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Predictors of All-Cause Mortality in Patients With Severe COPD and Major Depression Admitted to a Rehabilitation Hospital

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BACKGROUND: COPD is a major cause of all-cause mortality. We examined predictors of 1-year mortality in patients with severe COPD and major depression after inpatient treatment in a rehabilitation hospital.

METHODS: We screened 898 consecutively admitted patients. Of these, 138 patients received the diagnoses of COPD according to American Thoracic Society Guidelines and major depression by *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* and signed consent; 67 were randomized to a treatment adherence enhancement intervention and 71 to usual care. We assessed history of falls, dyspnea-related disability, severity of depression, medical burden, and cognitive functioning. Following discharge from inpatient rehabilitation, participants were prospectively followed, and mortality was ascertained over 52 weeks from hospital notes and reports of primary care physicians and relatives.

RESULTS: One-year, all-cause mortality was 22% (31 of 138). Multivariate Cox regression analysis showed that history of falls in the 6 months preceding hospital admission was the strongest predictor of mortality (OR, 3.05; 95% CI, 1.40-6.66; $P < .005$). Dyspnea during activities (Pulmonary Functional Status and Dyspnea Questionnaire-Modified domain) was also associated with mortality (OR, 1.05; 95% CI, 1.02-1.08; $P < .002$). Depression severity, medical burden, and cognitive impairment were not predictors of mortality.

CONCLUSIONS: Recent falls and dyspnea during activities identify subgroups of depressed patients with COPD at increased risk for all-cause mortality. These subgroups are in need of clinical attention and follow-up and can serve as targets for prevention research aiming to inform clinical strategies and public health planning. CHEST 2016; 149(2):467-473

KEY WORDS: COPD; depression; dyspnea; falls; mortality

ABBREVIATIONS: CCI = Charlson Comorbidity Index; HAM-D = Hamilton Depression Rating Scale; PFSDQ-M = Pulmonary Functional Status and Dyspnea Questionnaire-Modified; PID-C = personalized intervention for depression and COPD; WHODAS-II = World Health Organization Disability Assessment Schedule-II

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COPD is a major cause of mortality worldwide.[1,2] COPD is the only common chronic disease in which mortality has continued to increase over the past 30 years.[3] Currently, COPD is the fourth most frequent cause of death in the United States, and its prevalence is increasing in women and minorities. Twenty-four percent of patients with COPD have major depression, and another large percentage have milder depressive syndromes or symptoms.[4-6]

Depression may be associated with higher excess mortality in COPD than in other medical diseases. A recent comprehensive meta-analysis of 293 studies and 1,813,733 participants confirmed the association of depression with excess mortality, with a relative risk of 1.52. Depression-related excess mortality was comparable across individuals with heart disease, cancer, kidney disease, and other diseases.[5] An exception was COPD, in which depression conferred a disproportionately higher mortality risk than in other diseases. In addition to increasing all-cause mortality,[5] depression afflicting patients with COPD is associated with worse general and pulmonary health and greater disability.[7,8]

Given the high mortality of depressed patients with COPD, identifying predictors of mortality in such patients may inform clinical practice and public health prevention strategies. We sought to identify predictors of all-cause mortality in patients with severe COPD with major depression admitted to a rehabilitation hospital who participated in a treatment adherence intervention trial. This analysis tested the hypotheses that indices of overall disability, including falls, dyspnea-related disability, medical burden, and cognitive impairment, as well as depression severity predict increased all-cause mortality.

Materials and Methods

This analysis is based on data of a randomized clinical trial (1:1 ratio) comparing personalized intervention for depression and COPD (PID-C) with usual care.[9,10] PID-C is a manualized treatment that consists of individualized behavioral interventions targeting adherence to treatments for both depression and COPD prescribed by the patients' own physicians. The first session of PID-C was conducted prior to hospital discharge and the rest in the patients' homes by the social workers at weeks 3, 4, 8, 12, 16, 20, 24, and 26.

Details on participant flow and primary outcomes have been published earlier.[9,10] Briefly, 898 patients admitted to the inpatient pulmonary unit of a rehabilitation hospital were screened. Of these, 138 patients met criteria for COPD and major depression and signed informed consent approved by the Institutional Research Board of Weill Cornell Medical College.

The diagnosis of COPD was made by a pulmonologist after clinical examination and lung function tests based on the American Thoracic Society guidelines.[11] The diagnosis of major depression was made after a structural clinical interview (SCID R) according to *the Diagnostic and Statistical Manual of Mental Disorders, 4th edition* criteria.[12] Patients with *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* diagnoses other than unipolar major depression (except anxiety disorders and dysthymia) or severe cognitive impairment (Mini-Mental State Examination[13] score $\leq$ 20) were excluded.

Research Assessments

Severity of depression was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D).[14] A history of falls in the 6 months preceding entry was obtained from patient interviews. Patients were asked: "Have you fallen during the last 6 months?" If a fall was reported, patients were asked to detail the circumstances of the fall and any resultant injury using a standardized questionnaire.

Dyspnea-related disability was quantified with the Functional Status and Dyspnea Questionnaire-Modified (PFSDQ-M), an interviewer-administered scale consisting of three domains: dyspnea during activities, fatigue caused by activities, and change in activities related to dyspnea.[15] A subdomain score, ranging from 0 to 100, is calculated for each of the three domains. Higher PFSDQ-M scores correspond to greater dysfunction. PFSDQ-M has good psychometric properties and significant correlations with FEV_1 and "dyspnea" quantified with the Medical Council Dyspnea Scale.[16,17] Medical burden was quantified with the Charlson Comorbidity Index (CCI).[18] The World Health Organization Disability Assessment Schedule (WHODAS-II) was used to determine overall functional disability.[19] Mortality was ascertained by contacting the patients' homes and from notes of their primary care physicians or hospital records.

Data Analysis

Baseline demographic and clinical variables between those who died and those who remained alive 1 year after entry were compared using *t* tests or χ^2. Univariate Cox regression analyses were performed to further assess the relationship of each baseline demographic and clinical variable to mortality.

Multivariate Cox regression was used to identify predictors of mortality. The model included history of falls and each of the three dyspnea-related domains (PFSDQ-M domains: dyspnea during activities, fatigue caused by activities, and change in activities). We also examined whether removing age, sex, HAM-D, CCI, and WHODAS-II one domain at a time or all together improved the mortality model's fit using likelihood ratio χ^2 test. We retained age, sex, overall medical burden (CCI), and severity of depression (HAM-D) in the final multivariate model because they may influence mortality.[20] Interactions between history of falls and individual PFSDQ-M domains were included in the model to evaluate significance and assess improvement in model fit. Analyses were conducted with R 3.0.1[21] R/rms, Regression Modeling Strategies,[22] and SAS 9.3 (SAS Institute Inc). Two-tailed significance was set at 5%.

Results

Participants with COPD and major depression (N = 138) were followed for 1 year. They were aged 52 to 89 years (mean = 71.4, SD = 8.1). Ninety-one (66%) were women. In addition to major depression, 15.2% (21 of 138) of participants also had dysthymia, 10.1% (14 of 138) generalized anxiety disorder, and 11.6% (16 of 138) panic disorder.

By the end of 1 year, 31 participants had died (22%). There were no significant differences in mortality between those receiving the PID intervention and those receiving usual care ($\chi^2 = 0.182$, degrees of freedom = 1, $P = .669$). Baseline demographic and clinical characteristics were similarly distributed among those who survived and those who died, including pulmonary functions, overall medical burden severity of depression, cognitive impairment, dyspnea-related disability, and overall disability (Table 1).

Fifty patients (36%) had a history of falls in the 6 months prior to study entry. Of these, 22% (11 of 50) had no injury, 42% (21 of 50) had only minor injuries not requiring medical attention, and 36% (18 of 50) required attention (eg, sutures, treatment of fractures, or hospitalization). There was no difference in number of medications taken at baseline between those who had history of falls and those without (mean [SD], 10.72 [3.10] vs 11.38 [3.94]; $t = -1.07$; $P = .285$).

Univariate Cox regression analysis of demographic and clinical variables showed that history of falls during the 6 months prior to study entry was a predictor of mortality (Table 2). Multivariate analysis confirmed that history of falls within 6 months prior to entry was a significant predictor of mortality with a threefold increase in the hazard of death (Fig 1, Table 3). Dyspnea during activities (PFSDQ-M domain) was also a significant predictor of mortality. For every additional point on the dyspnea during activities domain, the hazard of mortality increased by 4.7%. Therefore, a depressed participant with COPD with a dyspnea score 1 SD above the mean of 49.7, (SD, 22.29) had 105% higher risk of mortality than a participant with a score at the mean. Removing age, sex, HAM-D, CCI, and WHODAS-II one domain at a time or all together did not improve the mortality model's fit using likelihood ratio χ^2 test. Age, sex, medical burden, and severity of depression were retained in the final multivariate model as they could influence mortality.[20] Interactions between history of falls and individual PFSDQ-M domains were not statistically significant and did not improve the model's fit. The above analysis was repeated using the PFSDQ-M total score instead of individual PFSDQ-M domains in the model. The hazard for the total PFSDQ-M score was not significant ($P = .21$).

Discussion

The principal finding of this study is that falls occurring 6 months preceding inpatient rehabilitation led to a threefold increase in 1-year all-cause mortality in patients with severe COPD and major depression. Dyspnea during activities increased mortality risk

TABLE 1] Baseline Characteristic of 138 Patients With an Exacerbation of COPD and Major Depression Followed for 12 Months

Variables	Died, Mean (SD) (N = 31)	Alive, Mean (SD) (n = 107)	Statistics	*P* Value
Sex, male (female)	9 (22)	36 (69)	$\chi^2 = 0.29$	.585
Age, y	71.87 (6.45)	70.49 (8.50)	$t = -0.83$	.407
FEV_1, L	0.79 (0.29)	0.87 (0.40)	$t = 0.67$	.506
FEV_1 %	0.34 (0.11)	0.37 (0.16)	$t = 0.69$	.492
Charlson Comorbidity Index	3.34 (2.13)	3.10 (2.06)	$t = -0.57$	.570
HAM-D	18.97 (3.34)	19.14 (2.90)	$t = 0.28$	.777
MMSE	27.48 (2.14)	27.39 (1.85)	$t = -0.23$	.820
PFSDQ-M dyspnea during activities	55.63 (18.34)	48.24 (23.31)	$t = -1.57$	.118
PFSDQ-M fatigue during activities	49.35 (19.85)	49.86 (21.88)	$t = 0.11$	.909
PFSDQ-M change in activities	54.06 (22.77)	52.40 (22.21)	$t = -0.35$	.724
PFSDQ-M total	159.0 (53.55)	150.5 (61.93)	$t = -0.67$	.502
WHODAS-II	38.19 (7.48)	37.51 (6.31)	$t = 0.70$	. 48

HAM-D = 17-item Hamilton Depression Rating Scale; MMSE = Mini-Mental State Examination; PFSDQ-M = Pulmonary Functional Status and Dyspnea Questionnaire-Modified; WHODAS-II = World Health Organization Disability Assessment Schedule II.

TABLE 2] Univariate Cox Regression Analysis of 1-Year Predictors of Mortality in Participants With Exacerbated COPD and Major Depression

Variables	HR	$\chi^2(1)$	*P* Value	95% CI
Sex	0.89	0.096	.76	0.41-1.91
Age	1.03	1.30	.25	0.98-1.08
Falls within 6 mo from entry	2.19	4.87	.03	1.09-4.39
PFSDQ-M dyspnea during activities	1.01	2.46	.12	0.997-1.03
PFSDQ-M fatigue during activities	1.00	0.03	.86	0.98-1.02
PFSDQ-M change with activities	1.00	0.09	.77	0.99-1.02
PFSDQ-M total score	1.00	0.41	.52	0.996-1.008
Charlson Comorbidity Index	1.03	0.13	.72	0.87-1.23
MMSE	0.96	0.18	.67	0.79-1.16
WHODAS-II	1.02	0.39	.53	0.97-1.07
HAM-D	0.98	0.15	.70	0.87-1.10

$\chi^2(1) = \chi^2$ statistic with 1 degree of freedom; HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

independently of history of falls; a participant with a "dyspnea during activities" score 1 SD above the mean had 105% higher mortality risk than a participant with a score at the mean. These observations suggest that history of falls and dyspnea during activities identify vulnerable depressed COPD subgroups in need of careful medical attention and follow-up. Although PID-C led to a higher remission rate of depression and greater improvement of dyspnea-related disability than usual care,[9] it did not influence mortality in this sample.

To our knowledge, this is the first prospective study of clinical predictors of mortality in patients with severe COPD and major depression, a population with a high mortality rate.[5,23,24] Most studies of depressed patients with COPD have included outpatients with depressive symptoms rather than major depression and report lower mortality than that of our sample.[5] However, the mortality rate in our sample of inpatients with COPD with major depression (22% in 12 months) is consistent with that of a national population-based study of patients hospitalized for first-ever COPD exacerbations.[25]

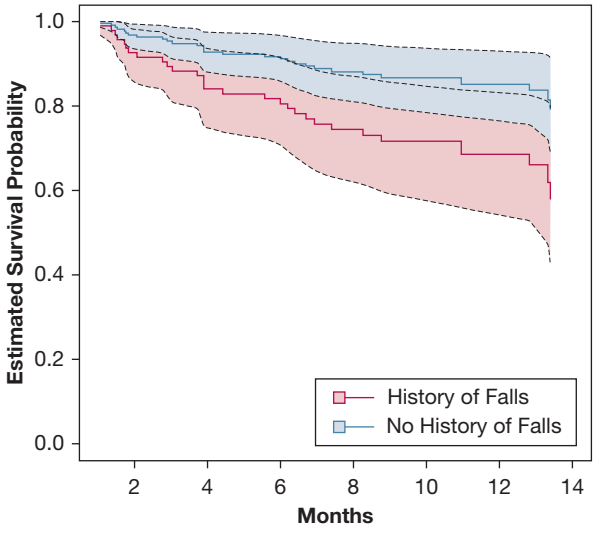

Figure 1 – *Survival curves estimated from a multivariate Cox model for participants with COPD and major depression with and without history of a fall, after adjusting for dyspnea-related disability (Pulmonary Functional Status and Dyspnea Questionnaire-Modified) domains (held at the mean value for each group).*

TABLE 3] Multivariate Analysis of 1-Year, All-Cause Mortality in Patients With an Exacerbation of COPD and Major Depression

Variables	HR	$\chi^2(1)$	*P* Value	95% CI
Sex, male vs female	0.68	0.69	.408	0.28-1.68
Age	1.04	2.54	.111	0.99-1.10
HAM-D	1.00	0.00	.969	0.88-1.14
Baseline Charlson total	0.99	0.02	.888	0.83-1.18
Falls status at baseline	3.05	7.82	.005	1.40-6.66
PFSDQ dyspnea during activities	1.05	9.59	.002	1.02-1.08
PFSDQ fatigue during activities	0.98	3.66	.056	0.95-1.00
PFSDQ change in activities	0.99	0.50	.479	0.96-1.02

See Table 1 and 2 legends for expansion of abbreviations.

Unlike osteoporosis, in which the most common cause of mortality is fractures,[26,27] mortality related to COPD is multifactorial and includes exacerbations of COPD, respiratory infections, and worsening of other medical illnesses that are commonly comorbid with COPD, including coronary artery disease, heart failure, hypertension, and stroke.[25,28,29] Literature in nondepressed patients with COPD has shown that advanced age, overall medical burden, exercise tolerance, daily physical activity, home oxygen therapy use or noninvasive mechanical ventilation, altered mental status, and use of inspiratory accessory muscles or paradoxical breathing are associated with mortality on follow-up.[25,30-32] These findings suggest that overall debility predicts mortality in patients with COPD.

Identifying the mechanisms by which recent history of falls increases mortality in depressed patients with COPD is beyond the scope of this analysis. One possibility is that falls constitute a composite index of frailty in a depressed, medically compromised, chronically ill population. The lack of an association of mortality with overall disability, medical burden, and cognitive impairment suggests that falls capture a broader dimension of ill health than each of these parameters alone. A related path from falls to increased mortality may involve inactivity. Falls increase "fear of falling"[33] and enhance the perception of dyspnea,[34] which, combined with physiologic causes of dyspnea, may increase inactivity, reduce self-efficacy (sense of being in control),[35] and worsen depression. The net effect of these processes is demoralization, giving up efforts at rehabilitation and socialization and promoting a spiral of physical deterioration leading to death. A similar mechanism may explain the relationship of dyspnea during activities with mortality. This view is consistent with studies of nondepressed COPD populations in whom dyspnea-related limitation of activities predicted mortality at 12 months in patients with moderate to severe COPD.[36,37]

Depression severity at entry did not influence mortality in this sample. A study of depressed and nondepressed patients with congestive heart failure documented that the diagnosis of major depression was associated with increased mortality.[38] Unlike this study, all our participants suffered from major depression with a narrow range in severity of depressive symptoms and signs.

PID-C did not reduce mortality in these participants, although PID-C was more effective than usual care in improving depression and dyspnea-related disability over a period of 1 year.[9,10] This is an intriguing finding suggesting that improvement of depression and dyspnea are insufficient to decrease mortality. A potential explanation for the failure of PID-C to reduce mortality is that PID-C is focused on patient adherence to treatment and did not adequately influence clinical decisions related to mortality, which were made by the patients' own physicians.

Limitations of this study include its relatively small sample and the rather short follow-up. However, the high mortality rate (22%) suggests that the sample and the study duration captured the outcome of interest in this vulnerable population. Our assessment of falls and of causes of death does not allow definitive conclusions of the mechanisms by which falls are linked to mortality. History of falls relied on interviewing patients during an exacerbation of COPD and may have been unreliable to some extent. However, the participants of this study did not have severe cognitive impairment (Table 1). The study did not assess the causes of falls, some of which might have been due to factors unrelated to debility, including sedation and a poorly arranged home setup. Further, the causes of death were reported by either the participants' relatives or their primary care physicians. Some of this information may have been unreliable. For these reasons, the study can only assert that there is an association between falls and all-cause mortality but cannot provide information about mechanisms explaining this relationship.

Conclusions

In this study of patients with severe COPD and major depression, history of falls was associated with a threefold increase in the risk of 12-month all-cause mortality. Dyspnea during activities was an independent predictor of mortality. COPD is perhaps the chronic medical illness with the strongest deleterious interaction with depression leading to death.[5] An intervention increasing adherence to treatment of COPD and depression prescribed by the patients' own physicians did not lower mortality, although it improved both depression and dyspnea-related disability. This observation suggests the need for novel appropriately targeted interventions. The subgroups of depressed patients with COPD with history of falls and dyspnea during activities require clinical attention and follow-up and can serve as a target for prevention research aiming to inform clinical strategies and public health planning.

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Author contributions: A. M. Y. has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. A. M. Y. contributed to data analysis and manuscript preparation and reviewing the final submission. P. J. R., J. A. S., and R. S. N. contributed to the development of research design, data analysis, and manuscript writing; D. K. and J. K. S. contributed to data management and analysis and manuscript writing; A. M., D. N. K., and S. B. contributed to data analysis and manuscript writing; G. S. A. was the principal investigator of the NIMH grant that supported this study and contributed to the development of research design, data analysis, and manuscript writing.

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