

Incidence and Risk Factors of Tuberculosis-Associated Chronic Obstructive Pulmonary Disease

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Purpose: Chronic obstructive pulmonary disease (COPD) is influenced by multiple factors. Varying prevalences of tuberculosis-associated COPD exist. However, studies on its incidence or risk factors are limited. We evaluated the incidence of tuberculosis-associated COPD and compare the characteristics of patients with and without COPD.

Patients and Methods: This multicenter, retrospective cohort study included 351 patients treated with anti-tuberculosis drugs for more than 6 months in four hospitals in Korea, followed for 11 years (132 months). The follow-up duration was divided into quartiles (Q1-Q4) to evaluate the change in the incidence of COPD over time. Clinical data and radiological findings were collected, and the incidence rate ratios were compared using Poisson regression and multivariable logistic regression analysis to identify risk factors.

Results: Overall, 71 participants developed tuberculosis-associated COPD, with an overall crude incidence of 20.56/1000 person-years. Patients with tuberculosis-associated COPD were older, more likely to be smokers, and had lower forced expiratory volume in 1 s (FEV1) (L) and lower FEV1/forced vital capacity. The incidence over 132 months was significantly lower than those during follow-up, with an incidence rate ratio of 0.49 ($p=0.027$). Multivariate analysis revealed that a tuberculosis diagnosis at an older age (adjusted odds ratio [aOR] 1.04; 95% confidence interval [CI]: 1.01–1.07), lower baseline FEV1 <80% (aOR 3.98; 95% CI: 1.92–8.24), smoking (aOR 3.23; 95% CI: 1.14–9.17), and multilobar involvement of tuberculosis (aOR 2.04; 95% CI: 1.08–3.85) were risk factors for tuberculosis-associated COPD. The incidence in the Q4 (>132 months, approximately 11 years) was significantly lower than that in the Q1 (18–71 months), with incidence rate ratio of 0.49 ($p=0.027$).

Conclusion: Older age at tuberculosis diagnosis, lower baseline FEV1 <80%, smoking history, and multilobar involvement were identified as risk factors for tuberculosis-associated COPD. The incidence of tuberculosis-associated COPD decreased 11 years after tuberculosis treatment.

Keywords: tuberculosis, post-tuberculosis lung disease, radiologic findings, spirometry

Introduction

Chronic obstructive pulmonary disease (COPD) was the fourth leading cause of death worldwide in 2021, accounting for approximately 5% of all global deaths.¹ Lancet Commission suggested that COPD should be classified into five types called etiologies, including type 3: infection-related COPD included tuberculosis-associated COPD.² According to the Global Tuberculosis Report 2020, the Republic of Korea was the Organisation for Economic Co-operation and

Development (OECD) country with the highest incidence of 59 cases per 100,000 people relative to the OECD average of approximately 9.95 cases per 100,000 people.³

Previous studies have suggested that a history of tuberculosis is associated with a higher risk of COPD development, with an odds ratio ranging from 1.37 to 2.94, compared with no history of tuberculosis.^{4,5} The estimated prevalence of tuberculosis-associated COPD varies widely from 8% to 58%.⁶ This variation across studies reflects differences in the study design (eg, non-cohort designs such as case-control or cross-sectional studies), TB definition and treatment practices, diagnosis of COPD, smoking prevalence in the study population, and the burden of TB. For instance, several studies defined COPD based on pre-bronchodilator forced expiratory volume in one second (FEV1)/ forced vital capacity (FVC) values below the lower limit of normal, or based on symptoms of chronic bronchitis, rather than using the GOLD guidelines.⁶⁻⁸ Similarly, tuberculosis was often defined based on self-reported TB history without microbiological, radiological, or treatment confirmation,^{6,9,10} and many studies did not specify the duration or adequacy of anti-TB treatment among participants. These studies are also limited by recall bias and uncertainty of the causal association between tuberculosis and COPD owing to the study methods, e.g cross-sectional study design, and sample size. Furthermore, spirometry was not performed before tuberculosis, leading to an inability to control for preexisting airway disease. In addition, several population-based studies are limited by a vague definition of tuberculosis history such as radiological evidence suggestive of inactive tuberculosis, further complicating interpretation.^{11,12} Andrew et al published a large population-based study of patients with tuberculosis confirmed by culture positivity, but the characteristics of tuberculosis, including radiologic findings and bacterial burden, were not described.¹³ Importantly, the true incidence of tuberculosis-associated COPD and the risk factors for the development of COPD after tuberculosis treatment remain largely unknown. One study reported that smear-positive TB was associated with lung function decline over a median follow-up of 16 months, which is insufficient to accurately assess the incidence of COPD or identify long-term risk factors following tuberculosis treatment.¹⁴

According to the World Bank 2022 data, the Republic of Korea has the second highest incidence of tuberculosis among the countries in the OECD.¹⁵ This high disease burden makes Korea a suitable setting for studying the long-term sequelae of pulmonary tuberculosis. Among these sequelae, COPD is of particular concern, as it contributes substantially to disability-adjusted life years and leads to considerable economic loss and poor quality of life.^{16,17} Therefore, understanding and managing tuberculosis-associated COPD should be a national healthcare priority, particularly in countries with a high tuberculosis burden such as the Republic of Korea. Well-designed research with detailed radiologic and microbiologic data and a sufficient follow-up period is essential to elucidate the relationship between tuberculosis and the development of tuberculosis-associated COPD. Such evidence is not only critical for informing public health strategies in Korea but also has broader implications for other countries with similar tuberculosis burdens.

Therefore, the objective of this study was to evaluate the incidence of tuberculosis-associated COPD and compare the characteristics of patients with tuberculosis who progressed to COPD with those who did not.

Materials and Methods

Study Design

We conducted a multicenter, retrospective cohort study in four hospitals in Korea: Seoul National University of Bundang Hospital (SNUBH); Seoul National University of Hospital (SNUH); National Medical Centre (NMC); and Veterans Health Service Medical Centre (VHS). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The institutional review board of each center approved the study, and each hospital waived the requirement for written informed consent considering that the research involved no greater than minimal risk and that obtaining consent was infeasible because of the retrospective nature of the study. All patient data were anonymized and handled with strict confidentiality to protect the privacy of the participants (IRB number B-2212-798-104).

Patient Population

This study included patients who had official records under the health insurance benefit extension policy for pulmonary tuberculosis in South Korea, which ensures a standardized diagnosis of pulmonary tuberculosis and uniform treatment

protocol including medications and duration across all medical institutions. Data of patients treated with anti-tuberculosis drug for over six months recorded in the health insurance benefit extension policy from January 1, 2013, to October 31, 2018, were initially screened at the four centers. We sequentially excluded, in descending order, patients who had no spirometry data before tuberculosis and patients who had spirometry data only within 5 years or no spirometry after tuberculosis (cases confirmed as COPD in pulmonary function test (PFT) performed within 5 years were included; those revealed as cases of nontuberculous mycobacteria [NTM]; and patients confirmed as having COPD before tuberculosis). COPD was diagnosed based on spirometry results (forced expiratory volume in 1 s [FEV₁]/ forced vital capacity (FVC) <0.7), regardless of pre- or post-bronchodilator use. PFT was conducted at each center in accordance with the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines.² After applying these criteria, 352 patients were included in the final analysis.

Data Collection

Demographic data and the burden of tuberculosis at baseline were reviewed from medical charts. They included age, sex, Acid-Fast Bacilli (AFB) staining, endobronchial tuberculosis (EBTB), treatment duration, multidrug-resistance (MDR), and chest computed tomography (CT) findings (bronchiolitis, cavitation, bronchiectasis, tuberculosis involvement sites, airway stenosis, mass, and pleurisy). The CT findings, which were interpreted and reported by board-certified chest radiologist of each center, were collected. Although a standardized reporting system was not used across the center and there was no central radiologic review, the following operational definition were applied: (a) bronchiolitis: characterized by centrilobular nodules and tree-in-bud pattern and sometimes included mosaic attenuation and air trapping;¹⁸ (b) cavity: characterized by abnormal air-filled spaces that replace the normal lung parenchyma and surrounded by wall;¹⁹ (c) mass: characterized by a mostly solid, circumscribed pulmonary lesion with a diameter > 30mm;²⁰ (d) TB pleurisy: characterized by pleural thickening and in certain stages, a pleural effusion may be present,²¹ with co-existing parenchymal lesions of tuberculosis;²² (e) bronchiectasis: characterized by increased bronchoarterial ratio, lack of tapering, bronchial wall thickening, or mucoid impaction;^{20,23} and (f) airway stenosis: characterized by the narrowing from the trachea to the subsegmental bronchi. Representative examples of each finding, obtained from patients included in this study, are shown in [Supplementary Figure 1](#). Multilobar involvement was operationally defined in this study as the presence of tuberculosis-affected lesions involving two or more lobes, based on radiologic interpretation. Spirometry data were collected before and after tuberculosis treatment and predicted for FEV₁, FVC, and FEV₁/FVC ratio, according to the American Thoracic Society/European Respiratory Society guidelines. In principle, post-bronchodilator data should be imputed; however, if post-bronchodilator data are missing, pre-bronchodilator data are used. Radiological findings from chest CT scans were collected; however, only those noted by the radiologist in the report were included. For example, even if other findings were observed on chest CT, such as bronchiectasis, we did not categorise them as tuberculosis-related findings if the radiologist did not mention them in the report.

Statistical Analysis

The baseline demographic data of the patients who progressed to COPD following tuberculosis were compared with the characteristics of patients who showed normal spirometry following tuberculosis using the chi-squared test for categorical variables and *t*-test for continuous variables. All continuous variables were non-normally distributed and are presented as medians and interquartile ranges (IQR). The intergroup comparisons of these variables were performed using the Mann–Whitney *U*-test.

Tuberculosis-associated COPD events were reported as events per 1000 person-years (PY), and Poisson-based 95% confidence intervals (CI) of the incidence rates were calculated. We used Poisson regression to investigate the relationship between the follow-up duration and incidence. The follow-up period was divided into four quartiles based on the distributions. The incidence for each quartile were compared using Poisson regression to model the number of COPD cases after tuberculosis as a function of the follow-up duration. The Incidence Rate Ratios (IRRs) were used to assess the relative risk of events in each quartile relative to the reference quartile. We performed multivariate logistic regression analysis to identify the factors associated with COPD progression by adjusting for age, sex, smoking history, baseline

lung function, and radiologic findings associated with tuberculosis-associated COPD in the univariate analysis ($p < 0.1$). Statistical analyses were performed using STATA version 14 software (StataCorp, College Station, TX, USA).

Results

Figure 1 shows the flow chart of the patients in this study who had a median follow-up duration of 90 months (69–128). Of the 11,250 patients with pulmonary tuberculosis who were treated with anti-tuberculosis medication over 6 months across the four hospitals, those who lacked PFT data, those diagnosed with COPD before tuberculosis treatment, those with confirmed NTM but not pulmonary tuberculosis, or those with extrapulmonary tuberculosis were excluded. Finally, 352 patients were analysed. During follow-up, 71 patients with tuberculosis (20.2%) who were treated for more than 6 months developed tuberculosis-associated COPD. The overall crude incidence of tuberculosis-associated COPD was 20.56/1000 PY.

The baseline characteristics of the normal and newly diagnosed tuberculosis-associated COPD groups are compared in Table 1. Compared to the patients with normal lung function, those with tuberculosis-associated COPD were older (55.6 ± 14.3 vs 60.4 ± 10.4 , $p = 0.009$), more likely to have smoked before (42.4 vs 60.5%, $p = 0.002$), and had lower FEV₁ (L) (2.6 vs 2.5 , $p = 0.029$) and FEV₁/FVC ratio (80 vs 75%, $p < 0.001$) at baseline. The proportion of cases of multidrug-resistant tuberculosis and the burden of tuberculosis did not differ between the two groups, as determined by AFB staining. The proportion of EBTB was significantly higher for the group that developed COPD after tuberculosis, and radiological findings showed a trend towards higher rates of bronchiectasis, airway stenosis, and multilobar involvement in the group that developed COPD after tuberculosis; however, the difference was not significant.

The incidence of tuberculosis-associated COPD was compared across the follow-up period and divided into quartiles (Table 2). The incidence in Q4 (over 132 months) was significantly lower than those for the other follow-up durations, with an IRR of 0.49 (p -value = 0.027). Figure 2 shows the incidence by quartiles of the follow-up duration and a trend of

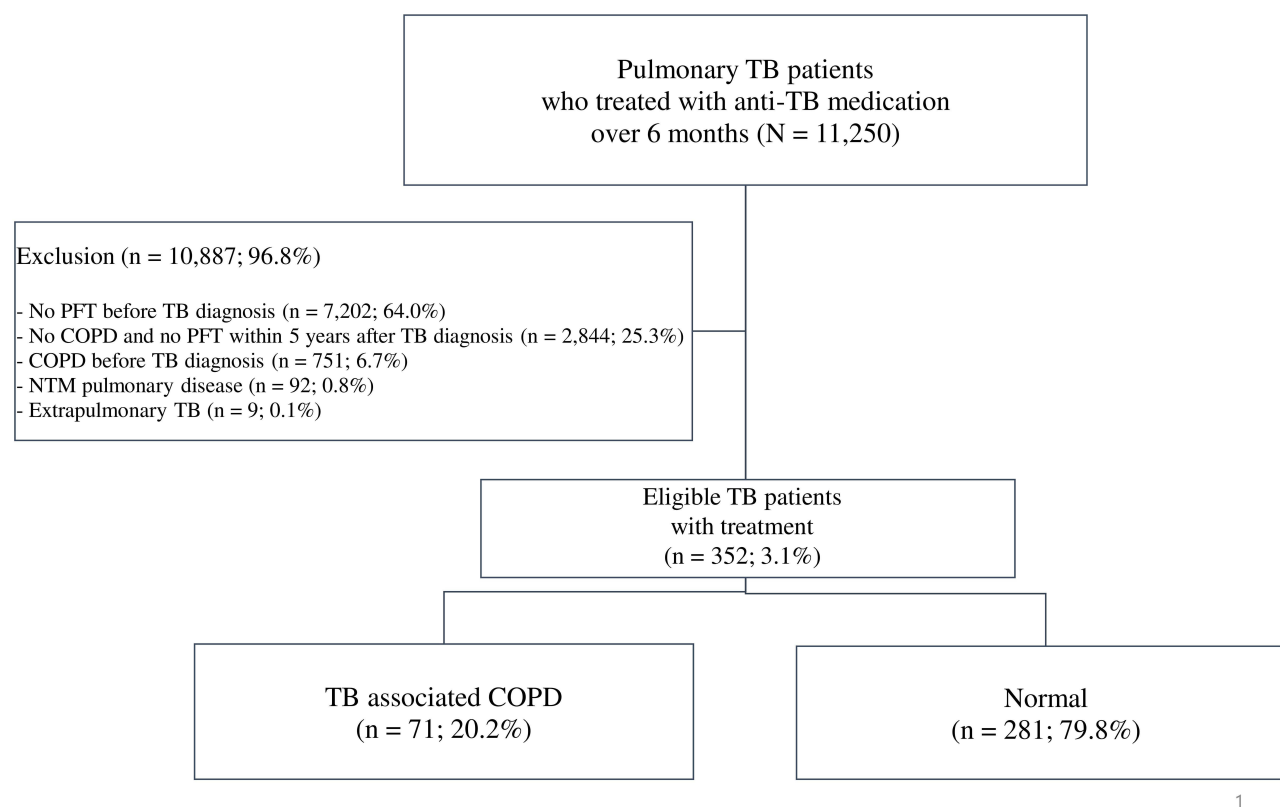


Figure 1 Flow chart of the patient population.

Table 1 Baseline Characteristics of Study Patient

Variables	Normal (n=281)	TB Associated COPD (n=71)	p
Age, year (at TB diagnosis)	55.6 ± 14.3	60.4 ± 10.4	0.009
Sex, male	165 (58.7%)	50 (70.4%)	0.077
BMI	22.3 ± 3.2	22.5 ± 3.1	0.689
Smoking			0.002
Never	125 (44.5%)	24 (33.8%)	
Former	71 (25.3%)	17 (23.9%)	
Current	50 (17.1%)	26 (36.6%)	
Unknown	38 (13.5%)	4 (5.6%)	
Smoking, Pack-year	26.9 ± 18.5	37.9 ± 27.1	0.008
Follow-up duration (month)	90 [70–126]	102 [72–139]	0.194
Baseline PFT			
FEV₁ (L)	2.6 [2.1; 3.1]	2.5 [1.8; 3.0]	0.029
FEV₁ (% predicted)	99.0 [87.0; 112.0]	95.0 [82.0; 105.0]	0.046
FVC (L)	3.2 [2.7; 4.0]	3.3 [2.4; 4.0]	0.592
FVC (% predicted)	92.0 [80.5; 103.0]	92.0 [80.0; 102.0]	0.898
FEV₁ /FVC	80.0 [76.0; 85.0]	75.0 [72.0; 78.0]	< 0.001
Follow-up PFT			
FEV₁ (L)	2.3 [1.8; 2.9]	2.0 [1.5; 2.6]	0.001
FEV₁ (% predicted)	99.0 [83.0; 111.0]	88.0 [71.0; 97.5]	< 0.001
FVC (L)	2.9 [2.3; 3.7]	3.0 [2.4; 4.0]	0.253
FVC (% predicted)	89.0 [74.5; 101.0]	91.0 [80.0; 102.0]	0.155
FEV₁ /FVC	78.0 [74.0; 84.0]	66.0 [63.0; 68.0]	< 0.001
Multidrug resistance tuberculosis	13 (4.5%)	4 (5.6%)	0.753
Endobronchial tuberculosis	14 (4.8%)	8 (11.3%)	0.040
Sputum AFB staining (≥ 1+)			
AFB ≥ 1+	44 (16.5%)	18 (26.9%)	0.051
AFB ≥ 2+	27 (10.2%)	8 (11.9%)	0.669
AFB ≥ 3+	11 (4.1%)	5 (7.5%)	0.255
Radiologic finding			
Bronchiolitis	198 (70.7%)	51 (76.1%)	0.377
Cavity	47 (16.8%)	12 (18.2%)	0.795
Mass	36 (13.0%)	10 (15.2%)	0.644
TB pleurisy	36 (12.8%)	7 (10.6%)	0.625

(Continued)

Table 1 (Continued).

Variables	Normal (n=281)	TB Associated COPD (n=71)	p
Bronchiectasis	46 (16.5%)	17 (25.8%)	0.082
Airway stenosis	13 (4.6%)	7 (10.4%)	0.067
Multilobar involvement	91 (32.7%)	30 (45.5%)	0.052

Abbreviations: AFB, Acid-Fast Bacilli; BMI, Body Mass Index; FEV₁, Forced Expiratory Volume in 1 s; FVC, Forced Vital Capacity; PFT, Pulmonary Function Test; TB, Tuberculosis.

Table 2 Incidence Rate and Incidence Rate Ratio of Tuberculosis-Associated Chronic Obstructive Pulmonary Disease Stratified by the Follow-Up Duration Quartile

Follow-up Duration [min-max]	Incidence Rate (1000 PY)	Incidence Rate Ratio	P
Q1 [18–71 months]	40.48	Reference	–
Q2 [72–95 months]	26.58	0.66	0.241
Q3 [96–131 months]	21.89	0.54	0.083
Q4 [132–235 months]	19.61	0.49	0.027

a lower incidence of tuberculosis-associated COPD with an increasing follow-up duration; however, the trend was not significant.

Table 3 presents the univariate and multivariate analyses of risk factors associated with the development of tuberculosis-associated COPD. In the multivariate logistic regression analysis, the probability of developing COPD following tuberculosis significantly increased as the age at the time of tuberculosis diagnosis increased (adjusted odds ratio [aOR] 1.04, 95% confidence interval [CI] 1.01–1.07). Using FEV₁ $\geq$ 90% as the reference group, patients with FEV₁ < 80% had a significantly higher risk of developing tuberculosis-associated COPD, with an aOR of 3.98 (95% CI: 1.92–8.24). Patients who had ever smoked had a 3.23-fold higher risk than those who had never smoked (aOR 3.23, 95% CI 1.14–9.17). Patients with multilobar involvement had a 2.04-fold higher risk of developing tuberculosis-associated COPD than those with single-lobe involvement.

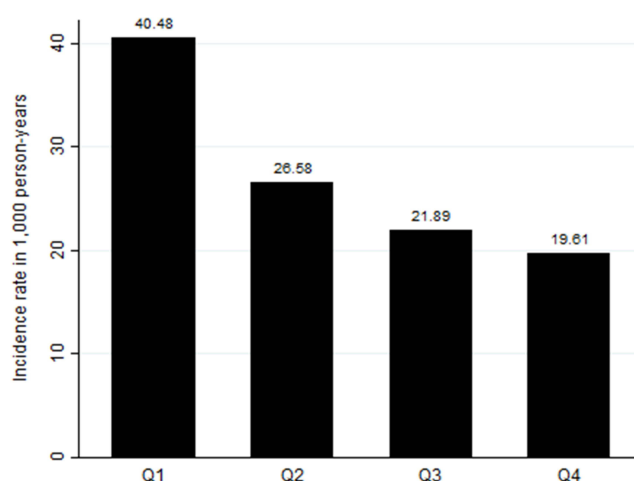
**Figure 2** Incidence rate of tuberculosis-associated chronic obstructive pulmonary disease stratified by the follow-up duration quartile.

Table 3 Univariate and Multivariate Logistic Regression Models for the Development of Tuberculosis-Associated Chronic Obstructive Pulmonary Disease

Variables	Univariate Logistic Regression				Multivariate Logistic Regression			
	OR	Lower CI	Upper CI	P	aOR	Lower CI	Upper CI	P
Sex (Ref, Male)	0.60	0.34	1.05	0.073	1.21	0.42	3.48	0.724
Age, year (TB diagnosis)	1.02	1.01	1.05	0.010	1.04	1.01	1.07	0.009
Ever smoker	1.90	1.09	3.32	0.025	3.23	1.14	9.17	0.028
Baseline FEV ₁ (%), (Ref, ≥90%)								
80%≤FEV ₁ <90%	1.58	0.73	3.38	0.242	1.72	0.68	4.39	0.255
FEV ₁ <80%	2.97	1.64	5.39	P <0.001	3.98	1.92	8.24	p <0.001
Endobronchial tuberculosis	2.42	0.97	6.02	0.057	2.58	0.73	9.18	0.142
Multidrug resistant tuberculosis	1.47	0.45	4.75	0.524				
Sputum AFB ≥ 1+	1.84	0.98	3.45	0.059	1.09	0.51	2.33	0.830
Airway stenosis in Radiography	2.32	0.89	6.08	0.085	3.01	0.93	9.79	0.067
Bronchiectasis in Radiography	1.69	0.89	3.19	0.106				
Multilobar involvement in Radiography	1.69	0.98	2.93	0.059	2.04	1.08	3.85	0.028
Pleurisy in Radiography	0.96	0.40	2.29	0.921				
Bronchiolitis in Radiography	1.24	0.66	2.30	0.504				
Volume loss in Radiography	1.61	0.55	4.70	0.380				
Cavity in Radiography	1.12	0.55	2.25	0.759				
Destroyed lung in Radiography	0.79	0.33	1.86	0.591				
Mass in Radiography	1.19	0.56	2.56	0.648				
Bronchial wall thickening in Radiography	1.18	0.24	5.85	0.836				

Abbreviations: AFB, Acid-Fast Bacilli; aOR, adjusted odds ratio; CI, confidence interval; FEV₁, Forced Expiratory Volume in 1 s; OR, odds ratio; TB, tuberculosis.

Discussion

In this multicenter retrospective cohort study, 20.2% of the patients progressed to COPD following tuberculosis treatment for more than 6 months, with an incidence of 20.56 /1000 PY and a median follow-up duration of 90 months. Furthermore, our study is the first to show that the incidence of COPD stratified by follow-up durations provides insights into the optimal follow-up duration required to minimise the risk of missing a COPD diagnosis after tuberculosis, and that patients with tuberculosis may develop COPD based on demographic data, treatment duration, radiological findings, and bacterial burden during tuberculosis diagnosis. When stratified by sex, the incidence rate was particularly higher among women, contributing to the overall higher rate observed in our cohort compared to a previous Korean community-based study (17.80 vs 14.48 per 1,000 person-years; [Supplementary Table 1](#)).²⁴ In a population-based cohort study of Korean published in 2024, 9.6% of tuberculosis survivors developed COPD, which is lower than the 20.2% observed in our study.¹⁵ Interestingly, the incidence rate of tuberculosis-associated COPD reported in the population-based study was 36.7 per 1,000 person-years, which is higher than 20.56 per 1,000 person-years reported in our study.¹⁵ This discrepancy may be attributed to differences in case definitions and data sources. The population-based study relied solely on diagnostic codes, which may have led to misclassification, including patients with asthma, extrapulmonary TB, or NTM. In our study, despite selecting patients using TB diagnostic codes combined with the prescription of anti-TB medications for more than 6 months, we identified 92 patients with NTM and 9 with extra-pulmonary TB upon detailed

review (Figure 1). Additionally, COPD diagnostic codes can be entered at the primary care setting without spirometry, which may also contribute to discrepancies in incidence estimation. Moreover, a recent large prospective cohort study of the European population reported an incidence of tuberculosis-associated COPD of 2.48 per 1,000 person-years, which is considerably lower than the incidence observed in our study (20.56 per 1,000 person-years).²⁵ This difference may be explained by a lower tuberculosis burden in European populations, where the TB incidence rate is approximately 24 per 100,000 population, compared to 38 per 100,000 in Korea, according to the World Health Organization (WHO) Global Tuberculosis Report in 2023.²⁶ Although this European study utilized UK Biobank data with reliable pulmonary function tests, it lacked radiologic findings. Therefore, our study, which included detailed clinical and radiological reviews to confirm tuberculosis and exclude misclassified cases, may provide a more accurate estimation of the true burden of tuberculosis-associated COPD.

We demonstrated that age at tuberculosis diagnosis, lower baseline FEV₁, smoking, and multilobar tuberculosis involvement were associated with an increased risk of COPD. The European study also identified age at tuberculosis diagnosis and smoking history as independent risk factors for COPD development, which is consistent with our findings.²⁵ COPD is a condition of accelerated lung ageing with complex mechanisms, including oxidative stress induced by smoking and an increased number of senescent cells within the airways.²⁷ As expected, tuberculosis diagnosis at an older age and smoking history were associated with an increased risk of COPD. In addition, patients with FEV₁ > 90% were significantly less likely to develop COPD than those with an FEV₁ < 80%. However, individuals with FEV₁ between 80% and 90%, while within the normal range, did not show a statistically significant reduction in risk compared to the patients with FEV₁ < 80%. This indicates that an FEV₁ value greater than 80% does not necessarily eliminate the risk of developing COPD after tuberculosis, although it is often considered normal. These findings underscore that optimal lung function (FEV₁ > 90%) may provide a more substantial protective effect, suggesting the need for continued monitoring and preventive strategies, even among individuals with FEV₁ in the 80–90% range. Sputum AFB staining was not associated with COPD progression, which is contrary to that of a previous study.¹⁴ We hypothesised that almost all patients had a low bacterial burden, considering that AFB negativity accounts for 81.4% of all patients with tuberculosis, resulting in no statistical significance. Instead, we observed an association between multilobar involvement and COPD progression after tuberculosis. This suggests that the burden of tuberculosis should be assessed with AFB in conjunction with radiographic findings.

According to the 2023 global tuberculosis report by the WHO, the estimated global tuberculosis incidence in 2022 was 134/100,000 population years, and the target incidence for ending the tuberculosis epidemic was less than 10 cases per 100,000 population per year.²⁶ The Republic of Korea has a lower incidence (38/100,000 population years) than the global value but is markedly greater than the global goal (<10/100,000 population/year). The Republic of Korea also has the second highest incidence of tuberculosis among the 38 member countries of the OECD 2021.^{15,28} Therefore, the prevalence of tuberculosis-associated COPD is expected to be high in Korea; however, all studies conducted in Korea are limited by the population-based approach and vague definitions of tuberculosis, such as suspected tuberculosis lesions in CXR or self-administered questionnaires of tuberculosis history.^{12,29}

The exact mechanism of tuberculosis-associated COPD is unclear. However, four potential mechanisms have been considered: small airway involvement, post-tuberculosis bronchiectasis, airway remodelling after parenchymal destruction, and alteration of the lung microenvironment during active tuberculosis infection.^{5,30} In tuberculosis, small airway involvement is characterised by granulomatous bronchiolitis, and this pathological abnormality presents as a tree-in-bud pattern on chest CT.^{31,32} In our study, 249 (68.6%) patients showed bronchiolitis with a tree-in-bud pattern on chest CT performed at the time of tuberculosis diagnosis. Small-airway dysfunction is considered a precursor of chronic airway diseases, including COPD and asthma.^{33,34} Second, tuberculosis can induce bronchiectasis owing to the destruction of elastin and muscles in the bronchial wall and post-tuberculosis bronchiectasis. According to a Korean bronchiectasis prospective cohort study, 19.7% of bronchiectasis cases were identified as post-tuberculosis bronchiectasis based on questionnaires, and patients with post-tuberculosis bronchiectasis showed higher airflow obstruction than those with bronchiectasis of other etiologies.³⁵ Another bronchiectasis study also demonstrated that more than half of the patients with post-tuberculosis bronchiectasis had airflow obstruction.^{36–38} However, we did not find a statistically significant effect of bronchiectasis detected by baseline chest CT on the development of COPD after tuberculosis. This could be

explained by the severity of bronchiectasis. The median FEV₁ predicted value for progression to COPD was 57.2–63% in another bronchiectasis study, whereas that of our study was 88%.³⁷ Therefore, the severity of bronchiectasis rather than the presence of bronchiectasis may have greater effects on COPD progression. In Korea, CT has increased rapidly since the early 2000s, and according to the 5th National Health and Medical Survey report of South Korea published in 2022, the number of CT scanners per 1,000,000 persons was 39.6 in 2019, which was higher than the OECD average of 25.8 per 1,000,000 persons.³⁹ Thus, tuberculosis was detected before the progression to severe bronchiectasis, considering that 89.2% of patients with tuberculosis had negative or 1+ AFB staining, which could be explained by the difference in the severity of bronchiectasis between bronchiectasis in our study and post-tuberculosis bronchiectasis in previous studies. Third, airway remodelling in the direction of thickening and stiffening from fibrosis leads to bronchodilator-resistant airway narrowing.⁴⁰ However, restrictive pulmonary impairment can manifest after tuberculosis. This heterogeneity may be linked to the host response to tuberculosis; however, the characteristics of those who will progress to airflow limitation or restrictive ventilator defects are not known.⁴¹ One hypothesis is that different matrix metalloproteinases (MMPs) are produced during mycobacterial infections. Lastly, the lung microenvironment was altered, and dysregulation was caused by mycobacterium and anti-tuberculosis therapy, which may contribute to chronic inflammation to facilitate the occurrence of COPD. Previous studies have demonstrated that *Mycobacterium* infection causes an acidic microenvironment in infected tissues. This promotes the upregulation of extracellular matrix degradation with increased MMPs by macrophages; such processes are commonly observed in COPD.⁴² Studies on the types of microbiomes that increase in abundance after *M. tuberculosis* infection are limited. One study reported that *Staphylococcus aureus*, *Klebsiella*, *Enterobacter species*, and *Pseudomonas* were identified in bronchial washing among patients with EBTB, although not compared to the control group of healthy participants.⁴³ These pathogens are associated with worsening symptoms, especially the frequent exacerbation of COPD.^{44–46} We assumed that dysbiosis in the direction of an increase in these bacteria following tuberculosis infection or treatment might play a role in predisposing the environment to COPD.

The main strengths of our study include the long-term follow-up (at least 5–19 years), which allowed for a comprehensive analysis of the incidence of tuberculosis-associated COPD over time. By examining the development of COPD across different follow-up intervals, our study provides an understanding of risk and offers practical guidance on the optimal duration of follow-up required for effective monitoring and early intervention. Second, we investigated detailed radiologic information, which shows factors associated with COPD following tuberculosis. Third, we included an objective assessment of pulmonary tuberculosis considering that patients who received a benefit extension policy for tuberculosis and had taken anti-tuberculosis drugs such as rifampin for more than six months were ultimately diagnosed with NTM (n=92). The use of standardized diagnostic and procedural protocols across all study sites ensured uniformity in data collection and analysis throughout the study period, thereby enhancing the reliability of tuberculosis-related classification and exclusion. Finally, the probability of misdiagnosis of tuberculosis-associated COPD based on analysis of spirometry data before tuberculosis treatment was low. This study has some limitations. First, spirometry was not originally intended to determine if COPD developed after tuberculosis. Second, we defined COPD solely based on an FEV₁/FVC ratio <0.7, without considering clinical symptoms or relevant risk factors. However, such a simplified spirometry-based definition is commonly used in large-scale epidemiological studies to estimate the incidence of COPD. Third, a small subset of patients (n=8, 2.2%) underwent spirometry without bronchodilators, which may have introduced minor variability in COPD diagnosis. Nonetheless, this minimal proportion is unlikely to have significantly affected the overall results. Lastly, there was no standardized assessment of CT findings. As there was no central radiologic review, CT interpretations were performed independently at each participating center, based on institutional practices. This may have introduced inter-observer variability in the evaluation of radiologic features, potentially affecting the consistency.

Conclusion

Our results suggest that a tuberculosis diagnosis at older age at, lower baseline FEV₁ (especially FFV₁ <80%), having smoked before, and multilobar involvement were significantly associated with the development of tuberculosis-associated COPD. Notably, the incidence of tuberculosis-associated COPD decreased significantly 11 years after

tuberculosis treatment. These findings suggest the importance of long-term spirometry surveillance. Therefore, physicians must follow up these patients, and spirometry should be performed regularly for at least 11 years for patients who have a high risk of COPD. Further prospective studies with standardized imaging interpretation and long-term spirometry follow-up are needed to validate these findings and to determine whether risk-based screening strategies can effectively facilitate the early identification and management of tuberculosis-associated COPD.

Data Sharing Statement

All data analyzed during this study are not publicly available due to ethical approvals from each institutional review board. The de-identified data used and analyzed during this study are available from the corresponding author upon reasonable request.

Ethics Approval Statement

The study was approved by the institutional review board of each participating hospital (IRB number B-2212-798-104) in Seoul National University Bundang Hospital, IRB Number J-2212-015-1382 in Seoul National University Hospital, IRB Number 2023-12-138 in National Medical Center, and IRB Number 2022-11-012 in Veteran Health Service medical center.

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Disclosure

Hye-Rin Kang and Jin Hwa Song's current affiliation is at Division of Pulmonology and Allergy, Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Republic of Korea. The authors report no conflicts of interest in this work.

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