis, such as lung cancer, bronchiectasis, and pneumonia, were also excluded. Acute exacerbation of COPD was defined similarly for readmissions.

Potential contributing comorbidities such as coronary artery disease, congestive heart failure, diabetes mellitus, hypertension, chronic kidney disease, gastroesophageal reflux disease (GERD), depression, and anxiety were recorded. Comorbidities were defined either by physician diagnosis or by use of medications as documented in the electronic medical record. Clinical variables including laboratory values and vital signs were also recorded at the time of index admission. Immunization status for pneumococcal and influenza vaccines was recorded. Subjects were deemed to have received in-hospital tobacco cessation counseling if counseling from either physicians or tobacco cessation counselors was recorded in the chart. The Hospital Tobacco Consult Service at our center provided bedside smoking cessation counseling, together with pharmacotherapy prescriptions, to patients who were referred by their health care providers or who indicated at admission that they wanted to quit smoking, and patients were referred to the state quit line for follow-up. The consult staff assessed patients' nicotine withdrawal discomfort, need for pharmacotherapy, and interest in quitting smoking, assisting those interested in developing a personalized quit plan. Patients provided with quit counseling were called within a month after discharge to encourage progress in quitting and use of the state quit line, if referred.

In the current analysis, we investigated risk factors for both short- and long-term readmission for acute exacerbation of COPD. We defined short-term readmission as readmission for acute exacerbation of COPD within 30 days and 90 days of index admission and long-term readmission as within 1 year. The institutional review board at the University of Alabama at Birmingham approved the study (X121221005).

Statistical Analysis

Baseline data were expressed as means with standard deviations (SD) for normally distributed values. Univariate analysis was performed using independent *t* test or Mann-Whitney U test where appropriate for comparing continuous variables and chi-square test for discrete variables for two groups defined by 1-year readmission status. Variables significant on univariate analysis ($P < 0.05$) were included in multivariable logistic regression analyses to identify independent predictors of readmission within 1 year of index admission. Additional variables found to be significant predictors of readmission in previous studies and important clinical variables such as age, race, sex, and smoking status were forced into the multivariable models. FEV_1 data within 2 years before admission were available in one-half the subjects, and hence we performed a secondary sensitivity analysis by adding FEV_1 to the multivariable model for 1-year readmission in this group. Because depression and anxiety can frequently coexist, collinearity diagnostics were performed using variance inflation factor (VIF) assessments. A VIF greater than 10 was considered significant for collinearity. Similar analyses were performed to identify predictors for 30-day and 90-day readmissions. Statistical Package for the Social Sciences 20.0 software (SPSS Inc., Chicago, IL) was used for all analysis. All statistical tests were two-sided, with significance assigned to tests with $P < 0.05$.

Results

Of the 901 patients discharged with primary *International Classification of Diseases, Ninth Revision* codes for acute exacerbation of COPD during the time period of the current analysis, 422 were confirmed by physician review to meet the study definition of exacerbation and to not have alternative primary respiratory illnesses, and were included in the study. These patients were separated into groups on the basis of 1-year readmission, as readmitted

(n = 132) and non-readmitted (n = 290). As seen in Table 1, participants overall had a mean ± SD age of 64.8 ± 11.7 years. Of these, 146 (34.5%) were African American, and 212 (50.1%) were male. Mean percent predicted FEV_1 was 48.1 ± 18.7%. Depression and anxiety were present in 131 patients (31%) and 89 patients (21%) in the cohort, respectively (Table 1). There was no collinearity between depression and anxiety (VIF = 1).

There were no significant differences between groups regarding age, sex, race, body mass index, or smoking history (Table 1). Those readmitted had lower percent predicted FEV_1 (44.9 ± 17.3% vs. 50.2 ± 19.4%; $P = 0.05$), a higher prevalence of GERD (36.4% vs. 25.2%; $P = 0.02$), and more frequent depression (47.7% vs. 23.4%; $P < 0.001$) and anxiety (28.8% vs. 17.6%; $P = 0.009$) (Table 1). Of those who were current smokers, patients readmitted had a significantly lower rate of tobacco cessation counseling (16.1% vs. 38.1%; $P < 0.001$) (Table 1). Mean sodium levels were higher in patients who were readmitted within 1 year. No baseline differences were observed in other comorbidities including coronary artery disease, congestive heart failure, hypertension, obstructive sleep apnea, and diabetes mellitus.

As seen in Table 2, depression (odds ratio [OR], 2.98; 95% confidence interval [CI], 1.93–4.61; $P < 0.001$), anxiety (OR, 1.89; 95% CI, 1.16–3.06; $P = 0.010$), and GERD (OR, 1.70; 95% CI, 1.09–2.65; $P = 0.019$) were associated with increased risk of 1-year readmission on univariate analysis, whereas tobacco cessation counseling was associated with reduced 1-year readmission (unadjusted OR, 0.37; 95% CI, 0.20–0.67; $P = 0.001$). After adjusting for variables significant on univariate analysis (GERD, anxiety, serum sodium, and tobacco cessation counseling) and other variables (age, race, sex, and current smoking status) that could potentially influence readmissions, depression remained significantly associated with increased risk of 1-year readmission (adjusted OR, 2.67; 95% CI, 1.59–4.47; $P < 0.001$), and tobacco cessation counseling was associated with reduced risk of 1-year readmission (adjusted OR, 0.34; 95% CI, 0.18–0.66; $P = 0.001$) (Figure 1). FEV_1 data were not available in all subjects; however, when FEV_1 was entered into the multivariable model, depression was significantly associated with 1-year readmission (*see* Table E1 in the online supplement).

Table 1. Baseline characteristics of participants by 1-yr readmission from index hospitalization

	Overall (N = 422)	Patients Not Readmitted (n = 290)	Patients Readmitted (n = 132)	*P* Value
Age, yr	64.8 ± 11.7	65.1 ± 12.0	64.3 ± 11.3	0.52
Male sex	212 (50.1)	74 (56.1)	138 (47.6)	0.11
African American	146 (34.5)	99 (34.1)	47 (35.6)	0.30
Body mass index, kg/m^2	27.6 ± 8.3	27.7 ± 8.3	27.2 ± 8.2	0.58
Smoking history, pack-years	50.0 ± 26	49.7 ± 27.2	50.6 ± 24.3	0.78
Current smoker	276 (65.2)	188 (64.8)	100 (67.1)	0.74
FEV_1 (% predicted)*	48.1 ± 18.7	50.2 ± 19.4	44.9 ± 17.3	0.05
FEV_1/FVC*	52.5 ± 14.3	53.8 ± 14.9	50.6 ± 13.1	0.13
Serum sodium, mmol/L	136.7 ± 4.2	136.4 ± 4.3	137.4 ± 3.9	0.03
Serum bicarbonate, mmol/L	29.1 ± 7.0	28.9 ± 7.7	29.6 ± 5.3	0.36
Serum creatinine, mg/dl	1.1 ± 0.7	1.1 ± 0.7	1.1 ± 0.7	0.55
White blood cell count, 10^3/mm^3	10.2 ± 4.7	10.3 ± 4.8	10.1 ± 4.6	0.63
Hematocrit	39.1 ± 6.1	39.3 ± 6.1	38.7 ± 6.3	0.37
Coronary artery disease	113 (26.7)	73 (26.4)	40 (31.0)	0.34
Atrial fibrillation	54 (12.8)	40 (14.4)	14 (10.9)	0.32
Congestive heart failure	107 (25.3)	75 (26.4)	32 (24.2)	0.64
Cerebrovascular accident	45 (10.6)	30 (10.3)	15 (11.4)	0.75
Hypertension	296 (70.0)	201 (69.3)	95 (72.0)	0.65
Diabetes mellitus	99 (23.4)	73 (25.2)	26 (19.7)	0.22
Chronic kidney disease	51 (12.1)	37 (12.8)	14 (10.6)	0.53
Obstructive sleep apnea	44 (10.4)	29 (10)	15 (11.4)	0.67
Gastroesophageal reflux disease	121 (28.6)	73 (25.2)	48 (36.4)	0.02
Depression	131 (31.0)	68 (23.4)	63 (47.7)	<0.001
Anxiety	89 (21.0)	51 (17.6)	38 (28.8)	0.009
Tobacco cessation counseling†	86 (31.2)	72/189 (38.1)	14/87 (16.1)	<0.001

Data are presented as mean ± SD or No. (%) unless otherwise specified.
*Lung function date available on 202 participants.
†276 current smokers.

To investigate the role depression played in short-term readmission, we analyzed 30-day (Table E2) and 90-day readmission proportions by univariate and multivariable modeling. Forty-seven patients (11%) were readmitted within the first 30 days of index admission; 23 (5%) were readmitted between days 31 and 90, and 62 (15%) were readmitted between days 91 and 365 after index admission. The cumulative 1-year readmission rate was 31%. Depression was associated with increased 30-day readmission on univariate analysis (unadjusted OR, 4.31; 95% CI, 2.30–8.10; $P < 0.001$) and remained significant after multivariable adjustment

Table 2. Predictors of readmission at 1 yr

Variables	Unadjusted OR (95% CI)	*P* Value
Age, yr	0.99 (0.98–1.01)	0.520
African American	1.06 (0.69–1.64)	0.783
Male	0.71 (0.47–1.08)	0.107
Current smoking	0.99 (0.64–1.57)	0.972
GERD	1.70 (1.09–2.65)	0.019
Depression	2.98 (1.93–4.61)	<0.001
Anxiety	1.89 (1.16–3.06)	0.010
Serum sodium, mmol/L	1.06 (1.01–1.12)	0.029
Tobacco cessation counseling	0.37 (0.20–0.67)	0.001

Definition of abbreviations: CI = confidence interval; GERD = gastroesophageal reflux disease; OR = odds ratio.

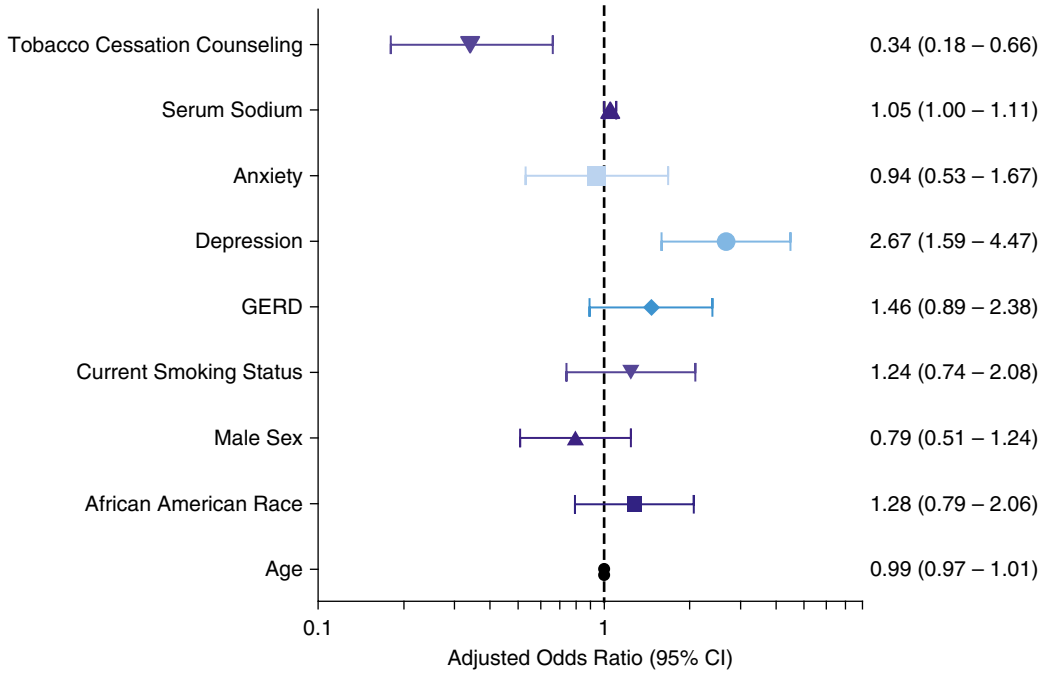

Figure 1. Independent predictors of readmission for acute exacerbation of COPD at 1 year. Variables shown are those significant on univariate comparisons between subjects with and without readmission within 1 year of index admission. The following variables were included in the multivariable model: age, race, sex, current smoking status, GERD, depression, anxiety, serum sodium, and tobacco cessation counseling. CI = confidence interval; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease.

for age, race, sex, smoking status, GERD, sodium level, anxiety, and tobacco cessation counseling (adjusted OR, 3.83; 95% CI, 1.84–7.96; $P < 0.001$) (Figure 2). After adjustment for these variables, depression was also independently associated with increased risk of 90-day readmission (adjusted OR, 2.47; 95% CI, 1.34–4.55; $P = 0.004$) (Figure 2). Anxiety was associated with increased risk of 30-day readmission on univariate analysis (unadjusted OR, 2.65; 95% CI, 1.39–5.04; $P = 0.003$) but did not achieve statistical significance after multivariable adjustment (adjusted OR, 1.44; 95% CI, 0.68–3.05; $P = 0.342$).

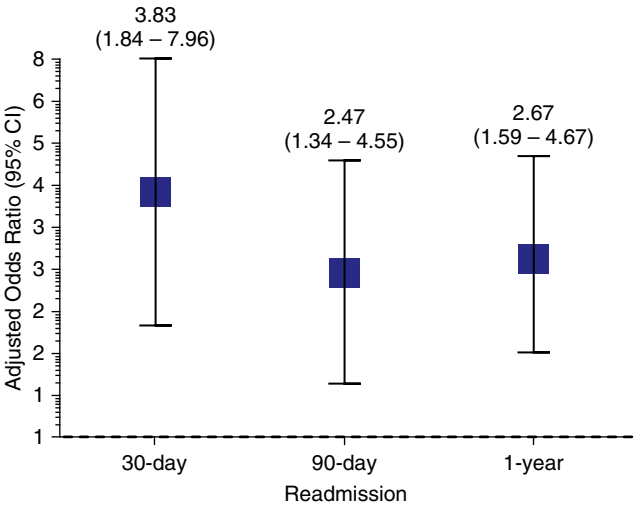

Figure 2. Depression and risk of readmission for acute exacerbation of COPD at 30 days, 90 days, and 1 year. Black boxes represent adjusted odds ratio with bars representing the 95% CIs. The following variables were included in the multivariable model: age, race, sex, current smoking status, gastroesophageal reflux disease, depression, anxiety, serum sodium, and tobacco cessation counseling. CI = confidence interval; COPD = chronic obstructive pulmonary disease.

Discussion

We found that depression is a risk factor for both short-term (30-d and 90-d) and 1-year readmission for acute exacerbation of COPD. Furthermore, we showed that tobacco cessation counseling was associated with reduced risk of 1-year readmission. Because both depression and smoking status are potentially modifiable, they may be valuable targets for interventions aimed at reducing COPD readmissions.

It is estimated that as many as 40% of patients with COPD have comorbid depression or suffer from depressive symptoms (29, 30), and we found a comparable prevalence in our population. However, the percentages in our study and in the general COPD population likely underestimate the actual prevalence of depression, partly because COPD and depression share a number of overlapping symptoms such as decreased energy and fatigue (31), and the effect of COPD

symptoms or acute exacerbations of COPD on a patient's psychological state is poorly understood (32). Importantly, although depression has been shown to be an independent risk factor for mortality in patients with COPD and is linked with an increased risk of exacerbations (27, 33–35), little is known about the association between depression and readmissions for acute exacerbation of COPD. As far as we know, our study is the first to show that depression is associated with an increased risk of both short- and long-term readmissions for acute exacerbation of COPD (36).

Patients with COPD and comorbid depression represent a potentially unique subgroup with difficult-to-control disease (32). Patients with COPD and depression report increased dyspnea, worse quality of life, and decreased treatment adherence, thus making it less likely that proven medical therapies or behavioral interventions such as tobacco cessation or pulmonary rehabilitation would be effective or their benefits maintained (37, 38). Although the underlying mechanistic links remain uncertain, the association between depression and COPD hospitalization is likely bidirectional, wherein depression worsens COPD-related morbidity and mortality, and COPD increases the risk of depression (39, 40).

Previous studies have linked psychological comorbidities with increased risk of mortality in patients with COPD, although data about readmissions are less definitive (38, 41). Coventry and colleagues prospectively examined psychosocial risk factors, including depressive symptoms and social support, and readmissions in a small cohort of patients with COPD in the United Kingdom and found a modest correlation with readmission risk in 1 year (26). Ng and colleagues also prospectively examined outcomes in patients with COPD and depressive symptoms, and although they found an increased risk of mortality and hospital stay, they did not find an increased risk of readmission (42). Xu and colleagues found an independent effect of depression on acute exacerbation of COPD risk but did not examine the risk of readmissions (27). We now report a robust association between depression and risk of readmission for acute exacerbation of COPD in a well-defined patient population, not only in the short term but also over a 1-year period, suggesting that depression is a sustained risk factor for readmission after an index hospitalization.

Although there are no prospective randomized studies of medical therapy for depression and readmission rates, retrospective studies suggest that antidepressant medication use is associated with a significantly lower mortality rate in this population (34). Furthermore, in one randomized clinical trial in patients with COPD and depression, a personalized outpatient intervention program composed of education and counseling improved not only depressive symptoms and adherence to antidepressants, but also dyspnea-related disability (43). Pulmonary rehabilitation can modify both depression symptoms and readmission rates (44, 45), but whether there is a causative link between reduction in depression scores and readmission rates has not been tested. In a retrospective analysis of Medicare data, Ahmedani and colleagues showed that patients with congestive heart failure, pneumonia, and acute myocardial infarction experienced increased risk of 30-day hospital readmission in the presence of comorbid depression (46). Given that reducing 30-day readmission for acute exacerbation of COPD is now a target set forth by the Centers for Medicare and Medicaid Services, these studies, together with our data, support the need for further research, including testing of pharmacologic and behavioral interventions, to examine psychological comorbidities such as depression as potentially modifiable risk factors for readmission for acute exacerbation of COPD. Anxiety has also been linked to a worse sensation of dyspnea in COPD (47) and increased risk of acute exacerbation of COPD (36, 47), but data on the risk of readmission are limited. Although we found an association between anxiety and readmissions on univariate analysis, this did not remain significant after multivariable modeling. Depression and anxiety frequently coexist, and depression appears to be a stronger risk factor for readmissions.

In our analysis, we also found that in-hospital tobacco cessation counseling reduced 1-year readmission rates, despite a low percentage (11.4%) of patients readmitted at 1 year who received tobacco cessation education. Persistent smoking is a known risk factor for acute exacerbation of COPD (48). Coultas and colleagues found a correlation between current smoking status and increased risk of depressive symptoms (49). Depression can also play a role in lack of adherence to tobacco cessation in patients with COPD (42). Although the creation of tobacco cessation groups in the stable outpatient setting has been shown to decrease hospitalizations, there is limited evidence regarding the effect of instituting in-hospital tobacco cessation interventions and their effect on readmission rates for acute exacerbation of COPD (48, 50). The mechanisms underlying the positive effects of tobacco cessation are likely related to airway remodeling and reduction in pulmonary inflammation (51). This represents an additional approach that should be tested prospectively.

Although hyponatremia has been shown in other retrospective studies to be a predictor of COPD hospitalization (52), perhaps reflecting the syndrome of inappropriate antidiuretic hormone release, volume overload, and/or cor pulmonale, we found on univariate analysis that higher serum sodium was associated with readmission risk over 1 year. Although high sodium may reflect dehydration as often seen in COPD exacerbations, we did not find a relationship between readmission and hemoconcentration. Further studies are needed to prospectively assess the predictive value of serum sodium. We also found on univariate analysis that GERD was a predictor of readmissions at 1 year, a finding supported by recent studies (53, 54).

Limitations

This retrospective study was based on administrative data from a single center. However, we reviewed all charts and included only those patients confirmed by physicians to have met the standardized criteria for acute exacerbation of COPD. In addition, because data were not available on the severity of depression using depression scales, we used physician diagnosis and medication use as our diagnostic criteria for depression. This may have underestimated the prevalence of depression and not allowed for stratification on the basis of depressive symptoms or disease severity. However, our findings do suggest that it would be prudent for physicians to be vigilant in assessing their patients with COPD for comorbid depression. Regarding this, the American Association of Cardiovascular and Pulmonary Rehabilitation recommends screening for depression at enrolment in

rehabilitation programs (55). Furthermore, our findings of an association between depression and both short- and long-term readmissions for acute exacerbation of COPD should inform a randomized controlled trial to assess whether this is a truly modifiable risk factor.

We recognize that socioeconomic factors such as education and financial resources are important factors that could potentially modify readmission risk; however, we do not have reliable information on these variables. Comorbidities were defined on the basis of their presence in physician notes in the medical record, which reflects a combination of physician-confirmed and self-reported conditions, and inaccuracies in the latter could have biased our results.

We did not have lung function data for all patients, but our secondary sensitivity analyses for only those patients with FEV_1 data showed that depression remained a strong predictor of readmissions. Although we were able to capture data accurately for readmissions to our center, we may have missed capturing data for readmissions to other hospitals. Finally, our study is subject to the usual limitations of retrospective design, including selection bias, misclassification bias, and residual confounding.

Conclusions

Depression is associated with both short- and long-term readmissions for acute exacerbation of COPD. Tobacco cessation counseling before hospital discharge also represents an important target that can potentially decrease 1-year readmission rates. Further studies are needed to assess the impact of interventions targeting depression and tobacco cessation counseling on the rate of readmissions for acute exacerbation of COPD. ■

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

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