Cognitive dysfunction in chronic obstructive pulmonary disease

Mohamed M. Metwally[a], Eman M. Khedr[b], Olfat M. El-shinnawy[a], Alaa EL-din Th. Hassan[a], Ahmad M. Shaddad[a]

Departments of [a]Chest Diseases and Tuberculosis, [b]Neurology and Psychiatry, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Ahmad M. Shaddad, MSc, Department of Chest Disease and Tuberculosis, Faculty of Medicine, Assiut University, Assiut, Egypt
Tel: +20 111 117 1930; Fax: +20882332278; e-mail: shaddad-ahmad@yahoo.com

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Background
Chronic obstructive pulmonary disease (COPD) is an increasingly common disease among older adults that has been linked to other comorbid conditions with serious morbidity and mortality, including cognition impairment. However, it remains poorly understood in COPD.

The aim of the study
The aim of this study is to evaluate cognitive dysfunction in COPD and to relate it to the severity obtained from spirometric and gasometric evaluation of COPD patients.

Patients and methods
In this case–control study design, 25 COPD patients and 25 age-matched and sex-matched healthy control patients were compared. Wechsler Adult Intelligence Scale-III (WAIS-III) and Mini-Mental State Examination (MMSE) were used to evaluate cognition in COPD patients.

Results
There was significant impairment of MMSE with a cognitive dysfunction reported in 72% of the COPD group. There was significant impairment in all components of WAIS-III, namely the verbal IQ, performance IQ, total scale IQ, and deterioration index in the COPD group than in the control group.WAIS-III scale was positively correlated to both oxygen tension and saturation, denoting the utmost role of hypoxemia in the pathogenesis of cognitive dysfunction in COPD patients. Receiver operator characteristics curves were plotted for the use of both oxygen tension and saturation, denoting good use of oxygen tension and saturation as a predictive value for impairment of MMSE and WAIS-III scale and hence cognitive dysfunction.

Conclusion
Cognitive dysfunction is a fixed finding that occurs in the course of COPD. Hypoxemia seems to play the principal role in cognitive disorders. Spirometric parameters seem to be closely related to the progression and prediction of the course of those disorders.

Keywords:
chronic obstructive pulmonary disease, cognitive dysfunction, Mini-Mental State Examination in chronic obstructive pulmonary disease, Wechsler Adult Intelligence Scale in chronic obstructive pulmonary disease

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Introduction

Cognitive impairment has been demonstrated in 77% of patients with chronic obstructive pulmonary disease (COPD) and hypoxemia [1]. Furthermore, it has been suggested that impaired performance in neuropsychological tests may be a predictor of mortality and disability in certain COPD populations [2-4]. However, despite their potential importance, the understanding of cognitive problems in COPD remains incomplete [5]. Cognition is a collective term for high-order neural processes that underpin information handling. These have been variously subclassified according to conceptual frameworks. In practice, cognitive abilities are mainly inferred from behavior, which itself is determined by a wide variety of neurological, psychological, and emotional factors [6]. The relationships between many processes involved in an everyday cognitive task are complex, but cognitive ability is usually broken up into discrete domains, although it is rarely possible to study single domains in isolation. Neuropsychological tests aim to provide standardized domains. Performance within each domain depends on one or more of the main classes of cognitive function. The tasks performed as part of neuropsychological testing often closely resemble mental challenges encountered in everyday life [6]. In the present study, we are aiming to evaluate cognitive dysfunction in COPD and compare it with the control

group, and to assess the relationship between cognitive dysfunction and COPD severity indices obtained from spirometric and gasometric evaluation of COPD patients.

Patients and methods

Patients

This study was conducted in Assuit University Hospital at the Chest Diseases and Tuberculosis Department and the Neurology and Psychiatry Department during the period between May 2013 and October 2015. We enrolled 25 stable COPD patients and 25 adult age-matched and sex-matched healthy controls.

Sampling and sample size

Sampling

Sampling was done by nonprobability convenient sampling technique. Patients were selected from those consecutively attending the Chest Diseases and Tuberculosis Department and those attending the outpatient clinic.

Sample size

There are many local studies for the estimation of prevalence of COPD among the risk group (age above 45 years with a history of smoking or ex-smoking or exposure to outdoor pollution). On the basis of the results of Said *et al.* [7] and El Hasnaoui *et al.* [8], the prevalence of COPD in Egypt was considered to be ~ 6%, and our patient and control sample size was calculated to be 25 using the Open Epi V.3.01 (Open source program, Atlanta,USA) computer program.

Chronic obstructive pulmonary disease diagnosis

A diagnosis of COPD is considered in any patient who has cough, sputum production, or dyspnea, and/or a history of exposure to known risk factors. The diagnosis is confirmed by an objective measure of airflow limitation (spirometry). Chronic cough, usually the first symptom of COPD to develop, may be intermittent in the beginning, but later it is present everyday, often throughout the day. Small quantities of tenacious sputum are usually raised by COPD patients after coughing bouts. Physical signs of airflow limitation are usually present. Spirometry is indicated to diagnose COPD. Spirometry should measure forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1), and the ratio of these two measurements (FEV1/FVC) is then calculated. Patients with COPD classically show a decrease in both FEV1 and FVC. The presence of a postbronchodilator FEV1of less than 80% of the predicted value in combination with an FEV1/FVC of less than 70% confirms the presence of airflow limitation that is not fully reversible [9].

Inclusion and exclusion criteria

Inclusion criteria

All stable COPD patients who met the diagnostic criteria mentioned above, with age ranging between 45 and 75 years old, who were admitted to the Chest Diseases and Tuberculosis Department in Assuit University Hospital and COPD patients who attended out patients' clinic, as well as healthy volunteers of the same age, residence, smoking habits, and educational level, were eligible to participate in the study.

Exclusion criteria

COPD patients who were associated with any of the following comorbidities were excluded from the study:

(1) Left-sided heart failure, renal insufficiency, or liver impairment
(2) COPD patient with exacerbation
(3) Electrolyte disturbance that may impair the neurological studies
(4) Diabetic patients
(5) Chronic use of systemic steroids or any other drug affecting results
(6) Severe decompensated respiratory failure impeding the study
(7) Previous cerebral stroke or any neuropsychiatric condition.

Ethical approval

The study was approved by the Institutional Ethics Committee of Assuit University. In addition, written informed consent was given by all patients and the control group before participation in the study.

Work-up scheme

All patients were subjected to careful history taking. Height, body weight, and BMI were recorded, and full chest and neurological examination were performed. All routine investigations to apply exclusion criteria were performed. All patients eligible to participate had undergone the following:

(1) Spirometric evaluation: Conventional spirometry by Zan 300; Sensor (Company nSpire Health™, Medics MGA USB, Germany), was performed to COPD and control groups. The reference values used were those of the American Thoracic Society standards. The following parameters were observed and recorded for the research: FEV1 percent of predicted and volume in liters, FEV1/FVC ratio, and FVC percent of predicted and volume in liters

(2) Gasometric evaluation: Arterial blood gases sample was analyzed using the Radiometer blood gas analyzer. Arterial blood acidity (pH), partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), arterial oxygen saturation (SaO_2), arterial bicarbonate level (HCO_3^-), and base excess or deficit were recorded
(3) Psychometric evaluation study including the following:
    (a) Wechsler Adult Intelligence Scale-III (WAIS-III)

    The procedures for administering and scoring the three Wechsler scales are similar. Each test has two batteries of subtests grouped into two general areas: The verbal scales measure general knowledge, language, reasoning, and memory skills, and the performance scales measure spatial, sequencing, and problem-solving skills. The tests are administered to individual examinees by trained examiners, using a complex set of test materials. Testing requires ~90 min. Raw scores on each test are converted to standard scores with a mean of 10 and a SD of 3 [10]. Scale scores in the verbal battery are summed and converted to a verbal IQ score; the same is done for the performance scale scores, which yield the performance IQ score. In turn, the verbal and performance IQ scores were summed and converted to obtain the full-scale (overall) IQ score [11]

    Interpretation: The verbal, performance, and full-scale IQ scores are normative IQs, having a mean of 100 and a SD of 15. Full-scale scores beyond 130 place an individual in the superior or 'gifted' range. Scores between 120 and 129 are classed as 'very high.' Scores between 110 and 119 are 'bright normal.' Classifications of other scores are as follows: 90–109, average; 85–89, low average; 70–84, borderline mental functioning; 50–69, mild mental retardation; 35–49, moderate retardation; 20–34, severe retardation; and below 20–25, profound retardation. Therefore, a cutoff value below 84% was considered impairment [12].

    (b) Mini-Mental State Examination (MMSE).

The MMSE measures various domains of cognitive function including orientation to time and place; registration, concentration, short-term recall, naming familiar items, and repeating a common expression; and the ability to read and follow written instructions, write a sentence, construct a diagram, and follow a three-step verbal command. The MMSE takes ~10 min to administer. It provides a baseline score of cognitive function and pinpoints specific deficits that can aid in forming a diagnosis [13].

The MMSE or Folstein test is a 30-point questionnaire and examines functions including registration, attention, calculation, recall, language, ability to follow simple commands, and orientation.

Interpretation

Dementia was classified according to the MMSE score as 21–17 for mild and 16–9 for moderate in illiterate patients; these values correspond to the values of 23–19 and 18–11 for mild and moderate dementia, respectively, using the full score of 30 points in case of educated patients [14].

Statistical analysis

Data were recorded to Statistical Package for Social Science statistical software computer program, version 20, Medcalc v. 11.6. (MedCalc Software company, Belgium), and Open Epi V.3.01.

Data were described using mean±SD and frequencies according to data are quantitative or qualitative, respectively. Nonparametric tests were used in the current study; Mann–Whitney test was used for comparison of results between COPD and control groups, and Spearman's correlation coefficient was used for correlation between cognitive dysfunction and spirometric, as well as gasometric, parameters of COPD patients. *P*-value below 0.05 was accepted as significant.

Recipient operator curves (ROC) were plotted to investigate the probability of some gasometric and spirometric parameters, which could be a detector of some cognitive dysfunction in COPD patients and to detect the cutoff value for these parameters.

Results

We enrolled 25 stable COPD patients and 25 age-matched and sex-matched healthy controls. Mean age and sex were 57.28 ± 5.55 years, 14 male, in the CODP group and 56.36 ± 5.17 years, 13 male, in the control group with no significant difference. Detailed demographic data of both groups are represented in Table 1.

However, spirometric evaluation showed that there was a significant difference between the COPD group and the control group in all gasometric and spirometric parameters, except for blood acidity (pH). Table 2 shows detailed spirometric and gasometric parameters.

The mean values of WAIS-III edition in the COPD group were compared with those of the control group.

There were significantly lower scores in all components of the WAIS-III scale, namely verbal IQ, performance IQ, and full-scale IQ, and COPD patients had higher deterioration index than in the control group, with a *P*-value less than 0.0001, as shown in Table 3. The frequency of cognitive dysfunction using WAIS-III scale among COPD patients was 56%.

There was a significant positive correlation between performance IQ of WAIS-III and both SaO_2 and PaO_2 (r = 0.506, P = 0.004 and r = 0.440, P = 0.028, respectively).

ROC curves were plotted to evaluate the use of SaO_2 level as a screening tool for the decrease of WAIS performance IQ in the COPD group. They denoted good use of SaO_2 level as screening tool for the decrease of WAIS performance IQ in the COPD group, as represented in Fig. 1. ROC curve was also plotted to evaluate the use of PaO_2 level as a screening tool for the decrease of WAIS performance IQ in the COPD group. It revealed the usefulness of PaO_2 level as a screening tool for decrease of WAIS performance IQ in the COPD group, as shown in Fig. 2.

Evaluation of the COPD group and control group using MMSE showed significant impairment of intellectual function in the COPD group compared with the control group. Total MMSE score among COPD versus control group was 23.72 ± 1.45 versus 27.24 ± 1.1, with a *P*-value less than 0.0001. The overall frequency of cognitive impairment among COPD group using MMSE was 72%.

There was a significant positive correlation between MMSE and SaO_2 with r of 0.494 and P-value of 0.012.

ROC curve was plotted to evaluate the use of SaO_2 level as a screening tool for the decrease of MMSE in the COPD group. It denoted excellent use of SaO_2 level as a screening tool for the decrease of MMSE in the COPD group, as represented in Fig. 3.

Discussion

COPD is an increasingly common disease among older adults that has been linked to other comorbid conditions with serious morbidity and mortality, including cardiovascular conditions, such as hypertension, stroke, and other heart diseases, and psychiatric illnesses [15]. In this study, we found that severe patients with COPD were also associated with lower cognitive performance using population-based longitudinal data. Our findings should raise awareness that adults with severe COPD are at a greater risk of

Table 1 Detailed demographic data of chronic obstructive pulmonary disease and control groups

	COPD group (*n*=25)	Control group (*n*=25)	*P*
Sex			
Male	14	13	0.777
Female	11	12	
Age (years)			
Mean±SD	57.28±5.55	56.36±5.17	0.448
Smoking			
Smoker	5	4	0.691
Ex-smoker	11	9	
Nonsmoker	9	12	
Residence			
Urban	8	10	0.556
Rural	17	15	
Dominant hand			
Right-handed	22	21	0.684
Left-handed	3	4	
Education			
Literate	9	11	0.627
Illiterate	16	14	
Duration of illness in years (mean±SD)		14.6±4.6	

COPD, chronic obstructive pulmonary disease.

Table 2 Detailed spirometric and gasometric parameters of the studied groups

	COPD group (*n*=25) (mean±SD)	Control group (*n*=25) (mean±SD)	*P*
FEV1 (l)	1.28±0.55	3.18±0.92	<**0.0001***
FEV1 (%)	45.72±16.65	93.88±8.91	<**0.0001***
FVC (l)	2.77±0.71	3.65±0.96	**0.001***
FVC (%)	82.64±15.67	95.40±11.13	**0.003***
FEV1/FVC (%)	46.16±13.27	85.68±4.76	<**0.0001***
BMI (kg/m^2)	22.74±5.52	28.50±6.36	**0.001***
PH	7.40±0.04	7.41±0.02	0.152
$PaCO_2$ (mmHg)	67.32±12.98	39.64±3.67	<**0.0001***
PaO_2 (mmHg)	61.88±5.18	84.64±5.97	<**0.0001***
SaO_2 (%)	91.12±2.05	96.80±1.19	<**0.0001***
HCO_3 (meq/l)	38.23±4.71	18.00±2.27	<**0.0001***
BE/BD (mmol/l)	13.48±5.09	2.16±1.40	<**0.0001***

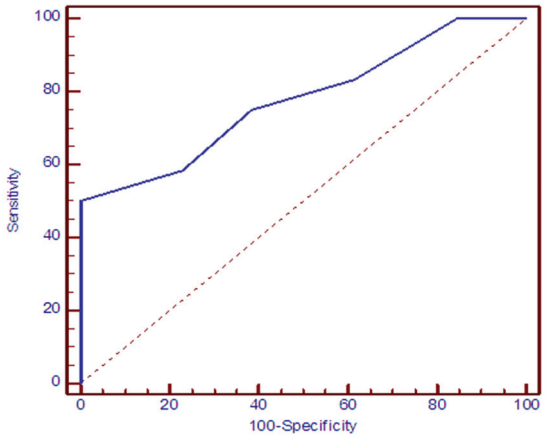
Bold and * value means the presence of statistically significant difference between the two groups. BE/BD, base excess/deficit; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in the first second; FEV1/FVC, forced expiratory volume/forced vital capacity ratio; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HCO_3, serum biocarbonate level; PCO_2, partial arterial pressure of carbon dioxide; PH, blood arterial acidity; PO_2, partial arterial pressure of oxygen; SaO_2, arterial oxygen saturation.

Table 3 Detailed results of Wechsler Adult Intelligence Scale-III scale

Groups	COPD group (mean±SD)	Control group (mean±SD)	*P* value
Verbal WAIS IQ	78.84±6.08	90.68±3.79	<0.0001*
Performance WAIS IQ	87.36±8.03	100.56±4.73	<0.0001*
Total WAIS IQ	80.67±17.30	93.36±3.19	<0.0001*
Deterioration index	17.30±7.53	4.59±3.38	<0.0001*

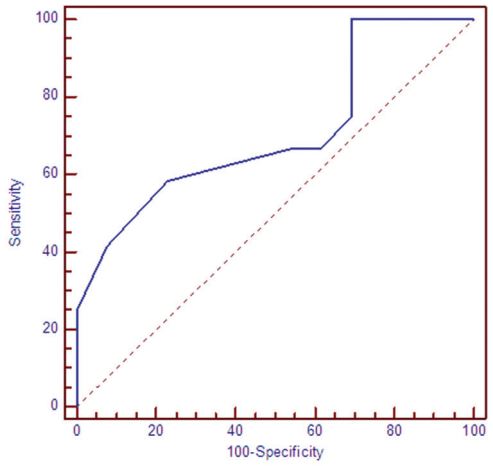
*Statistically significant difference between the two groups. COPD, chronic obstructive pulmonary disease; WAIS, Wechsler Adult Intelligence Scale.

Figure 1



Receiver operating characteristics curve was plotted to evaluate the use of SaO_2 level as a screening tool for the decrease of Wechsler Adult Intelligence Scale (WAIS) performance IQ in the chronic obstructive pulmonary disease (COPD) group. It denoted good use of SaO_2 level as screening tool for decrease of WAIS performance IQ in COPD group with, with a sensitivity of 50%, a specificity of 100%, positive predictive value of 100%, negative predictive value of 68%, cutoff value for oxygen saturation of up to 89%, and area under the curve of 0.776.

Figure 2



Receiver operating characteristics curve was plotted to evaluate the use of PaO2 level as a screening tool for the decrease of Wechsler Adult Intelligence Scale (WAIS) performance IQ in the chronic obstructive pulmonary disease (COPD) group. It revealed the usefulness of PaO_2 level as a screening tool for the decrease of WAIS performance IQ in the COPD group, with a sensitivity of 58%, specificity of 76%, positive predictive value of 70%, negative predictive value of 66%, cutoff value for oxygen tension of up to 59 mmHg, and area under the curve of 0.708.

developing cognitive impairment, which may make managing their COPD more challenging, and will likely further worsen their general health and quality of life, both of which can be severely affected by COPD.

Our study revealed that the frequency of cognitive impairment in COPD patients evaluated by WAIS-III scale and MMSE was 56 and 72%, respectively. Scores of these patients were positively correlated with oxygen tension and saturation.

The key mechanism proposed for cognitive dysfunction in COPD is neuronal damage mediated through hypoxia, but it has also been suggested that oxygen-dependent enzymes, which are important in the synthesis of neurotransmitters, such as acetylcholine, may be affected [16]. Moreover, a magnetic resonance spectroscopy study in patients with nonhypoxic severe COPD showed that cerebral metabolism was significantly altered and that the pattern of derangement differed from that seen in heart failure and diabetes [17].

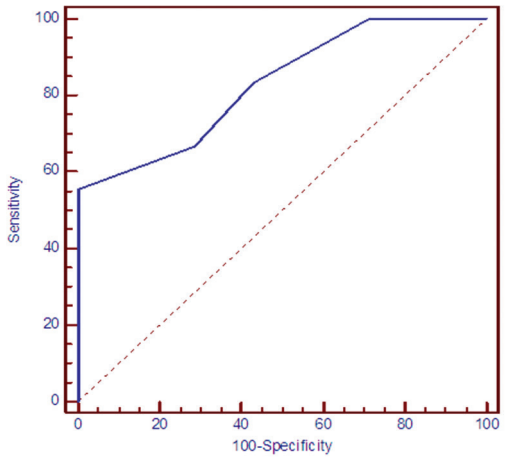
Inflammation may play a role, as there is evidence that C-reactive protein may be associated with cognitive decline, either through a direct neurotoxic effect or an effect on cerebral atherosclerosis. Other inflammatory mediators have also been linked to cognitive dysfunction, including interleukin-6, interleukin-1b, tumour necrosis factor-α, and α1-antichymotrypsin. However, these studies suggest an association rather than a causal link [18].

In concomitance with our results [19], they enrolled 54 COPD patients divided into two groups. Group I COPD without respiratory failure (n = 2), group II COPD with respiratory failure (n = 33), and controls (n = 40). Cognitive dysfunction was evaluated using MMSE scale and Kufman Short Neuropsychological Assessment Procedure. There was a significant impairment in cognitive function in both COPD groups and in the control group. There was also significant worse cognitive function in the COPD group with than in the group without respiratory failure. In addition, there was a positive correlation between FEV1% and MMSE recall score results.

In comparison with values of the control group, our results were in agreement with a case–control study by Orth *et al.* [15] who compared 32 patients with COPD (moderate) and 10 healthy controls. The tests used were ZVT, MWT, VLMT, WRG S5, Cognitrone S2, WDG, and TAP. Patients with COPD had significantly worse results in 14 out of 20 tests, compared with healthy controls. Domains such as intelligence and attention were significantly impaired, whereas memory, speed, and coordination were not impaired.

Another descriptive study of 149 patients with COPD (severe) supported our results by Antonelli-Incalzi *et al.* [20]. The tests used were Raven progressive matrices, verbal fluency, verbal memory, Albert's test, copying drawings, and Wechsler sentence construction. Results showed that 35% of

Figure 3



Receiver operating characteristics (ROC) curve was plotted to evaluate the use of SaO_2 level as a screening tool for the decrease of Mini-Mental State Examination (MMSE) in the chronic obstructive pulmonary disease (COPD) group. It denoted excellent use of PaO_2 level as a screening tool for the decrease of MMSE in the COPD group, with a sensitivity of 55%, specificity of 100%, positive predictive value of 100%, negative predictive value of 46%, cutoff value of 90 or less, and AUC of 0.829.

patients (52/149) had significantly lower cognitive performance in five out of 12 tests. Visual attention, verbal fluency, and memory were the most affected domains among those patients.

To evaluate the direct influence of hypoxemia on cognition in two COPD subgroups and a control group, Borson *et al.* [21] studied 18 patients with COPD (severe and very severe) compared with nine healthy controls. The tests used were wide-range achievement test 3, Wechsler Memory Scale, and WAIS. Results revealed that COPD patients differed significantly from healthy controls in some of the intelligence ($P < 0.03$) and memory ($P < 0.05$) tests, but not in all. Moreover, lower scores of cognitive performance were measured in oxygen-dependent COPD patients than in nonoxygen-dependent COPD patients.

Our results were supported by another large study by Hung *et al.* [22]. In a community sampled case–control study, they enrolled 4150 COPD patients –29% severe (oxygen depended or disease relatedactivity limited, age = 62.6 ± 1.8 years) and 71% nonsevere (age = 62.9 ± 2.1 years). Results of these patients showed that only severe COPD was associated with lower cognitive performance.

Another large study was performed in agreement with our results by Schurea *et al.* [5]. They enrolled 301 stable COPD patients who completed the Trail Making Test (TMT-A: psychomotor speed and TMT-B: executive control) and 198 patients who completed the Memory Impairment Screen. Using multivariable regression, they examined the relationship between the TMT-A, TMT-B, and Memory Impairment Screen with physical functioning (physical activity, 6 min walk test, and grip strength) and health-related quality of life measured with the Chronic Respiratory Questionnaire and the SF-36. Results of those patients showed that nearly 30% of patients had either borderline or impaired cognition on the TMT-A or TMT-B. Adjusted models indicated that those with either borderline or impaired cognitive functioning had weaker grip strength (TMT-A borderline: $\beta = -2.9$, $P < 0.05$; TMT-B borderline: $\beta = -3.0$, $P < 0.05$; TMT-B impaired: $\beta = -2.5$, $P < 0.05$) and lower scores on the mental health component summary score (MCS-SF-36 HRQOL) measure (TMT-A impaired: $\beta = -4.7$, $P < 0.01$).

Alternatively, the studies by Emery *et al.* [23] and Watanabe *et al.* [24] aimed to evaluate the role of lung reduction surgery and rehabilitation in improving cognition, and they proved that improving indices of COPD severity improves cognition. Emery and his colleagues enrolled 29 patients – age = 67.8 ± 7.4 years, FEV1 = 43 ± 17% – and 29 controls. They studied the exercise effects and found improved performance in verbal fluency test with exercise. However, Watanabe *et al.* [24]reported that one patient – aged 71 years old, FEV1 = 39% – showed improvement of all cognitive functions after lung volume reduction surgery.

Conclusion

Cognitive dysfunction is a fixed finding that occurs early in the course of COPD. It should be monitored and followed up early. Hypoxemia seems to play the principal role in cognitive disorders. Spirometric parameters seem to be closely related to the progression and prediction of the course of those disorders.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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