International Journal of Chronic Obstructive Pulmonary Disease Dovepress
open access to scientific and medical research

Open Access Full Text Article

STUDY PROTOCOL

The Clinical Characteristics, Treatment and Prognosis of Tuberculosis-Associated Chronic Obstructive Pulmonary Disease: A Protocol for a Multicenter Prospective Cohort Study in China

Zhihan Jiang[1,*], Yingying Dai[2,*], Jing Chang[2], Pingchao Xiang[3], Zhenyu Liang[4], Yan Yin[5], Yongchun Shen[6], Ruiying Wang[7], Bianba Qiongda[8], Hongling Chu[9], Nan Li[9], Xiaoyan Gai[1,10], Ying Liang[1,10], Yongchang Sun[1,10]

[1]Department of Respiratory and Critical Care Medicine, Peking University Third Hospital, Beijing, People's Republic of China; [2]School of Basic Medical Sciences, Peking University, Beijing, People's Republic of China; [3]Department of Respiratory and Critical Care Medicine, Peking University Shougang Hospital, Beijing, People's Republic of China; [4]Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Health, GuangZhou, People's Republic of China; [5]Department of Respiratory and Critical Care Medicine, The First Hospital of China Medical University, Shenyang, People's Republic of China; [6]Department of Respiratory and Critical Care Medicine, West China Hospital of Sichuan University, Chengdu, People's Republic of China; [7]Department of Respiratory and Critical Care Medicine, Shanxi Bethune Hospital, Taiyuan, People's Republic of China; [8]Department of Respiratory and Critical Care Medicine, Tibet Autonomous Region People's Hospital, Lhasa, People's Republic of China; [9]Clinical Epidemiology Research Center, Peking University Third Hospital, Beijing, People's Republic of China; [10]Research Center for Chronic Airway Diseases, Peking University Health Science Center, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ying Liang; Yongchang Sun, Department of Respiratory and Critical Care Medicine, Peking University Third Hospital, North Garden Road 49, Haidian District, Beijing, People's Republic of China, Tel +86 13810964766; +86 13910979132, Fax +86 108 226 6989, Email bysyliangying@126.com; suny@bjmu.edu.cn

Background: Tuberculosis and chronic obstructive pulmonary disease (COPD) are significant public health challenges, with pulmonary tuberculosis recognized as a pivotal risk factor for the development of COPD. Tuberculosis-associated COPD is increasingly recognized as a distinct phenotype of COPD that potentially exhibits unique clinical features. A thorough understanding of the precise definition, clinical manifestations, prognosis, and most effective pharmacological strategies for tuberculosis-associated COPD warrants further investigation.

Methods: This prospective, observational cohort study aims to enroll over 135 patients with tuberculosis-associated COPD and 405 patients with non-tuberculosis-associated COPD, across seven tertiary hospitals in mainland China. The diagnosis of tuberculosis-associated COPD will be established based on the following criteria: (1) history of pulmonary tuberculosis with standard antituberculosis treatment; (2) suspected pulmonary tuberculosis with radiological evidence indicative of tuberculosis sequelae; (3) no definitive history of pulmonary tuberculosis but with positive interferon-gamma release assay results and radiological signs suggestive of tuberculosis. At baseline, demographic information, medical history, respiratory questionnaires, complete blood count, interferon-gamma release assays, medications, spirometry, and chest computed tomography (CT) scans will be recorded. Participants will be followed for one year, with evaluations at six-month intervals to track the longitudinal changes in symptoms, treatment, lung function, and frequencies of COPD exacerbations and hospitalizations. At the final outpatient visit, additional assessments will include chest CT scans and total medical costs incurred.

Discussion: The findings of this study are expected to delineate the specific characteristics of tuberculosis-associated COPD and may propose potential treatment options for this particular phenotype, potentially leading to improved clinical management and patient outcomes.

Keywords: chronic obstructive pulmonary disease, COPD, pulmonary tuberculosis, tuberculosis-associated COPD, protocol

Received: 20 June 2024
Accepted: 16 September 2024
Published: 25 September 2024

Introduction

Chronic obstructive pulmonary disease (COPD), characterized by chronic respiratory symptoms and persistent airflow limitation,[1] is the third leading cause of death worldwide and results in approximately 3.3 million deaths annually, which imposes a substantial health and economic burden worldwide, especially in developing countries.[2,3] Pulmonary tuberculosis, another global health problem,[4] has been confirmed as an important risk factor for COPD development in numerous studies, increasing the risk of COPD by 3 to 4 fold.[5,6] Pooled prevalence of COPD is 21% among people with a history of pulmonary tuberculosis, which is similar to the result of a study conducted in China.[5,7] Despite the decreasing trend of incidence of tuberculosis, China still accounts for 7.4% of global tuberculosis incidence in 2021, ranking behind India and Indonesia.[8] Tuberculosis participates in the development of COPD through distinctive pathophysiological mechanisms compared to smoking-related COPD, characterized as excessive inflammation and elevated expression of lung matrix-degrading proteases, and this specific phenotype has been thereby named as "tuberculosis-associated COPD", accounting for 6.9% to 16% of COPD population.[6,9–11]

Although this concept had been raised by Allwood et al as early as in 2014, few studies focused on clinical and prognostic characteristics of tuberculosis-associated COPD and several relevant problems need to be addressed:[12] (1) Precise definition of tuberculosis-associated COPD. The initial definition of "tuberculosis-associated COPD" was proposed at the 1st International Post-Tuberculosis Symposium, which was defined as presence of airway obstruction (FEV_1/FVC ratio <0.7 or LLN) thought to be primarily related to small airway disease, on the basis of meeting the diagnosis of post-tuberculosis lung disease. However, this definition had not been fully discussed, and high-quality clinical evidence to support it was still lacking.[13] Additionally, pulmonary tuberculosis can be a potential comorbidity of COPD, for increased risk induced by tobacco smoking or biomass smoke inhalation, making the causal relation complicated to clarify.[1,14] (2) Unclear interaction between tuberculosis and other risk factors in the course of COPD. In addition to tuberculosis, other risk factors for COPD may be concomitant and the relation between tuberculosis and these factors seems to be unclear within non-smokers.[6,11] (3) The relevant predictors of morbidity and mortality among patients with tuberculosis-associated COPD need to be further explored. Previous studies have reported that COPD patients with prior tuberculosis were younger and experienced more acute exacerbations and hospitalizations during follow-up, indicating a worse prognosis than those without a history of tuberculosis.[15,16] Another study conducted in Korea found that the levels of serum inflammatory biomarkers such as C-reactive protein (CRP) and interleukin (IL)-6 were elevated in tuberculosis-associated COPD, which would be susceptible to cardiovascular diseases.[17–19] Nevertheless, evidence regarding the prognostic features of this condition was still limited. (4) Lack of evidence regarding pharmacological interventions and disease management. An early study found that COPD patients with a history of tuberculosis were featured by higher airflow resistance and lower response to bronchodilators.[20] Moreover, administration of inhaled corticosteroids (ICS) may increase the risk of tuberculosis recurrence.[21,22] Therefore, determining which patients would benefit from bronchodilators and ICS and avoiding relevant adverse effects is of clinical significance.

In this study, we aim to investigate the clinical characteristics and prognostic predictors, explore plausible therapeutic regimens, and promote precise diagnosis and treatment of tuberculosis-associated COPD in a well-defined COPD cohort.

Materials and Methods

Study Design and Objective

We design to conduct a nationwide, multicenter, prospective, observational cohort study enrolling consecutive tuberculosis-associated COPD patients (study group) and non-tuberculosis-associated COPD patients (control group) across mainland China, in which seven tertiary hospitals will participate (Table 1). The study is planned to be initiated in January 2024 and will last for two years. We intend to recruit patients in these hospitals during the first year and follow-up all participants for one other year by scheduled outpatient visits. The geographical distribution of these hospitals is shown in Figure 1, indicating regional representativeness.

Comprehensive baseline data will be collected from the initiation of the study, including demographics, medical history (related to COPD and pulmonary tuberculosis), risk factors for COPD, comorbidities, medication administration, blood routine examination, results of interferon gamma release assays (IGRAs), lung function tests, and chest computed tomography (CT). Patients will be followed-up at an interval of 6 months (within a 15-days variance) in the respective

Table 1 Participating Affiliations and Respective Responsibility

No.	Participating Affiliation	Allocated Responsibility
1 (Leading affiliation)	Peking University Third Hospital	Study design, project conduction, patient enrollment and follow-up, data collection
2	Peking University Shougang Hospital	Patient enrollment and follow-up, data collection
3	The First Affiliated Hospital of Guangzhou Medical University (Guangzhou Institute of Respiratory Diseases)	Patient enrollment and follow-up, data collection
4	The First Hospital of China Medical University	Patient enrollment and follow-up, data collection
5	West China Hospital of Sichuan University	Patient enrollment and follow-up, data collection
6	Shanxi Bethune Hospital	Patient enrollment and follow-up, data collection
7	Tibet Autonomous Region People's Hospital	Patient enrollment and follow-up, data collection

hospitals. Health conditions, respiratory symptoms, exacerbation history, blood routine examination, lung function, chest CT, and relevant cost of COPD will be reassessed. The flowchart of the study is presented in Figure 2.

Main objectives of this study are about the following aspects:

1. Elucidate the clinical characteristics, progression and prognosis of tuberculosis-associated COPD.
2. Evaluate the relationship between different drug regimens and the prognosis of tuberculosis-associated COPD, as well as recurrence or deterioration of pulmonary tuberculosis, serving as personalized medical management.
3. Optimize the definition of tuberculosis-associated COPD.

Participants and Inclusion and Exclusion Criteria

Individuals with stable COPD are eligible. The inclusion criteria of this study are as follows: (1) patients who have dyspnea, chronic cough, or sputum production, and have definite airflow limitation with a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <0.7; (2) in stable condition; and (3) aged 35 years or older.

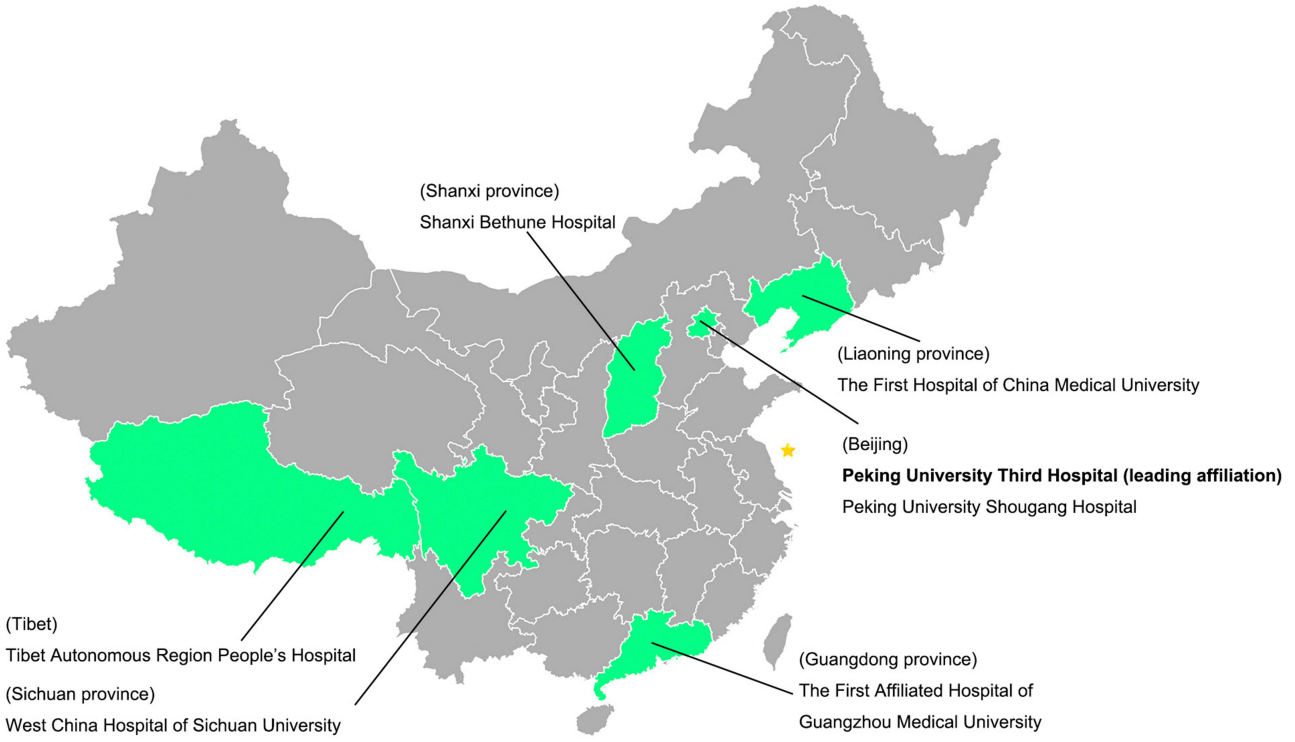

Figure 1 Geographical distribution of seven participating tertiary health centers in the mainland of China. There are two hospitals located in Beijing. Peking University Third Hospital is the leading affiliation.

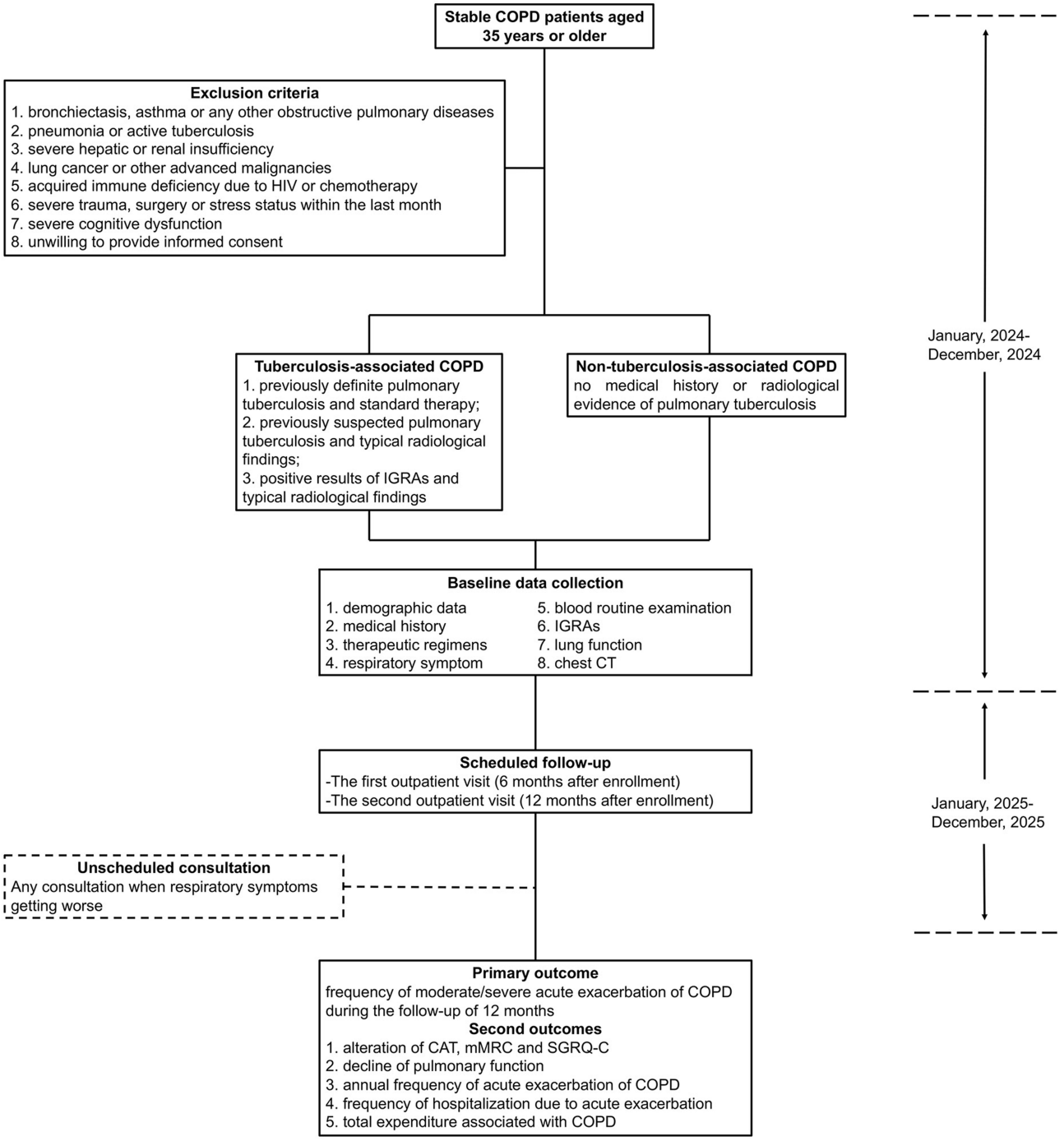

Figure 2 Flow chart of this cohort study.
Abbreviations: HIV, human immunodeficiency virus; IGRAs, interferon gamma release assays; CT, computed tomography; CAT, COPD Assessment Test; mMRC, modified Medical Research Council dyspnea scale; SGRQ-C, St. George's Respiratory Questionnaire for COPD patients.

The exclusion criteria are as follows: (1) bronchiectasis, asthma, or any other obstructive pulmonary diseases; (2) pneumonia or active tuberculosis; (3) severe hepatic or renal insufficiency; (4) lung cancer or other advanced malignancies; (5) acquired immune deficiency due to HIV infection or chemotherapy; (6) severe trauma, operation or stress status in the past month; (7) severe cognitive dysfunction; and (8) unwilling to provide informed consent.

Diagnosis of tuberculosis-associated COPD is made in our study if any of the following criteria is met: (1) previously definite pulmonary tuberculosis and ever receiving standard antituberculosis therapy; (2) previously suspected pulmonary

tuberculosis and having typical radiological findings consistent with tuberculosis sequelae, including calcification (isolated or multiple), fibrotic lesions (sharp margin), dense nodules, cavitation, or pleural scarring at the common site of tuberculosis; and (3) no definite history of pulmonary tuberculosis but having positive results of IGRAs accompanied by typical radiological findings consistent with tuberculosis sequelae. Patients in whom neither medical history nor chest CT indicates evidence of pulmonary tuberculosis are diagnosed as non-tuberculosis-associated COPD. All patients meeting the inclusion and exclusion criteria will be enrolled in the outpatient of each center and divided into tuberculosis-associated or non-tuberculosis-associated COPD based on the above criteria.

Baseline Data Collection

Demographic Data

Age, gender, ethnicity, height, weight, residential address, education level, and annual household income will be collected. Residential address is divided into urban or rural. Education level includes "primary school or less", "middle and high school" as well as "college and higher". Annual household income is stratified into four levels: ≤¥50,000, ¥50,000–10,000, ¥100,000–200000 and >¥200,000.

Medical History

Medical history includes smoking status (current smoker, former smoker or never-smoker), smoking index (pack-year), pulmonary tuberculosis history (when pulmonary tuberculosis was diagnosed, antituberculosis regimens and course), when COPD was diagnosed, other risk factors of COPD (including biomass fuel and air pollution exposure, early life events and childhood respiratory infection), comorbidities related to COPD (including hypertension, heart failure, arrhythmia, ischemic heart disease, diabetes, anemia, or polycythemia), and the frequency of exacerbation in the past 12 months.

Former smokers are defined as people who have smoked 100 cigarettes in their life and ceased smoking. Biomass fuels contain woody fuels and animal waste used for cooking or heating during the past six months or longer.[23] An exacerbation of COPD is defined as an event characterized by increased dyspnea and/or cough and sputum that worsens in <14 days.[1]

Therapeutic Regimens

The drug types administered for COPD are recorded, including short-acting β_2 agonists (SABA), short-acting muscarinic antagonists (SAMA), long-acting β_2 agonists (LABA), long-acting muscarinic antagonists (LAMA), SABA+SAMA, LABA+LAMA, methylxanthines, ICS, LABA+ICS, LABA+LAMA+ICS, theophylline and acetylcysteine. The drug names are also recorded.

Respiratory Symptoms

The COPD Assessment Test (CAT) score,[24] the modified Medical Research Council (mMRC) dyspnea scale,[25] and St George's Respiratory Questionnaire for COPD patients (SGRQ-C) will be used to comprehensively evaluate respiratory symptoms of the patients comprehensively.[26]

Blood Routine Examination

Blood routine examination will be performed at the clinical laboratory of the respective hospital. Counts of white blood cells, red blood cells, eosinophils, neutrophils, platelets, percentage of eosinophils and neutrophils, hemoglobin, and hematocrit are collected.

IGRAs

Peripheral venous blood samples (5mL) are obtained from each participant. QuantiFERON-TB Gold Plus (QFT-Plus, Cellestis, Australia) is used for detecting the tuberculosis infection using the following procedure: i) 1mL of blood is added into four tubes and incubated with ESAT-6 (specific antigen), CFP-10 (specific antigen), negative control, and mitogen (positive control) at 37°C for 16–24 hours, respectively; ii) the sample is centrifuged at 2000–3000 RCF for 15 minutes and plasma is extracted; and iii) then ELISA is used to measure the concentration of γ-interferon (γ-IFN). Result is interpreted as "positive" if either TB1-nil or TB2-nil γ-IFN level ≥0.35 IU/mL and >25% of nil value; "negative" if both TB1-nil and TB2-nil γ-IFN levels <0.35 IU/mL or <25% of nil value.

Lung Function

Standard pre-bronchodilator and post-bronchodilator (400 μg of salbutamol) spirometry are performed according to current ATS/ERS recommendations.[27] The percentage of predicted values for forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) will be calculated by using a reference equation of Chinese people. FEV_1, FEV_1 %predicted, FVC, FVC %predicted, FEV_1/FVC, residual volume (RV), total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLCO) are collected for evaluation of pulmonary ventilation and diffusion function.

Chest CT

Chest CT examinations and reports will be performed separately by two experienced radiologists from each participating affiliation. Radiographs are assessed for tuberculosis sequelae, emphysema, and bronchiectasis. Radiological findings of tuberculosis sequelae include calcification (isolated or multiple), fibrotic lesions (sharp margins), dense nodules, cavitation, or pleural scarring in common site of tuberculosis, as previously mentioned.

Goddard score is used for evaluating the severity of emphysema on pulmonary images by dividing the entire lung field into three areas: the upper, middle and the lower, with a total of six areas for both sides. The severity of emphysema is assessed in each area with a score ranging from 0 to 4 points and Goddard score values of six areas are summed up with a maximum score of 24.[28,29] Bronchiectasis is considered present if abnormal dilation of bronchi with the ratio of the diameter of bronchus to that of the accompanying pulmonary artery being >1.1 or the lack of tapering of bronchi are shown in chest CT.[30] Smith score and Bhalla score are used for estimating the extent and severity of bronchiectasis, respectively.[31,32]

Follow-Up and Outcomes

As a dynamic cohort, all participants will be prospectively followed up for at least one year from enrollment until December 2025. Outpatient visits will be arranged at an interval of 6 months (within a variance of 15-days) for disease and quality of life evaluations. Alteration of respiratory symptom, lung function and blood routine examination, therapeutic regimen, frequency of exacerbation and hospitalization, as well as recurrence of pulmonary tuberculosis will be collected. Chest CT will be reevaluated and the cost related to COPD will be summed up in the second outpatient visit. Besides scheduled visit, patients can consult their physicians whenever their symptoms worsen as a supplement to reduce recalling bias. Reasons for patient attrition are also recorded. Detailed procedures are shown in Table 2.

Table 2 Baseline Data Collection and Follow-Up Assessment

	Baseline	Follow-Up	
		After 6 Months	After 12 Months
Demographic data	☑		
Risk factors of COPD	☑		
Medical history of COPD	☑		
Comorbidity related to COPD	☑		
Respiratory symptoms[a]	☑	☑	☑
Frequency of exacerbation in the past 1 year	☑		
Blood routine examination	☑	☑	☑
IGRAs	☑		
Therapeutic regimens	☑	☑	☑
Lung function	☑	☑	☑
Chest CT	☑		☑
Frequency and severity of exacerbation[b]		☑	☑
Frequency of hospitalization due to COPD exacerbation[b]		☑	☑
Specific medical expenditure			☑

Notes: [a]Respiratory symptoms are assessed using the CAT score, mMRC dyspnea scale and SGRQ-C score. [b]Besides scheduled visit, patients are encouraged to consult the physicians and report their condition to the researchers, whenever their symptoms worsen.
Abbreviations: IGRAs, interferon gamma release assays; CT, computed tomography; CAT, COPD Assessment Test; mMRC, modified Medical Research Council dyspnea scale; SGRQ-C, St George's Respiratory Questionnaire for COPD patients.

Primary outcome of this study is the frequency of moderate/severe acute exacerbation of COPD over a follow-up period of 12 months. Exacerbations of COPD are classified as mild if patients are treated with short acting bronchodilators only, as moderate if patients are treated with short acting bronchodilators plus antibiotics or oral corticosteroids, and as severe if hospitalization or emergency room admission is required.[1]

The secondary outcomes include alteration of CAT score, mMRC dyspnea scale and SGRQ-C score, decline of pulmonary function, the frequency of acute exacerbation of COPD and hospitalization due to COPD exacerbation during the follow-up period, total expenditure associated with COPD within one year in follow-up and recurrence of pulmonary tuberculosis. Total expenditure is the summation of each medical expense, related to therapeutic regimen, ventilator support in hospital, long-term oxygen therapy and respirology rehabilitation training. Recurrence of pulmonary tuberculosis is defined as positive sputum acid-fast bacillus (AFB) and culture or active tuberculosis lesions on CT imaging.

Sample Size Estimation

This study plans to recruit participants by consecutive enrollment and registration from January 2024 to December 2024. Sample size estimation is based on the primary outcome variable of the frequency of moderate/severe acute exacerbations during follow-up, and an unpaired two-sided *t*-test will be used. With regard to participants who are followed up for more than 12 months, their annual frequency of moderate/severe acute exacerbation is calculated by dividing documented frequency over time. In view of the fluctuant frequency of exacerbation among different regions, data from other studies may have restricted significance for sample size estimation in specific districts.[33] The presumed annual frequency of exacerbation of tuberculosis-associated COPD patients is 0.85 ± 0.79 per year according to the medical history of COPD patients with prior pulmonary tuberculosis, and the presumed annual frequency of exacerbation of non-tuberculosis-associated COPD patients is 0.59 ± 0.65 per year. Assigning the non-tuberculosis-associated COPD group a three-times sample size and allowing for 10% attrition, we conservatively estimate that a minimum sample size of 135 patients allocated to tuberculosis-associated COPD group and 405 patients allocated to non-tuberculosis-associated COPD group will give 90% power and a significance level of 5%.

Statistics

Data will be analyzed using SPSS, version 26.0 (IBM Corp., Armonk, N.Y., USA). For descriptive statistics of baseline clinical data, normality of continuous variables (including age, BMI, frequency of acute exacerbation of COPD in the past 1 year, blood routine examination measurements, lung function measurements and chest CT-related scores) are tested using Kolmogorov–Smirnov test and quantile-quantile plot (QQ plot). Continuous variables with normal distribution are recorded as mean ± standard deviation (SD) and unpaired *t*-test is administered for difference evaluation; while those not following a normal distribution are recorded as median together with interquartile range, and Mann–Whitney test is administered for difference evaluation. Categorical variables (gender, education level, household income, risk factors of COPD, comorbidity, therapeutic regimens and GOLD stage) are recorded as numbers (%) and Chi-square test is used. P-value <0.05 is considered statistically significant.

All outcomes except recurrence of pulmonary tuberculosis are processed as continuous variables. For statistical tests of continuous outcome variables, unpaired *t*-test is administered for those with normal distribution, and Mann–Whitney test is administered for those not following normal distribution. Linear regression will be used for exploring independent risk factors related to continuous outcome variables. Logistic regression will be used for analyzing the independent factor associated with recurrence of pulmonary tuberculosis by controlling underlying confounders. Clustering analysis will be used for refining potential tuberculosis-associated COPD patients who accord with nature medical course of tuberculosis sequelae.

Quality Control, Data Management and Monitoring

With access to the exclusive data management platform constructed by Peking University Third Hospital based on REDCap, we utilize the electronic medical records and database for information entry, which will be accomplished by leading affiliation together with each collaborative institution. All private information that may indicate the personal identity will be concealed by a unique coded ID. Managers who are appointed will manually verify the data entered and check the logic of the data at regular intervals.

Discussion

This is a nationwide, multicenter, prospective, observational cohort study, which will be conducted among 7 tertiary hospitals across mainland China. The baseline clinical characteristics, including respiratory symptom burden, lung function measurements and radiological features, will be described and compared between the subjects with tuberculosis-associated COPD and non-tuberculosis-associated COPD. All eligible subjects will be followed up for one year. During the follow-up period, the frequency of COPD exacerbation, as well as dynamic changes of respiratory symptoms, lung function, and chest radiological features will be evaluated. Our study will provide a more detailed profile of tuberculosis-associated COPD and propose potential treatment options for this special phenotype.

Both tuberculosis and COPD are major public health problems, especially in developing countries. Meanwhile, tuberculosis is an important risk factor for COPD, which has been confirmed by several observational studies as well as meta-analysis.[5–7,34] Previous studies have generally concentrated on the relationship between tuberculosis and COPD, while few have attached attention to this phenotype per se, indicating that more clinical studies regarding disease characteristics, evolution, prognosis, and even the definition of this phenotype are warranted. In addition to the definition of tuberculosis-associated COPD proposed on the 1st International Post-Tuberculosis Symposium, diverse definitions applied in previous studies indicate that classical radiological TB sequel findings play an important role in diagnosing and categorizing.[18,20,35–37] Nevertheless, whether these definitions can accurately describe or reflect the essence of tuberculosis-associated COPD still requires further researches. Our study puts forward an innovative diagnosis criterion of tuberculosis-associated COPD, which integrates the medical history of pulmonary tuberculosis, IGRAs results, and chest CT radiological signs, and may embody improved sensitivity and specificity.

COPD exacerbations are important events in the management of COPD for accelerating the deterioration of health status, causing frequent hospitalization and readmission and increasing the risk of mortality.[1] A retrospective study conducted in Korea found that COPD patients with a history of tuberculosis had higher exacerbation prevalence, compared to those without prior tuberculosis history.[38] Another prospective study with a small sample size found that patients with post-Tuberculosis Obstructive Airway Disease (Post-TB OAD) experienced more severe exacerbation and frequency of hospitalization than those patients with "classic" COPD, during 12 months follow-up.[15] However, the evidences regarding disease exacerbation and relevant clinical outcomes in patients with tuberculosis-associated COPD are still limited. Heterogeneity among studies was noticeable, including the study design, region, participants and endpoint of observation. In addition, the patterns of lung function among patients with tuberculosis-associated COPD also had heterogeneity, and the response to bronchodilators was different.[20,39] Therefore, the risk factors and characteristics for disease exacerbation in this population will be significantly different from those without tuberculosis, and our study may address this issue.

The mechanism underlying tuberculosis-associated COPD is distinctive from smoking-related COPD. Previous studies revealed that submucosal tuberculosis and nonspecific inflammation, as well as bronchiectasis lesions, were frequently seen in patients with tuberculosis.[40] Lymph node involvement in primary infection syndrome could result in bronchial obstruction and dilation.[41] In addition, the destruction of lung parenchyma after pulmonary tuberculosis could affect lung compliance and cause the collapse of peripheral small airways, which in turn led to the occurrence of air trapping and emphysema.[42] Therefore, the clinical features and chest imaging findings in patients with tuberculosis-associated COPD were distinctive. Our previous study found that COPD patients with prior tuberculosis had unique features of emphysema and more bronchiectasis, which was consistent with previous studies.[15,43,44] Air trapping due to small airway obstruction was more often in tuberculosis-associated COPD in expiration CT scan, compared to those with smoking-related COPD.[45] Patients with tuberculosis-associated COPD had an increased decline in forced expiration volume in 1 second than those without prior tuberculosis.[38] In this prospective study, we will also investigate the clinical features including respiratory symptoms, quality of life, and the dynamic changes of spirometry function and chest imaging findings, in order to better understand this disease phenotype.

Long-acting bronchodilators are the foundation medications for patients with COPD, while inhaled glucocorticoids are conditionally recommended for certain patients, who have concomitant asthma, a blood eosinophil count ≥300/μL or experiences moderate exacerbation ≥2, or severe exacerbation requiring hospitalization ≥1.[1] However, there is a lack of evidence regarding the effect of bronchodilators in tuberculosis-associated COPD. The efficacy of bronchodilators in this

group of patients is still worth exploring. How to determine the "treatable traits" of patients with tuberculosis-associated COPD is of clinical significance. In addition, inhaled glucocorticoids may increase the risk of tuberculosis recurrence and thereby are not recommended in patients with prior tuberculosis history. However, for those patients with tuberculosis-associated COPD concomitant with asthma-like manifestations or high eosinophil counts in blood or sputum, whether they can benefit from inhaled glucocorticoids also requires further researches.

Another prominent strength of this study is that participants are recruited from seven tertiary hospitals located in six provinces across mainland China. Economic level and medication accessibility have an intense influence on tuberculosis prevalence and COPD treatment compliance, and this multicenter study will help to make the results more representative. With the application of more plausible screening criteria, it is expected that more insights into the clinical significance will be disclosed, in terms of the characteristics of tuberculosis-associated COPD.

This study has some limitations. Firstly, although the criteria we propose are comprehensive, their sensitivity and specificity still need to be verified for the lack of "gold standard". Secondly, we choose the annual moderate/severe exacerbation as primary outcome, while comorbidity as well as long-term outcome will not be evaluated in this study, which both have an influence on the life quality of COPD patients.

Abbreviations

COPD, chronic obstructive pulmonary disease; CT, computed tomography; CAT, COPD Assessment Test; CRP, C-reactive protein; DLCO, diffusing capacity for carbon monoxide; ELISA, enzyme-linked immunosorbent assay; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; γ-IFN, γ-interferon; ICS, inhaled corticosteroids; IGRAs, interferon gamma release assays; IL, Interleukin; LABA, long-acting β_2 agonists; LAMA, long-acting muscarinic antagonists; mMRC, the modified Medical Research Council dyspnea scale; RV, residual volume; SABA, short-acting β_2 agonists; SAMA, short-acting muscarinic antagonists; SGRQ-C, St. George's Respiratory Questionnaire for COPD patients; TLC, total lung capacity.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Informed consents will be obtained from all participants or their close relatives before data collection. This study will be conducted in accordance with the Declaration of Helsinki. This protocol has been approved by the Ethics Committee of Peking University Third Hospital (M2023573). This study has been registered in ClinicalTrials.gov (NCT06074042).

Acknowledgment

This paper has been uploaded to Research Square as a preprint: https://www.researchsquare.com/article/rs-3852584/v1.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception and study design 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.

Funding

The study was granted by China International Medical Foundation [Z-2017-24-2301].

Disclosure

The authors declare that they have no competing interests.

References

1. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, global initiative for chronic obstructive lung disease (GOLD) 2024 report. Available from: http://www.goldcopd.org/. Accessed November 13, 2024.
2. Safiri S, Carson-Chahhoud K, Noori M, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990–2019: Results from the global burden of disease study 2019. *BMJ*. 2022:e069679. doi:10.1136/bmj-2021-069679.
3. Soriano JB, Kendrick PJ, Paulson KR, et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: A systematic analysis for the global burden of disease study 2017. *Lancet Resp Med*. 2020;8:585–596. doi:10.1016/s2213-2600(20)30105-3
4. Dheda K, Barry CE, Maartens G. Tuberculosis. *Lancet*. 2016;387:1211–1226. doi:10.1016/s0140-6736(15)00151-8
5. Fan H, Wu F, Liu J, et al. Pulmonary tuberculosis as a risk factor for chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Ann Transl Med*. 2021;9:390. doi:10.21037/atm-20-4576
6. Kamenar K, Hossen S, Gupte AN, et al. Previous tuberculosis disease as a risk factor for chronic obstructive pulmonary disease: A cross-sectional analysis of multicountry, population-based studies. *Thorax*. 2022;77:1088–1097. doi:10.1136/thoraxjnl-2020-216500
7. Xing Z, Sun T, Janssens JP, et al. Airflow obstruction and small airway dysfunction following pulmonary tuberculosis: A cross-sectional survey. *Thorax*. 2023;78:274–280. doi:10.1136/thoraxjnl-2021-218345
8. World Health Organization. Global Tuberculosis Report 2022. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022. Accessed October 27, 2022.
9. Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: From epidemiology to pathophysiology. *Eur Respir Rev*. 2018;27:170077. doi:10.1183/16000617.0077-2017
10. Brilha S, Wysoczanski R, Whittington AM, Friedland JS, Porter JC. Monocyte adhesion, migration, and extracellular matrix breakdown are regulated by integrin αVβ3 in mycobacterium tuberculosis Infection. *J Immunol*. 2017;199:982–991. doi:10.4049/jimmunol.1700128
11. Zamzam MA, Agha MA, Said NA, Eldahdouh SS. Relation between pulmonary tuberculosis and chronic obstructive pulmonary disease. *Egypt J Chest Dis Tuberc*. 2022;71:15–19. doi:10.4103/ejcdt.ejcdt_74_20
12. Siddharthan T, Gupte A, Barnes PJ. Chronic obstructive pulmonary disease endotypes in low- and middle-income country settings: Precision medicine for all. *Am J Respir Crit Care Med*. 2020;202:171–172. doi:10.1164/rccm.202001-0165ED
13. Allwood BW, van der Zalm MM, Amaral AFS, et al. Post-tuberculosis lung health: Perspectives from the first international symposium. *Int J Tuberc Lung Dis*. 2020;24:820–828. doi:10.5588/ijtld.20.0067
14. Menezes AM, Hallal PC, Perez-Padilla R, et al. Tuberculosis and airflow obstruction: Evidence from the PLATINO study in Latin America. *Eur Resp J*. 2007;30:1180–1185. doi:10.1183/09031936.00083507
15. Swain S, Pothal S, Behera A, Manjhi R, Dutta P, Pradhan G. Treatment outcome among post TB obstructive airways diseases and COPD: A prospective cohort study. *J Fam Med Prim Care*. 2021;10:3411–3416. doi:10.4103/jfmpc.jfmpc_2391_20
16. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*. 2005;60:925–931. doi:10.1136/thx.2005.040527
17. Kunisaki KM, Dransfield MT, Anderson JA, et al. Exacerbations of chronic obstructive pulmonary disease and cardiac events. A post hoc cohort analysis from the SUMMIT randomized clinical trial. *Am J Resp Crit Care*. 2018;198:51–57. doi:10.1164/rccm.201711-2239oc
18. Oh JY, Lee YS, Min KH, et al. Difference in systemic inflammation and predictors of acute exacerbation between smoking-associated COPD and tuberculosis-associated COPD. *Int J Chronic Obstr Pulm Dis*. 2018;13:3381–3387. doi:10.2147/copd.s177371
19. Thomsen M, Dahl M, Lange P, Vestbo J, Nordestgaard BG. Inflammatory biomarkers and comorbidities in chronic obstructive pulmonary disease. *Am J Resp Crit Care*. 2012;186:982–988. doi:10.1164/rccm.201206-1113oc
20. Lee JH, Chang JH. Lung function in patients with chronic airflow obstruction due to tuberculosis destroyed lung. *Respir Med*. 2003;97:1237–1242. doi:10.1016/s0954-6111(03)00255-5
21. Kim JH, Park JS, Kim KH, Jeong HC, Kim EK, Lee JH. Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. *Chest*. 2013;143:1018–1024. doi:10.1378/chest.12-1225
22. Miravitlles M, Auladell-Rispau A, Monteagudo M, et al. Systematic review on long-term adverse effects of inhaled corticosteroids in the treatment of COPD. *Eur Respir Rev*. 2021;30:210075. doi:10.1183/16000617.0075-2021
23. Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): A national cross-sectional study. *Lancet*. 2018;391:1706–1717. doi:10.1016/S0140-6736(18)30841-9
24. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. *Eur Resp J*. 2009;34:648–654. doi:10.1183/09031936.00102509
25. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the medical research council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax*. 1999;54:581–586. doi:10.1136/thx.54.7.581
26. Meguro M, Barley EA, Spencer S, Jones PW. Development and validation of an improved, COPD-specific version of the St. George respiratory questionnaire. *Chest*. 2007;132:456–463. doi:10.1378/chest.06-0702
27. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Resp J*. 2005;26:319–338. doi:10.1183/09031936.05.00034805
28. Goddard PR, Nicholson EM, Laszlo G, Watt I. Computed tomography in pulmonary emphysema. *Clin Radiol*. 1982;33:379–387. doi:10.1016/s0009-9260(82)80301-2
29. Kagimoto A, Mimura T, Miyamoto T, Nakashima C, Yamashita Y. Severity of emphysema as a prognosticator of resected early lung cancer: An analysis classified by Goddard score. *Jpn J Clin Oncol*. 2020;50:1043–1050. doi:10.1093/jjco/hyaa084
30. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J. Fleischner society: Glossary of terms for thoracic imaging. *Radiolo*. 2008;246:697–722. doi:10.1148/radiol.2462070712
31. Smith IE, Jurriaans E, Diederich S, Ali N, Shneerson JM, Flower CD. Chronic sputum production: Correlations between clinical features and findings on high resolution computed tomographic scanning of the chest. *Thorax*. 1996;51:914–918. doi:10.1136/thx.51.9.914
32. Bhalla M, Turcios N, Aponte V, et al. Cystic fibrosis: Scoring system with thin-section CT. *Radiolo*. 1991;179:783–788. doi:10.1148/radiology.179.3.2027992
33. Yang T, Cai B, Cao B, et al. Exacerbation in patients with stable COPD in China: Analysis of a prospective, 52-week, nationwide, observational cohort study (REAL). *Ther Adv Respir Dis*. 2023;17:17534666231167353. doi:10.1177/17534666231167353

34. Sarkar M, Srinivasa, Madabhavi I, Kumar K. Tuberculosis associated chronic obstructive pulmonary disease. *Clin Respir J*. 2017;11(3):285–295. doi:10.1111/crj.12621
35. Baig IM, Saeed W, Khalil KF. Post-tuberculosis chronic obstructive pulmonary disease. *J Coll Physicians Surg Pak*. 2010;20:542–544.
36. Aggarwal D, Gupta A, Janmeja AK, Bhardwaj M. Evaluation of tuberculosis-associated chronic obstructive pulmonary disease at a tertiary care hospital: A case-control study. *Lung India*. 2017;34:415–419. doi:10.4103/lungindia.lungindia_522_16
37. Yakar HI, Gunen H, Pehlivan E, Aydogan S. The role of tuberculosis in COPD. *Int J Chronic Obstr Pulm Dis*. 2017;12:323–329. doi:10.2147/COPD.S116086
38. Park HJ, Byun MK, Kim HJ, et al. History of pulmonary tuberculosis affects the severity and clinical outcomes of COPD. *Respirol*. 2018;23:100–106. doi:10.1111/resp.13147
39. Gupte AN, Paradkar M, Selvaraju S, et al. Assessment of lung function in successfully treated tuberculosis reveals high burden of ventilatory defects and COPD. *PLoS One*. 2019: 14:e0217289. doi:10.1371/journal.pone.0217289.
40. Thompson JR, Kent G. Occult tuberculosis endobronchitis in surgically resected lung specimens. *Am Rev Tuberc*. 1958;77:931–939. doi:10.1164/artpd.1958.77.6.931
41. Jones EM, Peck WM, Woodruff CE, Willis HS. Relationships between tuberculosis and bronchiectasis; A study of clinical and of post-mortem material. *Am Rev Tuberc*. 1950;61:387–398. doi:10.1164/art.1950.61.3.387
42. Snider GL, Doctor L, Demas TA, Shaw AR. Obstructive airway disease in patients with treated pulmonary tuberculosis. *Am Rev Respir Dis*. 1971;103:625–640. doi:10.1164/arrd.1971.103.5.625
43. Jin J, Li S, Yu W, Liu X, Sun Y. Emphysema and bronchiectasis in COPD patients with previous pulmonary tuberculosis: Computed tomography features and clinical implications. *Int J Chronic Obstr Pulm Dis*. 2018;13:375–384. doi:10.2147/COPD.S152447
44. Wang Y, Li Z, Li F. Impact of previous pulmonary tuberculosis on chronic obstructive pulmonary disease: Baseline results from a prospective cohort study. *Comb Chem High Throughput Screen*. 2023;26:93–102. doi:10.2174/1386207325666220406111435
45. Allwood BW, Gillespie R, Galperin-Aizenberg M, et al. Obstructive pulmonary disease in patients with previous tuberculosis: Pathophysiology of a community-based cohort. *S Afr Med J*. 2017;107:440–445. doi:10.7196/SAMJ.2017.v107i5.12118