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BIOBEHAVIORAL PROGNOSTIC FACTORS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: Results from the INSPIRE-II Trial

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Abstract

Objective—To examine the prognostic value of select biobehavioral factors in patients with chronic obstructive pulmonary disease (COPD) in a secondary analysis of participants from the INSPIRE-II trial.

Methods—Three hundred twenty six outpatients with COPD underwent assessments of pulmonary function, physical activity, body mass index, inflammation, pulmonary symptoms, depression, and pulmonary quality of life, and were followed for up to 5.4 years for subsequent clinical events. The prognostic value of each biobehavioral factor, considered individually and combined, also was examined in the context of existing Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 risk stratification.

Results—Sixty-nine individuals experienced a hospitalization or died over a mean follow-up time period of 2.4 (interquartile range = 1.6) years. GOLD classification was associated with an increased risk of clinical events (HR = 2.72 [95% CI 1.63, 4.54], per stage); Six Minute Walk (HR = 0.50 [0.34, 0.73] per 500 feet), total steps (HR = 0.82 [0.71, 0.94] per 1,000 steps), hsC-reactive protein (HR = 1.44 [1.01, 2.06] per 4.5 mg/L), depression (HR = 1.12 [1.01, 1.25] per 4 points), and pulmonary quality of life (HR = 1.73 [1.14, 2.63] per 25 points) were each predictive over and above the GOLD assessment. However, only GOLD group and Six Minute Walk were predictive of all-cause mortality and COPD hospitalization when all biobehavioral variables were included together in a multivariable model.

Conclusion—Biobehavioral factors provide added prognostic information over and above measures of COPD severity in predicting adverse events in patients with COPD.

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Keywords

COPD; stress; depression; quality of life; functional capacity

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex and relatively common lung disease that is a growing cause of morbidity and mortality throughout the world.(1, 2) COPD is an obstructive airway disease in which chronic inflammation is thought to result in structural changes including narrowing of the small airways and loss of elasticity.(3) COPD is considered to be the result of cumulative exposure to pollutants, of which smoking is the primary culprit. However, environmental pollution or occupational exposure also may be responsible;(4) in fact, it has been estimated that more than 10% of the reported cases of COPD may occur in persons who have never smoked.(5)

Unlike chronic conditions such as coronary heart disease and cancer, there are no known pharmacologic therapies that prolong survival in COPD patients. The severity of COPD is measured by pulmonary function testing, and the amount of air expired in one second (FEV_1) is considered a sensitive measure of disease severity, which is independently prognostic of clinical outcomes.(6–8) However, patients with COPD vary greatly in their clinical presentations and functional status, independent of FEV_1, and other factors have been shown to be predictive of clinical outcomes.(9) The Food and Drug Administration has noted that “with the exception of lung function tests, there are no well validated biomarkers or surrogate endpoints that can be used to establish efficacy of a drug for COPD.”(10) Although a number of potential prognostic factors have been examined, including biomarkers obtained from bronchial biopsies, sputum, and bronchoalveolar lavage, few have been validated.(11–13) Furthermore, while some studies have examined the prognostic value of biobehavioral factors such as the GOLD classification(14), Six Minute Walk Test (6MWT)(15), measures of inflammation(16, 17), physical activity(18), and depression(19, 20), most studies either collect such factors in isolation, or report their prognostic value individually rather than collectively. The INSPIRE-II study provides an opportunity to examine the relationship of a broad array of biobehavioral biomarkers, separately and together, to medical endpoints.

The INSPIRE-II trial was a dual site (Duke University Medical Center and Ohio State University), randomized clinical trial that evaluated the effects of a telephone-based coping skills training (CST) intervention for COPD patients and their respective caregivers on physical and psychosocial measures of quality of life and on medical outcomes (clinicaltrials.gov Identifier: NCT00736268). The methods and primary results of the trial have been published previously(21) (22). The CST intervention improved quality of life (QoL), reduced distress and somatic symptoms, and increased functional capacity compared to health education controls. However, the intervention did not improve clinical outcomes. The present ancillary study from INSPIRE-II evaluated the prognostic significance of biobehavioral factors collected at baseline, prior to treatment, on the combined endpoint of all-cause mortality and COPD-related hospitalizations, independent of disease severity

determined by FEV_1, age, and medical comorbidities. We also examined the predictive value of these biobehavioral factors in relation to the recently revised Global Initiative for Chronic Obstructive Lung Disease 2011 (GOLD 2011) assessment, which classifies patients on the basis of FEV_1, exacerbation history and symptoms, and has been shown to be associated with increased mortality risk.(14, 23–26)

Methods

Eligibility and Trial Overview

INSPIRE-II enrolled outpatients diagnosed with COPD, with FEV_1 25–80% of predicted within 6 months of study enrollment, and FEV_1/FVC <70%. The protocol was approved by the Institutional Review Boards at Duke and Ohio State and all participants provided written informed consent. The first patient was enrolled in January, 2009 and the last follow-up was completed in June, 2014. Details related to the methods and primary outcomes have been previously (21, 22).

Assessment procedures

Prior to randomization, patients completed a baseline assessment battery of biobehavioral prognostic factors, including measures of pulmonary function, inflammation, somatic symptoms, functional capacity and physical activity, depression and pulmonary QoL.

Pulmonary Function and Body Mass Index—Forced Expiratory Volume (FEV_1) was determined by a standard pulmonary function test performed in accordance with guidelines established by the American Thoracic Society.(27) Patients were instructed to breathe normally into a spirometer and then to inhale quickly to total lung capacity (TLC) and immediately thereafter perform a rapid and complete forced exhalation to determine the forced vital capacity (FVC). The forced expiratory volume in the first second determined the FEV_1.

Body Mass Index (BMI): Height and body weight were measured by a standard balance scale; body mass index (BMI) was calculated as weight (kg) divided by height in meters squared

Functional Capacity and Physical Activity

Six-Minute Walk Test Distance (6MWD): A standard protocol to determine exercise tolerance by measuring the distance walked within a 6-minute time limit was used.(28) Patients were asked to cover as much distance as possible at a self-selected pace, and, if needed, were provided with enough oxygen to maintain saturations of 90% or greater.

Physical Activity/Accelerometry: Physical activity (PA) during daily life was quantified on two successive days using the Kenz Lifecorder Plus accelerometer NL-2160 (LC; Suzuken Co. Ltd., Nagoya Japan). The average number of steps per day and time spent in moderate physical activity were recorded.

Somatic Symptoms—St. George's Respiratory Questionnaire (SGRQ)(29) is a 50-item scale that evaluates symptomatology (e.g., frequency of cough, sputum production, wheeze, breathlessness), activity (activities that cause or are affected by breathlessness), and impacts (on employment, need for medications, disruption of daily life). Scores range from 0 to 100, with higher scores indicating more pulmonary symptoms. The Cronbach's alpha in the present sample was 0.91.

Depression and Quality of Life—Beck Depression Inventory II (BDI-II)(30) is a 21-item self-report measure assessing cognitive, affective, and somatic symptoms of depression. Scores range from 0 to 63 with higher scores indicating greater depressive symptoms. The Cronbach's alpha for the present sample was 0.91.

Pulmonary Quality of Life (PQoL)(31) is a 36-item scale derived from the SF-36 that is designed to specifically assess quality of life (QoL) in patients with end stage lung disease. Scores range from 25 to 125, with higher scores indicating better pulmonary QoL. The Cronbach's alpha for the present sample was 0.89.

Inflammation—High sensitivity C-Reactive Protein (hsCRP) was quantified by Lab Corp using commercial ELISA kits (R&D Systems). Blood samples were obtained only from participants at Duke University (N=226).

Medical Co-morbidities—Charlson Medical Comorbidity Index(32) was used to assess the cumulative burden of medical comorbidity. The presence of each of 20 medical conditions was determined from patient report. The index assigns a weight to each condition, with the weighting coefficients derived from the approximate 1-year adjusted relative risk of mortality associated with that condition in a general medical population.

GOLD Classification—GOLD classification is the most widely used approach used to diagnose and manage COPD. The revised GOLD 2011 categorizes patients into one of four groups: A-low risk, less symptoms with mild-moderate airflow limitation, 0–1 COPD exacerbations per year and few pulmonary symptoms; B-low risk, more symptoms, with mild-moderate airflow limitation, 0–1 exacerbations per year and more symptoms; C-high risk, less symptoms with severe or very severe airflow restrictions and/or more than 2 exacerbations per year or 1 or more hospitalized exacerbations per year and few symptoms; D-high risk, more symptoms with severe or very severe airflow restrictions and/or more than 2 exacerbations per year or 1 or more hospitalized exacerbations per year and more symptoms. For the purpose of this study, GOLD 2011 was based upon FEV_1, prior COPD hospitalizations, and symptom severity. A SGRQ score of ≥ 25 was used in place of the COPD Assessment Test (CAT) cutoff of ≥ 10, in keeping with prior studies.(23)

Staff performing all biobehavioral assessments was blinded to treatment condition and clinical outcomes.

Clinical Endpoints—Patients documented all medical encounters every 6 months. Medical records were reviewed by a conference of study pulmonologists, blinded to treatment condition and biobehavioral results, who adjudicated all medical events. The

primary endpoint was the combined endpoint of time to death from any cause or first COPD-related hospitalization.

Statistical Analysis

We first performed a series of analyses using general linear models comparing patients with and without a clinical event for each biobehavioral factor adjusting for known predictors of COPD exacerbations including age, medical comorbidities (Charlson score), duration of COPD, and FEV_1. In order to provide meaningful data on the magnitude of difference between patients with and without events, standardized effect size data using Cohen's d are also presented.(33) Site (Duke and OSU) and Treatment group (CST and UC) were included in the models initially, but neither were significant and consequently were omitted in the final analyses. We next examined the relationship between prognostic factors and clinical outcomes using Cox regression, with the first clinical event coded as the event, and those with no events or who dropped out of the trial censored at the time of last contact. Separate models were conducted to examine the relationship between each biobehavioral factor--functional capacity (6MWD), physical activity during daily life (accelerometry total steps), BMI, inflammation (CRP), depression (BDI-II), and pulmonary quality of life (PQoL). In our analyses of hs CRP, we also controlled for whether participants were taking either inhaled corticosteroids or prednisone because of the known influence of these medications on inflammation. In the Cox regression models, predictors were scaled such that the hazard ratios reflected clinically meaningful comparisons on that predictor. The 6MWD was scaled so that one unit was equivalent to 150-meters; age to 10 years; total steps to 1,000 steps, and the BDI-II to 4-points. Both hsCRP (4.5 mg/L) and the PQoL (25 points) were scaled to their interquartile ranges (IQR), which allows the coefficient to be interpreted as comparing a "typical" person in the middle of the upper half of the predictor distribution with a "typical" person in the middle of the lower half of the predictor distribution.

Because GOLD is the most widely accepted risk stratification system for COPD patients, we examined the predictive ability of each biomarker after accounting for GOLD 2011 classification in addition to age, Charlson score, and COPD duration. In a final model, we examined the independent association of all biobehavioral predictors simultaneously. Given the number of candidate predictors in relation to the number of events in this final model and, in the interest of parsimony, we followed the recommendations of Steyerberg (34), in which candidate predictors with p-values < 0.50 are maintained in the model and those with p-values ≥ 0.50 are removed. We also used the bootstrap validation procedure in the rms package within R (http://cran.r-project.org/) to evaluate the extent to which overfitting may have produced optimism in overall model fit.(35) Finally, we also examined the extent to which physical activity (total accelerometry steps) and inflammation (hsCRP) explained any observed relationships between psychological predictors (BDI-II and PQoL) and clinical events using the MEDIATION package within R.

Results

Patient Characteristics

Three hundred twenty six individuals were enrolled in the INSPIRE II trial. The majority of participants (77%) were aged 60 years or older (range 38 – 81 yrs), Caucasian, and male (Table 1). Generally, participants had few medical comorbidities and most were not current smokers.

Demographic and Clinical Characteristics and Survival

Sixty-nine individuals experienced a hospitalization or died over a mean follow-up time period of 2.4 (IQR = 1.6) years (range 0.1 to 5.4 years). There was no difference in follow-up times between patients with and without events. The median follow-up time for individuals who did not experience a clinical event was 2.8 (IQR = 1.0) years and was 2.2 (IQR = 1.6) years among individuals who were either hospitalized or died during follow-up (P = .09). Among individuals who died (N=9), three experienced a hospitalization prior to death, which was counted as their first event in the time-to-event analyses. Among the 60 individuals with hospitalizations, 38 individuals were hospitalized once (63%), 12 individuals were hospitalized twice (20%), and 10 individuals were hospitalized three or more times (17%). Similar to results presented in the primary paper, now with a longer follow-up period, there was no difference between CST and COPD-ED in time to death or first COPD-related hospitalization (P = .584).

Examination of demographic and clinical characteristics of patients with and without events revealed that participants with events were older (P = .005), had lower FEV_1 (P < .0001), a longer duration of COPD (P < .001), were more likely to be on supplemental oxygen (P < .0001), and taking prednisone (P = .001) (Table 1).

Biobehavioral Predictors of Survival

Functional Capacity, Physical Activity and BMI—Individuals who experienced a clinical event had lower 6MWD distance (d = 0.77 [95%CI 0.52, 1.02], P < .001), fewer total steps (d = 0.58 [95%CI 0.32, 0.84], P = .016), and fewer moderate intensity steps (d = 0.54 [95%CI 0.28, 0.80], P = .029) (Table 2). Time-to-event analyses revealed that greater 6MWD (HR = 0.54 [95% CI 0.37, 0.80], P = .002), total steps (HR = 0.84 [95% CI 0.73, 0.95], P = .007) and moderate intensity steps (HR = 0.40 [95% CI 0.20, 0.80], P = .01), and higher BMI (HR = 1.04 [95% CI 1.00, 1.08], P = .043) were associated with lower likelihood of a clinical event.

Quality of Life, Depression and Dyspnea—Participants who experienced a clinical event had higher scores on the BDI-II (d = 0.27 [95%CI 0.0, 0.53], P = .023) and SGRQ (d = 0.56 [95%CI 0.30, 0.82], P = .001), and lower PQoL (d = 0.60, [95%CI 0.34, 0.86], P = .004) (Table 2). Separate time-to-event models showed that the BDI-II (HR = 1.14 [95% CI 1.02, 1.27] per every 4 points higher BDI-II score, P = .016), SGRQ (HR = 1.11 [95% CI 1.04, 1.18] per every 4 points higher SGRQ score, P < .001), and PQoL (HR = 1.66 [95% CI 1.11, 2.49] per every 25 point higher PQoL score, P = .015) were each predictive of clinical events.

Inflammation—Participants with clinical events had higher hsCRP (d = 0.49 [95%CI 0.18, 0.79], P = .007) (Table 2). In time-to-event analyses, higher hsCRP (HR = 1.38 [95% CI 0.97, 1.97], P = .078) tended to be associated with a greater likelihood of an event.

Association between GOLD Classification and Biobehavioral Measures: Because the GOLD classification is widely considered to be the 'gold' standard for risk stratification in individuals with COPD, we conducted ancillary analyses in which we evaluated the prognostic value of the individual biomarkers over and above GOLD classification. As shown in Table 3, lower GOLD classification was associated with poorer functional capacity, fewer steps, greater depression, and poorer pulmonary QoL (P's< .01). Consistent with prior studies(14, 25, 26), we found that the relationship between GOLD classification and risk of adverse clinical outcomes was linear (P = .037 for test of linear trend) and therefore modeled GOLD as a continuous predictor (A = 0, B = 1, C = 2, D = 3) (note: results were essentially the same when GOLD was modeled categorically). After controlling for GOLD (which includes FEV_1 and pulmonary symptoms [SGRQ]), age, medical comorbidities, and duration of COPD, 6MWD (HR = 0.50 [95%CI 0.34, 0.73]), P < .001), accelerometry (HR = 0.82 [95%CI 0.71, 0.94], P = .003), hsCRP (HR = 1.44 [95%CI 1.01, 2.06], P = .042), BDI-II (HR = 1.12 [95%CI 1.01, 1.25], P = .039), and PQOL (HR = 1.73 [95%CI 1.14, 2.63], P = .011) were each predictive over and above GOLD (Table 4).

Examination of the magnitude of risk associated with the combined endpoint of death or COPD hospitalizations, quantified as the probability of an event at 3 years, indicated that every 150m lower 6MWD was associated with an 17% greater 3-year probability of an event, every 1,000 fewer steps with a 6% increased probability, every 4.5-point higher CRP level a 10% increased probability, every 4-point higher score on the BDI-II a 4% increased probability, and every 15-point lower score on the PQOL a 9% increased probability of an event. The GOLD index also remained predictive of events in these ancillary models (P's < .032), with each lower GOLD level (e.g., from A to B, B to C, and C to D) associated with a 7–13% increased risk of mortality or hospitalization. These associations tended to remain significant when corrected for multiple testing using the Benjamini-Hochberg False Discovery rate: 6MWD (P = .002), total steps (P = .009), BMI (P = .020), hsCRP (P = .050), BDI-II (P = .050), and PQoL (P = .120).

In a final model controlling for the biobehavioral predictors most predictive of outcomes, only 6MWD (P = .043), and GOLD classification (P = .038) remained predictive, whereas all other predictors were no longer significant (P's > .186). Examination of parameter estimates in our final model suggested that for every one-level decrease in GOLD (i.e., A–D), the 3-year probability of a clinical event increased by 6%, whereas every 150m decrease in 6MWD increased the probability of an event by 14%. The estimated optimism for fit was modest-for this final model (12%), suggesting minimal bias from overfitting.

Mediators of Depression, PQOL, and Clinical Events

In order to better understand the relationship between depression, quality of life, and clinical outcomes, we examined whether levels of physical activity and inflammation explained the relationship between our psychological predictors and subsequent clinical events. We first

examined whether baseline levels of PQOL and the BDI-II were associated with total accelerometry steps. We then examined whether baseline PQOL and BDI-II levels remained predictive of clinical outcomes after controlling for total accelerometry steps in separate models. We found that both higher PQOL (β = .34, P <.0001) and lower BDI scores (β = −.18, P < .001) were associated with greater total accelerometry steps, that the relationships between both PQOL (HR = 1.48, P = .089) and BDI-II (HR = 1.10, P = .090) with clinical events were attenuated after controlling for total accelerometry steps, and the formal tests for mediation were significant (Ps = .03).

We then examined whether the association of PQOL and the BDI-II with clinical outcomes were explained by CRP levels. We found that depressive symptoms assessed by the BDI-II were not associated with hsCRP levels (β = .10, P = .144) and a formal test of mediation could therefore not be examined. In contrast, higher levels of CRP were associated with lower PQoL (β = .16, P = .030) but PQoL remained a significant predictor of events (HR = 1.7, P = .014) after controlling for CRP, which was attenuated (HR = 1.03, P = .519); the formal test for mediation was not significant (P = .20).

Discussion

The results of this study demonstrated the prognostic importance of biobehavioral factors in COPD patients, independent of age and objective measures of COPD severity. Although FEV_1 is widely considered to be the best single measure of disease severity and is prognostic of all-cause mortality,(36) we found that low physical activity and functional capacity, higher BMI, greater dyspnea, increased depression, poorer quality of life, and higher levels of inflammation were each independently associated with worse clinical outcomes over and above age and disease severity determined by standard pulmonary function testing. Previous studies have largely examined the association of each of these biobehavioral risk factors with clinical outcomes individually, including such factors as physical activity,(37) dyspnea,(38) depression,(39) quality of life,(40) 6MWD(15, 41) and CRP.(42–44) One important exception is the ECLIPSE observational cohort(45). This 3-year, prospective, multi-center study of 2180 COPD patients sought to identify potential risk factors for disease progression in patients with different COPD subtypes, as well as biomarkers that serve as intermediate endpoints. Results showed that a prior history of exacerbations was associated with more frequent exacerbations during prospective follow-up across all GOLD categories (46) and that COPD-related hospitalizations were associated with reduced survival. (47) A broad array of biobehavioral measures were obtained, including measures of inflammation, quality of life, functional status, and depression(47); however, the prognostic value of each biobehavioral measure was apparently not considered in the context of the full range of other measures, although some findings were reported individually(48, 49) or were described in relation to GOLD classification.(14) The present study not only examined each of these factors separately, but established their independent prognostic value over and above the GOLD 2011 classification. Furthermore, when all the biobehavioral prognostic factors were considered simultaneously, only reduced functional capacity and greater pulmonary symptoms were significant predictors of clinical outcomes over and above the FEV_1 and age.

We also examined the relation of the biobehavioral measures to GOLD 2011 criteria and confirmed the prognostic significance of GOLD 2011. Increasing severity of GOLD 2011 classification generally was associated with worse biobehavioral risk factors. For example, depression scores were twice as high in GOLD category D compared to Category A (BDI-II = 5.4 vs 11.7) and patients in category A had the greatest exercise tolerance and activity levels, while patients in category D had the poorest exercise tolerance and lowest activity level. We note that the observed differences in 6MWD across GOLD 2011 groups in our INSPIRE-II cohort were similar to both COPDgene(23) and ECLIPSE.(14) The pattern of total daily steps across GOLD 2011 groups revealed that patients in group A were most physically active, while patients in group C were actually slightly more physically active than those in group B, despite having greater airflow obstruction, reaffirming the observation that compromised pulmonary function only partially explains the reduced functional capacity and limited ability to perform activities of daily living in COPD patients.

GOLD classification is determined by way of two independent axes: one determined by symptoms and the other by a combination of airflow obstruction (FEV_1) and prior exacerbation history. GOLD B is characterized by higher prevalence of cough, wheezing and frequent exacerbations driven by airway inflammation, whereas GOLD C tends to have more severe airflow obstruction but comparatively fewer symptoms. Thus, GOLD B patients by definition have more respiratory symptoms than GOLD C, despite higher FEV_1 and may have more comorbidities (thus additional causes for dyspnea and cough) and be more likely to have a “chronic bronchitis” (i.e. inflammatory) phenotype rather than an “emphysema-predominant” phenotype, which is marked by poor lung function but less inflammation. Therefore, GOLD categories B and C can be difficult to distinguish and some studies have shown that patients classified in GOLD B may actually be sicker relative to patients classified as GOLD C.(50) In the present study, GOLD classification was predictive of adverse outcomes when modeled either linearly or categorically.

Even after adjusting for age, duration of COPD, GOLD 2011 classification, and medical comorbidities, a broad range of biobehavioral risk factors were associated with increased risk of COPD-related hospitalization or all-cause mortality, including measures of systemic inflammation, pulmonary quality of life and depression, in addition to physical activity measures as we have previously reported.(51) The significance of these risk factors, even in the context of the established GOLD 2011 risk index, highlights the potential value of biobehavioral factors associated with mortality and COPD-related hospitalization as part of efforts to improve medical outcomes in COPD patients.

Although all of the biobehavioral risk factors that we considered had significant prognostic value over and above GOLD 2011, only functional capacity and accelerometry added significantly to GOLD 2011 once all other biobehavioral variables were included in the model. As reported previously in the INSPIRE-II study population, 6MWD and total daily physical activity are more predictive of combined COPD-related hospitalization or all-cause mortality compared to GOLD 2011 classification.(51) Thus, our findings confirm the importance of functional capacity as an independent risk marker in patients with COPD, even when evaluated in the context objectively measured pulmonary function (i.e., FEV_1) along with of a broader set of biobehavioral risk factors. These findings add to the growing

literature that greater 6MWD is associated with better survival in COPD patients. (15, 51–56) and validate its inclusion as an important and independent predictor of risk over and above impaired pulmonary function and symptom severity.

In addition to the laboratory-based 6MWD measure of functional capacity, we assessed physical activity during routine activities of daily living. Previous studies have shown that physical activity can be measured reliably in COPD patients,(57) is lower in patients with COPD than in controls(58) and in patients with higher scores on the BODE index.(59) Low daily life activity is associated with reduced quality of life,(60) acute exacerbations of COPD,(61) and increased mortality.(62) Both self-reported(56) and accelerometry-measured(61) physical activity have previously been shown to predict acute exacerbations of COPD. Moy et al. reported that daily steps and inflammation were associated with increased acute exacerbations of COPD.(18) Waschki et al.(62) found that physical activity based on step counts and estimated energy expenditure was more strongly associated with mortality compared to FEV_1, SGRQ, and 6MWD. We previously reported that fewer total daily accelerometry steps at baseline were associated with increased risk of COPD-related hospitalization or all-cause mortality among patients in INSPIRE-II;(51) the current report extends these findings, demonstrating that this relationship is independent of other biobehavioral risk factors, including measures of systemic inflammation, depression, pulmonary QoL and burden of other medical comorbidities. Thus, functional capacity as measured by 6MWD and reflected in activity during daily life may provide a useful barometer of risk in COPD patients and actually was used in INSPIRE II to inform activity prescriptions for home exercise.(21) The relationship between improvements in pulmonary symptoms and functional capacity and changes in risk of COPD-related hospitalizations or mortality in interventional studies has not been clearly established. The effect of pulmonary rehabilitation on clinical outcomes has been inconsistent, with no significant mortality benefit in most large controlled studies, but more favorable effects on hospitalization risk.(63–66) Although the CST intervention in INSPIRE-II resulted in improved symptoms and functional capacity, CST did not result in better medical outcomes. It is possible that the magnitude of improvement in these biobehavioral risk factors was not sufficient to improve medical endpoints, or that they were not in the pathway by which CST may affect clinical outcomes. Therefore, the effect of reducing symptoms and increasing functional capacity on clinical outcomes remains an empirical question worthy of further research.

Limitations

Although our sample was relatively large, the number of participants in GOLD 2011 categories A and C were relatively small, which also may have contributed to some of the variability in our findings (e.g., low BDI-II scores and high PQoL scores in category C). However, other studies also have found GOLD B and C to be difficult to distinguish with respect to outcomes.(50) Prior studies also have demonstrated significant within-group variability in risk of COPD exacerbation and related hospitalization in GOLD groups C and D,(14, 23, 24) which may be due to differences in the symptom scale used to assess dyspnea. While we did not use the MRC or CAT to classify patients according to GOLD criteria, the SGRQ correlates strongly with the CAT,(67) and has been used to classify patients into GOLD 2011 groups in prior studies such as GOPDGene.(23) Although prior

exacerbation history was assessed in INSPIRE-II, our categorization scheme precluded the use of the threshold of ≥ 2 exacerbations to define higher risk as in GOLD 2011.

Summary

We have demonstrated that when adjusted for age, comorbidities and history of prior COPD exacerbations, markers of depression, pulmonary symptoms and quality of life, systemic inflammation and functional status and physical activity level are all strongly associated with clinical outcomes. Functional capacity as measured by 6MWD adds predictive value to GOLD 2011 classification with respect to first COPD-related hospitalization or death from any cause, after adjusting for the full range of these biobehavioral risk factors. These findings suggest that somatic symptoms and physical function are important biomarkers of risk in COPD, over and above objective measures of pulmonary function, and that interventions directed at reducing risk through improving symptoms and increasing physical activity need further study.

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Table 1

Demographic characteristics of study sample stratified by the presence of an event during the follow-up time period.

Variable	Full Cohort (n = 326)	No Event (Censored) n = 257)	Event (n = 69)	P-value
Age**	66.1 (8.3)	65.4 (8.3)	68.6 (8.0)	.005
Sex (% Female)	127 (39%)	98 (38%)	29 (42%)	.556
Caucasian, n (%)	285 (87%)	225 (88%)	60 (87%)	.895
Duration of COPD**	5.4 (3.8)	5.0 (3.7)	7.1 (3.7)	<.001
Smoker				
Current†	58 (18%)	51 (20%)	7 (10%)	.061
Former	253 (78%)	197 (77%)	56 (81%)	.425
Never†	15 (5%)	9 (4%)	6 (9%)	.068
FEV_1, % predicted**	45.3 (16.7)	47.7 (16.6)	36.5 (14.5)	<.001
SSRI medication	63 (19%)	45 (17%)	18 (26%)	.127
Other depression medication	34 (10%)	24 (9%)	10 (14%)	.235
Inhaled Corticosteroid	220 (67%)	170 (66%)	50 (72%)	.320
Prednisone**	32 (10%)	18 (7%)	14 (20%)	.001
Supplemental Oxygen (Y/N)**	119 (37%)	74 (29%)	45 (66%)	<.001
Charlson Comorbidity Index	2.5 (2.2)	2.5 (2.2)	2.4 (2.2)	.733
Hx of heart failure	13 (4%)	10 (4%)	2 (4%)	.948
Hx of heart disease	53 (16%)	45 (18%)	8 (12%)	.232
Hx of stroke	26 (8%)	21 (8%)	5 (7%)	.801
Hx of diabetes	56 (17%)	41 (16%)	15 (22%)	.126
GOLD Index (A=0, B=1, C=2, D=3)**	2.15 (1.1)	2.02 (1.1)	2.58 (0.8)	.001

Note: FEV_1 = forced expiratory volume; GOLD = Global initiative for chronic Obstructive Lung Disease. Some percentages may sum to >100% due to rounding.

Table 2

Mean (± SD) Biobehavioral variables as a function of whether patients died or experienced a COPD-related hospitalization over the follow-up period.

Variable	No Event (Censored)	Event	Unadjusted P-value	No Event	Event (Censored)	Adjusted P-value	Cohen's d
	Unadjusted, mean (SD)			Adjusted, mean (SE)			
hs C-Reactive Protein, mg/L	3.4 (3.2)	5.0 (3.6)	.002	3.4 (0.3)	4.9 (0.5)	.006	0.49 (0.18, 0.79)
Body Mass Index, kg/m^2	28.8 (6.4)	29.3 (7.0)	.523	28.5 (0.4)	30.2 (0.8)	.057	0.09 (−0.18, 0.35)
Six Minute Walk Test, m	373 (109)	286 (100)	<.001	364 (6)	320 (12)	<.001	0.77 (0.52, 1.02)
Total Accelerometer Steps	4292 (3062)	2570 (2127)	<.001	4132 (172)	3173 (346)	.013	0.58 (0.32, 0.84)
Pulmonary Quality of Life	82.8 (16.0)	73.4 (12.3)	<.001	81.8 (0.9)	76.8 (1.8)	.010	0.60 (0.34, 0.86)
Beck Depression Inventory II	10.3 (8.4)	12.6 (8.9)	.047	10.2 (0.5)	12.7 (1.1)	.046	0.27 (0, 0.53)
St. George's Respiratory Questionnaire	43.0 (17.8)	52.9 (14.1)	<.001	43.7 (1.0)	50.9 (2.0)	.004	0.56 (0.30, 0.82)

Note: Event-group differences are adjusted for age, Charlson comorbidity index, duration of COPD, FEV_1, and INSPIRE-II treatment group. Unadjusted standardized effect sizes between participants with and without events were examined using Cohen's d. By convention, Cohen's d of 0.2 is considered small, 0.5 is considered medium, and 0.8 is considered a large effect.

Table 3

Mean Biomarker Measures (± SD) as a function of GOLD Classification.

Variable	GOLD A (n=27)	GOLD B (n=91)	GOLD C (n=17)	GOLD D (n=191)	P-value
hs C-Reactive Protein, mg/L	3.0 (3.6)	3.5 (3.4)	3.0 (2.6)	4.1 (3.4)	.178
Body Mass Index, kg/m^2	27.7 (4.4)	30.8 (7.1)	25.5 (5.0)	28.4 (6.4)	.721
Six Minute Walk Distance, m	472 (75)	392 (105)	435 (79)	313 (102)	<.001
Accelerometry Total Steps	6791 (3568)	4216 (2797)	5456 (3133)	3247 (2634)	<.001
Pulmonary Quality of Life Scale	101.8 (7.7)	82.2 (13.2)	102.0 (7.6)	75.3 (14.0)	<.001
Beck Depression Inventory-II	5.4 (4.9)	11.8 (8.4)	3.4 (2.9)	11.7 (8.8)	<.001

Note: P-values represent differences between groups A and D; variables are expressed as mean (SD).

Table 4

Relationship between individual biobehavioral predictors and the combined endpoint of COPD-related hospitalization or death.

Variable	Model 1: 6MWD	Model 2: Accelerometry	Model 3: BMI	Model 3: CRP	Model 4: BDI-II	Model 5: PQOL	Model 6: Multivariate Model
Age	1.29	1.31	1.51*	1.57*	1.58*	1.51*	1.31
Charlson	0.94	0.95	0.94	0.94	0.95	0.97	0.93
Duration of COPD	1.07†	1.08*	1.10**	1.05	1.09*	1.07†	1.07†
GOLD	1.39*	1.44*	1.68**	1.73**	1.60**	1.46*	1.39*
Coping Skills Training	1.18	1.17	1.10	1.06	1.14	1.18	----------
6MWD	0.50**	----------	----------	----------	----------	----------	0.62*
Total Steps		0.82**	----------	----------	----------	----------	0.93
BMI			1.03	----------	----------	----------	----------
Prednisone or ICS				1.02	----------	----------	----------
hsCRP				1.44*	----------	----------	1.13
BDI-II					1.12*	----------	----------
PQOL						1.74**	1.08

Note: Biobehavioral predictors are shown in the far left column with each individual predictive model in a unique column. All models were adjusted for age, medical comorbidities, duration of COPD, and GOLD classification. Values are hazard ratios. After examining each individual biobehavioral predictor, a final model is reported in the far right column using predictors initially associated with clinical outcome P < .50. BDI-II = Beck Depression Inventory-II; BMI = Body Mass Index; COPD = chronic obstructive pulmonary disease; hsCRP = high sensitivity C-Reactive Protein; GOLD = Global initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids; PQOL = Pulmonary Quality of Life Scale. 6MWD is scaled in 150 meter increments; age is scaled by 10-year increments; total steps are scaled by 1,000 steps; BDI was scaled by 4-point increments; CRP was scaled in 4.5-point increments; GOLD was scaled in 1-point increments (A = 0, B = 1, C = 2, D = 3); PQOL was scaled in 25-point increments.

†P ≤ .10;

*P ≤ .05;

**P ≤ .01.

Note: Models 1–6 adds a single predictor to the model after accounting for age, Charlson score, duration of COPD, and GOLD score. Model 6 examines the influence of all biomarkers simultaneously.