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ORIGINAL RESEARCH

Cognitive status among patients with chronic obstructive pulmonary disease

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Purpose: We investigated the association between cognitive impairment and chronic obstructive pulmonary disease (COPD), taking into account demographic and clinical variables evaluated during routine practice.

Patients and methods: We performed a post hoc analysis of a cross-sectional study that included subjects with stable COPD. Sociodemographic and clinical information was recorded using the Body mass index, airflow Obstruction, Dyspnea and Exacerbations index and the Charlson comorbidity index. Cognitive performance was studied by the mini-mental state examination, with a score less than 27 indicating clinical impairment. Depressive symptoms, physical activity, and quality of life (EuroQoL-5 dimensions and COPD Assessment Test) were also evaluated.

Results: The analysis included 940 subjects. The prevalence of cognitive impairment was 39.4%. Multivariate logistic regression models revealed that cognitive impairment was associated with educational level (odds ratio [OR] =0.096, 95% confidence interval [CI] =0.011–0.447) and poorer quality of life measured by the EuroQoL-5 dimensions social tariff (OR =0.967, 95% CI =0.950–0.983). When questionnaires were not included in the analysis, cognitive impairment was associated with educational level (OR =0.063, 95% CI =0.010–0.934), number of exacerbations (OR =11.070, 95% CI =1.450–84.534), Body mass index, airflow Obstruction, Dyspnea and Exacerbations index score (OR =1.261, 95% CI =1.049–1.515), and the Charlson comorbidity index (OR =1.412, 95% CI =1.118–1.783).

Conclusion: Cognitive impairment is common in COPD and is associated with low educational level, higher disease severity, and increased comorbidity. This could have therapeutic implications for this population.

Keywords: chronic obstructive pulmonary disease, cognitive function, mini-mental state examination, depression, quality of life, comorbidity

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive and partially reversible airflow limitation, and it is among the leading causes of mortality worldwide.[1] COPD is a multicomponent disease, and patients present a range of comorbidities that have an impact on prognosis and may increase the risk of mortality.[2] The effects of COPD on respiratory and physical function have been well studied; moreover, due to the heavy burden of psychological disturbance, psychiatric morbidity, and disability in daily life, the mental health of COPD patients has received growing attention in recent years.[3,4] The prevalence of cognitive impairment in patients with COPD ranges from 12% to 88%[5] and is associated with depression, poor quality of life, which may affect patients' ability to manage their disease, and reduced compliance with medication and oxygen therapy,[6,7] leading to adverse clinical outcomes.[8–11]

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Therefore, cognitive function as well as emotional function are important aspects of the overall clinical care of patients with COPD.

It has been suggested that a multidimensional assessment and personalized disease management approach could be an optimal strategy for addressing comorbidities, self-management education, and risk factor modification in COPD patients.[7] The early identification of cognitive dysfunction is critical if outcomes are to be improved in this population, and an understanding of the characteristics associated with a higher risk of cognitive impairment may assist health care professionals to address this challenge.

The primary aim of this study was to examine the cross-sectional prevalence of cognitive impairment in an unselected population of COPD patients; the secondary objective was to determine the relationships between cognitive impairment and major demographic and clinical variables, such as lung function, depression, and quality of life.

Materials and methods

Study design and sample

The present study is a post hoc analysis of a cross-sectional, observational study conducted in respiratory medicine departments and primary care centers in Spain.[11] This study was aimed at examining the prevalence of depressive symptoms and moderate-to-severe depression in COPD and included ambulatory patients who were 40 years of age or older, with stable COPD (confirmed by postbronchodilator forced expiratory volume in 1 second/forced vital capacity $<70\%$ and absence of exacerbations in the previous 3 months). All patients that completed the mini-mental state examination (MMSE) were included in this post hoc analysis. The study was approved by the Institutional Ethics Committee of the Hospital Clinic (Barcelona, Spain) and was conducted in accordance with the principles of the Declaration of Helsinki. Prior to participation, all patients signed written documentation that the informed consent process was completed.

Study assessments

Investigators recorded patients' sociodemographic data and clinical information on COPD severity using the Modified Medical Research Council Dyspnea scale[12] and the Body mass index, airflow Obstruction, Dyspnea and Exacerbations (BODEx) index,[13] comorbidity according to the Charlson index,[14] exacerbations in the previous year, and treatment. Cognitive status was assessed by the MMSE,[15,16] widely used to screen for cognitive impairment. This instrument explores spatial and temporal orientation, registration, attention, and calculation, recall, language, and visual construction in 12 items and 30 questions. A correct answer to one question was given 1 score point (total from 0 to 30). A score of less than 27 indicated cognitive impairment.[17]

Depressive symptoms were measured using the short Beck Depression Inventory questionnaire.[18,19] This tool is a 13-item self-administered inventory that assesses affective, cognitive, motivational, and vegetative symptoms of depression. Items use a 4-point scale that ranges from 0 to 3 and a total score is calculated by adding up the item responses. An additional question was included about suicidal ideation and suicidal attempts.

Health-related quality of life was assessed by the generic EuroQoL-5 dimensions (EQ-5D) questionnaire and the specific COPD Assessment Test (CAT). The EQ-5D consists of a 5-item descriptive system (including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with each item rated as no problems, some problems, or severe problems, and an overall health state score for the day of the assessment, measured on a visual analog scale (0–100; 100 represents best overall health).[20] The CAT is a short, specific quality of life questionnaire for measuring the impact of COPD on the patient's well-being and daily life. It consists of eight items, each presented as a 6-point semantic differential scale, providing a score out of 40, indicating the impact of the disease.[21] We used the validated Spanish version of CAT.[22] Physical activity was measured by asking patients how many minutes, on average, they walked every weekday, as previously described.[23,24] Depending on their daily walking activity, patients were classified into three groups: patients who walked <30 minutes, patients who walked between 30 and 60 minutes, and patients who walked ≥ 60 minutes.

Statistical analysis

Continuous variables were expressed as the mean and the standard deviation. Categorical values were described as absolute and relative frequencies. Fisher's exact test was used for comparisons of qualitative variables, with the Bonferroni correction for all pairwise comparisons. Student's *t*-test was used to determine the relationship between qualitative variables by group. Odds ratio (OR) univariates were calculated by logistic regression to evaluate the different risks contemplated in the study, including all demographic, clinical, and questionnaires variables. Only significant associations are shown in the Tables 2 and 3. After stepwise analysis, the various adjusted ORs were calculated using multivariate logistic regression. The first model was developed with cognitive status as a dependent variable and all variables that showed a significant association with cognition in univariate

analysis as independent variables (model 1). A second model (model 2) excluded any variables derived from the use of the questionnaires from the independent variables. The objective of model 2 was to identify the factors associated with cognitive impairment that could be identified in routine clinical practice without the administration of questionnaires.

All statistical tests were considered significant when P was <0.05. Statistical analyses were performed using SAS version 9.1.3 Service Pack 3 software (SAS Institute Inc., Cary, NC, USA).

Results

Sample characteristics and cognitive status

Of 1,273 screened patients, 333 had not had the MMSE evaluation and were excluded from the analysis. Both populations (excluded and included ones) were compared and their characteristics are described in Table 1. Included patients were predominantly male, with an age ranging from 40 to 90 years. A total of 370 patients (39.4%) scored below the threshold of 27 for suspicion of mild cognitive impairment

Table 1 Characteristics of all patients with and without cognitive impairment according to MMSE scores

Variable	Excluded patients	Included patients	MMSE <27	MMSE ≥27	*P*-value
Sex, males (n, %)	233 (73.1%)[a]	762 (81.6%)	299 (81.7%)	463 (81.5%)	>0.99
Age, years (mean, SD)	66.8 (9.4)	67.7 (10.0)	69.6 (9.5)	66.5 (10.1)	<0.001
Coexistence (n, %)					
Alone	55 (17.1%)	121 (13.0%)	50 (13.6%)	71 (12.5%)	<0.001[b]
With partner	212 (66.0%)	646 (69.2%)	224 (61.0%)	422 (74.4%)	
With family	47 (14.6%)	141 (15.1%)	75 (20.4%)	66 (11.6%)	
Institutionalized	1 (0.3%)	12 (1.3%)	8 (2.2%)	4 (0.7%)	
With professional caregiver	6 (1.9%)	14 (1.5%)	10 (2.7%)	4 (0.7%)	
Educational level (n, %)					
Basic literacy	47 (14.7%)[a]	74 (7.9%)	42 (11.4%)	32 (5.7%)	<0.001[c]
Primary level	190 (59.6%)	540 (57.9%)	251 (68.4%)	289 (51.1%)	
Secondary level	62 (19.4%)	193 (20.7%)	52 (14.2%)	141 (25.0%)	
Completed university	20 (6.3%)[a]	125 (13.4%)	22 (6.0%)	103 (18.2%)	
COPD duration (mean, SD)	10.4 (6.4)	11.6 (7.7)	12.9 (8.0)	10.8 (7.4)	<0.001
Active smoker (n, %)	77 (25.8%)	206 (22.4%)	66 (18.4%)	140 (25.0%)	>0.99
Pack-years (mean, SD)	37.1 (20.4)	39.5 (21.8)	42.3 (24.8)	37.7 (19.4)	0.002
BMI (mean, SD)	27.5 (4.7)	27.8 (4.7)	27.9 (4.7)	27.7 (4.7)	0.52
Postbronchodilator spirometry (mean, SD)					
FVC, mL	2,945 (977)	3,046 (977)	2,912 (922)	3,132 (1,001)	0.001
FVC, %	65.4 (21.2)[a]	71.0 (17.0)	71.3 (15.8)	70.8 (17.70)	0.55
FEV_1, mL	1,805 (846)	1,886 (852)	1,778 (767)	1,957 (897)	0.002
FEV_1, %	54.4 (21.0)	55.2 (17.8)	55.7 (17.9)	54.9 (17.7)	0.59
FEV_1/FVC	56.6 (16.0)	58.5 (20.9)	57.2 (13.8)	59.4 (24.4)	0.13
Cough (n, %)	264 (85.7%)	770 (83.2%)	322 (89.7%)	448 (79.1%)	<0.001
Expectoration (n, %)	233 (78.4%)	669 (73.0%)	286 (79.7%)	383 (68.7%)	<0.001
Dyspnea, (n, %)	296 (94.0%)	891 (95.0%)	359 (97.5%)	532 (93.3%)	0.003
mMRC dyspnea score (mean, SD)	2.8 (0.9)	2.8 (0.9)	3.1 (0.9)	2.6 (0.9)	<0.001
Patient with exacerbations (n, %)	265 (79.6%)[a]	808 (86.0%)	351 (94.9%)	457 (80.2%)	<0.001
Number of hospital-treated exacerbations (emergency + admission) (mean, SD)	1.3 (0.5)[a]	1.4 (2.2)	1.8 (2.7)	1.0 (1.5)	<0.001
Oxygen therapy at home, (n, %)	65 (23.0%)	204 (23.4%)	130 (37.0%)	74 (14.2%)	<0.001
BODEx (mean, SD)	2.7 (1.8)	2.8 (1.9)	3.3 (1.8)	2.4 (1.9)	<0.001
Charlson comorbidity index (mean, SD)	1.3 (1.4)[a]	1.4 (1.4)	1.6 (1.5)	1.0 (0.6)	<0.001
BDI score (mean, SD)	9.3 (6.1)	9.0 (6.5)	11.7 (6.4)	7.2 (5.7)	<0.001
Suicidal ideation (n, %)	29 (9.4%)	123 (13.1%)	78 (21.2%)	45 (7.9%)	<0.001
Health status according to EQ-5D (mean, SD)	57.9 (17.1)	57.4 (19.2)	52.4 (18.2)	60.5 (19.2)	<0.001
Social tariff EQ-5D (mean, SD)	0.6 (0.2)	0.6 (0.2)	0.5 (0.2)	0.7 (0.2)	<0.001
CAT score (mean, SD)	21.6 (7.3)	21.6 (8.6)	25.2 (6.9)	19.3 (8.7)	<0.001
Physical activity grade (mean, SD)	4.1 (1.6)	4.3 (1.5)	3.7 (1.4)	4.6 (1.5)	<0.001
Minutes walked per day (mean, SD)	73.5 (68.2)[a]	64.2 (52.3)	56.1 (45.8)	68.8 (55.2)	0.001

Notes: [a]Excluded vs included patients. [b]Alone vs professional caregiver. [c]Basic literacy vs completed university.

Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index; BODEx, Body mass index, airflow Obstruction, Dyspnea and Exacerbations index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; EQ-5D, EuroQoL-5 dimensions; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, Modified Medical Research Council scale; MMSE, mini-mental state examination; SD, standard deviation.

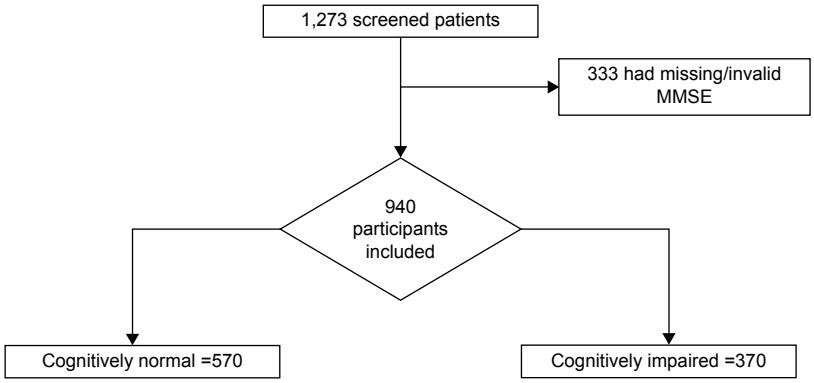

Figure 1 Flow diagram for the analysis.
Abbreviation: MMSE, mini-mental state examination.

(MCI; Figure 1). Patients with MMSE scores <27 were older, had a lower level of formal education, had heavier smoking exposure, presented more respiratory symptoms, had more frequently domiciliary oxygen, suffered a higher number of and more severe exacerbations during the previous year, and had a greater comorbidity burden. In addition, higher levels of depression, more suicidal ideation, poorer quality of life, and less physical activity were more frequent in cognitively impaired patients.

Factors associated with the presence of cognitive impairment

In the univariate analysis, cognitive impairment was associated with higher age, lower educational level, worse lung function and more severe COPD, more frequent respiratory symptoms and exacerbations, and oxygen therapy requirement. Higher comorbidity burden, more depressive symptoms, and more impaired health status (EQ-5D and CAT) were also associated with cognitive impairment. Higher levels of physical activity were associated with better cognitive function (Table 2).

In the multivariate analysis, only educational level and the EQ-5D social tariff were independently and significantly associated with cognitive impairment (Table 2). When the analysis was limited to the usual demographic and clinical variables, and the questionnaires were excluded from the model, the significant factors in the multivariate analysis were educational level, history of exacerbations,

Table 2 Factors associated with cognitive impairment in univariate and multivariate analysis

Variable	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (per 5-year increment)	1.177	1.099–1.262	<0.001			
Educational level (completed university vs basic literacy)	0.160	0.080–0.310	<0.001	0.069	0.011–0.447	0.014
Postbronchodilator FVC	0.977	0.963–0.991	0.001			
Postbronchodilator FEV_1	0.975	0.959–0.991	0.003			
Cough	2.290	1.540–3.410	<0.001			
Expectoration	1.780	1.300–2.430	<0.001			
Presence of dyspnea (yes vs no)	2.850	1.360–5.960	0.005			
Exacerbations in the previous year (yes vs no)	4.570	2.750–7.570	<0.001			
Oxygen therapy	3.180	1.070–9.440	0.037			
BODEx	1.280	1.179–1.389	<0.001			
Charlson comorbidity index	1.590	1.435–1.762	<0.001			
BDI score	1.125	1.098–1.152	<0.001			
Suicide ideation	3.150	2.120–4.670	<0.001			
Health status according to EQ-5D	0.799	0.742–0.860	<0.001			
Social tariff EQ-5D	0.971	0.965–0.977	<0.001	0.967	0.950–0.983	<0.001
CAT score	1.098	1.078–1.118	<0.001			
Physical activity grade	0.648	0.587–0.715	<0.001			
Minutes walked per day	0.994	0.991–0.998	0.001			

Abbreviations: BDI, Beck Depression Inventory; BODEx, Body mass index, airflow Obstruction, Dyspnea and Exacerbations index; CAT, COPD Assessment Test; CI, confidence interval; EQ-5D, EuroQoL-5 dimensions; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio.

Table 3 Factors associated with cognitive impairment in univariate and multivariate analysis, including only demographic and clinical variables

Variable	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age (per 5-year increment)	1.177	1.099–1.262	<0.001			
Educational level (completed university vs basic literacy)	0.160	0.080–0.310	<0.001	0.063	0.010–0.394	0.010
Postbronchodilator FVC	0.977	0.963–0.991	0.001			
Postbronchodilator FEV_1	0.975	0.959–0.991	0.003			
Cough	2.290	1.540–3.410	<0.001			
Expectoration	1.780	1.300–2.430	<0.001			
Dyspnea	2.850	1.360–5.960	0.005			
Exacerbations	4.570	2.750–7.570	<0.001	11.070	1.450–84.534	0.020
Oxygen therapy	3.180	1.070–9.440	0.037			
BODEx	1.280	1.179–1.389	<0.001	1.261	1.049–1.515	0.014
Charlson comorbidity index	1.590	1.435–1.762	<0.001	1.412	1.118–1.783	0.004
Suicide ideation	3.150	2.120–4.670	<0.001			
Physical activity grade	0.648	0.587–0.715	<0.001			
Minutes walked per day	0.994	0.991–0.998	0.001			

Abbreviations: BODEx, Body mass index, airflow Obstruction, Dyspnea and Exacerbations index; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio.

the BODEx index, and the Charlson comorbidity index (Table 3).

Discussion

COPD is a multicomponent inflammatory disease that affects physical and nonphysical functions, one of which is cognition. In our study, we found some degree of cognitive impairment in almost 40% of unselected COPD patients, as determined by a MMSE score <27. Previous estimates of cognitive dysfunction in COPD patients ranged from 12% to 88%, depending on the study population and the tools used for neuropsychological assessment.[5,9] A recent study in a very similar population (including not only elderly patients, but also young patients) to ours[17] found MCI in 36% of COPD patients after comprehensive neuropsychological testing. The authors reported that a MMSE score of 27 provided optimal maximum accuracy and a diagnostic cutoff (<27 indicated impairment), with 97% specificity and 73% of patients correctly classified. However, they also found that the Montreal Cognitive Assessment performed better as a screening test for detecting MCI in patients with COPD. So, this threshold for mild impairment is not necessarily indicative of a clinically significant cognitive decline associated with functional impairment, but could serve as an early identification of an affected cognitive function.

Cognitive symptoms are core symptoms in many mental disorders;[25] they impact on cognitive functioning, which deteriorates as patients get older, particularly after the age of 60.[26] COPD patients score lower on standard cognitive performance tests over time, compared with individuals of the same age without the disease.[27] One hypothesis for this accelerated decline in COPD patients is altered brain perfusion.[28] Changes in brain perfusion due to hypoxemia in subjects with severe COPD may increase cognitive impairment.[29] In our population, more cognitively affected patients were receiving domiciliary oxygen that could be a correlate of higher disease severity and sustained periods of hypoxemia. In contrast, a recent study indicated that long-term home oxygen therapy allowed to preserve cognitive functions from the COPD-induced deterioration,[30] so the role of supplemental oxygen in preventing COPD-induced cognitive deterioration is still controversial. Indeed, other factors, such as hypercapnia or oxidative stress, may also be involved.[31] Other authors have suggested that intermittent and continuous hypoxia resulting from poor lung function may lead to transient deficits in neurotransmitter metabolism in the central nervous system.[32–34] Several mechanisms, then, appear to be involved in cognitive decline in this population. Prospective neuroimaging studies are required to characterize brain changes and corresponding disturbances in cognitive function in these patients over time.

Cognitive impairment represents a critical health care burden in terms of costs.[35] Individuals with MCI have a higher risk of developing dementia than the general population.[36] Moreover, cognitive dysfunction in COPD has been associated with poorer outcomes and even with an increase in disability and mortality.[8,37,38] Thus, it is essential that this condition is identified early in COPD patients, in order to

prevent or delay progression to clinical dementia or increased morbidity. If the factors affecting cognition are recognized, cognitive impairment may be detected earlier and COPD patients at higher risk may be identified. In our study, the multivariate analysis showed that educational level and quality of life assessed by EQ-5D were significantly and independently associated with the presence of cognitive impairment. However, the use of health-related quality of life or other questionnaires is not a routine practice in most primary care offices, so we ran a multivariate model, discarding the scores of these questionnaires and including only demographic and clinical variables. In this model, cognitive impairment was associated with exacerbations in the previous year, the severity of COPD measured by the BODEx index, and a higher comorbidity burden.

Exacerbations in COPD are of great importance. They have been associated with increased health care costs,[39] a significant decline in health status,[40] and substantial mortality.[41] Our results suggest that frequent exacerbations also have negative consequences on cognitive function. This is in line with a previous study that investigated the cognitive function of COPD patients who were hospitalized following an acute exacerbation. These patients had significantly poorer cognitive function compared with control participants 3 months after discharge from the hospital.[10] Other studies have shown that cognitive impairment during the exacerbation period resolves during periods of stability.[42–44] More exacerbations and increased COPD severity could reflect the poorer compliance with medication associated with cognitive impairment.[6,7] The systemic inflammation seen in severe COPD and during acute exacerbations[45] may participate in neurocognitive impairment via a direct neurotoxic effect or by affecting cerebral atherosclerosis.[9] A high comorbidity burden may also contribute to persistent brain injury: multiple concomitant diseases, such as cerebrovascular disease and related mechanisms, including endothelial dysfunction and oxidation, may lead to neuronal death, synaptic dysfunction, and cognitive impairment.[46]

All these data confirm that the cognitive impairment that occurs in COPD patients is associated with disease severity. Neuropsychiatric assessment should become a routine part of the diagnostic procedure for these patients, to help physicians grade the overall impact of COPD and determine the most effective treatment and strategies.

The cross-sectional design of our study limits any type of causal inferences, and the directionality between COPD and cognition remains unclear. Despite the frequent use of the MMSE in clinical research and practice, this tool for cognitive impairment detection could have missed key domains of cognition often affected in COPD (ie, executive functioning). An additional limitation of our study is the lack of data on our patients' medical treatment. As treatment may have great impact on the symptom burden and mental health of the patients, such information should be collected in future studies. In particular, prospective studies are urgently needed to determine the most effective behavioral and medical interventions for reducing the risk of poor neurocognitive outcomes in patients with COPD.

Conclusion

Cognitive impairment is common in COPD and has important clinical implications. Early detection of cognitive decline is crucial, in view of its association with poorer COPD outcomes, including increased mortality, and patients with frequent exacerbations and or when the BODEx index appears concerning the clinician may want to ask the patient and/or caregivers about cognitive function. These patients may need more individualized educational and care interventions to help them manage their daily lives. Clinicians must involve family caregivers in the care plan of patients with severe COPD and cognitive deficits.

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