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## Pre-COPD : a New Advance in COPD

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## Pre-COPD: a New Advance in COPD

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## Pre-COPD: a New Advance in COPD

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**【Abstract】** Chronic obstructive pulmonary disease (COPD) is a common chronic disease of the respiratory system that has high morbidity and mortality across the world. Like other chronic diseases, the development of COPD is a long process, and its prognosis could be improved significantly by early prevention and intervention. As the understanding of COPD in the international academic community gradually deepens, the 2022 Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) report first proposed the concept of pre-COPD. We reviewed the development of pre-COPD, analyzed its definition and diagnostic criteria, and summarized the significance of early identification of pre-COPD patients. Pre-COPD results from the widening and deepening of the existing concept of COPD prevention and treatment. A full understanding of pre-COPD will contribute to guiding the direction of COPD pathogenesis research and basic COPD research, and to improving the awareness of primary prevention of COPD in clinical practice, thereby reducing the prevalence and mortality of COPD and the burden of COPD on families and society.

**【Key words】** Pulmonary disease, chronic obstructive; Pre-COPD; Global initiative for chronic obstructive lung disease; Diagnosis; Prevention; Early medical intervention; Review

Chronic obstructive pulmonary disease (COPD) is a common type of chronic airway disease in respiratory departments, characterized by irreversible airflow limitation and persistent respiratory symptoms. The pathogenesis of COPD is not completely clear, it is usually believed that oxidative stress and inflammatory reaction in the airway due to significant exposure to harmful particles such as smoking or harmful gases is the main mechanism of COPD pathogenesis, factors such as genetics, age and sex, lung growth and development, and socioeconomic status also play a role in the pathogenesis.

Currently, COPD has become the third leading cause of death in the world, and the global prevalence of COPD in people over 30 years old is reported to be about 11.7%<sup>[1]</sup>. In 2018, the survey results of "China Adult Lung Health Research" led by Academician Wang Chen showed that the prevalence rate of people over 40 years old in China is as high as 13.7%, and the total number of patients is nearly 100 million<sup>[2]</sup>. In addition, the prevalence of COPD will

increase sharply with the growth of age. In the context of the deepening degree of aging in China, the economic burden and social burden brought by COPD will be further increased. How to better prevent and manage COPD and reduce its prevalence and mortality is a major task for clinical research and basic research. The new Global Initiative for Chronic Obstructive Pulmonary Disease (the global initiative for chronic obstructive lung disease, GOLD) in 2021 presents a new concept: pre-chronic obstructive pulmonary disease (pre-COPD)<sup>[3]</sup>, this concept not only marks the development of the research field of COPD to the early disease, but also means the transformation of the prevention concept of COPD to prevention and early intervention, which will have a positive impact on improving the prognosis of COPD patients, thus achieving the purpose of reducing the COPD prevalence and mortality. The Literature search strategy of this article: With "Pre-COPD, Early COPD, Mild COPD" as the English keywords to search for PubMed, Medline, Web of Science; with "Chronic obstructive pulmonary disease early, early chronic obstructive pulmonary disease, mild chronic obstructive pulmonary disease" as the Chinese keywords to search for CNKI, China Biomedical Literature Service System, VIP from inception to 2022 June. Literature inclusion criteria: clinical studies on early or early chronic obstructive pulmonary disease, sexual lung disease, basic research, guidelines/consensus, reviews related to the topic of this study. Literature exclusion criteria: literature unrelated to the research question, repeated publication, unable to find full text information, and poor quality literature.

## **1 The development course of the pre-COPD**

1.1 The GOLD 0 stage In 1998, the National Institute of Heart, Lung, and Blood Diseases, the National Institute of Health and WHO worked together to launch GOLD under the principles of evidence-based medicine to raise awareness of COPD and promote the concerted efforts of all people involved in healthcare to promote the prevention and management of COPD. 2001 GOLD Report: Global Strategy for Diagnosis, Management and Prevention of COPD (Global Strategy for the Diagnosis, Management, and Prevention of COPD) divide COPD into four stages: Stage 0: "high risk"; Stage I: mild COPD; Stage III: moderate and severe COPD<sup>[4]</sup>. The characteristics of stage GOLD 0 (GOLD stage 0) can be summarized as risk factors (smoking) and symptoms (chronic cough and sputum), and no airflow limitation in lung function tests. For some people, stage 0 does not appear to be a health issue, but this stage emphasizes early identification of people "at risk" and intervention before developing airflow limitation. However, this concept was removed in the 2006 GOLD revision for two main reasons: (1) GOLD 0 population characteristics; (2) not all GOLD 0 populations eventually develop airflow limitation<sup>[5-6]</sup>.

1.2 GOLD-Unclassified (Global Initiative for Obstructive Lung Disease-Unclassified, GOLD-U) Although the concept of stage GOLD 0 was removed, it was found that smokers without airflow limitation but with chronic respiratory symptoms are more likely to have severe respiratory diseases, a phenomenon that has attracted increasing

clinical and research attention. In 2011, WAN et al<sup>[7]</sup> made the first attempt to describe the clinical characteristics and imaging characteristics of this group by defining  $FEV_1/FVC \geq 0.7$  and  $FEV_1 \leq 80\%$  predicted value as GOLD-U, confirms that BMI can affect lung function, reducing  $FEV_1$  and FVC in proportion, but  $FEV_1/FVC$  may remain within the reference range; the study also describes the following characteristics of the GOLD-U population: (1) The total lung (TLC) and functional residual volume (FRC) are not associated with BMI in the GOLD-U population; (2) Race (African American), gender, diabetes, and congestive heart failure are all helpful to predict the onset of the GOLD-U population. Although this view and definition has not been deeply explored in future studies, WAN et al<sup>[7]</sup> have realized that the GOLD-U population has some characteristics different from COPD patients.

1.3 pre-COPD With the continuous development and progress of modern medicine, people realize that in the occurrence and development process of disease, they generally experience a transitional stage, that is, the special stage from the normal state to the disease state. A correct understanding of this stage and control and intervention is of great significance to prevent the progress of disease. Therefore, in the prevention and diagnosis and treatment of hypertension and diabetes, more and more clinical attention is paid to the management of pre-hypertension and prediabetes<sup>[8-9]</sup>. For COPD, some "high-risk" groups do not meet the current diagnostic criteria for COPD, but this population is at increased risk of airflow limitation over time<sup>[5]</sup>. To better identify this part of the population, based on borrowed classification methods in other areas of medicine. In 2018, CELLI et al<sup>[5]</sup> suggested to improve the classification of COPD and propose the concept of pre-COPD, in 2020, HAN et al<sup>[10]</sup> once again suggested the introduction of the concept of pre-COPD, because it is increasingly clear that when airflow limitation as defined by lung function occurs, the lungs. The pathological changes of this injury are mostly concentrated in the small airways with an inner diameter of  $<2$  mm, and with the extension of time, the pathological damage will gradually accumulate and aggravate, until the occurrence of persistent airflow limitation. The GOLD 2022 report released in 2021-11-15 clarifies four confusing concepts, including early chronic obstructive pulmonary disease (early COPD), mild chronic obstructive pulmonary disease (mild COPD), chronic obstructive pulmonary disease (COPD in young people) in young people, and pre-COPD. In 2022, MARTINEZ et al<sup>[11]</sup> further detailed the above four concepts and proposed the necessity of randomized controlled clinical trials in patients with pre-COPD. At this point, the concept of pre-COPD has officially entered everyone's vision. The characteristics of the concepts related to COPD are shown in Table 1<sup>[12]</sup>.

**Table 1** Criteria for early detection of COPD

Item	Early COPD <sup>a</sup>	COPD in young people	pre-COPD	Mild COPD
History of smoking	Exist	Exist	No requirement	Exist
Symptom	No requirement	No requirement	Chronic cough and sputum	The mMRC score was 0 to 1 points, and the CAT score was <10 points
FEV <sub>1</sub> /FVC	<LLN	<0.7	>0.7	<0.7
Rate of FEV <sub>1</sub> decline	>60 ml/year	No requirement	Heterogeneity	No requirement
FEV <sub>1</sub> %pred	No requirement	<80%	>80%	>80%
Age	<50	20~50	Any age	Any age
Imaging findings	Emphysema, air stagnation, and residual or bronchial thickening	May be a pulmonary emphysema	With or without pulmonary emphysema	N/A

## 2 The definition and diagnostic criteria of pre-COPD

2.1 Definition In the views of the GOLD 2022 report, pre-COPD means: (1) Respiratory symptoms (of any age group); (2) With or without detectable structural and / or functional abnormalities; (3) There is no current airflow limitation; (4) It may or may not develop into persistent airflow limitation over time.

In the 1980s, SCADDING<sup>[13]</sup> proposed that diseases were defined by four key features, including clinical features, structural abnormalities, dysfunction, and etiology. The clinical features, structural abnormalities, and etiology of pre-COPD and COPD are similar, with the key difference in the function, so whether there is airflow limitation is defined by lung function<sup>[10]</sup>.

2.2 Diagnostic criteria FEV<sub>1</sub> / FVC <0.7 after bronchodilator inhalation is the criterion for the diagnosis of COPD, but it is unable to indicate the early changes in COPD. In conjunction with the GOLD 2022 edition report's definition of pre-COPD, regardless of the presence of risk factors, structural or functional abnormalities, if the respiratory symptoms are present and pulmonary function does not reveal airflow restriction, a diagnosis of pre-COPD can be considered.

Based on the above diagnostic criteria, many people may be diagnosed with pre-COPD, but this part of the population will not develop COPD, so it is necessary to develop further diagnostic methods with good sensitivity and specificity and can be implemented clinically. CHEEN et al<sup>[14]</sup> have proposed that actigraphy can provide a large amount of out-of-hospital information to help understand and diagnose pre-COPD. In addition, some screening

methods may be used to improve clinicians' awareness of pre-COPD, such as risk factors and symptom-based screening questionnaire<sup>[15]</sup>, chest CT<sup>[16]</sup>, pulmonary magnetic resonance examination (MRI)<sup>[17]</sup>, carbon monoxide diffusion(DLCO)<sup>[18]</sup>, and probe-based confocal laser microendoscopy (pCLE)<sup>[19]</sup>. These diagnostic methods and ideas still need to be confirmed by large-scale clinical trials, more methods and specific markers are also expected to help in the diagnosis of pre-COPD.

### 3 The promoting effect and practical significance of pre-COPD

3.1 Improve the early diagnosis of COPD Early diagnosis and intervention to reduce "high-risk" individuals with rapid decline in lung function are essential to reducing morbidity and mortality in COPD<sup>[20]</sup>. However, large amount of research evidence shows that the diagnosis rate of COPD is still low in global<sup>[21-22]</sup>, which poses serious challenges to the early intervention of COPD. RAY et al<sup>[23]</sup> used TargetCOPD scores to identify undiagnosed COPD patients in UK primary care clinics and invited them for further diagnostic evaluation, about 16.6% of patients had undiagnosed mild airflow limitation and about 9.7% of patients had undiagnosed moderate airflow limitation; after 12 months, only 10.6% of the undiagnosed patients were eventually diagnosed with COPD. PRETEROTI et al<sup>[24]</sup> used a population-based case-finding strategy to assess the prevalence of patients with undiagnosed airflow limitation in adults with respiratory symptoms in Canada, in approximately 20% of subjects, and in patients with undiagnosed airflow limitation. Moreover, the reported prevalence of undiagnosed COPD in people with a history of smoking is about 13.1% in Japan<sup>[25]</sup> and about 34.8% in Denmark<sup>[26]</sup>.

In order to prevent COPD and better stabilization management, the GOLD Committee recommended in version 2006 that any patient with a history of respiratory symptoms and related risk factors (such as cigarette smoke and indoor biofuels) exposure should be considered for the diagnosis of COPD. The US Preventive Services Task Force (USPSTF) published a systematic review to encourage clinicians to actively detect COPD patients with risk factors, such as cigarette exposure or the presence of respiratory symptoms<sup>[27]</sup>. However, COPD may be asymptomatic in its early stages, and those with self-reported good health and no comorbidities may be at risk for COPD even if they are exposed to it. In fact, COPD may be asymptomatic in its early stages, and those with self-reported good health status and no comorbidities may be overlooked even when exposed to COPD risk factors<sup>[6]</sup>. The concept of pre-COPD proposed in this GOLD report can detect COPD and patients in a wider range, and actively guide and intervene for them to prevent the aggravation in the future.

3.2 Strengthen the early intervention of COPD FLETCHER et al tested 800 male patients in West London aged 30 to 59 years for FEV<sub>1</sub> since 1961 every 6 months for 8 years, found that FEV<sub>1</sub> decreased slowly with age. In addition, FEV<sub>1</sub> decline slowly in non-smokers without airflow limitation, while smokers have "sensitive" and

"insensitive" population, FEV<sub>1</sub> decline rates in "insensitive" smokers are similar to non-smokers. However, FEV<sub>1</sub> in "sensitive" smokers fell relatively fast and eventually showed airflow limitation<sup>[29]</sup>. At first, their research results did not receive much attention, until modern cohort studies delineated the trajectory of lung function from birth to death<sup>[30]</sup>, and the progressive changes in COPD were fully recognized. According to the existing evidence and the progress of the disease course of COPD, more and more scholars began to reach a consensus that the earlier the intervention, the greater the recovery of pulmonary function in COPD patients.

The concept of pre-COPD opens new windows of opportunity for prevention and early intervention<sup>[31-32]</sup> includes smoking cessation, pharmacological intervention, and pulmonary rehabilitation. The current clinical data and evidence on early intervention are based on early COPD or mild COPD, but these evidences are more or less useful for pre-COPD, and it is believed that there will be clinical studies on preCOPD in the future. Firstly, smoking cessation is the focus of early intervention in COPD, which can slow the decline in lung function<sup>[33]</sup> and reduce the hospitalization and mortality rates in COPD patients<sup>[34]</sup>. SCANLON et al<sup>[35]</sup> studied 3 926 smokers with mild and moderate COPD, maintained annual lung function measurements in these smokers for 5 years, and found that among smokers with mild and moderate COPD, the annual decline in FEV<sub>1</sub> was only 50% of that of smokers. In order to study the influencing factors of COPD patients, BAI et al<sup>[34]</sup> included 204 patients and followed them for 5 years. They found that the risk of death in the persistent smoking group was significantly higher than that in the smoking cessation group, suggesting that smoking cessation can significantly affect the natural course of COPD. In addition, Fan Jing et al<sup>[36]</sup> investigated the smoking cessation situation of 5 791 COPD patients aged 40 years old in 2014-2015. The results showed that the smoking cessation rate of this population was 25.0%, the successful smoking cessation rate was 19.1%, and the smoking cessation ratio was 23.1%. According to the previous data, the smoking cessation situation of COPD patients in China is still not optimistic, and it is necessary to further strengthen the health and health education of COPD patients to quit, and admonish COPD patients to actively quit smoking. Secondly, medical therapy plays a key role in the intervention of patients with COPD, and increasing evidence supports the benefit of conventional drug therapy in patients with early COPD<sup>[37]</sup>. Both the UPLIFT trial<sup>[38]</sup> and the TORCH trial<sup>[39]</sup> demonstrated that pharmacological intervention (tiotropium or salmeterol/fluticasone propionate) slowed the deterioration of lung function, improved health-related quality of life and reduced mortality relative to placebo. Moreover, the study of Li et al<sup>[40]</sup> confirmed that in patients with early COPD, the annual decline rate of FEV<sub>1</sub> and FVC after tiotropium withdrawal was not different from the control group, indicating that the withdrawal of tiotropium caused to sustained improvement in lung function. Finally, pulmonary rehabilitation is an effective non-pharmacological intervention for patients with all stages of COPD. A systematic evaluation demonstrated that



pulmonary rehabilitation significantly improved mild COPD, patient exercise capacity and health-related quality of life<sup>[41]</sup>. In addition, SAHIN et al<sup>[42]</sup> confirmed that COPD patients who smoke can also benefit from pulmonary rehabilitation.

**3.3 Reduce the burden on families and society** With the deepening of aging in China, the number of COPD patients will continue to rise, which will bring a heavy burden to the family and society. It is reported that the annual hospitalization cost per COPD patient in the United States is US \$6 852, and the annual hospitalization cost per COPD patient in China is US \$1 477<sup>[43]</sup>. In addition to the above hospitalization costs, COPD patients also face outpatient costs and other costs related to diagnosis and treatment, such as transportation, accommodation and nutrition costs<sup>[44]</sup>. In addition, as one of the important global disability diseases, COPD will not only cause the loss of patients' labor force, but also make family members bear different degrees of burden and pressure when taking care of COPD patients.

It is well known that the cost of disease treatment will increase significantly with the severity of the disease, prevention and early intervention can effectively delay the disease process, thus then reduce the economic burden of the family and society. MENN et al<sup>[45]</sup> compared healthcare utilization between patients with mild and moderate COPD and calculated associated direct medical costs and found that patients with mild COPD were 75% higher than those with moderate COPD, highlighting the economic importance of prevention and interventions of early diagnosis and disease progression delay. The proposal of pre-COPD can attract attention to COPD prevention and early intervention to a greater extent, promote the early prevention and control of COPD, and achieve higher health performance at a lower cost.

#### **4 Summary and Outlook**

The theme of the 18th World COPD Day of 2019 is "All Together to End COPD". Can such a vision ultimately be realized? SORIANO et al<sup>[46]</sup> predict that by 2040, only East Asia, South Asia and Oceania will remain high for COPD, while the rest of the world will be much lower than 0.03%. At the same time, AGUSTI et al<sup>[47]</sup> believe that the eradication of COPD could be achieved within this century. To realize this vision, China needs to do more to prevent and control COPD to stay behind the rest of the world. In 2019, the prevention and treatment of chronic respiratory diseases was one of 15 major actions in the Healthy China Initiative (2019-2030). This document set goals for medical workers in the respiratory community and pointed the way forward<sup>[48]</sup>. At the same time, GOLD 2022 puts forward the concept of pre-COPD, which once again provides opportunities for medical workers in the respiratory field, which will provide a wider basic population for the prevention of COPD, and also provide a new perspective for researchers to study COPD. More importantly, more potential "high-risk" groups will be valued,

which will advance the front line of COPD prevention and delay or even prevent the progression of pre-COPD to COPD.

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