

# Chronic Obstructive Pulmonary Disease and Extrapulmonary Effects: Cognitive Impairment

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### Abstract:

Chronic Obstructive Pulmonary Disease (COPD) is a public health problem which is increasing worldwide. Comorbidities usually occur in patients with COPD because COPD affects the physiological functions in a systemic manner. It has been reported that the ratio of cognitive impairment in COPD patients is higher than that of age-matched populations. Cognitive impairment thus has been proposed as a clinical manifestation in patients with COPD. Understanding all aspects of COPD and the effects of cognitive impairment on health outcomes for COPD patients therefore is essential for developing a holistic treatment.

**Keywords:** clinical assessment, cognitive function, cognitive impairment, comorbidities, COPD

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## Introduction

The World Health Organization (WHO) reports that chronic obstructive pulmonary disease (COPD) is the fifth leading cause of death and may become the third leading cause of death by 2030.<sup>1,2</sup> COPD often occurs as multi-morbidity, associated with 2 or more pathologic conditions.<sup>3</sup> Although multimorbidity frequently occurs in patients with COPD, its impact on clinical outcomes is still inconclusive.

COPD is prevalent in older populations and it can induce systemic physiological effects including cognitive impairment.<sup>4,5</sup> The literature suggests that cognitive dysfunction may have an impact on COPD regression.<sup>6</sup> This review thus aimed to examine COPD features and cognitive impairment in COPD patients. Online publications on COPD and cognitive impairment in COPD patients were researched and discussed. The review focused on recent publications in English and Thai up to 2018.

## Definition and cause

WHO has stated that “COPD is not simply a smoker’s cough, but an umbrella term for the diagnosis of chronic lung diseases causing respiratory airflow limitation, i.e., chronic bronchitis and emphysema. The usual symptoms of COPD are breathlessness, excessive sputum, and chronic cough”.<sup>2</sup> This definition is similar to the explanation from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), which states “COPD is identified by lung airflow limitation and continued respiratory symptoms. The airflow limitation arises from a mixture of small airway abnormalities and parenchymal destruction. The relative contribution of that mixture individually differs. Although COPD symptoms progressively increase, it is a common, preventable and treatable disease”.<sup>7</sup> The American Thoracic Society (ATS) and the European Respiratory Society (ERS) state that “COPD is a preventable and treatable disease classified by airflow limitation that is not fully reversible and is usually progressive. The airflow limitation is associated

with an inflammatory response of the lungs to noxious particles. Besides the effects on lungs, COPD also leads to systemic consequences”.<sup>8</sup> The definition of COPD from ATS and ERS emphasizes the extrapulmonary effects of COPD.

Tobacco smoking is a well-known cause of COPD.<sup>1</sup> However, it has been found that worldwide exposure to occupational pollution (i.e., organic and inorganic dusts, chemical agents, and fumes) and indoor air pollution (i.e., particles from burning biomass fuels) is increasing, particularly in low-income and middle-income countries, while the proportion of tobacco smokers is diminishing. Therefore, inhalation of these pollutants may pose a greater risk of COPD.<sup>9</sup> Besides causing COPD, repeatedly breathing in noxious agents has been widely reported to increase the risk of acute exacerbation and hospitalization. Therefore, prevention of exposure to pollution is the most important strategy for counteracting COPD.<sup>8</sup> Rather than a cumulative exposure to deleterious particles, other factors including genetics, airway hyper-responsiveness, childhood respiratory infection, and poor lung growth during gestation and in the early stages of life are also conducive to developing COPD, but in a smaller proportion.<sup>10</sup>

## Epidemiology and burden

A Global Burden of Disease study in 2015 reported the prevalence of COPD to be approximately 174 million cases worldwide.<sup>9</sup> In the same year, Adeloide et al. estimated that the prevalence was 384 million cases.<sup>11</sup> The estimation of COPD prevalence varies significantly among studies because there are various approaches for determining that prevalence.<sup>1,12-14</sup> Since collecting data for estimating COPD prevalence is costly, the available data of the prevalence mainly comes from high-income countries.<sup>1</sup> In Thailand, the Ministry of Public Health reported that COPD prevalence had increased from 2,268/100,000 people in 2,000 to 7,035/100,000 people in 2010.<sup>15</sup> Regarding gender differences: Although COPD occurs more often in men, a

higher exposure to indoor air pollution and a higher susceptibility to develop airflow limitation in women might alter the future prevalence, making it less gender predominant.<sup>16-18</sup>

It is well known that chronic diseases cause an economic burden, which has both direct and indirect costs.<sup>19</sup> The direct costs of COPD come from detection, treatment, and rehabilitation, whereas the indirect costs come from disease-related morbidity and mortality.<sup>19,20</sup> Hospitalization is estimated to account for 45.0–50.0% of the direct costs of COPD.<sup>20</sup> Hospitalization is usually required due to the exacerbation of the condition; thus, preventing frequent exposure is the most effective strategy for decreasing the adverse effect of COPD on the economy.<sup>13,19</sup> Regarding morbidity and mortality of COPD patients: It has been recognized that COPD often coexists with other pathologic conditions that can affect the patient's prognosis and mortality rate.<sup>21-25</sup> The high prevalence of COPD makes it one of the leading causes of mortality worldwide.<sup>1,8,20</sup> WHO estimates that more than 3 million people die from COPD per year, which accounts for 5.0% of all deaths globally. Approximately 90.0% of COPD deaths are in low- and middle-income countries.<sup>2</sup> In Thailand, COPD is reported as the fifth leading cause of death among Thais, although few studies of mortality in patients with COPD have been conducted.<sup>15</sup> It is believed that mortality is underestimated because it is difficult to specify COPD as the cause of death.

## Pathophysiology

The principle pathophysiologic characteristic of COPD is an expiratory airflow limitation caused by reduced lung elastic recoil and increased lung airway resistance. The pathogenesis of COPD is due to an abnormal progressive inflammation of airways, alveoli, and microvasculature, which mostly represents the immune reaction to long-term inhalation of noxious particles.<sup>26</sup> Chronic inflammation occurs as the disease progresses, resulting in emphysematous

destruction of lung parenchyma and restructuring and narrowing of the small airways. The physiologic change of COPD is complicated because of the heterogeneity of the pathology, in which some patients get a predominant emphysema pattern (emphysema) and others have mainly small airway disease (bronchitis). Moreover, it is also associated with severity and comorbidity.<sup>27</sup> Nevertheless, to manage the disease effectively, disease development and overall physiological changes need to be clarified.<sup>27</sup>

A progressive decline of forced expiratory volume in 1 s (FEV<sub>1</sub>) wholly represents the respiratory impairment of COPD. However, other symptoms such as exercise intolerance in the patients cannot be explained by FEV<sub>1</sub> at all.<sup>28</sup> A comparison of a respiratory compliance diagram and rest-exercise spirogram between healthy subjects and patients with COPD was conducted in O'Donnell's study. The healthy participants on the respiration graph nearly all fall in the central linear portion of the pressure-volume loop. By contrast, patients with COPD fall on the steep portion of that curve, indicating that higher pressure is required for a given lung volume. In the patients, the inspiratory muscles must work against the increased lung elastic recoil pressure at end-expiration. This overload thus weakens the inspiratory muscles. According to the spirogram, the end-expiratory lung volume (EELV) and inspiratory capacity (IC) are maintained at rest and throughout exercise in healthy adults, whereas tidal volume (TV) needs to be increased during exercise for supporting a higher oxygen demand. In contrast to healthy populations, the expiration of the patients with COPD cannot allow EELV to decrease to the optimal volume; thus, lung hyperinflation occurs and a larger IC is observed, respectively. Despite the resting TV of normal subjects and patients with COPD being comparable, TV can increase marginally in patients with COPD during exercise because of hyperinflation.<sup>29</sup> Taken together, hyperinflation is a critical factor inducing exercise intolerance in patients with COPD and can be

detected by increased EELV and IC. Although exercise aggravates hyperinflation because of the shortened expiratory time and consequent elevated EELV (dynamic hyperinflation), exercise training or pulmonary rehabilitation can overcome those effects by reducing the ventilatory requirement and improving breathing efficiency. Therefore, patients require exercise training or pulmonary rehabilitation in order to reduce the effects of hyperinflation.<sup>28</sup>

## Assessment

In accordance with GOLD, there are 4 aspects of COPD assessment: (1) the presence and severity of the spirogram abnormality, (2) current symptoms, (3) exacerbation history and its future risk, and (4) presence of comorbidities.

COPD severity classification is based on the asperity of airflow limitation because it principally impacts the patient's health status, the risk of exacerbation and death. Classification of airflow limitation in COPD patients is performed by using specific spirometric cut-points. In order to minimize variability, spirometry is carried out after the administration of an adequate dose of short-acting inhaled bronchodilator.<sup>7</sup> Although lung function is a strong predictor of mortality in COPD patients, its classification cannot totally reveal the multidimensional component of COPD.<sup>30</sup> Weak correlations between FEV<sub>1</sub>, symptoms, and patient's health status have also been observed in some studies.<sup>30,31</sup> Regarding COPD symptoms, it is now recognized that various respiratory symptoms can occur in patients with COPD and that likewise affects health status.<sup>31</sup> A comprehensive assessment of symptoms is thus recommended. Various questionnaires were developed to determine the overall symptoms of COPD, e.g., the modified British Medical Research Council (mMRC) questionnaire and the COPD Assessment Test (CAT) score. Since it is known that exacerbation inducing hospitalization is an important factor causing death in COPD patients, the

"ABCD" assessment tool was used to emphasize the importance of exacerbation. This tool incorporates exacerbation sorting (number of exacerbation induced hospital admissions in the past year) with a symptomatic level (the mMRC questionnaire or the CAT score).<sup>7</sup> The patients thereby can be divided into 4 groups: A, B, C, and D. This classification can benefit targeting individual therapies, i.e., exacerbation prevention versus symptom relief.<sup>7</sup> Comorbidity has been reported to affect the mortality rate of patients with COPD.<sup>24,25</sup> Patients with COPD and comorbidities, such as diabetes and coronary artery disease, have been reported to be admitted for exacerbations more often than patients without comorbidities. To prevent the risk of complications and to promote the overall health of patients with COPD, comorbidity thus also needs to be detected early and managed. GOLD therefore has emphasized the importance of comorbidity assessment in COPD.<sup>24</sup> In agreement with GOLD, the study of Sin and colleagues showed that comorbidity screening incorporating lung function and dyspnea score monitoring can better predict mortality in patients.<sup>32</sup> It is clear that no single assessment can be the standard method for evaluating the degree of COPD; therefore, multicomponent approaches are necessary for targeting treatment, prognosis, and predicting mortality, as they can better reflect all the health outcomes of patients with COPD.

## Systemic effects

COPD does not affect solely the respiratory system. It can also have an impact on physiological function in a systemic manner.<sup>33</sup> The extrapulmonary effect also contributes to the high burden of COPD because it further deteriorates health status and affects mortality in the patients.<sup>33,34</sup> The following systemic effects frequently appear in patients and have been found to be clinically relevant.<sup>23</sup>

### Systemic inflammation

Elevated plasma C-reactive protein was found to be associated with an increased risk of comorbidities in COPD; therefore, systemic inflammation has been proposed to play a key role in the development of the concomitant diseases in COPD, e.g., coronary artery disease. Several studies have stated that an increase in the plasma oxidative stress of patients with COPD is a main cause inducing systemic inflammation.<sup>35-37</sup> Rahman and colleagues examined the plasma indicators of systemic oxidative stress in nonsmokers, healthy smokers and patients with COPD while in both clinically stable and exacerbation conditions. The indicators were significantly elevated in smokers and patients, especially during exacerbation.<sup>36</sup> Praticò et al. found that the urinary level of isoprostane F<sub>2α</sub>-III formed by reactive oxygen species-dependent peroxidation of arachidonic acid was higher in patients with COPD than for age, sex, and smoking habit-matched health controls.<sup>37</sup>

### Nutritional abnormality

Unexplained weight loss is a common clinical expression of nutritional abnormality in patients with COPD. This nutritional aberration can be explained by the imbalance of caloric intake and the metabolic rate of the patients in which the prior is normal, and the latter is usually increased. Therefore, it has been suggested that weight loss in patients with COPD may result from cachexia rather than malnourishment.<sup>38,39</sup>

### Skeletal muscle dysfunction and osteoporosis

Skeletal muscle dysfunction (SMD) in patients with COPD is probably explained by 2 mechanisms: (1) reduction of muscle mass, and (2) dysfunction of the remaining muscle. Mitochondrial abnormalities, loss of contractile proteins, hypoxia, hypercapnia, and acidosis have been reported to induce SMD in COPD patients.<sup>40</sup> It has further

been found that SMD significantly affects exercise capacity in patients with COPD.<sup>41</sup> Killian and colleagues determined that many patients with COPD stop exercising because of muscle fatigue rather than dyspnea.<sup>42</sup> Regarding osteoskeletal effects, excessive bone loss has been noticed in patients with COPD compared with age-matched populations.<sup>43</sup> Osteoporosis in COPD can result from multiple causes, e.g., smoking, steroid treatment, systemic inflammation, and SMD.<sup>44</sup>

### Nervous system impairment

Various abnormal aspects of the nervous system have been reported in patients with COPD.<sup>45</sup> Chronic hypoxia has been proposed as a cause of those problems, but the mechanisms are unclear. However, there is evidence showing the relationship between abnormal and the systemic inflammation. Nitric oxide, TNF- $\alpha$  and other cytokines including interleukin (IL)-6, IL-1b, and  $\alpha$ 1-anti-chymotrypsin have been reported to increase in patients with COPD and nervous system impairment.<sup>46</sup> Moreover, increased plasma C-reactive protein in the patients may be associated with cognitive decline, either through a direct neurotoxic effect or via an effect on cerebral arteries.<sup>47</sup> Cognitive dysfunction has currently been proposed as a clinical manifestation in COPD patients. This has been supported by magnetic resonance imaging of the patients showing altered cerebral perfusion and brain bioenergetic metabolism.<sup>48,49</sup>

## Cognitive impairment in COPD

### Definition of cognitive impairment and whether its development in COPD is different from normal aging

Cognition is a term signifying the high-order neural mechanisms that process information management. Cognitive ability is determined by a variety of neurological, psychological, and emotional factors and it is mainly inferred from behavior in practice.<sup>6</sup> Cognitive ability is usually divided into

discrete domains, i.e., receptive, learning and memory, processing, expressive function, and mental activity variables. Each domain performance depends on one or more main class of related cognitive function.<sup>50</sup> Cognitive impairment causes a decline in cognitive abilities, including memory and thinking skills, resulting in an increased risk of developing Alzheimer's or another type of dementia. Nevertheless, in some individuals, mild cognitive impairment (MCI) could revert to a normal state or remain stable. Therefore, cognitive impairment should be diagnosed early and treated.<sup>51</sup>

One principle proposed mechanism of cognitive dysfunction in COPD patients is neuronal damage caused by hypoxia.<sup>6</sup> Many factors have been reported to present a risk of cognitive impairment in both healthy populations and the patients with COPD, i.e., activity, smoking, sleep quality/obstructive sleep apnea, inflammation, health status, BMI, depression, and fatigue. However, various determinants are obvious either in the general population or in COPD patients. In the general population, age, education, hypertension, diabetes, atrial fibrillation, B12/folate, thyroid stimulating hormone, and drugs have been reported to be associated with the development of cognitive impairment, whereas the factors relating to the development of cognitive impairment, including hypoxemia, hypercapnia, poor lung function, and exacerbations, which are quite unique, appear in COPD patients.<sup>6</sup> Therefore, it is suggested that cognitive impairment in COPD patients is not solely due to the overlapping factors. In other studies of the pattern of cognitive dysfunction in COPD patients, a specific pattern of neuropsychological impairment in the patients has been observed, in which attention, memory, and executive function have a moderately severe deficit compared to those with Alzheimer's disease or multi-infarct dementia and healthy controls.<sup>52</sup> It also has been reported that memory is more impaired in patients with chronic cerebrovascular disease than in patients with COPD.<sup>53</sup> However, some studies have suggested that cognitive deterioration in COPD patients is

consistent with age-related cognitive decline. The heterogeneity of observed cognitive dysfunction in COPD patients in various studies is perhaps due to differences in the severity of the disease in the studied populations or deviations in neuropsychological tests. Nevertheless, current evidence mostly suggests that cognitive dysfunction in COPD patients mainly involves attention, memory, motor and executive functions, and the pattern of deterioration may be different from that seen in Alzheimer's disease or multi-infarct dementia.<sup>6</sup>

#### **Prevalence and impact of cognitive impairment in COPD**

Many studies have shown that patients with COPD usually have cognitive impairment either globally or in certain cognitive domains. It has been reported that 42.0% of patients with COPD had moderate to severe cognitive impairment, whereas 14.0% of control subjects had cognitive dysfunction<sup>54</sup>. Concerning hypoxemia, the rate of neuropsychological deficit was 27.0% for mild hypoxemia but 62.0% for severe hypoxemia. It was found that the patients with hypoxemia also had poorer verbal fluency compared with a control group.<sup>52,55</sup> Hypoxemia thus has been reported as the main factor in developing and aggravating cognitive dysfunction in patients with COPD.<sup>56</sup>

In the general population, cognitive dysfunction has been found to be associated with the management of medicines, instrumental activities of daily living (IADL), and mortality.<sup>57</sup> Few studies have examined the impact of cognitive impairment in COPD patients; however, it has been found that incorrect inhaler use was associated with executive dysfunction.<sup>58</sup> Cognitive problems also have been found to be associated with poor IADL in the patients with COPD.<sup>59</sup> In addition, it was observed that cognitive dysfunction in patients with COPD was closely related to impaired functioning in daily life.<sup>56</sup> Since cognitive dysfunction reduces the level of functioning in daily living, it also

decreases patient's quality of life.<sup>60</sup> Lower Mini-Mental State Examination (MMSE) scores have been noticed in elderly patients admitted to hospital with an exacerbation of COPD. However, it was not related to 6-month mortality.<sup>61</sup> In another study using MMSE, significantly impaired cognitive function during discharge was reported in patients using a mechanical ventilator during the exacerbation. Nevertheless, MMSE had improved after 6 months in these patients.<sup>62</sup> This suggests that cognitive function may be reversibly-impaired during exacerbation.<sup>63</sup> However, cognitive impairment in the patients during exacerbation has been associated with poor compliance with medication and oxygen therapy. This poor compliance increases the risk of repeated acute exacerbation.<sup>62</sup> Although MMSE was developed for dementia screening, using MMSE as a single test might not be suitable for detecting an alteration of subtle cognitive impairment.<sup>6</sup> The Montreal Cognitive Assessment (MoCA) has been reported to be superior to MMSE in detecting MCI in patients with COPD.<sup>64</sup> It has been found that patients with COPD with acute exacerbation have a significantly lower MoCA score compared to stable COPD and controls. Moreover, the MoCA score was significantly correlated with FEV<sub>1</sub> and reverse correlated with C-reactive protein and the partial pressure of CO<sub>2</sub>.<sup>65</sup>

In summary, cognitive impairment in COPD patients may be associated with health outcomes, including functional activity and quality of life; however, these associations are still not consistent among studies.

#### **Management in COPD with cognitive impairment**

Since it has been found that a significant proportion of patients with COPD have MCI, a known risk factor for dementia, determination of cognitive function in these patients is needed in order to determine and prevent the risk of developing more severe cognitive impairments. Because COPD mostly occurs in the elderly, the demand for homecare services has increased. Regarding home-

based interventions, patients should be involved in monitoring and treating themselves, as it is important to maintain the self-care of the patients.<sup>66</sup> Cognitive dysfunction has been reported as a limiting factor of self-care in patients with COPD.<sup>67</sup> Therefore, the level of cognitive function of these patients must be considered before planning treatment.<sup>66</sup> In addition to the risk of developing dementia, maintenance or improvement of cognitive function in the patients with COPD may also enhance self-care of the patients and support other interventions.

Generally, treatment of COPD consists of smoking cessation, vaccination, increased physical activity, pulmonary rehabilitation, pharmacotherapy, interventional treatments, oxygen and ventilatory support, and treatment of comorbidities.<sup>1</sup> However, the evidence showing treatment of COPD patients with comorbidities is weak. Regarding cognitive impairment in patients with COPD, it appears that there is a link between increased physical activity, exercise, and cognitive function.<sup>23</sup> A number of studies have shown that physical activity is associated with the maintenance and improvement of cognitive function in patients with COPD.<sup>68,69</sup> Impaired visual attention, verbal memory, and visuospatial functions have been reversed after 3 weeks of pulmonary rehabilitation which mainly consists of endurance exercise.<sup>70</sup> In patients with mild COPD, reasoning and problem-solving skills were heightened after performing short- and long-term exercise.<sup>71</sup> The acute improvement effect of exercise (after 20 minutes of exercise) on verbal fluency was also reported.<sup>72</sup> Although increased physical activity and exercise are related to cognitive function improvement, the mechanism is still elusive and there are no studies indicating that these interventions are the best management for patients with COPD and cognitive impairment. Cleutjens et al. reported the effect of pulmonary rehabilitation on percentage of dropout of participants with severe COPD, 6-min walk distance, CAT, St George's respiratory questionnaire-COPD specific, hospital anxiety and

depression scale, and lung information needs questionnaire in patients with and without cognitive impairment. It was found that pulmonary rehabilitation could increase 6-min walk distance and quality of life in both groups, but the 6-min walk distance of the patients with cognitive impairment was lower than that of the patients without cognitive impairment. The dropout number in the cognitive impairment group was higher than that in the patients without cognitive impairment. This indicates that the patients with cognitive impairment had a higher risk of not performing continued pulmonary rehabilitation.<sup>73</sup> Recently, we reported that home-based pulmonary rehabilitation plus a cognitive improvement program can enhance cognitive function, 6-min walk distance, and quality of life in patients with moderate to severe COPD with cognitive impairment, whereas a pulmonary rehabilitation program alone does not change the parameters. The results also indicate that patients with COPD and cognitive impairment have a risk of ineffective home-based pulmonary rehabilitation. A cognitive improvement program may enhance the effectiveness of pulmonary rehabilitation through decreasing that risk.<sup>69,74</sup>

## Conclusion

COPD causes critical systemic effects. Clinical assessment thus ought to take into account that consequence. The presence of cognitive impairment in patients with COPD can affect self-care ability and may be associated with health status and mortality. A better understanding of this extrapulmonary effect may provide new therapeutic strategies that could result in better health outcomes and prognoses for patients.

## Conflict of interest

None.

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