Risk factors of cognitive dysfunction among patients with chronic obstructive pulmonary disease

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Background
Cognitive dysfunction is one of the most common comorbidities related to chronic obstructive pulmonary disease (COPD), with ~70% of patients developing such condition. Besides, cognitive dysfunction has been established to be a potential predictor of mortality and morbidity.
Aim
This study was conducted to assess the possible causes of cognitive dysfunction among patients with COPD.
Patients and methods
Patients with COPD aged more than 40 years were included in the current study. Patients were further assorted into two groups based on the assessment of cognition state using Mini Mental State Examination: patients who had COPD without cognitive dysfunction (control group) and patients who had COPD with cognitive dysfunction (case group).
Results
A total of 120 participants were included in the study. Of them, 60 patients experienced COPD without cognitive dysfunction (control group) whereas 60 patients experienced COPD with cognitive dysfunction (case group). There was a statistically significant difference between both groups regarding the education level (P=0.038), intelligence quotient levels (P=0.004), duration of symptoms (P=0.042), and Modified Cumulative Illness Rating Scale (MCIRS) (P=0.001). The results of regression model showed that patient's age (P=0.01), MCIRS (P=0.041), duration of symptoms (P=0.03), and education state (P=0.029) were statically significant predictors of Mini Mental State Examination score.
Conclusion
The findings of our investigation increase the awareness that despite the controlled COPD, elderly obese patients with high MCIRS score and long duration of symptoms were more susceptible to develop cognitive dysfunction.

Keywords:
causes, chronic obstructive pulmonary disease, cognitive dysfunction

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Introduction

Chronic obstructive pulmonary disease (COPD) is deemed to be a life menacing disease (Lopez-Campos *et al.*, 2016). To date, COPD affects ~600 million patients worldwide; thereafter, it is estimated to be the third leading cause of death and the fifth leading cause of disability by 2020 (Jemal *et al.*, 2005; Smith and Wrobel, 2014). The burden of COPD is still mounting owing to the increased smoking rate and air pollution, principally among the elderly population (Negewo *et al.*, 2015).

Noteworthy, COPD is a multisystem disease with numerous extrapulmonary consequences (Celli *et al.*, 2018). In particular, COPD is characterized by pulmonary manifestations apart from progressive and irreversible airflow obstruction along with extrapulmonary manifestations such as impairment of brain function (Lopez-Torres *et al.*, 2016). The brain is more susceptible to the systemic effects of COPD, which in turn lead to the development of abundant neurological impairment and cognitive dysfunction (Kakkera *et al.*, 2018; Lawi *et al.*, 2018). Cognitive dysfunction is one of the most common comorbidities related to COPD, whereby nearly 70% of patients with COPD developed such condition (Lawi *et al.*, 2018). In addition, cognitive dysfunction has been established to be a potential predictor of mortality and morbidity among patients with COPD (Yohannes *et al.*, 2017). Accordingly, patients showed inadequate compliance to oxygen

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therapy and medication, which in turn enhance considerably the risk of acute exacerbation (Bajaj *et al.*, 2019). In addition, cognitive dysfunction had multiple repercussions on health status, patient function, and quality of life (Cleutjens *et al.*, 2017).

Of note, COPD is often associated with many comorbidities, comprising hypertension, ischemic heart disease, lung cancer, and diabetes (Cleutjens *et al.*, 2018). These factors coupled with the sequential hypoxia and hypercapnia might be attributed to the pathogenesis of cognitive dysfunction among patients with COPD (Dag *et al.*, 2016). Recently, the prevalence of cognitive dysfunction is rising, particularly with the increasing awareness of such condition along with the advancement in the neurodiagnostic tools (Cleutjens *et al.*, 2018). However, the literature is still doubtful about the detection of the possible risk factors and predictors of cognitive dysfunction among patients with COPD. To shed light on this issue, this study was conducted to assess the possible causes and predictors of such condition among patients with COPD.

Patients and methods

Ethical consideration

The present study was executed based upon the recommendations of the Ethical Research Board of the Faculty of Medicine, Al-Azhar University, Cairo, Egypt. The potential risk events and complications were illustrated obviously for the included patients, legal trustee, or their relatives before study implementation. Informed consents were obtained before study conduction. Furthermore, all clinical procedures were carried out along with the guidelines of the Declaration of Helsinki.

This is a prospective observational case–control study that was implemented at the Psychiatry and Pulmonology Departments, Sayed Galal and Al-Zahraa University Hospitals, Faculty of Medicine, Al-Azhar University, Cairo, throughout the entire period of June 2017 to January 2019.

Inclusion criteria

Patients with COPD, established clinically based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, and aged more than 40 years were included in the current study. Patients were further assorted into two groups based on the assessment of cognition state using Mini Mental State Examination (MMSE): patients who had COPD without cognitive dysfunction (control group) and patients who had COPD with cognitive dysfunction (case group).

Exclusion criteria

Patients with COPD who experienced exacerbation attacks within 4 weeks before the study conduction were excluded. Similarly, patients with severe decompensated respiratory failure and uncontrolled coronary heart disease, diabetes, hypertension, heart failure, liver impairment, renal insufficiency, encephalitis, or epilepsy were omitted.

Patients having a history of brain tumor, head injury, previous stroke, or having a major psychiatric illness or dementia were ousted (based on the American Psychiatric Association). Eventually, patients treated by cortisone for a long period were excluded as well.

Patient evaluation

Clinical assessment

All patients were subjected to history taking to reveal the following data: age, sex, BMI, duration of symptoms, history of COPD exacerbation, and symptoms. Besides that, patients were clinically evaluated to reveal the evidence of visual and hearing impairment along with complete neurological examination.

The Modified Cumulative Illness Rating Scale

It is a method for recording all the associated comorbidities of the included participants. It assorted the diseases of 14 organ systems, whereas each organ was scored 0–4 based on the severity of affection (Miller *et al.*, 1992).

Pulmonary function tests

Conventional spirometry was used to evaluate the pulmonary function for each participant via portable dry rolling SpiroBank spirometer (Company nSpire Health; Medics MGA USB, Oberthulba, Germany). The reference values were calculated based on the guidelines of the American Thoracic Society. Spirometry measured forced vital capacity and forced expiratory volume in 1 s (FEV1), and the ratio of these two measurements (FEV1/forced vital capacity) is then calculated.

Blood gas analysis

With the patients holding their breath, radial arterial blood was aspirated using a heparinized syringe, positioned on ice, and taken to a blood gas laboratory for analyses. Using the radiometer blood gas analyzer, arterial blood acidity (pH), partial

pressure of arterial oxygen, partial pressure of arterial carbon dioxide, arterial oxygen saturation, arterial bicarbonate level, and base excess or deficit were calculated.

Psychological assessment

Mini Mental State Examination

It evaluated the overall assessment of cognitive function, as it is associated with extensive memory testing and cognitive decline among patients with COPD. Patients were given a score between 0 and 30, whereby patients scored more than 24 were considered having normal cognitive function (Incalzi *et al.*, 1993, Incalzi *et al.*, 1998).

Assessment of psychological well-being

Manifestations of anxiety and depression were assessed based on the hospital anxiety and depression scale (HADS). This scale is composed of a subscale, which ranged from 0 to 21 points. The patients were assorted based on their score into normal (0–7), borderline (8–10), and abnormal (11–21) levels of anxiety and depression. Subsequent to that, the Beck Depression Inventory was carried out to evaluate the depth, intensity, and severity of depression using a 21-item questionnaire. This score ranged from 0 to 63, where patient scores 0–9 represent not depressed, patient scores 10–18 and 19–29 represent mild–moderate and moderate–severe depression, respectively; and patient scores 30–63 represent severe depression (Zigmond and Snaith, 1983; Beck *et al.*, 1961).

Using the Symptom Checklist 90 (SCL-90), the psychological system intensity for each participant was assessed (Derogotis *et al.*, 1973).

Statistical analysis

Continuous variables were explicated in the form of mean and SD, and its confidential groups were compared using Student *t* test. On the contrary, categorical variables were expressed using the number and percentage, and its particular groups were compared using Pearson's χ^2 test with Fisher's exact test. In addition, correlation analysis was conducted using Spearman's rank correlation coefficient. The univariate linear regression model was established to reveal the possible predictors of cognitive dysfunction among patients with COPD using MMSE scale. The significance is established when *P* value less than 0.05. Statistical analysis was performed using SPSS software, version 23 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Patients' demographic characteristics

A total of 120 participants were included in the study. Based on MMSE, 60 patients experienced COPD without cognitive dysfunction (control group), whereas 60 patients experienced COPD with cognitive dysfunction (case group). The mean age of the included patients was 55.31±7.23 and 56.48±6.41 years (*P*=0.81) among case and control groups, respectively. There was a statistically significant difference between both groups regarding the education level (*P*=0.038), where 45 (65%) patients among the case group were illiterates and 31 (51.6%) patients among the control group were illiterates. In this respect, there was a statistically significant low intelligence quotient level (*P*=0.004) among the case group, with a mean of 73.98±6.45, in contrast to the control group, with a mean of 91.77±4.87. Furthermore, the patients among the case group showed statistically significant (*P*=0.042) long duration of symptoms (18.61±4.29 years), relative to the patients among the control group (13.7±3.5 years). Subsequent to that, there was a statistically significant (*P*=0.001) high Modified Cumulative Illness Rating Scale (MCIRS) among the case group when compared with the control group, with a mean of 26.79±3.87 and 19.51±2.31, respectively (Table 1 and Figs 1 and 2).

Based on pulmonary function tests, there was no statistically significant difference between the case and the control groups regarding the levels of FEV1 (*P*=0.059), partial pressure of arterial oxygen (*P*=0.73), and partial pressure of arterial carbon dioxide (*P*=0.905). Similarly, there was no statistically significant difference between both groups regarding the number of patients received oxygen therapy (*P*=0.86) (Table 1 and Fig. 3).

Patients' psychological assessment

The mean levels of MMSE scores differed substantially (*P*=0.002) between the case and the control groups, with a mean of 19.203±3.41 and 27.3±3.1, respectively. On the contrary, there was no statistically significant difference between both groups regarding HADS depression score (*P*=0.8), HADS anxiety score (*P*=0.61), Beck Depression Inventory score (*P*=0.79), SCL-90 anxiety score (*P*=0.804), SCL-90 agoraphobia score (*P*=0.58), and SCL-90 depression score (*P*=0.091) (Table 2 and Fig. 4).

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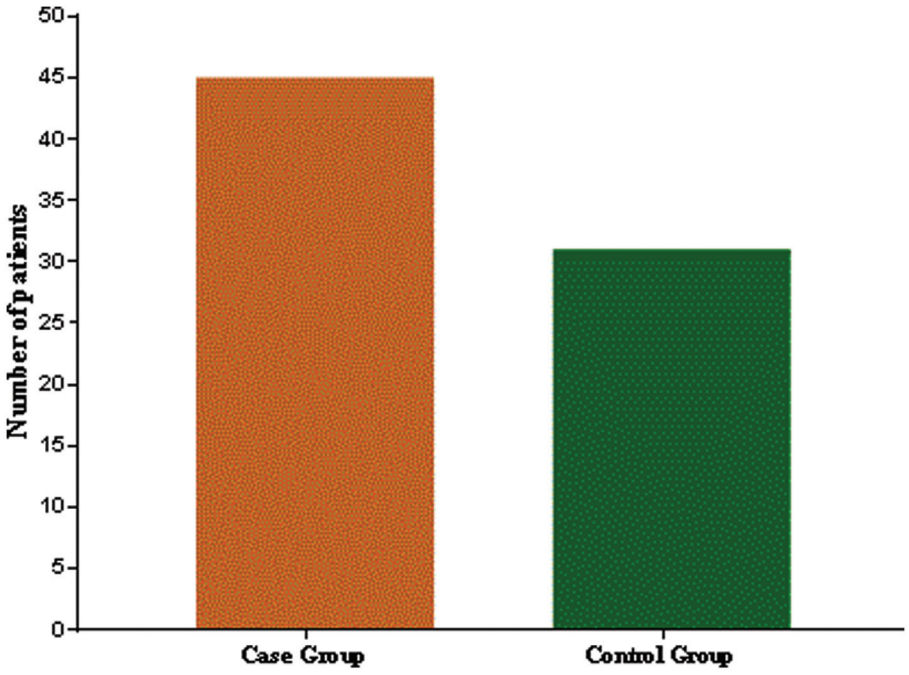
Correlation analysis showed that there was a significant negative correlation between MMSE score and the age of the patients (*r*=–0.4, *P*=0.039), BMI (*r*=–0.37,

Table 1 Patients' demographic characteristics

Variables	Case group (*N*=60) [mean (SD)/*n* (%)]	Control group (*N*=60) [mean (SD)/*n* (%)]	*P* value
Age	55.31±7.23	56.48±6.41	0.81
Sex (male)	39 (65)	41 (68.3)	0.92
BMI (kg/m^2)	26.41±3.31	27.8±4.56	0.46
Education level (illiterate)	45 (75)	31 (51.6)	0.038
IQ level	73.98± 6.45	91.77±4.87	0.004
Dominant right hand	52 (86.6)	49 (81.6)	0.67
Duration of symptoms (years)	18.61±4.29	13.7±3.5	0.042
Visual impairment	25 (41.66)	31 (51.6)	0.19
Hearing impairment	17 (23.3)	26 (43.3)	0.3
Oxygen therapy	22 (36.6)	28 (46.6)	0.86
Spirometry and arterial blood gases			
FEV1% predicted	56.6±14.21	53.22±11.21	0.059
PaO_2 (mmHg)	71.5±9.45	74.33±12.65	0.73
$PaCO_2$ (mmHg)	38.22±4.67	39.43±3.21	0.905
Smoking behavior			
Current smokers	47 (78.3)	38 (36.6)	0.82
Previous smokers	13 (21.6)	14 (23.3)	0.96
Never smoking	0	8 (13.3)	–
MCIRS	26.79±3.87	19.51±2.31	0.001

FEV1, forced expiratory volume in 1 s; IQ, intelligence quotient; MCIRS, Modified Cumulative Illness Rating Scale; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen.

Figure 1



Bar chart displaying the pattern of education (illiterate) among the studied group.

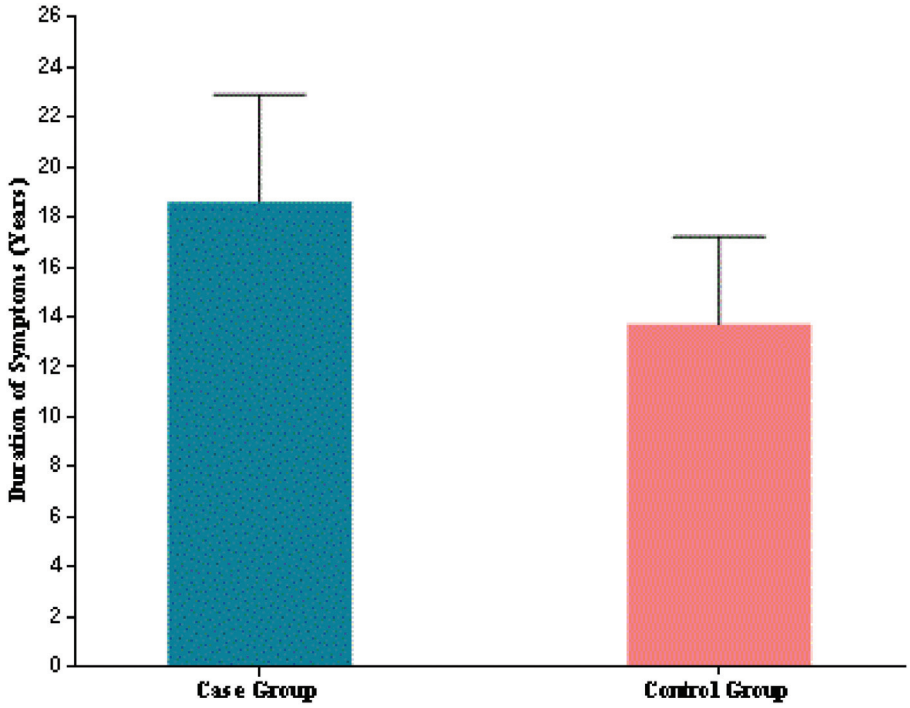
P=0.02), MCIRS (-0.61, *P*=0.001), and duration of symptoms (*r*=-0.54, *P*=0.04). Subsequently, there was a significant positive correlation between MMSE score and the number of literates (*r*=0.81, *P*<0.001), and intelligence quotient levels (*r*=0.45, *P*=0.046) (Table 3).

The results of regression model displayed that patients' age (*P*=0.01), MCIRS (*P*=0.041), duration of symptoms (*P*=0.03), and education state (*P*=0.029) were statically significant predictors of MMSE score (Table 4).

Discussion

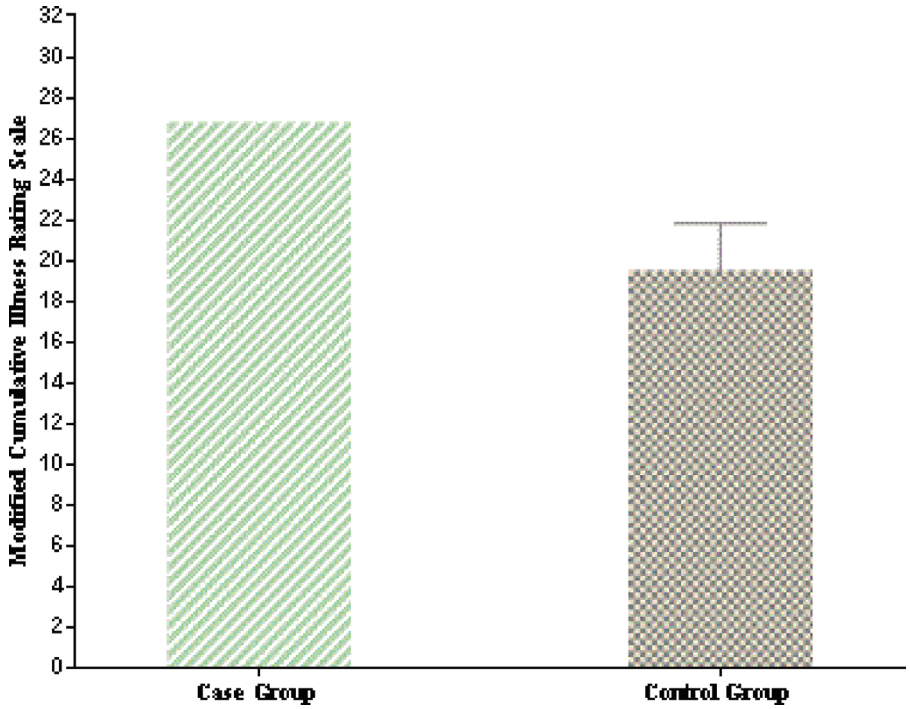
COPD is a progressive multicomponent disease that altered noticeably several functions of multiple organs

Figure 2



Error bar chart displaying the duration of symptoms among the studied group.

Figure 3



Error bar chart displaying the mean MCIRS among the studied group. MCIRS, Modified Cumulative Illness Rating Scale.

besides its significant effect on lung and heart (Dal Negro *et al.*, 2015). The presence of significant cognitive dysfunction was found to be related to the severity of the disease; however, some studies showed that cognitive deterioration may occur even among patients with controlled COPD (Metwally *et al.*, 2017).

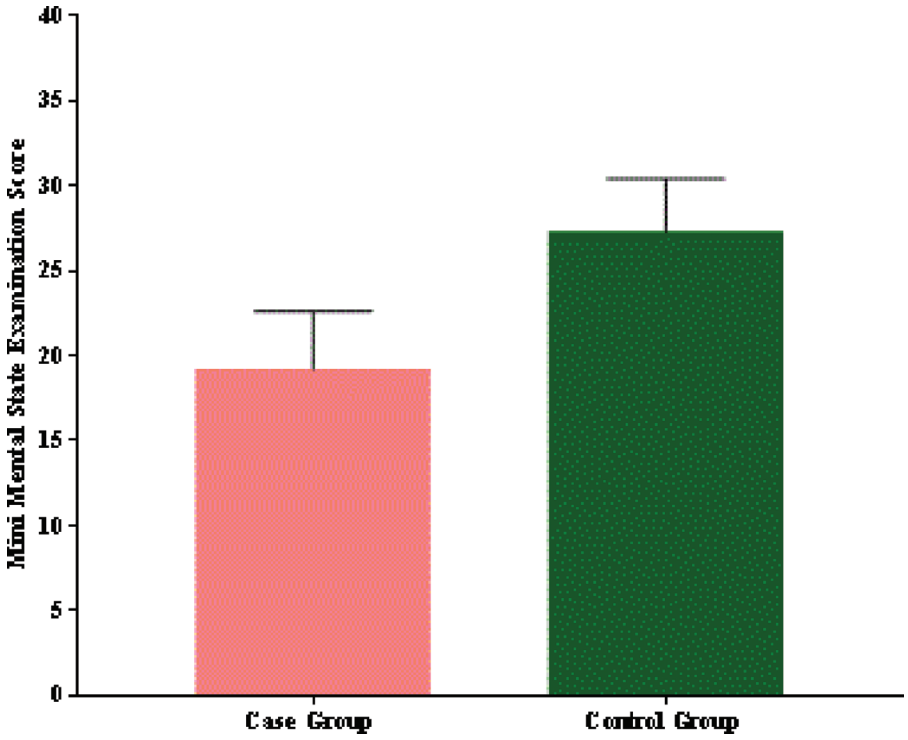
Finding the possible risk factors of cognitive deterioration among patients with stable COPD is a doubtful question in the literature. This is because the inadequate number of studies had abundant limitations. Herein, the evidence abbreviated in our investigation brings to light that even if

Table 2 Patients' cognitive and psychological assessment

Variables	Case group [mean (SD)/*n* (%)]	Control group [mean (SD)/*n* (%)]	*P* value
MMSE	19.203±3.41	27.3±3.1	0.002
Psychological well-being			
HADS depression score (points)	8.21±2.54	7.36±1.94	0.8
HADS anxiety score (points)	9.1±2.9	7.45±2.34	0.61
BDI score (points)	19.51±4.02	17.67±3.6	0.79
SCL-90 anxiety score (points)	16.42±2.3	17.02±1.69	0.804
SCL-90 agoraphobia score (points)	11.8±2.6	10.6±1.1	0.58
SCL-90 depression score (points)	29.66±3.79	26.4±2.09	0.091
SCL-90 somatization score (points)	24.88±3.42	22.6±307	0.17
SCL-90 insufficiency score (points)	19.08±2.4	18.3±3.1	0.4
SCL-90 sensitivity score (points)	27.4±1.9	25.3±2.04	0.59
SCL-90 hostility score (points)	7.55±1.3	7.07±1.2	0.69
SCL-90 insomnia score (points)	14.5±1.59	13.2±1.41	0.48
SCL-90 psychoneuroticism score (points)	159.63±12.92	149.2±11.043	0.062

BDI, Beck Depression Inventory; HADS, hospital anxiety and depression scale; MMSE, Mini Mental State Examination; SCL, Symptom Checklist.

Figure 4



Error bar chart displaying the mean MMSE scores among the studied group. MMSE, Mini Mental State Examination.

patients with COPD did not experience significant deterioration of their pulmonary function tests, they may develop cognitive dysfunction. Thereafter, patients with COPD should be subjected to comprehensive follow-up protocol comprehending cognitive assessment as a part of the respiratory assessment.

These results might be attributed to the associated persistent hypoxemia, which directly causes neural damage. In detail, the brain has the highest oxygen demand in the body; therefore, it is highly sensitive to ischemia (Lee *et al.*, 2000). If the oxygen supply is inadequate to fulfill the metabolic demands of the brain, this can lead to a lack of cerebral neurons (Lawi *et al.*, 2018). In addition, it also affects oxygen-dependent enzymes, which are extremely pivotal in the synthesis of different neurotransmitters likewise acetylcholine. Besides, elevated carbon dioxide tension along with hypercapnia plays a major role in the development of cognitive dysfunction (López-Torres *et al.*, 2016).

Table 3 Correlation between patients' demographics and Mini Mental State Examination score

Variables	Correlation coefficient (*r*)	*P* value
Age	–0.4	0.039
BMI	–0.37	0.02
MCIRS	–0.61	0.001
Duration of symptoms	–0.54	0.04
% predicted FEV1	0.1	0.69
PaO_2	0.08	0.078
$PaCO_2$	–0.01	0.092
Education (literates)	0.81	<0.001
IQ level	0.45	0.046

FEV1, forced expiratory volume in 1 s; IQ, intelligence quotient; MCIRS, Modified Cumulative Illness Rating Scale; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen.

Table 4 Univariate linear regression model to predict cognitive dysfunction based on Mini Mental State Examination score

Variables	*?*	*P* value
Age	–0.63	0.01
BMI	0.02	0.6
MCIRS	–0.3	0.041
Duration of symptoms	–0.5	0.03
Education (illiterate)	0.2	0.029

MCIRS, Modified Cumulative Illness Rating Scale.

For patients with stable COPD state, the underlying cause of cognitive impairment may be related to neurophysiological consequences such as continuous decline of prefrontal cortex circulation (Dal Negro *et al.*, 2014). In this respect, Shim *et al.* (2001), notified that cerebral metabolism was noticeably affected, whereas the pattern of derangement was considerably high based on the magnetic resonance spectroscopy among controlled patients with COPD. Subsequently, a study by Metwally *et al.* 2017 (Kozora *et al.*, 1999) showed that there was a significant impairment of cognitive dysfunction, based on MMSE scale, among patients with COPD despite the absence of respiratory failure.

The results of our study showed that elderly obese patients with high MCIRS score coupled with a long duration of symptoms were more vulnerable to develop cognitive dysfunction. This result might be attributed to the increase in the oxidative stress and inflammation process coupled with the decline of physical activity can express the process of aging, which in turn enhance considerably the neurodegenerative changes (Thakur *et al.*, 2018). In compliance with our results, Dag *et al.* (2016), reported that there was a significant difference between patients who developed cognitive dysfunction and those who did not develop regarding the age (*P*=0.001), education level (*P*=0.04), and MCIRS (*P*=0.01), which were also predictors of cognitive performance among patients with COPD.

Despite the evidence retrieved in our study, this study had some limitations, such as lack of randomization along with short-follow up period, which hinder the capability to detect long-term consequences of cognitive dysfunction and may hinder the feasibility of our study.

Conclusion

The findings of our investigation increase the awareness that despite the controlled COPD, elderly obese patients with high MCIRS score and long duration of symptoms were more susceptible to develop cognitive dysfunction. Thereafter, cognitive evaluation should be a part of the routine respiratory assessment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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