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STUDY PROTOCOL

Lung Health of Early COPD (LHEC): A Multi-Center Cohort Study—Rational and Design

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Introduction: Little is known about the early stage of chronic obstructive pulmonary disease (COPD), especially in nonsmokers. More efforts should be made to investigate the characteristics of this stage, as well as to identify biomarkers for early diagnosis. This study aimed to build a national cohort of patients with early COPD in China to address the current research gaps in this area.

Methods and Analysis: We intend to enroll 1500 participants aged 35 to 75 years with post-bronchodilator spirometry showing a forced expiratory volume in one second (FEV1)/forced vital capacity ratio below 0.8 and an FEV1% predicted of at least 80%, classified as early COPD subjects. Recruitment will take place across 24 centers located in various provinces throughout China. Participants will be categorized into four groups based on their smoking status and spirometry results: pre-COPD smokers, mild COPD smokers, pre-COPD nonsmokers, and mild COPD nonsmokers. Each participant will undergo three visits over a 2-year period, including one baseline visit and two follow-up visits. Comprehensive and follow-up questionnaires will be administered, and the participants will undergo physical examination, pulmonary function testing, high-resolution computed tomography (CT), routine blood tests, and biological sample collection. We will analyze the changes in lung function, CT images, symptoms, biomarkers, and other relevant parameters across the different groups.

Discussion: There is an urgent need for a more precise definition of early COPD for intervention at an earlier stage. By setting a narrower range of lung function thresholds to define pre- and mild-COPD, this study will effectively observe the early disease progression of COPD patients in a shorter period of time. By including a considerable proportion of nonsmokers, this study is more likely to identify new factors influencing early COPD.

Ethics and Dissemination: Ethical approval was obtained China–Japan Friendship Hospital (Beijing, PR China; approval number 2022-KY-141). Participants will provide written informed consent. Study findings will be disseminated through conferences and peer-reviewed scientific and professional journals.

Trail Registration Number: NCT05466396.

Keywords: early stage, non-smoking, mild-COPD, pre-COPD, protocol

Background

Chronic obstructive pulmonary disease (COPD) is the most prevalent chronic respiratory disease in China. According to the most recent epidemiological study in China,[1] the overall prevalence of spirometry-defined COPD is 8.6%, accounting for 99.9 million people in China.

The disease burden of COPD in the young population is also high; the prevalence of COPD is 7.1% and 2.9% in men and women aged 40–49 years, respectively, and 3.9% and 2.0% in men and women aged 30–39 years, respectively.[1]

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Studies focusing on lung function in early adulthood (25–40 years) showed that 9.6% of these individuals had poor lung function (forced expiratory volume in one second [FEV1] <80% predicted)[2] and were associated with earlier incidence of respiratory, cardiovascular, and metabolic abnormalities.

A number of people have shown lung function abnormalities but still cannot be diagnosed with COPD. Moreover, COPD patients with mild lung function impairment (GOLD stage I) also account for a large proportion of all COPD patients.[1] The gap between normal lung function and severe COPD is substantial. However, individuals within this gap may possess certain characteristics that remain unidentified but contribute to disease progression.

Recently, to stop the progression of COPD at an early stage to decrease the heavy economic and social burdens it causes, researchers have paid more attention to the pre- and mild stages of the disease. We defined pre- or mild COPD as Early COPD (as described in the Methods section). Early COPD has been studied for a long time; however, there has been no consensus on its definition. Researchers have identified some clues regarding patients with early COPD, such as special risk factors, early symptoms, lung function characteristics, and early signs on computed tomography (CT). However, these studies mostly excluded nonsmokers and focused on younger patients, who cannot represent all people in this stage of COPD.[3,4]

We aim to characterize individuals with early COPD, both smokers and nonsmokers, to determine unknown risk factors, changes in lung function and CT findings, and biomarkers.

Materials and Methods

Objectives

The major objectives of this study are as follows:

1. Characterizing pre- and mild-COPD patients in China and exploring their risk factors in smokers and nonsmokers.
2. Describing descending lung function in early COPD and identifying groups of people with different changing curves of lung function.
3. Recording the disease process of early COPD, including lung function, CT findings, symptoms, and treatment.
4. Exploring new indicators of early COPD, such as lung function parameters, CT characteristics, and biomarkers, that can help identify individuals who are most likely to develop COPD.

Design

This is a multicenter, observational, prospective cohort study with two follow-up periods of 2 years as the initial stage, external follow-up will be planned later.

Participants

We aim to enroll men and women aged 35–75 years, with post-bronchodilator spirometry FEV_1/forced vital capacity (FVC) <0.8 and forced expiratory volume in one second percent predicted (FEV1%pred) ≥80%, who are willing to participate in this study and sign the consent form. The exclusion criteria are as follows: (1) diseases that may cause lung function abnormalities, such as lung cancer, bronchiectasis, interstitial lung disease, and previous chest surgery; (2) body mass index >35 kg/m^2; (3) mental disease or cognitive disorders; (4) pregnancy or lactation; (5) participation in other interventional clinical studies; (6) heart attack in the last 3 months (eg, angina pectoris, myocardial infarction, malignant arrhythmia); (7) hospitalized for heart disease within the last 1 month; (8) receiving anti-tuberculosis drugs or having active tuberculosis; (9) Malignancy diagnosed recently or treated; (10) disease that researchers consider inappropriate for pulmonary function tests; and (11) inability to provide written informed consent.

Participants enrolled will be further divided into four groups named and defined as follows (Table 1). Group A: Pre-COPD smokers, defined as a population with 0.7≤ FEV_1/FVC <0.8 (post-bronchodilator) and >10 pack-years of smoking. Group B: Mild-COPD smokers, defined as a population with FEV_1/FVC<0.7 (post-bronchodilator) and >10 pack-years of smoking. Group C: Pre-COPD nonsmokers, defined as a population with 0.7≤ FEV_1/FVC <0.8 (post-bronchodilator) who never smoked or smoked fewer than 10 pack-years. Group D: Mild-COPD nonsmokers, defined as a population with FEV_1 /FVC<0.7 (post-bronchodilator) who never smoked or smoked < 10 pack-years.

Table 1 Grouping of the Subjects into 4 Groups

Group	Smoking Status	Spirometry (Post-Bronchodilator)
A: Pre-COPD smokers	≥10 pack years	$0.7 \leq FEV_1/FVC < 0.8$, $FEV_1\%pred \geq 80\%$
B: Mild-COPD smokers	≥10 pack years	$FEV_1/FVC < 0.7$, $FEV_1\%pred \geq 80\%$
C: Pre-COPD non-smokers	Never smoker or <10 pack years	$0.7 \leq FEV_1/FVC < 0.8$, $FEV_1\%pred \geq 80\%$
D: Mild-COPD non-smokers	Never smoker or <10 pack years	$FEV_1/FVC < 0.7$, $FEV_1\%pred \geq 80\%$

We plan to enroll 1500 participants, with 375 patients in each group. We will also enroll 50 individuals with normal pulmonary function as healthy controls, defined as $FEV_1/FVC \geq 0.8$ and $FEV_1\%pred \geq 80\%$. Participants will be enrolled from hospitals located throughout China, mainly in outpatient departments.

Distribution of Research Centers

This study was led by the China–Japan Friendship Hospital in Beijing, with 23 other sub-research centers located in different provinces of China distributed throughout the country (Figure 1).

Baseline and Follow-Up Assessments

Visit 1: Baseline Assessment

After enrollment, we will conduct a face-to-face baseline assessment of the participants, which will include questionnaires, physical examination, pulmonary function tests, high-resolution CT, blood tests, and biological sample collection.

Baseline questionnaires include demographic data, respiratory symptoms, tobacco use, biomass and environmental exposure, personal and family disease history, physical activity, diet, psychological status, quality of life, complications, and medical assessments.

The modified Medical Research Council (mMRC) and COPD Assessment Test (CAT) questionnaires were employed to assess symptom severity, the EQ-5D questionnaire was utilized to quantify quality of life (QoL), and the Short Form-12 (SF-12) was applied to evaluate psychological status.

Physical examinations include blood pressure, height, weight, and fingertip oxygen saturation measurements.

Pulmonary function tests include pre- and post-diastolic pulmonary function, diffusing capacity of the lung for carbon monoxide (DLCO), tomography, and pulse oscillation.

CT including breathing biphasic chest high-resolution CT.

A regular blood test is required.

Biological sample collection, wherein blood and urine are collected for further investigation.

Visit 2: 12-Month Telephone Follow-Up

We will make a 10-min phone call with the participants in the 12^{th} month after enrollment, employing an easy questionnaire, including respiratory symptoms, tobacco use, biomass, and environmental exposure, as well as medical visits in the past 12 months.

Visit 3: 24-Month Face-to-Face Follow-up

During the 24-month visit, we will perform a face-to-face follow-up that will include questionnaires, physical examinations, pulmonary function tests, high-resolution CT, blood tests, and biological sample collection.

Twenty-four-month questionnaires include respiratory symptoms, tobacco use, biomass and environment exposure, as well as medical visits in the past 12 months. Pulmonary function tests, high-resolution CT, blood tests, and biological sample collection are the same as those performed at baseline.

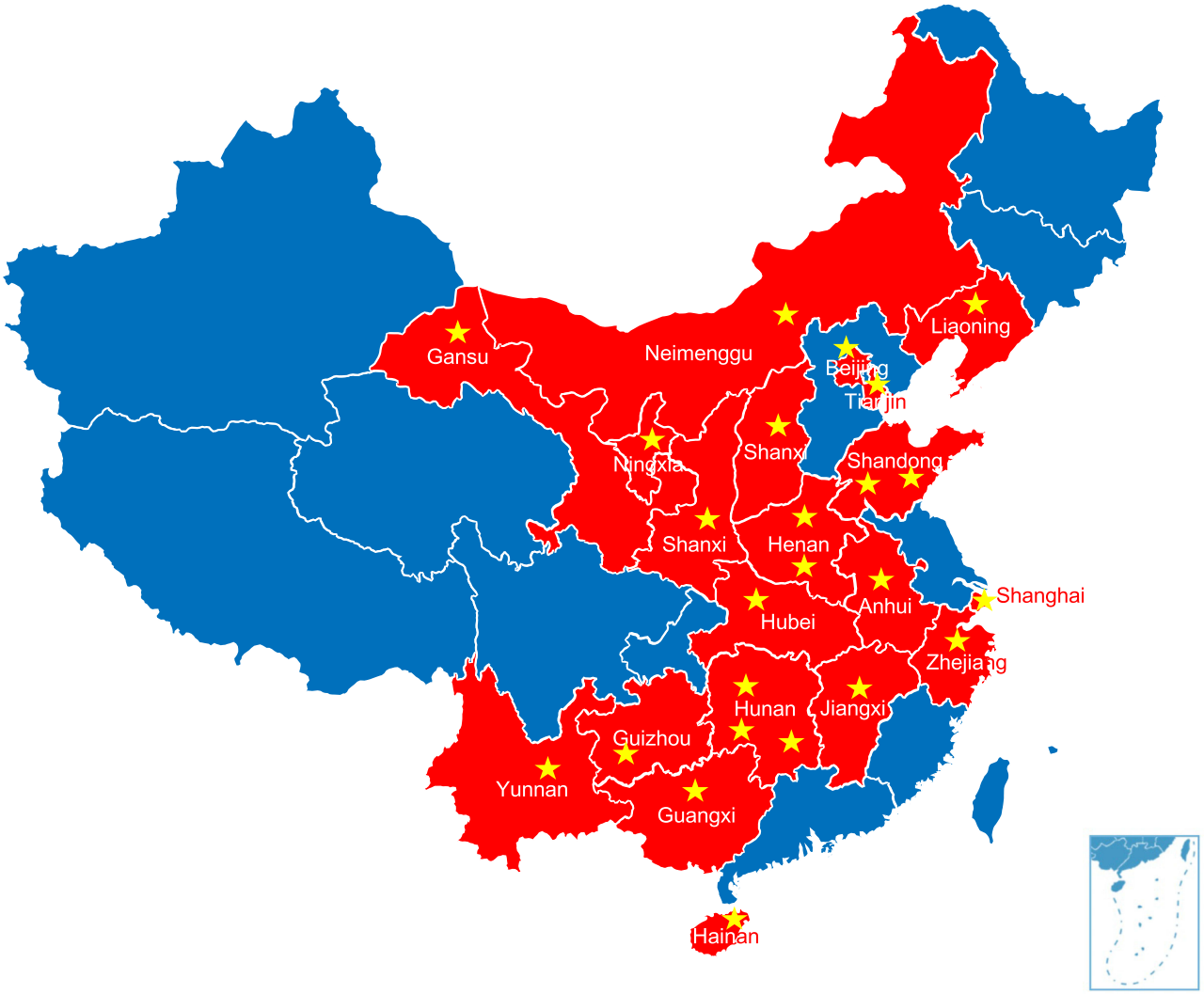

Figure 1 Distribution of research centers of this study located in China. Red: provinces with research centers located. Yellow star: research centers.

The overall study design and data collection at each visit are shown in Figure 2.

Management of Follow-up and Loss to Follow-Up

At enrollment, all participants provided contact information for themselves and their primary contacts. The telephone follow-up in this study was designed with brief interview duration. During the predefined one-month window before and after each scheduled follow-up time point, researchers will attempt to contact the participant at three distinct time slots over three days. If all three attempts fail, the participant will be classified as lost to follow-up. For individuals lost to follow-up at the 12-month assessment, additional attempts will be made during the 24-month follow-up window to re-establish contact.

All instances of loss to follow-up will be documented, including reasons for attrition, to evaluate whether missingness adheres to the missing completely at random (MCAR) assumption. Primary analyses will employ complete case analysis (CCA) to ensure validity in trajectory modeling. Should the overall attrition rate exceed 10%, a multiple imputation approach via iterative chained equations will be implemented to generate a complete dataset.

Outcome

The primary outcomes of this study are decline in pulmonary function (eg, FEV_1, FVC, DLCO) and changes of high-resolution CT in early and mild COPD. The secondary outcomes of this study are changes in the quality of life and symptoms reflected through the changes in the scale scores.

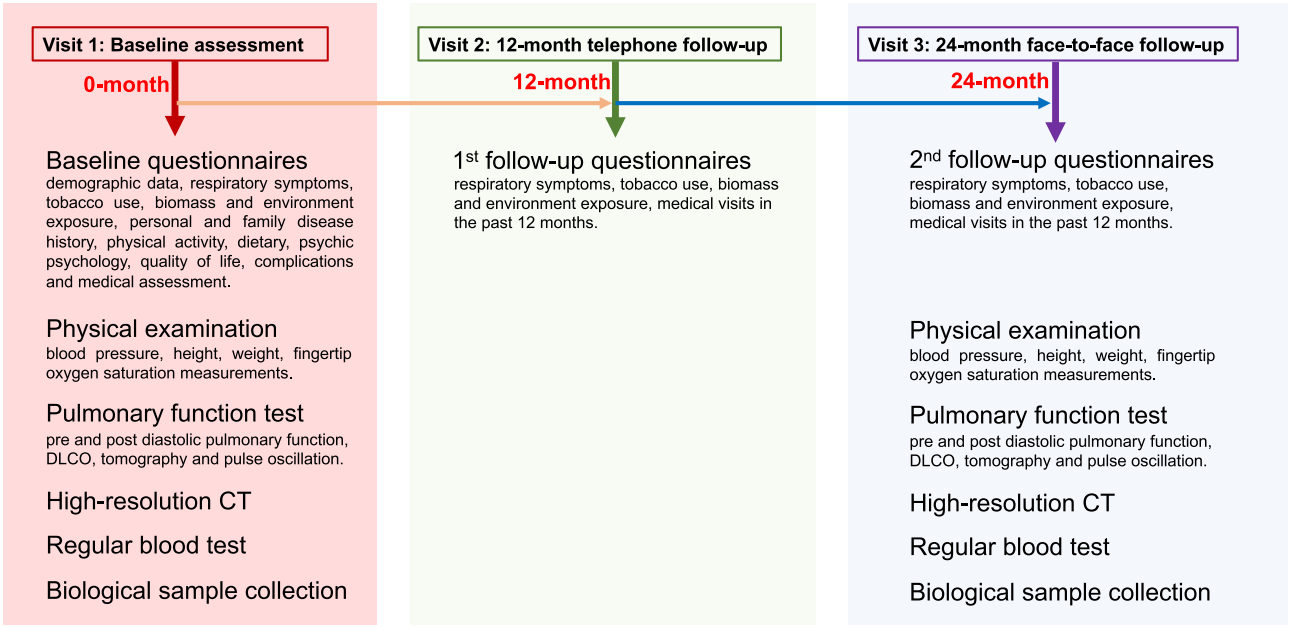

Figure 2 Study design and visits. The red box includes all the data that will be collected in visit 1, which is the baseline assessment. The green box shows data collected in visit 2 as the first follow-up in Month 12. The blue box shows data collected in visit 3 as the second follow-up in Month 24.

Sample Size

Based on a consensus discussion by five respiratory specialists, the probability of high-risk individuals developing early-stage COPD was estimated at 20%. With α=0.05 (significance level) and β=0.10 (statistical power), a survival analysis using a cohort study design indicated a minimum required sample size of 677 participants. To enhance statistical robustness and account for potential attrition, this study plans to enroll 1500 individuals.

To ensure adequate representation of the target subgroups (including non-smoking individuals and the pre-COPD subgroup), we implemented a balanced allocation strategy to maintain equal participant numbers across all groups.

Ethics and Registration

The project protocol, informed consent, and questionnaires were approved by the Institutional Review Board of China–Japan Friendship Hospital (Beijing, PR China; approval number 2022-KY-141). The program has been registered at ClinicalTrials.gov with the identifier NCT05466396. All the participants will be required to provide written informed consent. The trial will comply with the Declaration of Helsinki.

Planned Statistical Analysis

Continuous variables (eg, age, FEV1, FVC, tobacco use, biomass exposure, physical activity, and DLCO) will be summarized as the number of observed values, number of missing values, mean and standard deviation, or median, minimum, and maximum. Categorical data (eg, sex, complications, and disease history) will be summarized as the number of observed values, number of missing values, and numbers and percentages in each category.

For statistical comparison between study groups, when continuous data are normally distributed, the Student's *t*-test will be used. The Mann–Whitney *U*-test will be used for non-normally distributed data. Categorical data will be compared using $\chi 2$ or the Fisher exact test.

To control covariates in this study, primary analyses will adjust for covariates via linear/logistic mixed-effects models (eg, adjusting for age, sex, smoking status as fixed effects; study site as random effect). For exposure-outcome analyses (eg, air pollution effects), inverse probability weighting (IPW) will be applied to minimize selection bias.

Imaging data will be analyzed using the Digital Lung platform to quantify metrics such as emphysema extent, lung volume, and pulmonary nodules. Longitudinal statistical analyses will be performed to assess temporal changes in these quantitative parameters.

Biomarker analysis in this study primarily encompasses multi-omics profiling. Biological samples will undergo genomic, proteomic, and metabolomic analyses. Differential protein expression will be screened using *t*-tests, ANOVA (for multi-group comparisons), or non-parametric tests (eg, Mann–Whitney *U*-test), while population genomic analyses will employ linear/logistic regression models (eg, PLINK).

Differentially expressed molecules will undergo pathway enrichment analysis via databases such as Gene Ontology (GO), KEGG, and Reactome (utilizing tools like clusterProfiler) to identify COPD-associated pathways, including inflammation, oxidative stress, and fibrosis. Multi-omics integration will be conducted using Weighted Gene Co-expression Network Analysis (WGCNA) or Data Integration Analysis for Biomarker discovery using Latent variable methods (DIABLO) to identify cross-omics co-expression modules or biomarker combinations. Classification models based on random forest, support vector machines (SVM), or deep learning architectures (eg, convolutional neural networks) will be developed to predict early COPD risk.

Data Management

In this study, the data will be collected and processed by each research center following general data protection rules. The data will be further analyzed in a leading research center. Chest CT images will undergo quantitative CT analysis via the Dexin-FACT software (Dexin-FACT-V1.0, China) integrated into the Digital Lung measurement platform, generating CT-derived metrics specific to chronic obstructive pulmonary disease (COPD), including emphysema index, airway wall thickness, and parenchymal texture parameters, etc. Biological samples will be collected and roughly processed at each research center and then transported to the China–Japan Friendship Hospital for further processing and analysis. A research data management plan was developed to provide further operational details and procedures.

Discussion

This study aims to investigate the initial stages of COPD based on a national cohort, record the natural disease history at this stage, and clinically and biologically define early COPD.

COPD is a heterogeneous collection of diseases associated with different genetic backgrounds, environmental exposures, and physiological effects. People with FEV1/FVC<0.7 are likely to be diagnosed with COPD, and as the underlying causes of COPD have not been fully investigated, there is considerable interest in the initial stages of the disease. Studies on the lung function trajectory of COPD have shown that FEV1 declines faster at the early stage of COPD than at the terminal stage.[5] Owing to the lack of awareness in identifying early stage COPD, many patients are first diagnosed in moderate to severe stages, missing the optimal period for intervention.[1,6,7] The concept of early COPD was proposed quite some time ago, and its definition has been continuously updated over the past 20 years. GOLD 0 stage was introduced by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2001,[8] which is thought to be the origin of the concept of early COPD. GOLD 0 was defined as patients without airflow limitation on spirometry, but with risk factors and persistent respiratory symptoms. However, GOLD 0 has always been questioned because of its vague definition and unconfirmed clinical relevance, especially because of the lack of evidence that these patients will eventually develop COPD.[9–12] In 2006, the definition of GOLD 0 was removed from the GOLD guidelines because of the high heterogeneity of the defined population and insufficient evidence supporting the progression of the GOLD 0 population to stage 1.[13]

It has become increasingly evident that individuals classified as GOLD 0 experience a higher incidence of COPD exacerbations, greater respiratory impairment, poorer quality of life, and shorter 6-min walk distances compared to never-smokers.[14,15] Additionally, 42.3% of patients in the GOLD 0 group already exhibit CT evidence of emphysema or airway thickening. Consequently, the question of whether GOLD 0 should be reintegrated into the COPD staging system has sparked an ongoing debate since 2016. Many researchers have argued that a new definition of "early COPD" should be established.[16] In an effort to reduce confusion and support future research, the 2022 GOLD statement clarified the concept of "early COPD",[17] defining "early" as "near the beginning of a process" which should only be used to discuss

the "biological early" stage when appropriate. The aim is to promote the development of effective preventive interventions to halt these processes, thereby reducing the risk of COPD-related mortality.[18]

Currently, the majority of cohorts established for research on early COPD focus on smokers, with minimal attention given to nonsmokers.[19–21] These research cohorts are partially dedicated to patients classified as GOLD I–II, whereas others have adopted the definition of GOLD 0 as part of the early COPD definition. Furthermore, some studies have focused specifically on young individuals with COPD. However, research has demonstrated that factors other than smoking, such as biomass exposure, may be the predominant causes of early COPD. Moreover, GOLD 0 is not an optimal method for defining early COPD. There is a need for a more accurate definition of early COPD that encompasses both pre-COPD and mild COPD.

Our study has two notable strengths. First, it employs a narrower range of lung function thresholds to define pre-COPD and mild COPD. According to our preliminary studies (unpublished data), people with a FEV1/FVC of 0.7–0.8 have a higher probability of becoming COPD patients in 2 years, therefore we set this range for our study. This approach facilitates the identification of true COPD cases within a shorter timeframe. By focusing on a more precise range, we can more effectively distinguish between pre-COPD and mild-COPD. Observing patients at both ends of the initial disease stage allows for a deeper investigation of this particular phase. Second, the study included a significant proportion of nonsmokers. By excluding smoking, which is a prominent risk factor, we can better understand the true contributions of other risk factors and identify new ones. Additionally, we plan to utilize the collected biological samples for a variety of analyses, including various omics approaches, and employ large-scale biological models to track changes in biomarkers. This will enable us to identify truly meaningful indicators. This approach could potentially revolutionize the definition of COPD.

Our study has several limitations. First, the follow-up period may be insufficient to fully investigate the progression of early COPD. Given that COPD is a chronic condition, significant changes may not be observable within a 2-year timeframe. However, this study focuses on the early stage of the disease, which is meaningful to get a closer view, and we designated the initial 2 years as the first stage of this cohort. Following the completion of this initial follow-up phase, we will develop a subsequent follow-up plan for the cohort. Second, no interventions have been included. This investigation is designed as an observational study to better understand the natural processes of the disease, with the implementation of interventions being a crucial next step.

Abbreviations

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Patient and Public Involvement

No patient and/or the public were involved in the design of this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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