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Depression and Health-Related Quality of Life in Chronic Obstructive Pulmonary Disease

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Abstract

Background—Prior research on the risk of depression in COPD has yielded conflicting results. Furthermore, we have an incomplete understanding of how much depression versus respiratory factors contribute to poor health-related quality of life.

Methods—Among 1202 adults with COPD and 302 demographically-matched referents without COPD, depressive symptoms were assessed using the 15-item Geriatric Depression Score (GDS). We measured COPD severity using a multifaceted approach, including spirometry, dyspnea, and exercise capacity. We used the Airway Questionnaire 20 and the Physical Component Summary Score to assess respiratory-specific and overall physical quality of life, respectively.

Results—In multivariate analysis adjusting for potential confounders including sociodemographics and all examined comorbidities, COPD subjects were at higher risk for depressive symptoms (GDS ≥ 6) than referents (odds ratio [OR], 3.6; 95% confidence interval [CI], 2.1 – 6.1; $p < .001$). Stratifying COPD subjects by degree of obstruction on spirometry, all subgroups were at increased risk of depressive symptoms relative to referents ($p < .001$ for all). In multivariate analysis controlling for COPD severity as well as sociodemographics and comorbidities, depressive symptoms were strongly associated with worse respiratory-specific quality of life (OR, 3.6; 95% CI 2.7 – 4.8; $p < .001$) and worse overall physical quality of life (OR, 2.4; 95% CI, 1.8 – 3.2; $p < .001$).

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Conclusions—Patients with COPD are at significantly higher risk of having depressive symptoms than referents. Such symptoms are strongly associated with worse respiratory-specific and overall physical health-related quality of life, even after taking COPD severity into account.

Keywords

Depression; Health Status; Pulmonary Disease; Chronic Obstructive; Quality of Life

INTRODUCTION

A primary objective of treatment for patients with chronic disease is to improve health-related quality of life.¹ For patients with chronic obstructive pulmonary disease (COPD), pulmonary rehabilitation is known to improve health-related quality of life, but this benefit is not fully explained by improvement in cardio-respiratory function.^{2–4} For example, a recent Cochrane meta-analysis concluded that pulmonary rehabilitation programs significantly improved health-related quality of life, even though the improvement in exercise capacity was below the threshold of clinical significance.⁴ This finding raises the intriguing possibility that psychosocial factors, such as depression, are critical determinants of health status in COPD.

Depression is thought to be associated with worse health status in patients with COPD, but studies on this subject have generally been hampered by either small sample sizes or incomplete information to adjust for COPD severity.^{5–7} Moreover, while depression appears to be more common in COPD patients than in the general population, there have been few studies addressing this question.^{5, 8} One systemic review concluded that the evidence for a significant risk of depression in COPD patients remained inconclusive.⁹ Indeed, some studies have found an increased level of depression in patients with COPD,^{10, 11} while others have not.^{12, 13}

Our study uses a large observational cohort to study depressive symptoms in COPD. We hypothesized that individuals with COPD would be more likely to have depressive symptoms than demographically matched referent subjects without COPD, that more severe COPD would be associated with a higher likelihood of having depressive symptoms, and that depressive symptoms would be strongly associated with health-related quality of life even after controlling for COPD severity.

METHODS

Participants

The Function, Living, Outcomes, and Work (FLOW) study is an ongoing cohort study of patients with COPD and matched referents without COPD.¹⁴ The cohort was derived from members of Kaiser Permanente (KP),. Patient recruitment has previously been described in detail.¹⁴ Briefly, we identified all adult KP members, living within a 30-mile radius of our research clinic, who were recently treated for COPD.¹⁴ The age range was restricted to 40–65 years because an important focus of the FLOW study is examining the long-term prevention of COPD-associated morbidities. Using KP databases, we identified all patients who met each of two criteria: one based on health-care utilization and the second based on medication prescription. The health-care utilization criterion was ≥ 1 outpatient visits or hospitalizations for COPD over the prior 12 months. The medication criterion was ≥ 2 prescriptions for a COPD-related medication during a 12-month window surrounding the COPD utilization date. We previously compared this algorithm to medical record review and demonstrated that it accurately identifies adults with COPD.¹⁵

We recruited 1,212 COPD patients who completed both structured telephone interviews and research clinic visits. Ten subjects were excluded because they did not meet the Global

Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for COPD based on interviews and spirometry,¹⁶ yielding a COPD cohort of 1202 subjects.

We aimed to recruit 300 control subjects without COPD. We initially identified 373 referent subjects, without historical utilization for COPD, who were matched to COPD subjects by age, gender, and race. By design, we excluded 71 subjects who had spirometric evidence of airway obstruction at the time of research clinic evaluation, leaving 302 referent subjects.

The study was approved both by the University of California, San Francisco Committee on Human Research and the Kaiser Foundation Research Institute's institutional review board and all participants provided written informed consent.

Measurements

As previously described, subjects underwent structured telephone interviews followed by a research clinic visit.¹⁴ Interviews obtained medical comorbidities, tobacco history, sociodemographic characteristics, and the 15-item short-form Geriatric Depression Scale (GDS). We chose the GDS because it was developed to counter the problem of overlap between symptoms of a physical illness, such as COPD, and the somatic symptoms considered indicative of depression.⁹ The GDS has been validated both in non-geriatric populations generally as well as specifically in younger adults with obstructive lung disease.^{17–19} Using a cut-point of 6 or more symptoms, the GDS has a sensitivity of 88% and a specificity of 62% compared with structured clinical interview for diagnosing major depression.²⁰ Following precedent, we therefore defined depressive symptoms as present if subjects reported ≥ 6 out of 15 possible symptoms on the GDS.²¹

For COPD patients, respiratory-specific quality of life was assessed using the validated revised Airways Questionnaire 20 (AQ20-R).^{22–24} Lower scores reflect more favorable health status. Physical quality of life as reflective of generic health status was measured using the Short-Form (SF)-12 Physical Component Summary (PCS) score. The SF-12 PCS is derived from the Medical Outcomes Study SF-36 instrument, which has been extensively validated in the general population and among adults with COPD.^{25, 26} Higher scores reflect more favorable health status. Although both the PCS and AQ20-R scores are continuous variables, they can be grouped for clinical interpretability. On an *a priori* basis, we divided these scores into 4 strata based on the quartiles observed in the COPD cohort.

COPD Severity Assessment

For subjects with COPD, COPD severity was assessed in several ways. We conducted spirometry according to American Thoracic Society (ATS) guidelines.²⁷ Although we did not administer bronchodilators prior to spirometry, 90% of subjects had taken their own short-acting bronchodilator within 4 hours of spirometry or had taken a long-acting bronchodilator earlier in the same day.

Submaximal exercise performance was assessed using the Six Minute Walk Test (6MWT).^{28, 29} Subjects who routinely used home oxygen or who had a resting oxygen saturation $< 90\%$ were supplied with supplemental oxygen during the test. The primary outcome was meters walked in 6 minutes.

Oxygen saturation was assessed at rest using pulse oximetry. For subjects with prescribed supplemental oxygen ($n=61$), oxygen saturation was assessed on their prescribed oxygen.

We also used a previously-validated survey-based COPD severity score, which is based on responses to survey items that comprise five domains of COPD severity: (1) degree of respiratory symptoms, (2) prior systemic corticosteroid use, (3) other COPD medication use,

(4) previous hospitalization or intubation for respiratory disease, and (5) home oxygen use.³⁰ Potential scores range from 0 to 35.

We furthermore determined the BODE Index, which is a multidimensional score, predictive of death in COPD, that incorporates many of the above measures.³¹ Specifically, it includes body-mass index (BMI) [B], airflow obstruction as measured by FEV₁ [O] dyspnea [D], and exercise capacity [E], measured by the 6MWT.

Statistical Analysis

Differences in characteristics between COPD subjects and referents were compared using the t-test for continuous normally distributed variables and χ^2 tests for categorical variables. We used χ^2 tests for linear trend for ordinal variables.

Risk of Depressive Symptoms Relative to Referents—We used multivariate logistic regression to determine the adjusted odds ratio (OR) of having depressive symptoms in COPD subjects relative to referents, taking into account sociodemographics and comorbidities. We analyzed the COPD group as a whole relative to referents and also stratified by degree of airway obstruction as measured by FEV₁% predicted categorizations specified by GOLD.¹⁶ We used likelihood ratio testing to determine whether different OR's within a given multivariate logistic regression were different from each other.

COPD Severity and Risk of Depression—To further evaluate whether COPD is associated with depression, we examined whether higher COPD severity was associated with a greater likelihood of having depressive symptoms. To do so, we developed several multivariate logistic regression models. Each model used depressive symptoms as the outcome variable and included the same potential confounders (sociodemographics, comorbidities, tobacco history, and BMI) but included a different measure of COPD severity as a predictor variable.

Impact of Depression on Quality of Life among COPD Patients—We also evaluated the association between depressive symptoms and health-related quality of life, controlling for COPD severity. Here we developed two multivariate logistic regression models, each with a different quality of life outcome variable. Each model incorporated the same potential confounders, listed above, as well as both the BODE Index and COPD Severity Score to adjust for COPD severity. We chose the BODE index because, as a single measure, it incorporates multiple measures of COPD severity, including FEV₁ and 6MWT. We also incorporated the COPD Severity Score because, as a survey-based measure of such factors as COPD-specific utilization, it has the potential to capture a dimension of COPD severity not assessed by the BODE Index. Because our objective here was to determine the extent to which depressive symptoms are associated with quality of life after maximally adjusting for COPD severity, it was most conservative to simultaneously include both the BODE Index and COPD Severity Score. For our categorizations of overall physical and respiratory-specific quality of life, we used ordinal logistic regression.³² The ordinal logistic model invokes the proportional odds assumption and estimates a single OR for the association between a predictor and a multilevel categorical outcome (in this case, the 4 strata of the PCS and AQ20-R).

For all analyses, we used Stata/SE software (version 9.2, College Station, TX). For all logistic regression models, the Hosmer-Lemeshow test demonstrated adequate goodness-of-fit ($p>0.20$ for all models).³² The proportional odds assumption was verified for both ordinal logistic regression analyses ($p>0.20$ for both models).³²

RESULTS

Patient Characteristics

By design, patients with and without COPD were similar in age, gender, and race (TABLE 1). Compared with referents, patients with COPD had a higher prevalence of all examined comorbidities, higher average BMI, and greater prevalence of depressive symptoms ($p<.001$ for all).

COPD and the Risk of Depressive Symptoms

In multivariate analysis adjusting for sociodemographics and comorbidities, depressive symptoms were much more common in persons with COPD than in referents (OR, 3.6; 95% CI, 2.1 – 6.1; $p<.001$). In addition, when COPD subjects were stratified by FEV₁ categorization, all subgroups were more likely to have depressive symptoms relative to referents, with the OR highest among those with the lowest FEV₁ (TABLE 2). A χ^2 test for trend revealed that greater COPD severity, based on greater categorical impairment in FEV₁, was associated with increasing risk of depressive symptoms ($p<.001$).

To examine whether COPD severity unmeasured by lung function might explain why patients with higher FEV₁ manifest greater odds of depressive symptoms than referents, we dichotomized subjects based on the median value of the COPD Severity Score within each FEV₁ % predicted stratum (TABLE 3). Thus, for example, the median value of the COPD Severity Score in the subgroup of patients with FEV₁ $\geq 80\%$ predicted was 7. Patients in this subgroup whose COPD Severity Score was above the median (i.e. ≥ 7) were at greater risk of having depressive symptoms relative to the referent population (OR, 4.3, 95% CI 2.3 – 8.0) than patients in this subgroup whose COPD Severity Score was below the median (i.e. < 7) (OR, 1.8; 95% CI 0.9 – 3.8); likelihood ratio testing revealed that the OR of 4.3 was statistically significantly different than the OR of 1.8 ($p=0.009$). This result suggests that variability in COPD severity is related to variability in depressive symptoms even in subjects with higher FEV₁.

Among the subgroup with COPD, greater COPD severity was associated with increased likelihood of depressive symptoms after controlling for covariates. This was observed for each method used to assess COPD severity (TABLE 4).

Depressive Symptoms and Quality of Life in COPD

When examining the relationship between depressive symptoms and health-related quality of life, after adjusting for both potential confounders and COPD severity measures, we found that depressive symptoms were strongly associated with worse respiratory-specific quality of life (OR, 3.6; 95% CI 2.7 – 4.8; $p<.001$) and worse overall physical quality of life (OR, 2.4; 95% CI, 1.8 – 3.2; $p<.001$) (TABLE 5).

DISCUSSION

In a population-based sample, COPD was associated with a greater risk of depressive symptoms compared to a matched referent group. The fact that increasing COPD severity is associated with an increasing likelihood of depressive symptoms provides further evidence for an association between COPD and depression. Depressive symptoms also appeared to negatively impact quality of life, highlighting the importance of depression in these patients. Targeting depression in COPD could therefore be an attractive strategy to improve health status.

Previous research on the risk of depression faced by patients with COPD has yielded conflicting results.^{5–13} The study by van Manen and colleagues,¹¹ with 162 COPD subjects, is the largest

prior study on this subject that also included both a referent population and pulmonary function measurement. Interestingly, this study showed an increase in depressive symptoms among subjects with severe COPD ($FEV_1 < 50\%$ of predicted) but not in their cohort as a whole or in the less severe subgroups.¹¹ We cannot be sure of the reason for our differing conclusions, but this may have to do with higher rates of mood disorders generally in the United States relative to The Netherlands, where that study was performed.³³ Prior research has suggested that cultural differences between nations may affect the expression of depressive symptoms and be responsible for differing risk factors for major depression in various countries.³⁴

Our finding that higher COPD severity is associated with a higher likelihood of depressive symptoms provides further validity to the concept that COPD is associated with depression. However, our cross-sectional analysis cannot completely determine the causal pathway between COPD and depressive symptoms. It is possible that COPD causes depression or that depression causes COPD via its association with cigarette smoking.³⁵ Both pathways may also be operative. Alternatively, shared genetic and environmental factors may predispose independently to both smoking and depression.^{36, 37} Thus, because COPD may not be directory causing depression, targeting improved respiratory physiology in COPD may not alleviate depressive symptoms.

We found that depressive symptoms were strongly associated with health-related quality of life. Even though the risk of depressive symptoms increased with increasing COPD severity, the relationship between depressive symptoms and health-related quality of life was present taking into account such severity. These results are particularly important because depression complicating COPD is often overlooked in clinical practice.³⁷ Our results suggest that attempts to improve the quality of life of COPD patients should not underestimate the importance of depression as a potentially mediating factor. Moreover, there is evidence that treating depression in COPD improves quality of life.^{38, 39} Although this might include antidepressive pharmacotherapy,³⁹ interventions such as pulmonary rehabilitation, which often includes psychosocial support, may also improve mood and reduce depressive symptoms.^{4, 40–42} Alternatively, psychological counseling within the context of a physician visit may be important.⁴³ Because of the strong association between depressive symptoms and quality of life, further study regarding effective methods of treating depression in COPD appear clearly warranted.

Several study limitations must be considered. Although the inclusion criteria required healthcare utilization for COPD and COPD medication usage, it is possible that some subjects had asthma rather than COPD. However, all patients also had a physician diagnosis of COPD and reported having the condition. The observed lifetime smoking prevalence was similar to that in other population-based epidemiologic studies of COPD, supporting the diagnosis of COPD rather than asthma.^{44, 45} Nonetheless, we cannot exclude the possibility that some subjects, especially those with less obstruction on spirometry, may have conditions other than COPD. However, we note that reduced FEV_1 was associated with a higher likelihood of depressive symptoms; thus, eliminating subjects with higher FEV_1 from our cohort would only have strengthened our finding that subjects with COPD are at higher risk of depressive symptoms than referents.

Because an important focus in the prospective follow-up of our cohort will be studying the long-term prevention of COPD-associated morbidities, we intentionally sampled younger adults with COPD (ages 40–65). Although we adjusted for age within our multivariate models, we cannot be sure of the applicability of our results to older adults with COPD. In addition, KP members, because they have health care access, may also be different than the general population of adults with COPD. Mitigating this limitation, the sociodemographic characteristics of Northern California KP members are similar to those of the regional

population.^{46, 47} Moreover, selection bias could have been introduced by non-participation in the study and could in turn affect the generalizability of our results. However, our participation rates were comparable or better than many other studies on this subject.^{1, 6, 7, 9–13}

Our measure of depression, the GDS, is not intended to diagnose major depression but rather depressive symptoms. Nonetheless, patients with depressive symptoms warrant further evaluation in clinical practice, and treatment for depression is often recommended even in the absence of a diagnosis of major depression.⁴⁸ One advantage of the GDS over other measures of depressive symptoms is that it is less contaminated with somatic symptoms such as poor appetite and poor sleep that may be symptoms of either depression or of COPD itself.^{9, 11} This reduces the likelihood that we are over-estimating depression in this setting.

In conclusion, we found that patients with COPD, at all levels of airway obstruction, were at higher risk of depressive symptoms than referents. Furthermore, increasing COPD severity was associated with an increasing likelihood of depressive symptoms. Even so, after taking COPD severity into account, depressive symptoms were strongly associated with worse quality of life.

Clinical Significance

- COPD is associated with an increased risk of depressive symptoms. Clinicians should thus be alert to the possibility of depression in their COPD patients.
- Because depressive symptoms appear to strongly impact quality of life in COPD, even after adjusting for respiratory symptoms and impairment, clinicians should consider depression in COPD to be an important clinical problem in its own right.

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Table 1
 Characteristics of 1202 patients with COPD and 302 referents*

	Referents (n=302)	COPD Patients (n=1202)	P Value
Demographic Factors			
Age, mean (SD) years	58.5 (6.2)	58.2 (6.2)	.49
Female	185 (61)	691 (57)	.23
White (non-Hispanic)	200 (66)	810 (67)	.70
Married or Cohabiting	200 (66)	744 (62)	.16
College graduate	165(55)	326 (27)	<.001
Annual household income <\$20,000	9 (3)	129 (11)	<.001
Medical Co-morbidities			
Hypertension	118 (39)	657 (55)	<.001
Coronary artery disease	8 (3)	139 (12)	<.001
Congestive heart failure	0 (0)	136 (11)	<.001
Stroke	2 (1)	66 (5)	<.001
Diabetes mellitus	41 (14)	249 (21)	<.001
Lower back pain	98 (32)	707 (59)	<.001
Sleep apnea	27 (9)	265 (22)	<.001
Tobacco history			<.001
Never smoker	158 (52)	165 (14)	
Ex-smoker	132 (44)	644 (54)	
Current Smoker	12 (4)	393 (33)	
Body mass index (mean) (SD), kg/m ²	29.9 (6.4)	31.7 (8.2)	<.001
Depressive Symptoms [†]	17 (6)	330 (27)	<.001

* Data are presented as number (column percentage) except where indicated otherwise. Tobacco history percentages among COPD subjects do not add up to 100% because of rounding.

[†] Geriatric depression score ≥ 6 .

Table 2
Prevalence and odds of depression in patients with COPD compared to referents

	n	Depressive Symptoms [*]	OR [†] (95% CI)
COPD subjects[‡]			
FEV ₁ ≥80% predicted	283	75 (26.5%)	3.1 (1.7 to 5.6)
FEV ₁ ≥50–80% predicted	549	142 (25.9%)	2.9 (1.7 to 5.1)
FEV ₁ ≥30–50% predicted	258	74 (28.7%)	4.6 (2.5 to 8.4)
FEV ₁ <30% predicted	112	39 (34.8%)	8.0 (4.1 to 15.7)
Referents	302	17 (5.6%)	1.0 (referent)

^{*} Geriatric depression score ≥ 6

[†] Odds ratio for COPD vs. referents for each subgroup of COPD. Results are from multivariate logistic regression adjusted for age, gender, marital status, race, education, annual household income, body-mass index, and all comorbidities listed in Table 1. Other factors associated with depressive symptoms in multivariate analysis were age, gender, education, annual household income, bmi, and history of stroke, sleep apnea, and lower back pain (p<.05 for all). In χ^2 test for trend, decreasing FEV₁ categorizations were associated with increasing odds of depressive symptoms (p<.001)

[‡] Comparing the whole COPD group to referents in multivariate analysis adjusted for the same covariates yields an odds ratio for depressive symptoms of 3.6 (95% CI: 2.1 – 6.1).

Dichotomization of FEV₁ % predicted subgroups into high and low COPD Severity Scores: Examining the association of COPD severity with depressive symptoms within each strata of FEV₁

OR* (95% CI) for Depressive Symptoms [†]				
	Subgroup Median COPD Severity Score [‡]	Low COPD Severity Score (< Subgroup Median)	High COPD Severity Score (≥ Subgroup Median)	p-value for OR difference within FEV ₁ subgroup [§]
COPD subjects				
FEV ₁ ≥80% predicted	7	1.8 (0.9 – 3.8)	4.3 (2.3 – 8.0)	p=0.009
FEV ₁ ≥50–80% predicted	9	2.0 (1.1 – 3.7)	4.0 (2.2 – 7.2)	p<0.001
FEV ₁ ≥30–50% predicted	12	2.5 (1.2 – 5.1)	7.4 (3.9 – 14)	p<0.001
FEV ₁ <30% predicted	15	7.6 (3.4 – 17)	8.3 (3.8 – 18)	p=0.84

* Odds ratio of depressive symptoms is relative to referent group without COPD. Each FEV₁ stratum was dichotomized based on the median COPD Severity Score within that stratum. Results are from multivariate logistic regression adjusted for age, gender, marital status, race, education, annual household income, body mass index, and all comorbidities listed in Table 1

[†] Depressive symptoms defined as geriatric depression score ≥ 6

[‡] The COPD Severity Score is a survey-based measure of COPD severity that takes into account respiratory symptoms, COPD medication usage, prior hospitalizations and intubations for COPD, and home oxygen usage. See Methods.

[§] Based on likelihood ratio testing. For example, within the subgroup of patients with FEV₁ ≥ 80% predicted, those with a high COPD Severity Score had a significantly higher risk of depressive symptoms relative to referents without COPD (OR=4.3) than those whose COPD Severity Score was low (OR=1.8) (p=0.009 for difference between these two OR's).

Table 4

Relationship of various measures of COPD severity to depressive symptoms (GDS Score $\geq$ 6) among patients with COPD (n=1202)

	OR (95% CI)	P-Value
FEV ₁ % predicted *	1.26 (1.08 – 1.47)	0.003
6 Minute Walk Test *	1.96 (1.64 – 2.34)	<.001
Oxygen Saturation *	1.33 (1.15 – 1.55)	<.001
COPD Severity Score *	2.04 (1.72 – 2.42)	<.001
BODE Index *	2.13 (1.82 – 2.51)	<.001

Each row represents a separate multivariate logistic regression analysis that includes the following covariates: age, gender, race, marital status, education, annual household income, tobacco history, body-mass index, and all comorbidities listed in Table 1.

* Per 1 standard deviation in each of the measures: FEV₁ % predicted (unit decrement = 23%); 6 minute walk test (unit decrement = 120 meters); oxygen saturation (unit decrement 2.5%); COPD Severity Score (unit increment [higher score reflects ↑severity] = 6.1 points); BODE Index (unit increment [higher score reflects ↑severity] = 2.4 points).

Table 5

Multivariate analyses of the association between depressive symptoms, COPD severity measures, and health-related quality of life in patients with COPD in multivariate analysis

	Worse Respiratory-Specific Health-Related Quality of Life		Worse Overall Physical Health-Related Quality of Life	
	OR* (95% CI)	P Value	OR* (95% CI)	P Value
Depressive Symptoms [†]	3.6 (2.7 – 4.8)	<.001	2.4 (1.8 – 3.2)	<.001
BODE Index [‡]	1.7 (1.4 – 1.9)	<.001	2.0 (1.7 – 2.3)	<.001
COPD Severity Score [§]	2.9 (2.5 – 3.5)	<.001	1.9 (1.6 – 2.2)	<.001

The two columns of health-related quality of life measures represent two different multivariate models which simultaneously included the independent variables shown above as well as the following covariates: age, gender, race, marital status, education, annual household income, tobacco history, body mass index, and all comorbidities listed in Table 1.

* Odds ratio from ordinal logistic regression, representing the association between predictor variables (e.g. presence of depressive symptoms) and the multi-level categorical health-related quality of life outcomes (see Methods).

[†] Geriatric depression score ≥ 6 .

[‡] Odds ratios presented per 1 standard deviation increment in BODE Index. The BODE Index includes body-mass index, pulmonary function measurement, a dyspnea scale, and exercise capacity (see Methods). Higher BODE Index scores reflect greater COPD severity.

[§] Odds ratios presented per 1 standard deviation increment in COPD Severity Score. Higher COPD Severity Scores reflect greater severity.