Frequency and correlates of anxiety, depression, and cognitive dysfunctions in patients with chronic obstructive pulmonary disease: a case–control study

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Background
Appearance of anxiety, depression, and cognitive dysfunction represents important parameters that could complicate the outcome of chronic obstructive pulmonary disease (COPD).

Objective
The objective of this study was to assess the frequency of anxiety, depression, and cognitive dysfunctions among COPD patients and to find possible risk factors.

Methodology
A total of 80 COPD patients were assessed using severe combined immunodeficiency for establishing psychiatric diagnosis, Beck depression inventory for assessment of severity of depressive symptoms, Hamilton anxiety scale for severity of anxiety symptoms, trail making tests (TMTs) A and B for cognitive functions, and spirometry and arterial blood gases for ascertainment of COPD, and they were matched to 80 healthy controls.

Results
In all, 17.5% of patients had mild COPD, 35.5% had moderate COPD, 35.5% had severe COPD, and 12.5% had very severe COPD. Their mean pO_2 level was 65.62 (±15.90), and the mean level of forced expiratory volume in 1 s (FEV1) was 51.36 (±15.55). The patient group showed higher statistically significant difference in the presence of psychiatric illness (55%, $P=0.001$), anxiety level (22.5%, $P=0.06$), depression level (42.5%, $P=0.0001$), substance abuse (15%, $P=0.035$), TMT A ($P=0.0001$), and TMT B ($P=0.0001$). Anxiety and depressive scores were significantly associated with the severity of COPD ($P<0.001$). Anxiety score correlated with age ($r=-0.267$) and pO_2 ($r=0.326$). Depression score correlated with FEV1 ($r=-0.262$). Cognitive functions correlated with the level of pO_2 ($r=0.324$). Age, pO_2, FEV1, and substance abuse were independent predictors of cognitive dysfunction, whereas the former three predicted psychiatric symptoms.

Conclusion
COPD increases the risk for depression, anxiety, and cognitive impairments, and thus raising awareness of clinicians to screen for psychiatric risk factors is essential in improving COPD outcome.

Keywords:
anxiety, chronic obstructive pulmonary disease, cognitive functions, depression, neuropsychological functions, obstructive pulmonary disease, pulmonary functions

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation, being incompletely reversible, progressive course, and recurrent exacerbations [1]. These exacerbations are responsible for a substantial health, financial, and human burden, for example, frequent hospitalizations, increased medication consumption, functional impairment, and death [2]. COPD population prevalence rate ranges from 5 to 13%, which is directly related to tobacco smoking and is expected to rise as smoking rates continue to increase, especially in developing countries [3].

Two frequent and not sufficiently recognized comorbid disorders with COPD are anxiety and depression [4]. Previous research has shown that psychological distress is significantly elevated among patients with COPD, with up to 55% of patients suffering from a clinical diagnosis of anxiety and/or depression [5]. Psychological comorbidity is not only prevalent but is also associated with adverse outcomes such as impaired quality of life and higher treatment failure [6]. Evidence suggests that anxiety and depression may have direct impacts on health status, hospitalization, and exacerbation of COPD [7,8]. Furthermore, they represented very important parameters for the

estimation of quality of life in patients with COPD, no less important than patients' pulmonary function [4].

Despite the high prevalence and the association with increased morbidity and mortality, the symptom burdens of anxiety and depression frequently go unrecognized and undertreated in COPD patients [9].

In addition, studies have shown that patients with COPD have various cognitive impairments, which ranged from reports of affection of verbal learning and memory [10], slower reaction time, attentional deficits for simple, selective, and sustained attention but not for divided attention [11], frontal-type cognitive decline [12], to global impairment in cognitive functions, which were negatively influenced by accelerated aging and increased with disease severity [13].

Although abundant literature is present on the comorbidity of anxiety or depression in COPD patients, no such studies were conducted on Egyptian patients, and none included the effect on cognitive functions, which might cause even more impairments to COPD patients in their daily lives. Therefore, the aim of the present study was to investigate the frequency and severity of anxiety, depression, and cognitive dysfunctions among patients with COPD, to assess those differences compared with matched healthy controls, and to evaluate the correlation between anxiety, depression, and cognitive dysfunctions with the severity of COPD and other demographic variables of patients. Knowledge of these factors will help incorporate psychiatric consultation into the treatment program of COPD patients and therefore ameliorate patient suffering and improve treatment outcome.

Patients and methods

Site of the study

This is a cross-sectional pilot study that was carried out in the outpatient clinic and in the patient ward of the Chest Department, Ain Shams University (Ain Shams University is located in Cairo and serves a wide catchment area of East and Central Cairo). The study was conducted in compliance with the guidelines of the Research and Ethics committee of the Institute of Psychiatry. The research protocol was approved by the Research and Ethics committee of Ain Shams University.

Participants in the study

Patient group

A total of 80 adult patients with COPD both from the inpatient ward and outpatient clinic of the pulmonary medicine department were recruited in this study. They fulfilled the following preset inclusion criteria: a diagnosis of COPD based on the definition provided by the global initiative for chronic obstructive lung disease (GOLD, [14]), above 18 years of age, and both genders. The exclusion criteria were as follows: past history of psychiatric disorders, past history of previous lung volume reduction surgery such as pneumonectomy, and past history of other chronic medical disorders such as diabetes mellitus, hypertension, present history of fever, and chest infection that could confound the results.

Control group

A total of 80 adult healthy controls were recruited in the study; they were selected from the employees and visitors of patients coming to Ain Shams university hospitals in all departments. Chest examination and spirometry were performed to ensure good pulmonary functions before inclusion. Control subjects were matched for age and sex with the patient group.

Tools used in the study

We used the following tools for both groups:

(1) Designed questionnaire for obtaining patient's demographic data such as age, sex, smoking history, education level, occupation, marital status, onset of the illness, prior admission to intensive care, or mechanical ventilation as added stressors that may contribute to different psychological outcomes.
(2) Spirometry: assessment of pulmonary functions was performed using Flowmate Spirometer after administration of an adequate dose of short-acting inhaled bronchodilator to minimize variability. Classification of the severity of airflow limitation in COPD (patients with FEV1/forced vital capacity < 0.7) was carried out based on postbronchodilator FEV1, according to GOLD, 2013 [14]:
    (a) Mild COPD: FEV1 $> 80\%$ of predicted.
    (b) Moderate COPD: $50\% \leq$ FEV1 $\geq 80\%$ of predicted.
    (c) Severe COPD: $30\% \leq$ FEV1 $\geq 50\%$ of predicted.
    (d) Very severe COPD: FEV1 $< 30\%$ of predicted.
        (i) Arterial blood gases were assessed and patients were classified into patients with normal pO_2, hypoxemic patients with a pO_2 of 60–75 mmHg, and patients with respiratory failure with $pO_2 < 60$ mmHg.
(3) Structured clinical interview for *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. axis I disorders (SCID-I-clinician version) [15]. The SCID has seven diagnostic modules, which focused on different diagnostic groups: mood, psychotic, substance abuse, anxiety, somatoform, eating, and adjustment disorders. Its use in this study was to ascertain the presence of a psychiatric diagnosis; the clinician version was used rather than the research version for its relatively easier administration and coverage of the diagnoses most commonly encountered in clinical settings.
(4) Hamilton Anxiety Scale (HAM-A) [16,17]: The HAM-A was developed to measure the severity of anxiety symptoms, and it is still widely used today in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and it measures both psychological anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). A total score of 0–17 is considered to be mild, 18–25 is moderate, and 26–30 is severe. A total score above 30 indicates very severe anxiety.

(5) Beck Depression Inventory [18]: It measures the depth and behavioral manifestations of depression and consists of 21 items, each of which has four responses of increasing severity. Numerical values from 0 to 3 are assigned to each statement to indicate the degree of severity. A total score from 0 to 9 is considered normal, 10–16 reflects mild depression, 17–29 reflects moderate depression, and 30 or above is considered severe depression. It is a widely used standardized instrument.
(6) Trail making test (TMT) [19]: It is one of the most popular neuropsychological tests; it provides information on visual search, scanning, processing speed, mental flexibility, and executive functions. It consists of two parts: part A consists of encircled numbers from 1 to 25 randomly spread across a paper and subjects are asked to connect the numbers in order, whereas part B consists of numbers and letters. It is more complex because it requires subjects to connect numbers and letters in an alternating pattern. The score represents the amount of time required to complete the task [20]. Some cognitive functions are evaluated by both parts including spatial organization, graph-motor speed, recognition of numbers, visual pursuit, vigilance, and number sequences. Part A evaluates rote memory and part B is associated with the processes of distinguishing between numbers and letters, integration of two independent series, ability to learn an organizing principle and apply it systematically, serial retention and integration, problem solving, and planning [20].

Procedure of the study

A total of 97 patients were evaluated; five patients dropped out after the chest examination and spirometry and did not complete the psychiatric evaluation, eight patients were excluded because of past history of psychiatric treatment, three patients were excluded because of past history of reductive lung surgery, and one patient died before the assessment was complete because of severe respiratory failure. All patients and control subjects participating in the study were asked to sign an informed consent; they received full clinical evaluation including history taking and chest examination. Pulmonary function tests were performed for all participants. This was followed by SCID interview, Beck Depression Inventory, HAM-A, and TMT assessment.

The assessment of each subject took 3–4h. Therefore, it was undertaken over a two-session interview: the first session included pulmonary evaluation and spirometry. The second session pertained to psychiatric assessment and neuropsychological testing, which was performed within a week.

Statistical analysis

Continuous variables are expressed as mean and SD. Categorical variables are expressed as frequencies and percentages. Student's *t*-test and analysis of variance test were used to assess the statistical significance of the difference between two or more than two study group means, respectively. χ^2 and Fisher's exact tests were used to examine the relationship between categorical variables. Pearson's correlation was used to assess the correlation between quantitative variables. Multivariate linear regression was used to test and estimate the dependence of a quantitative variable based on its relationship with a set of independent variables. A significance level of P less than 0.05 was used in all tests. All statistical procedures were carried out using SPSS, version 15 for Windows (Chicago, Illinois, USA).

This study is the first of two publications in a research project assessing psychiatric symptomatology and cognitive functions in a sample of COPD patients.

Results

Sociodemographic data of the participants

The age of the patient group ranged from 33 to 85 years with a mean of 59.35 (± 10.09) years, and most of them were male (95%), whereas the age of the control group ranged from 35 to 84 years with a mean of 62.38 (± 10.52) years, and similarly most subjects were male (92.5%). Both groups showed no statistical significance except for smoking index (patients 83% vs. controls 50%, $P = 0.0001$), as shown in Table 1.

Clinical characteristics of the patient group

Analysis of the chest condition of the patient group showed that the duration of illness ranged from 2 to 40 years with a mean of 17.18 (± 9.29) years. The severity of COPD (according to GOLD standards) was as follows: 17.5% ($N = 14$) had mild COPD, 35.5% ($N = 28$) had moderate COPD, 35.5% ($N = 28$) had severe COPD, and 12.5% ($N = 10$) had very severe COPD. Their mean pO_2 level was 65.62 (± 15.90), and the mean level of FEV1 was 51.36 (± 15.55), denoting impairment of respiratory functions and hypoxemia in the majority of the patient group. In all, 32.5% of patients ($N = 26$) were previously admitted to the ICU, whereas 10% ($N = 8$) had a history of previous mechanical ventilation. Analysis of patients' hypoxemic state revealed that 35% of patients ($N = 28$) had mild hypoxemia, 37.5% ($N = 30$) had moderate hypoxemia, whereas 30.8% ($N = 24$) had severe hypoxemia and were on oxygen therapy.

Comparison between patient group and control group regarding psychiatric characteristics and cognitive function

Comparison between the two groups revealed high statistical significance in all studied domains as follows: the presence of psychiatric illness (patients 55% vs. controls 20%, $P = 0.001$), anxiety level (5% of patients with COPD had mild anxiety and 17.5% had moderate anxiety, vs. 10% in controls, $P = 0.06$), level of depression (35% of COPD patients had mild depression and 7.5% had moderate depression, vs. 12.5% in controls, $P = 0.0001$), substance abuse (patients 15% vs. controls 5%, $P = 0.035$), TMT A (patients scored a mean of 156.06 ± 82.62 vs. controls 57.95 ± 17.33, $P = 0.0001$),

Table 1 Comparison between patient group and control group regarding sociodemographic data

	n (%)			
	Patient group (*N*=80)	Control group (*N*=80)	*P*	Significance
Age (mean ±SD)	59.35±10.09	62.38±10.52	0.065[a]	NS
Duration of smoking (mean± SD)	33.49±13.33	29.23±11.41	0.052[a]	NS
Gender				
Male	76 (95.0)	74 (92.5)	0.514[b]	NS
Female	4 (5.0)	6 (7.5)		
Smoking status				
Smoker	32 (40.0)	32 (40.0)	0.089[b]	NS
Nonsmoker	10 (12.5)	20 (25.0)		
E-smoker	38 (47.5)	28 (35.0)		
Smoking index				
1	12 (16.2)	30 (50.0)	0.0001[b]	HS
2	50 (67.6)	24 (40.0)		
3	12 (16.2)	6 (10.0)		
Residence				
Cairo	52 (65.0)	60 (75.0)	0.168[b]	NS
Outside Cairo	28 (35.0)	20 (25.0)		
Occupation				
No dust exposure	60 (75.0)	58 (72.5)	0.719[b]	NS
Exposure to dust	20 (25.0)	22 (27.5)		
Marital status				
Married	60 (75.0)	66 (82.5)	0.246[b]	NS
Single	20 (25.0)	14 (17.5)		

HS, highly significant; NS, not significant.
[a]Student's *t*-test.
[b]χ^2-test.

and TMT B (patients had a mean of 321.57 ± 132.55 vs. controls 127.20 ± 28.98, $P = 0.0001$), as shown in Table 2.

Comparison between patients with different chronic obstructive pulmonary disease severities regarding personal, psychiatric, and cognitive variables

Our analysis revealed that patients with severe COPD had more anxiety symptoms compared with other groups ($P = 0.047$), and patients with severe and very severe COPD had more depressive symptoms compared with other groups ($P = 0.016$), as shown in Table 3.

Similarly, comparison between COPD patients with substance-related disorders versus COPD patients without such comorbidity regarding cognitive dysfunction showed a significant statistical difference between both groups as regards TMTs A and B ($P = 0.0001$ and 0.0001, respectively). On the other hand, COPD patients with a history of previous ICU admission or mechanical ventilation or those on oxygen therapy did not show any statistical significance regarding the presence of psychiatric symptoms or cognitive affection compared with those who were not exposed to those added stressors.

Correlations between personal data, chest condition, and psychiatric symptoms and cognitive functions among cases

Table 4 shows that anxiety score correlated with age ($r = -0.267$, $P = 0.017$) and the level of pO_2 ($r = 0.326$, $P = 0.003$). Depression score correlated with FEV1 ($r = -0.262$, $P = 0.019$). Moreover, the trail making test A correlated with the level of pO_2 ($r = 0.324$, $P = 0.011$).

Analysis of independent risk factors affecting psychiatric symptoms and cognitive function

Multivariate linear regression model was used to determine which factors were independently associated with psychiatric symptoms and cognitive functions. Age, pO_2, FEV1, anxiety score, depression score, and substance abuse were used as independent variables. The results showed that age, pO_2, and depression score were independent predictors for anxiety symptoms, whereas anxiety score was found to be an independent predictor for depressive symptoms. pO_2, depression score, and substance-related disorders were the independent predictors for TMT A, whereas age, pO_2, FEV1, and depression score were the independent predictors for TMT B, as shown in Table 5.

Discussion

COPD is a leading cause of disability and death worldwide, and by 2030 COPD is expected to represent the third leading cause of death in middle-income countries [21]. Appearance of anxiety and depression represents very important parameters for estimation of quality of life in patients with COPD, no less important than patients' pulmonary function [4]. Moreover, previous studies have shown that patients with COPD have various cognitive impairments; however, the exact pattern and course of the cognitive decline in patients with COPD is still not understood [13].

Therefore, the aim of the present study was to investigate the frequency and severity of anxiety, depression, and cognitive dysfunctions among patients with COPD, and to evaluate the correlation between anxiety, depression, and cognitive dysfunctions with the

Table 2 Comparison between patient group and control group regarding the psychiatric characteristics and cognitive function

	n (%)			
	Patient group (*N*=80)	Control group (*N*=80)	*P*	Significance
Anxiety score (mean±SD)	11.77±4.91	10.53±3.28	0.06[a]	NS
Depression score (mean±SD)	9.10±4.34	7.18±3.22	0.002[a]	HS
Trail making test A (mean±SD)	156.06±82.62	57.95±17.33	0.0001[a]	HS
Trail making test B (mean±SD)	321.57±132.55	127.20±28.98	0.0001*	HS
Present psychiatric disorder				
Yes	44 (55.0)	16 (20.0)	0.0001[b]	HS
No	36 (45.0)	64 (80.0)		
Anxiety level				
Normal	62 (77.5)	72 (90.0)	0.006[b]	HS
Mild	4 (5.0)	6 (7.5)		
Moderate	14 (17.5)	2 (2.5)		
Depression level				
Normal	46 (57.5)	70 (87.5)	0.0001[c]	HS
Mild	28 (35.0)	8 (10.0)		
Moderate	6 (7.5)	2 (2.5)		
Substance-related disorders				
Yes	12 (15.0)	4 (5.0)	0.035[b]	S
No	68 (85.0)	76 (95.0)		

HS, highly significant; NS, not significant.
[a]Student's *t*-test.
[b]χ^2-test.
[c]Fisher's exact test.

Table 3 Comparison between cases with different chronic obstructive pulmonary disease severities as regards personal, psychiatric symptoms, and cognitive functions

	n (%)					
	Mild COPD (*N*=14)	Moderate COPD (*N*=28)	Severe COPD (*N*=28)	Very severe COPD (*N*=10)	*P*	Significance
Age (mean±SD)	60.43±11.88	59.00±10.87	59.71±10.33	57.80±3.08	0.929[a]	NS
Duration of illness (mean±SD)	15.14±5.01	16.29±9.59	17.71±10.77	21.00±8.43	0.444[a]	NS
pO_2 (mean±SD)	65.47±16.35	62.89±19.73	65.57±11.77	73.60±12.43	0.346[a]	NS
Anxiety score (mean±SD)	10.43±4.40	10.29±3.47	13.57±6.11	12.80±3.85	0.047[a]	S[d]
Depression score (mean±SD)	8.57±2.34	7.43±3.48	10.00±4.47	12.00±6.32	0.016[ae]	S[e]
Trail making test A (mean±SD)	147.57±62.99	172.43±108.91	134.58±53.80	196.60±111.45	0.194[a]	NS
Trail making test B (mean±SD)	326.33±105.88	348.71±167.83	281.08±96.99	375.00±167.42	0.217[a]	NS
Hypoxemia						
Normal	2 (14.3)	12 (42.9)	4 (14.3)	4 (40.0)		HS
					0.0001[c]	
Mild	10 (71.4)	2 (7.1)	12 (42.9)	4 (40.0)		
Moderate	2 (14.3)	14 (50.0)	12 (42.9)	2 (20.0)		
Psychiatric disorder						
Yes	6 (42.9)	16 (57.1)	16 (57.1)	6 (60.0)		NS
					0.792[b]	
No	8 (57.1)	12 (42.9)	12 (42.9)	4 (40.0)		
Anxiety						
Normal	12 (85.7)	24 (85.7)	18 (64.3)	8 (80.0)		NS
					0.397[c]	
Mild	0 (0.0)	2 (7.1)	2 (7.1)	0 (0.0)		
Moderate	2 (14.3)	2 (7.1)	8 (28.6)	2 (20.0)		
Depression						
Normal	8 (57.1)	18 (64.3)	16 (57.1)	4 (40.0)		NS
					0.208[c]	
Mild	6 (42.9)	10 (35.7)	8 (28.6)	4 (40.0)		
Moderate	0 (0.0)	0 (0.0)	4 (14.3)	2 (20.0)		
Substance-related disorders						
Yes	4 (28.6)	4 (14.3)	4 (14.3)	0 (0.0)		NS
					0.334[c]	
No	10 (71.4)	24 (85.7)	24 (85.7)	10 (100.0)		

ANOVA, analysis of variance; HS, highly significant; NS, not significant; S, significant.
[a]ANOVA.
[b]χ^2-test.
[c]Fisher's exact test.
[d]Group 3 versus group 1 (S), group 3 versus group 2 (S) by post-hoc test.
[e]Group 4 versus group 1 (S), group 4 versus group 2 (HS), group 3 versus group 2 (S) by post-hoc test.

severity of COPD and some demographic patients' variables.

The present study found a higher prevalence of psychiatric disorders among patients with COPD (55%)

Table 4 Correlations between personal data, medical data, and psychiatric symptoms and cognitive functions among cases

	Anxiety score	Depression score	Trail making test A	Trail making test B
Age				
r	−0.267(*)	−0.063	0.059	0.227
P	0.017	0.581	0.650	0.081
Significance	S	NS	NS	NS
Duration of smoking				
r	0.022	0.226	0.250	0.249
P	0.854	0.053	0.054	0.059
Significance	NS	NS	NS	NS
Duration of illness				
r	−0.147	0.120	−0.106	0.029
P	0.194	0.288	0.412	0.826
Significance	NS	NS	NS	NS
Number of ICU admissions				
r	0.358	0.364	−0.056	−0.179
P	0.073	0.067	0.815	0.477
Significance	NS	NS	NS	NS
pO_2				
r	0.326	0.175	0.324	0.219
P	0.003	0.120	0.011	0.093
Significance	HS	NS	S	NS
FEV1				
r	−0.182	−0.262	0.033	0.145
P	0.107	0.019	0.797	0.267
Significance	NS	S	NS	NS

HS, highly significant; NS, not significant; S, significant.

Table 5 Multivariate linear regression analysis of risk factors affecting psychiatric symptoms and cognitive function

	Anxiety score		Depression score		Trail making test A		Trail making test B	
	Coefficients (95% CI)	*P*	Coefficients (95% CI)	*P*	Coefficients (95% CI)	*P*	Coefficients (95% CI)	*P*
Age	−0.107 (1.22–6.75)	0.018	0.038 (−0.05–0.12)	0.377	1.202 (−0.66–3.06)	0.201	3.985 (1.22–6.75)	0.006
pO_2	0.070 (0.38–4.34)	0.017	0.004 (−0.05–0.06)	0.895	1.849 (0.51–3.19)	0.008	2.364 (0.38–4.34)	0.020
FEV1	−0.008 (0.75–4.34)	0.801	−0.054 (−0.11–0.001)	0.56	1.059 (−0.14–2.26)	0.083	2.546 (0.75–4.34)	0.006
Anxiety score	–	–	0.471 (0.29–0.66)	0.0001	0.643 (−3.85–5.13)	0.775	0.125 (−6.51–6.76)	0.970
Depression score	0.542 (−6.51–6.76)	0.0001	–	–	5.687 (0.81–10.57	0.023	11.536 (4.3318.74)	0.002
Substance-related disorders	0.855 (4.33–18.74)	0.506	0.358 (−3.47–1.27)	0.358	82.280 (30.55–134.01)	0.002	165.099 (83.57–246.63)	0.0001

CI, confidence interval.

compared with a matched control group (20%). The most common psychiatric disorders found were depression (42.5%), anxiety disorder (22.5%), and substance-related disorders (15%) compared with the control group. These results were in agreement with the results of a previous study, which showed that 43% of patients with COPD were diagnosed with depression and 29% of them were diagnosed with anxiety [22]. Some studies had demonstrated that the prevalence of depression was between 11 and 30% in patients with mild to severe COPD [23,24], whereas in other studies the frequency of anxiety and depression in COPD patients is reported to vary from 25 to 80% [25,26]. This wide range in reported prevalence of depression and anxiety among patients with COPD is attributable to various factors, including sampling methods, varying screening instruments, and differences in diagnostic assessment tools used.

The scores for anxiety and depressive symptoms were higher among the patients with COPD than among control subjects. These results are in agreement with the results of previous studies that reported anxiety symptoms ranging from 9.57 to 49% and depressive symptoms ranging from 22.8 to 52% using the Hospital Anxiety and Depression Scale as the screening tool [27,28]. Moreover, Xu *et al.* [8] found that among patients with COPD those with anxiety and depression had significantly higher annual rates of exacerbations, more hospitalization, and longer hospital stays. These high rates emphasize the importance of screening and treatment of depression and anxiety in patients with COPD to maintain health-related quality of life [29].

The present study also showed that patients with severe and very severe COPD had more anxiety and depression compared with patients with mild and moderate COPD. Van Manen *et al.* [30] reported similar results on a larger sample size of COPD patients, and by means of Center for Epidemiologic Studies Depression Scale the study showed 2.5 times more frequent depression in patients with a severe degree of COPD (FEV1 < 50%) compared with the control group. Our results disagreed with the results of a study conducted by Regvat *et al.* [31], which reported that anxiety and depression were more common in patients with mild COPD. This disagreement is likely to be due to different study population, as their sample included a greater number of patients with mild COPD.

The present study showed a correlation between high levels of anxiety and younger patients with COPD and in patients with lower hypoxemia, whereas depression correlated with decreased pulmonary functions (lower FEV1). These results were partially consistent with the results of previous studies reporting that anxiety and depression were more common in younger COPD patients and more in patients with severe COPD [30]. In addition, Lou *et al.* [7] reported that patients who were younger, female, had higher education level, higher BMI, history of smoking, and dyspnea suffered from anxiety or depressive symptoms more frequently. Others showed that depression was more in female patients with COPD, in patients with decreased value of FEV1, and that depression and anxiety increased with number of hospitalizations and days of hospital treatment [4]. Our results also concur with previous research reporting that high pO_2 levels were correlated with the presence of anxiety or depression in patients with COPD; they further elaborated that those patients had lower partial pressure of carbon dioxide and higher pH [31]

Although previous studies showed significant correlation between depression and female gender in COPD [4,7,32], it was not found in our study most likely because of different sample characteristics, as the majority of the participants were male (95%). Similarly, there was no significant correlation between anxiety and/or depression and smoking in COPD patients, unlike some studies that showed that anxiety and depression were more common in smokers with COPD [33,34]. Nevertheless, other studies reported no association, and they reported that impaired lung function was associated with worse cognition and depressive and anxiety symptoms that are independent of current and lifetime smoking status [35,36].

Our study did not show significant correlation between anxiety and/or depression with duration of illness or ICU admission; this was in agreement with the study conducted by Obradovic *et al.* [4], who found no significant correlation between the presence of anxiety and depression and duration of the disease, and they attributed this result to COPD patients' understanding of the long duration of the illness and its chronicity, which may serve as an explanation why the duration itself was not associated with either anxiety or depression in COPD patients.

From the multivariate linear regression results, younger age, higher pO_2 level, and the presence of depressive symptoms were independent factors for anxiety, whereas the presence of anxiety symptoms was the independent factor for depression. This result highlights the importance of careful screening for depression and anxiety in patients with COPD from the early periods of the illness. Moreover, our results showed a significant correlation between anxiety and depression; therefore, general practitioners should be informed that when patients with COPD have symptoms of anxiety or depression the other condition should be suspected as well.

An astonishing finding in the present study was that 15% of patients with COPD had comorbid substance-related disorders; in addition, those patients showed more cognitive dysfunction compared with COPD patients without such comobidity. This was in agreement with Kuhl *et al.* [37], who found that 7.7% of patients with COPD had comorbid substance-related disorders. Furthermore, Yeatts *et al.* [38] in their study showed that COPD patients with comorbid substance-related disorders were more likely to have subsequent hospital admission compared with those without this comorbidity. Therefore, it is very important to screen for substance-related disorders in COPD patients, as the presence of such comorbidity could cause more cognitive dysfunction and worsen their health outcomes.

With respect to the cognitive functions of participants, which were assessed using the TMT that assesses the psychomotor speed and executive functions, efficient integration of attention, visual scanning, and cognitive sequencing, the present study showed that patients in the COPD group had high significant increase in test completion time compared with the control group. In addition, this cognitive dysfunction was correlated with the level of pO_2. This was in agreement with a previous study that showed that patients with COPD had a significantly slower overall reaction time measured with the attention network time compared with matched healthy controls; also, there were differences found in verbal and visual learning, and in logical thinking [13]. In addition, Hung *et al.* [39] found that patients with severe COPD showed lower cognitive performance over 6 years of follow-up. A year later another study showed that COPD was associated with a major risk of cognitive impairment, and the presence of hypoxemia was related to increased risk of cognitive impairment, whereas regular use of supplemental oxygen therapy decreased the risk for cognitive impairment [40]. This was further explained by Dodd *et al.* [41] who reported that it is reasonable to regard patients with COPD to be at an increased risk of neuronal injury, either through factors related to COPD such as hypoxemia or as a result of comorbidities, which adversely affect the brain such as vascular disease and smoking.

An earlier study by Richards *et al.* [35] examined the relationship between lung function and cognitive ability in middle-aged adults, although not directly studying COPD; they found that FEV1 and cognitive function were positively associated across the life course. Numerous prior clinical studies have observed that impaired cognitive performance was more pronounced in those with severe disease or oxygen dependence [25,27,30].

Using multivariate linear regression in the present study showed that age, pO_2 level, FEV1 level, presence of depressive symptoms, and substance-related disorders were the independent predictors for cognitive dysfunction. Our findings concur with previous studies that reported that pO_2 levels adversely affect cognition in COPD and postulated that it may be due to affection of oxygen-dependent enzymes, which are important in the synthesis of neurotransmitters, such as acetylcholine [41], and concur with previous studies reporting pulmonary functions (level of FEV1) to adversely affect cognitive

functions [39]. Our results similarly agree with previous studies on the effect of depressive symptoms on impairment in executive function, memory, and processing speed in COPD patients [42].

For patients with severe COPD, this decline in cognition is likely to have important clinical consequences. In order for patients with COPD to maintain independence, cognitive abilities are necessary for being adherent to complex medication regimens, such as inhalers and oxygen, and to manage other chronic diseases often associated with COPD, among other daily tasks made more difficult by activity limitations due to COPD. Often, patients with cognitive difficulties, if undetected and untreated, have lower adherence to their treatment and follow-up regimens, and as a consequence may deteriorate more rapidly and have worse health outcomes. Cognitive impairment often leads to functional disability and increases the need for additional care services. It is therefore important for clinicians to be sensitive to cognitive change of COPD patients [39].

There were a number of limitations to the present study: first was the small sample size; second, most of the participants were male, and thus we did not evaluate the prevalence of psychiatric disorders in female patients with COPD and whether they differ clinically from those in male patients with COPD; and third, the cross-sectional design of the study did not allow for evaluation of changes in anxiety and depression over time, nor their effect on the patient physical health and quality of life.

Conclusion

Patients with COPD are at an increased risk for depression, anxiety, and substance-related disorders. Therefore, early psychiatric evaluation should be done for each patient with COPD, particularly those with younger age, high pO_2 level, and decreased FEV1. Our finding should raise awareness that patients with COPD are at a greater risk of developing cognitive impairment, which may make managing their COPD more challenging; therefore, clinicians should consider periodic screening for cognition in such patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Quint JK, Baghai-Ravary R, Donaldson GC, Wedzicha JA. Relationship between depression and exacerbations in COPD. Eur Resp J 2008; 32:53–60.

2 Mittmann N, Kuramoto L, Seung SJ, Haddon JM, Bradley-Kennedy C, Fitz-Gerald JM. The cost of moderate and severe COPD exacerbations to the Canadian healthcare system. Respir Med 2008; 102:413–421.

3 Buist AS, Vollmer WM, McBurnie MA. Worldwide burden of COPD in high- and low-income countries. Part I. The burden of obstructive lung disease (BOLD) initiative. Int J Tuberc Lung Dis 2008; 12:703–708.

4 Obradovic LMN, Pesut DP, Maric D, Maskovic J, Maric NP, Milikic MM. Symptoms of anxiety and depression in patients with chronic obstructive pulmonary disease. Pneumologia 2012; 61:92–96.

5 Yohannes AM, Willgoss TG, Baldwin RC, Connolly MJ. Depression and anxiety in chronic heart failure and chronic obstructive pulmonary disease: prevalence, relevance, clinical implications and management principles. Int J Geriatr Psychiatry 2010; 25:1209–1221.

6 Venkata A, DeDios A, ZuWallack R, Lahiri B. Are depressive symptoms related to physical inactivity in chronic obstructive pulmonary disease? J Cardiopulm Rehab and Prevention 2012; 32:405–409.

7 Lou P, Zhu Y, Chen P, Zhang P, Yu J, Zhang N, *et al*. Prevalence and correlations with depression, anxiety, and other features in outpatients with chronic obstructive pulmonary disease in China: a cross-sectional case control study. Pulmonary Medicine 2012; 12:53.

8 Xu W, Collet JP, Shapiro S, Lin Y, yang T, Platt RW, *et al*. Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations. Am J Respir Crit Care Med 2008; 178:913–920.

9 Maurer J, Rebbapragada V, Borson S, Goldstein R, Kunik ME, Yohannes AM, *et al*. Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Chest 2008; 134 (Suppl):43S–56S.

10 Etnier JL, Berry M. Fluid intelligence in an older COPD sample after short- or long-term exercise. MedSci Sports Exerc 2001; 33:1620–1628.

11 Orth M, Kotterba S, Duchna K, Widdig W, Rasche K, Schultze-Werninghaus G, Duchna HW. Cognitive deficits in patients with chronic obstructive pulmonary disease (COPD). Pneumologie 2006; 60:593–599.

12 Antonelli Incalzi R, Marra C, Giordano A, Calcagni ML, Cappa A, Basso S, *et al*. Cognitive impairment in chronic obstructive pulmonary disease a neuropsychological and spect study. J Neurol 2003; 250:325–332.

13 Klein M, Gauggel S, Sachs G, Pohl W. Impact of chronic obstructive pulmonary disease (COPD) on attention functions. Respiratory Medicine 2010; 104:52–60.

14 Global Initiative of Chronic Obstructive Lung Disease. Global strategy for diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available at: *http://www.goldcopd.org*. [Accessed January 2013].

15 First MB, Spitzer RL, Williams W, Gibbon M. *Structured clinical interview for DSM-IV – clinician version (SCID-CV) (users guide and interview)*. Washington: American Psychiatric Press; 1997.

16 Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55.

17 Maier W, Buller R, Philipp M, Heuser I. The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. J Affect Disord 1988; 14:61–68.

18 Beck A, Ward C, Mendelson M. Beck Depression Inventory (BDI). Arch Gen psychiatry 1961; 4:561–571.

19 Reitan RM, Wolfson D. *The Halstead–Reitan neuropsycholgical test battery: therapy and clinical interpretation*. Tucson, AZ: Neuropsychological Press; 1985.

20 Reitan Ralph M, Deborah Wolfson. Category test and trail making test as measures of frontal lobe functions. Clin Neuropsychol 1995; 9:50–56.

21 Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. Plos Med 2006; 3:430–442.

22 Kunik M, Azzam P, Souchek J, Cully JA, Wray NP, Krishnan LL, *et al*. A practical screening tool for anxiety and depression in patients with chronic breathing disorders. Psychosomatics 2007; 48:16–21.

23 Julian LJ, Gregorich SE, Earnest G, Eisner MD, Chen H, Blanc PD, *et al*. Screening for depression in chronic obstructive pulmonary disease. COPD 2009; 6:452–458.

24 Balcells E, Gea J, Ferrer J, Serra I, Orozco-Levi M, de Batlle J, *et al*. Factors affecting the relationship between psychological status and quality of life in COPD patients. Health Qual Life Outcomes 2010; 8:108–116.

25 Andenaes R, Kalfoss MH, Wahl A. Psychological distress and quality of life in hospitalized patients with chronic obstructive pulmonary disease. J Adv Nurs 2004; 46:523–530.

26 Chavannes NH, Huibers MJH, Schermer TRJ. Associations of depressive symptoms with gender, body mass index, and dyspnea in primary care COPD patients. Fam Pract 2005; 32:604–607.

27 Kunik ME, Roundy K, Veazey C, Souchek J, Richardson P, Wray NP, Stanley MA. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. Chest 2005; 127:1205–1211.

28 Eisner MD, Blanc PD, Yelin EH, Katz PP, Sanchez G, Iribarren C, Omachi TA. Influence of anxiety on health outcomes in COPD. Thorax 2010; 65:229–234.

29 Cleland JA, Lee AJ, Hall S. Associations of depression and anxiety with gender, age, health-related quality of life and symptoms in primary care COPD patients. Fam Pract 2007; 24:217–223.

30 Van Manen JG, Bindels PJ, Dekker FW, IJzermans C, van der Zee JS, Schade E. Risk of depression in patients with chronic obstructive pulmonary disease and its determinants. Thorax 2002; 57:412–416.

31 Regvat J, Xmitek A, Vegnuti M, Kosnik M, Suskonvic S. Anxiety and depression during hospital treatment of exacerbation of chronic obstructive pulmonary disease. J int Med Res 2011; 39:1028–1038.

32 Di Marco F, Verga M, Reggente M, Maria Casanova B, Santus P, Blasi F, *et al*. Anxiety and depression in COPD patients: the roles of gender and disease severity. Respir Med 2006; 100:1767–1774.

33 Gudmundsson G, Gislason T, Janson C, Lindberg E, Suppli Ulrik C, Brøndum E, *et al*. Depression, anxiety and health status after hospitalization for COPD: a multicenter study in the Nordic countries. Respir Med 2006; 100:87–93.

34 Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med 2007; 167:60–67.

35 Richards M, Strachan D, Hardy R, Kuh D, Wadsworth M. Lung function and cognitive ability in a longitudinal birth cohort study. Psychosom Med 2005; 67:602–608.

36 Sachdev PS, Anstey KJ, Parslow RA, Wen W, Maller J, Kumar R, *et al*. Pulmonary function, cognitive impairment and brain atrophy in a middle-aged community sample. Dement Geriatr Cogn Disord 2006; 21:300–308.

37 Kuhl K, Schurmann W, Rief W. Mental disorders and quality of life in COPD patients and their spouses. Int J Obstruct Pulmon Dis 2008; 3:727–736.

38 Yeatts KB, Lippman SJ, Waller AE, Lich H, Travers D, Weinberger M, Donohue JF. Population-based burden of COPD-related visits in the ED: return ED visits, hospital admissions, and comorbidity. Chest 2013; 144: 784–793.

39 Hung WW, Wisnivesky JP, Al Siu, Ross JS. Cognitive decline among patients with chronic obstructive pulmonary disease. Am J Respir Grit Care Med 2009; 180:134–137.

40 Thakur N, Blanc PD, Julian LJ, Yelin EH, Katz PP, Sidney S, *et al*. COPD and cognitive impairment: the role of hypoxemia and oxygen therapy. Int J Chron Obstruct Pulmon Dis 2010; 5:263–269.

41 Dodd JW, Getov SV, Jones PW. Cognitive function in COPD. Eur Respir J 2010; 35:913–922.

42 Wamberg J, Gomez-Martinez S, Romeo J, Díaz LE, Marcos A. Nutrition, inflammation, and cognitive function. Ann N Y Acad Sci 2009; 1153:164–175.