



Review

Early chronic obstructive pulmonary disease: A new perspective

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Abstract

Chronic obstructive pulmonary disease (COPD) is a respiratory disease with a high incidence, mortality, and disability rate. Because there are few symptoms in the early stages of COPD, diagnosis and treatment are seriously insufficient. It is necessary to find effective clues for early COPD diagnosis and provide appropriate interventions. Several studies suggest that small airway disease is the earliest stage of COPD because it is correlated with subsequent development of airflow obstruction. However, there are currently no globally accepted criteria for defining early COPD. This study mainly introduced risk factors, definition, diagnosis, and treatment of early COPD from a new perspective.

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Keywords: Chronic obstructive pulmonary disease; Early diagnosis; Risk factors; Intervention; Treatment

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic airway disease characterized by persistent and

progressive airflow limitation.¹ In recent years, COPD has been considered a global problem, predicted to be the third most common cause of death by 2030 and ranked fifth in the global disease burden.² Although the morbidity and mortality of COPD are high, a long disease course and few symptoms in the early stage lead to insufficient diagnosis.^{3,4} Early COPD refers to the disease state within a period when the COPD course starts.⁵ This early stage may occur in the elderly, middle-aged, or the young.⁶ More than 70% of COPD patients are in the early stage of COPD with or without mild respiratory symptoms.^{3,7} As the disease progresses and lung function is damaged, the symptoms gradually increase and arouse the patient's attention. Several studies have shown that the rate of forced expiratory volume in the first second after inhalation of bronchodilator (FEV1) decline in early

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COPD patients is significantly faster than that in the terminal stage.⁸ Besides, early stage COPD patients are at higher risk of hospitalization for acute exacerbation of COPD, acute pneumonia, and all-cause mortality.^{9–11} Early detection and treatment might slow down disease progression, improve quality of life, and reduce medical costs.¹² There is no standard criteria in diagnosing early COPD; thus, we need to refine the definition so that the disease can be captured in the early stages of development, and preventive measures can be adopted before major lung damage occurs, to stop or delay disease progression.

Risk factors in COPD

In healthy individuals, lung function reaches a plateau at 20–25 years old, lasts about 10 years, then gradually declines.^{13–15} Lung development is a complex and intricate process that is affected by several factors (Table 1).¹ Risk factors take decades of continuous exposure before the spirometer detects an abnormal lung function.¹⁶ We need to find potential patients before lung function becomes abnormal. COPD was conventionally considered to be a disease caused by smoking in the elderly. Many researchers have confirmed that the pathogenesis of COPD may begin much earlier, even before birth.^{17,18} First and foremost, there are complex interactions between genes and the environment.¹⁹ Smoking, whether during pregnancy, or as children, adolescents or adults, and active or passive smoking, is associated with an increased risk of COPD.^{20,21} Parental asthma, parental smoking, premature delivery, and low birth weight may be risk factors for developing COPD.^{17,21–27} Bronchopulmonary dysplasia, childhood infections, and airway hyperresponsiveness lead to restricted lung

function growth and airflow limitation.^{17,23,28} Children with severe asthma are at increased risk of COPD.²⁹ Nutritional imbalance in pregnant women, children, and adolescents may cause lung development disorders.³⁰ Middle-aged people with symptoms of cough and sputum are at high risk of developing COPD.³¹ The existence of multifactorial pathogenesis is related to decreased lung function in early life and early adulthood (approximately 20–25 years old).¹⁵ Although these adverse exposure events are common, their exact contribution to lung function remains unclear. They should not be excluded when defining early COPD (Fig. 1).

Definition of early COPD

At present, there is no unified understanding of early COPD in academics. Rennard and Drummond⁶ proposed that early COPD should be an interval in time at the beginning of the disease course (Table 2), because pathogenic processes leading to COPD may occur at any time of life. Therefore, early COPD is not the same as mild COPD. Even in the mild stage, patients may have been suffering from the disease for several years.

Exposure to risk factors causes changes in molecules and cells, resulting in lung structural damage.^{32,33} Before lung function declines, even if no emphysematous destruction occurs, terminal and transitional bronchioles will be destroyed and lost, and the lumen of the surviving bronchus narrowed and the wall thickened.^{34–36} Airway stenosis or alveolar destruction are pathological changes that lead to early symptoms, such as coughing, expectoration, and exertional dyspnea.^{35,37} Patients with cough, sputum, dyspnea, and the detection of a low diffusing capacity of the lung for

Table 1
Risk factors for chronic obstructive pulmonary disease by age.

Risk factors	Prenatal	Perinatal	Childhood and adolescence	Adulthood
Environmental-genetic interactions	✓	✓	✓	✓
Active or passive smoking	✓	✓	✓	✓
Nutritional imbalance	✓	✓	✓	
Parental asthma	✓			
Parental smoking	✓			
Premature delivery		✓		
Low birth weight		✓		
Bronchopulmonary dysplasia			✓	
Infections			✓	
Airway hyperresponsiveness			✓	
Severe asthma			✓	
Cough/sputum				✓
Aging				✓

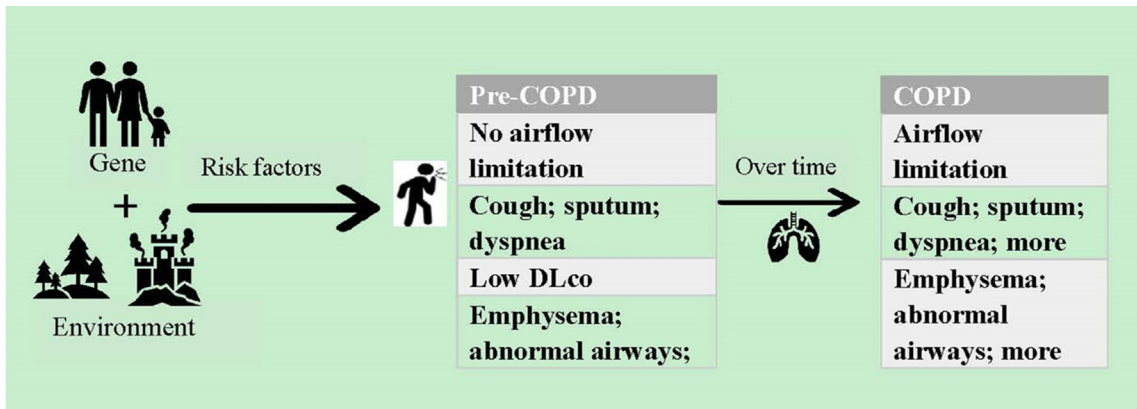


Fig. 1. COPD progression process. COPD: chronic obstructive pulmonary disease; DLco: diffusing capacity of the lung for carbon monoxide.

carbon monoxide (DLco), without airflow limitation, have been classified as having “pre-COPD”.³⁸

Siafakas et al³⁹ suggested that the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification 0 should be defined as early COPD (Table 2). They believed it was a pre-clinical stage and is consistent with early disease. GOLD 0 refers to patients without airflow limitation but with chronic cough and sputum expectoration. Since there was not enough evidence to show that patients with GOLD 0 were likely to develop COPD, GOLD canceled this concept in 2006.⁴⁰ However, the Subpopulations and Intermediate Outcome Measures in COPD (SPIROMICS) study found that current smokers or ex-smokers with normal pulmonary function but are symptomatic had

acute exacerbations, restricted activity, lower airway thickening in high resolution computed tomography (HRCT), and mild reductions in FEV1 and forced vital capacity (FVC).⁴¹ Existing smokers and ex-smokers with obvious respiratory symptoms may have normal lung function, but computed tomography (CT) shows a certain degree of airway wall thickening, emphysema, and gas trapping.⁴² The clinical significance of GOLD 0 should be correctly evaluated, and the diagnosis and treatment of COPD should be advanced.

Martinez et al³⁶ proposed a definition for early COPD as an individual younger than 50 years with 10 pack-years or more smoking history, and at least one of the following: (1) signs of airflow limitation (post-bronchodilator FEV1/FVC less than the lower limit of normal

Table 2
Diagnosis of early COPD as proposed.

Reference	Diagnosis
Rennard et al, 2015 ⁶ Celli et al, 2019 ³⁸	An interval in time at the beginning of the disease course Cough, sputum, dyspnea; A low DLco; No airflow limitation
Siafakas et al 2018 ³⁹	Chronic cough; Sputum expectoration; No airflow limitation
Martinez et al, 2018 ³⁶	Age <50 years; At least 10 pack-years of smoking history. Any one of: FEV1/FVC less than LLN; Compatible CT abnormalities; Accelerated FEV1 decline (≥60 mL/year)
Çolak et al, 2020 ⁹	Age < 50 years; FEV1/FVC less than LLN; At least 10 pack-years of tobacco consumption

COPD: chronic obstructive pulmonary disease; DLco: diffusing capacity of the lung for carbon monoxide; LLN: lower limit of normal; CT: computed tomography; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity.

[LLN]); (2) abnormal airways on CT imaging (emphysema, gas trapping, thickening of the tracheal wall); or (3) annual decline rate of FEV1 \geq 60 mL/year.

Çolak et al⁹ defined early COPD as FEV1/FVC less than the LLN in individuals under 50 years old with at least 10 pack-years of tobacco consumption.

However, these definitions lacked strong evidence of corresponding long-term cohort studies. COPD is caused by multiple, long-term, interactive, genetic, and environmental effects on lung development and function. To define early COPD, we should consider these factors comprehensively.

Causes of difficult diagnosis and treatment in early COPD

The symptoms of early COPD are insidious, with asymptomatic patients accounting for 35.5%–42.0% of cases.^{43–45} Only 30%–50% of COPD patients reach the severe stage, when symptoms are more typical and the condition can readily be diagnosed.⁴⁶ Smokers with COPD, who think that their symptoms are caused by smoking, ignore them and do not seek diagnosis and treatment.⁴⁷ Some patients deny that their respiratory symptoms are caused by aging or other complications.⁴⁸ Some patients feel that the symptoms are mild, and gradually adapt to the symptoms and ignore their existence.⁴⁹ The consequences of negligence and neglect of early symptoms are that patients remain unaware of the development of the disease, and as the disease progresses, patients will gradually reduce their activities, perceive more subtle symptoms, and cover-

up its progression.⁵⁰ The popularity rate of pulmonary function test is low, and the sensitivity of pulmonary function in the diagnosis of early COPD is not high.⁵¹ When undiagnosed, early COPD progresses to a serious disease stage; it will affect health-related quality of life (HRQoL) and increase medical costs.⁵² Therefore, timely identification and intervention are of great significance in early COPD.

Potential diagnostic methods for early COPD

There is a long incubation period in COPD, from chronic inflammation, injury, repair, and structural remodeling of the respiratory tract, to detectable pulmonary function changes. Lung structure changes occur before lung function damage. Several studies have proposed that small airway disease occurs as the earliest stage of COPD, before the development of emphysema.^{35,39} If it is diagnosed timely, during the phase of lung tissue structure change, it can significantly delay the progression of COPD and reducing disease, disability, and mortality.

The GOLD criteria, specifically FEV1/FVC $<$ 0.7, are typically used in the diagnosis and classification of COPD (Table 3).⁵³ FEV1 and FVC declines with age, and the reduction rate in FEV1 is faster. Regarding FEV1/FVC $<$ 0.7 as the COPD diagnostic criterion, there is a potential for underdiagnosis in younger people and overdiagnosis in older adults.⁵⁴ Lung function in asymptomatic smokers is usually within the normal range, but low-dose CT scan has confirmed early lung structure changes, such as emphysema, with

Table 3
Potential diagnostic methods for early COPD.

Methods	Characteristics
Spirometry	Potential to miss early disease
Chest CT	Detect small areas of emphysema early and small airway lesions
EB-OCT	Measure small airway pipe with diameter \leq 2 mm
V/PSPECT	Detect functional airway abnormalities before FEV1 decreases
Micro-CT	Detect emphysema
PRM	Identify small airway disease
PEF%pred	High sensitivity and specificity for airflow limitation
pCLE	Detect increased median cross-sectional area of alveolar duct openings
DLco	Identifies airway disease and emphysema before spirometry
IOS	Finding individuals with symptoms but normal spirometry
Hyperpolarized magnetic resonance imaging	Quantify alveolar enlargement
Potential biomarkers	Occur in the early stages
Screening questionnaires	Based on risk factors and symptoms

COPD: chronic obstructive pulmonary disease; CT: computed tomography; EB-OCT: endobronchial optical coherence tomography; V/PSPECT: ventilation-perfusion single photon emission computed tomography; PRM: parametric response mapping; PEF%pred: percentage of predicted peak expiratory flow; pCLE: probe-based confocal laser endomicroscopy; DLco: diffusing capacity of the lung for carbon monoxide; IOS: impulse oscillometry.

lung function damage gradually appearing when there is aggravation of lung structure damage.⁵⁵ Emphysema is asymptomatic for a long time in the early stage, and symptoms or changes in lung function occur only when lung parenchymal destruction is larger than 30%.^{44,56} Therefore, lung function tests should not be taken as the only diagnostic criterion of early COPD, but should be combined with other examination methods.⁵⁷

Imaging examination might be more advantageous for early diagnosis. Lutchmedial et al⁵⁸ proposed several kinds of CT to detect COPD patients with emphysema and respiratory symptoms. If the pulmonary function test was normal, emphysema can provide a basis for early COPD diagnosis. Asymptomatic smokers with lung functions within the normal range develop perifocal changes in lung tissue, detectable by CT scans.⁵⁵ Emphysema contains air vesicles instead of normal tissue. This leads to a substantial decrease in ray densitometry, which can be quantified by CT scan. Chest CT can detect small areas of emphysema early and distinguish phenotypes of emphysema and small airway lesions.⁵⁹ It can be used for predicting the possibility of smokers without airflow limitation to develop COPD with airflow limitation. A COPD gene study found that 68% of patients with mild COPD symptoms had emphysema on CT examination.⁴² Moreover, functional small airway diseases diagnosed by chest CT are closely related to emphysema and decreased FEV1 of lung function.^{59,60} Endobronchial optical coherence tomography (EB-OCT) can measure small airway pipes with a diameter ≤ 2 mm.^{61,62} Bajc et al⁶³ have found that ventilation-perfusion single photon emission computed tomography (V/PSPECT) can also detect functional airway abnormalities early, when FEV1 has not yet decreased. McDonough et al believed that micro-CT can detect early emphysema in patients with COPD. Extensive airway stenosis and small conduction airway loss in COPD patients with central lobular emphysema and total lobular emphysema are also confirmed to occur earlier than emphysema.³⁵

Parametric response mapping (PRM) technology has proven that functional small airway disease (fSAD) occurs earlier than emphysema.⁶⁴

The percentage of predicted peak expiratory flow (PEF%pred) $< 80\%$ produces a high sensitivity and specificity for airflow limitation. The sensitivities of the standard to COPD I and COPD II were 55.60% and 83.30%, respectively.⁶⁵

Probe-based confocal laser endomicroscopy (pCLE) can detect the increased median cross-sectional area of the alveolar duct openings in emphysematous patients,

which is a morphological change that can be correlated with lung function parameters.⁶⁶ It may contribute to identifying patients with emphysema. Harvey et al⁶⁷ considered that the DLco could also be used for early diagnosis of COPD.

Frantz et al⁶⁸ reported abnormal impulse oscillometry (IOS) findings in individuals with symptoms but normal spirometry. IOS may diagnose early COPD before spirometry impairment.

Hyperpolarized magnetic resonance imaging can measure the alveolar size by estimating the gas diffusion distance. This method can be used to quantify alveolar enlargement.⁶⁹ Gas diffusion can be quantified by spatial orientation, which can estimate small airway size.⁷⁰

Some potential biomarkers in the current study were found to be closely related to lung function and emphysema. Early COPD occurs at the biochemical and molecular cellular level, and inflammatory markers may play a key role in the early stages and disease prediction.⁷¹ C-reactive protein (CRP) is an acute-phase protein that serves as an early marker of inflammation or infection, and has been implicated in the pathogenesis, along with other metalloproteases of COPD. Elevated baseline CRP levels were associated with poorer lung function and a concomitant decrease in FEV1. Other inflammatory markers, such as matrix metalloproteinase-1, 7, and 9, have been found to be associated with similar changes.⁷² 8-isoprostanes, glucose-regulated protein 78 (GRP78), CD163, and transglutaminase-2 in lung tissue, sputum, and plasma from patients with COPD were also associated with decreased lung function.^{73–77} Due to the limitations in methods of detection, several biomarkers of early COPD are still in the research stage and need to be confirmed by further studies.

At present, there are many screening questionnaires for COPD based on risk factors and symptoms, such as the COPD Population Screener Questionnaire (COPD-PS), Lung Function Questionnaire (LFQ), and COPD Diagnostic Questionnaire (COPD-DQ). The specificity of the screening is between 25% and 73%.^{78,79}

Treatment of early COPD

Early is related to time, while severity refers to lung function loss; they may or may not be consistent in one individual.⁸⁰ No information is available on early COPD, so data must be extrapolated from what is known about mild COPD.⁸¹ For patients with moderate to severe COPD, the GOLD guidelines aim to relieve symptoms and improve their lives. As for early COPD,

the U.S. Preventive Services Task Force (USPSTF) and GOLD do not recommend screening and interventions.^{1,82} However, studies have confirmed that airway obstruction in patients with early COPD is reversible, and pulmonary function injury can be alleviated by treatment.⁴⁴ The clinical trial Towards a Revolution in COPD Health (TORCH) and the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study showed that the annual decline rate of FEV1 in the pulmonary function of patients with mild COPD was more rapid than that of severe patients.^{12,49,83,84} Therefore, early intervention is required to slow lung function decline.⁸⁵ The earlier the prevention and treatment, the better the improvement of the reversible degree of airflow obstruction.⁸⁶

In the earliest stage of COPD, pharmacological and non-pharmacological therapies can affect disease progression and outcome.⁸⁷ Smoking cessation is the priority in early COPD intervention, which can reduce the mortality of COPD patients, slow down lung function decline, and attenuate the continuous progression of the disease. Previous research has confirmed that the annual decrease in FEV1 in the early COPD smoking cessation group was significantly slower than that in the non-smoking group (31 mL/year vs. 62 mL/year), while the FEV1/predicted value significantly improved (+1.98% vs. -0.74%).⁸⁸ Quitting smoking has been shown to attenuate lung function decline at all levels of COPD. The earlier an individual quits, the greater influence there would be on lung function.^{89,90} The benefit of FEV1 improvement in mild COPD patients is more obvious than that in severe COPD patients.⁴⁶ Risk factors for COPD include air pollution, toxic and harmful gases and dust exposure, biofuels, and respiratory tract infections.¹ Therefore, reducing occupational and environmental exposure, improving kitchen ventilation equipment, and actively preventing and treating juvenile respiratory tract infections are of significance in the prevention and treatment of COPD.^{91,92}

Bronchodilators are the core drugs for the treatment of airway obstruction. However, the choice of short-acting beta-agonist (SABA), long-acting muscarinic antagonist (LAMA), long-acting beta-agonist (LABA), LABA/LAMA, or LABA/inhaled corticosteroid (ICS) for the treatment of early COPD also be controversial and more research is needed.⁸⁷

Compared with GOLD stage III or IV, the UPLIFT study revealed that tiotropium bromide can reduce the annual lung function decline rate and improve the symptoms of COPD patients in GOLD stage II.^{12,84}

Furthermore, in the tiotropium bromide group, the time to the first acute exacerbation and the time to hospitalization caused by acute exacerbation were extended, and the acute exacerbation risk was reduced.¹² The Mesure de l'Influence de Spirival sur les Troubles Respiratoires Aigus a Long terme (MISTRAL) study showed that in the subgroup of patients with moderate COPD with FEV1 \geq 50%, the frequency of exacerbations in the tiotropium bromide group was lower than that in the placebo group (1.21 vs. 1.97, $P < 0.01$).⁹³ Zhou et al¹⁰ conducted a randomized controlled trial (Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease; Tie-COPD) of inhaled tiotropium bromide and placebo in COPD patients. The results confirmed that tiotropium significantly improved FEV1 and quality of life, reduced acute exacerbation frequency and hospitalization risk, and reduced the FEV1 annual decline rate. Unfortunately, studies on this therapy in patients with early COPD are currently not available.

The TORCH study showed that salmeterol/fluticasone reduced FEV1 descent speed in patients with GOLD stage II,⁵² and annual acute exacerbation rate and death risk were reduced by 31% and 33%, respectively.^{52,93} Health status was also better than the placebo group.⁹⁴ Similarly, in the Study to Understand Mortality and Morbidity in COPD (SUMMIT), FEV1 decreased more slowly in the fluticasone furoate/vilanterol group than in the placebo group in patients with GOLD stage II (-46 mL vs. -38 mL, $P = 0.019$).⁹⁵ Currently, there is no evidence for its use in patients with early disease.

Pulmonary rehabilitation can lead to significant improvement in daily life activities, motor symptoms, and HRQoL, reducing acute exacerbation risk.^{43,96} Rehabilitation can provide short- and long-term benefits for mild COPD patients.⁹⁷ This evidence suggests its potential benefit even in early disease. Unfortunately, there is currently insufficient capacity to provide conventional pulmonary rehabilitation services for a large number of patients with early disease.

Conclusion

Further studies are required to establish early diagnostic criteria for COPD. Due to adverse early life exposures coupled with environmental–genetic interactions, lung function criterion alone cannot be suitable for early recognition and diagnosis. For high-risk populations with normal lung function, determination of respiratory symptoms and assessment of lung CT features are of great importance. It is recommended

that for high-risk groups with symptoms and with COPD on lung CT assessment, drug treatment may be beneficial to increase the expiratory flow rate, improve symptoms, and reduce the frequency of acute exacerbations. However, more long-term cohort studies are needed to confirm the benefits of drug therapy for early COPD.

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Conflicts of interest

None to declare.

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