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Tuberculosis Development in Chronic Obstructive Pulmonary Disease: A Nationwide Population-Based Study

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ABSTRACT

Background: Pulmonary tuberculosis is a major comorbidity of chronic obstructive pulmonary disease (COPD). However, the risk factors for tuberculosis development in patients with COPD have not been thoroughly studied. Thus, this study investigated the development of tuberculosis according to comorbidities and inhaler prescriptions for COPD.

Methods: A retrospective cohort study was conducted using data from the Korean Health Insurance Review and Assessment Service database from January 1, 2015 to December 31, 2020. This cohort included 139,589 COPD patients (≥ 40 years) with a new prescription of inhalers. Cox proportional hazards regression models were used to identify significant risk factors for predicting the development of tuberculosis.

Results: Multivariate analysis demonstrated that a history of tuberculosis (hazard ratio [HR], 18.14; 95% confidence interval [CI], 16.44–20.02) and hospitalization during the screening period (HR for one hospitalization, 1.30; 95% CI, 1.17–1.44; HR for two or more hospitalizations, 1.54; 95% CI, 1.39–1.70), along with older age and male sex, were associated with the development of pulmonary tuberculosis.

Conclusion: Our data indicate that a history of tuberculosis and hospitalization during the screening period, along with old age and male sex, are independent risk factors for the development of pulmonary tuberculosis in patients with COPD.

Keywords: Chronic Obstructive Pulmonary Disease (COPD); Tuberculosis; Comorbidity

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is projected to become the third leading cause of death globally by 2030, and its burden continues to rise, particularly in developing countries.^{1–4} The prognosis of COPD is closely linked to frequent exacerbations, primarily triggered by infections, including respiratory viruses and bacteria.⁵

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The authors have no potential conflicts of interest to disclose.

Data Availability Statement

Health Insurance Review and Assessment Service (HIRA) is an open public database that any researcher can access through the website (<https://www.hira.or.kr>).

Author Contributions

Conceptualization: Park JH. Data curation: Lee Y. Formal analysis: Lee Y, Park B. Investigation: Lee Y, Park JH. Methodology: Jeong H, Lee Y, Choi WI, Park B, Park JH. Project administration: Park JH. Supervision: Park JH. Writing - original draft: Jeong H. Writing - review & editing: Lee Y, Oh JH, Choi WI, Park JH.

According to the Lancet Commission report, infection-related COPD (COPD-I) is one of the five subtypes of COPD and is recognized as a significant contributing factor.^{1,2,6} The association between tuberculosis (TB) and COPD has been described in several studies.^{7,8} Structural lung damage caused by TB, including pleural changes, bronchial stenosis, and lung scarring, can predispose individuals to an increased risk of developing COPD.^{8,9} Conversely, increasing evidence suggests that patients with COPD are at a higher risk of developing pulmonary TB, mainly because of a compromised innate immune system and impaired pulmonary function.^{7,10} Furthermore, a previous study indicated that a TB diagnosis is associated with increased mortality in patients with COPD compared with that in patients with TB in the general population.¹¹ Therefore, the co-existence of COPD and TB is a serious health concern that necessitates targeted prevention and management strategies. Some studies have explored the relationship between inhaled corticosteroids (ICS) and TB risk in COPD.^{12,13} However, the factors contributing to TB development in patients with COPD, beyond smoking, have not been sufficiently investigated. Hence, this study aimed to identify the risk factors for the development of TB in patients with COPD, with a particular focus on inhaler prescriptions and comorbidities, using data from a nationwide cohort in Korea.

METHODS**Study design**

This study retrospectively analyzed data from the Korean Health Insurance Review and Assessment Service (HIRA) database, covering the period from January 1, 2015 to December 31, 2020. The HIRA database contains comprehensive medical service claim records, including diagnostic codes based on the International Statistical Classification of Diseases and Related Health Problems, 10th Edition (ICD-10), as well as medication data. It encompasses healthcare services across all geographic regions and covers 98% of the Korean population, all of whom are insured under the country's mandatory and universal national health insurance system.¹⁴ Key data fields, including drug names, quantities, dispensing dates, and durations, had minimal missing or out-of-range values, affecting less than 0.5% of the records.

The COPD cohort was constructed from the HIRA database based on the following criteria: 1) patients aged ≥ 40 years, 2) a primary diagnosis of COPD (J43–J44 of ICD-10 codes) recorded between January 1, 2016, and December 31, 2020, 3) at least three prescriptions of one of the following respiratory medications within one year of observation period: long-acting muscarinic antagonists (LAMA), long-acting β_2 -agonists (LABA), a combination of LAMA/LABA, a combination of ICS/LABA, triple therapy (LAMA + LABA + ICS), phosphodiesterase-4 inhibitors, mucolytics, or theophylline (Fig. 1).¹⁵

Each patient underwent a one-year screening period without any inhaler prescriptions prior to the index date. The index date was defined as the date when the patient was first prescribed inhaler medication (Fig. 2). During the screening period, the following exclusion criteria were applied: patients with a history of cancer; patients who had been prescribed respiratory inhalers before the index date; patients who had inhaler prescriptions switched after the index date; patients with prescriptions of immunosuppressants; patients diagnosed with diabetes mellitus without medications for diabetes mellitus; and patients diagnosed with osteoporosis without medications for osteoporosis. Subsequently, TB development during the observation period was assessed from the index date to December 31, 2020 (Fig. 2).

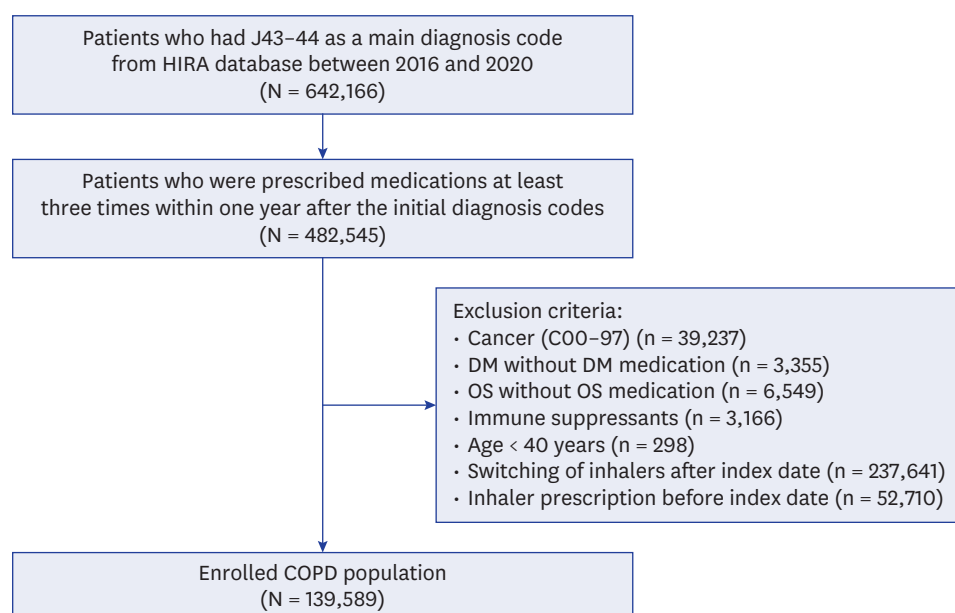


Fig. 1. Flow chart of study population selection.

HIRA = Health Insurance Review and Assessment Service, DM = diabetes mellitus, COPD = chronic obstructive pulmonary disease, OS = osteoporosis.

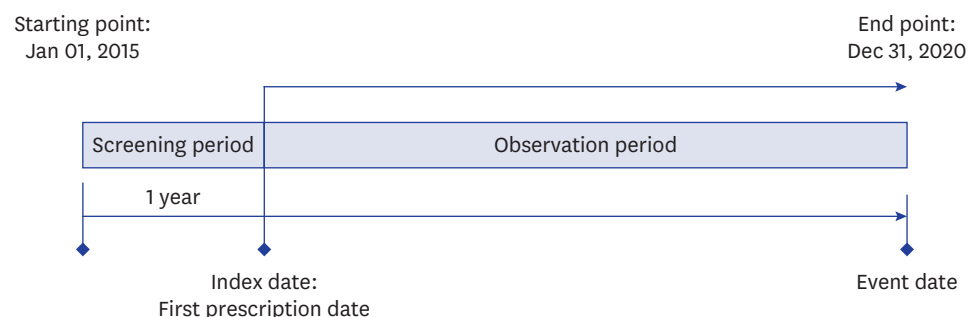


Fig. 2. Study design.

Case identification and comorbidities

Within the eligible cohort, TB cases that occurred after the index date were identified based on the following criteria: 1) a reported TB diagnosis with ICD-10 codes A15–A19, 2) treatment with two or more anti-TB drugs (Anatomical Therapeutic Chemical code J01), including isoniazid, rifampicin, ethambutol, pyrazinamide, prothionamide, 4-aminosalicylic acid, and cycloserine; 3) at least two claims for TB-related medical expenses submitted to HIRA. A history of TB was defined as the diagnosis of TB before the index date.

All comorbidities including a history of TB were detected using the ICD-10 codes during the screening period (Table 1). Oral corticosteroid (OCS) usage was identified by a prescription of 420 mg (15 mg/day for four weeks) or more prednisolone for COPD during the observation period.

Table 1. Baseline characteristics of this chronic obstructive pulmonary disease cohort

Characteristics	Values
Age, yr	68.9 ± 10.9
Age distribution, yr	
40–49	6,701 (4.8)
50–59	21,717 (15.6)
60–69	41,582 (29.8)
70–79	45,296 (32.5)
80–	24,293 (17.4)
Sex, male	105,447 (75.5)
Co-morbidities during screening period	
Asthma (J45–J46)	58,064 (41.6)
Hypertension (I10–I15)	73,885 (52.9)
Ischemic heart disease (I20–I25)	24,190 (17.3)
Heart failure (I50)	11,704 (8.4)
Cerebrovascular stroke (I60–I66)	12,035 (8.6)
Diffuse interstitial lung disease (J84)	1,149 (0.8)
Bronchiectasis (J47)	7,304 (5.2)
GERD (K21.0, K21.9)	62,171 (44.5)
Previous history of tuberculosis	2,696 (1.9)
Chronic liver diseases (K70.3, K71.7, K73, K74)	4,351 (3.1)
Chronic renal diseases (N18, N19, I12.0, I13.2)	4,293 (3.1)
Osteoporosis (M80–M82)	2,509 (1.8)
Diabetes mellitus (E10–E14)	23,865 (17.1)
Epilepsy (G40, G41)	3,100 (2.2)
Treatment	
LAMA, LAMA/LABA	77,505 (55.5)
LAMA/ICS	30,417 (21.8)
LAMA/ICS/LABA	3,913 (2.8)
LABA	27,754 (19.9)
CCI score	2.64 ± 1.95
CCI score	
0 (CCI score = 0)	11,190 (8.0)
1 (CCI score = 1)	35,189 (25.2)
2 (CCI score = 2)	32,034 (23.0)
3 (CCI score ≥ 3)	61,176 (43.8)
OCS use (hydrocortisone equivalent)	
Cumulative dose	900 [400–2,190]
Cumulative dose = 0	67,355 (48.25)
Cumulative dose ≤ 1,000 mg	38,247 (27.4)
Cumulative dose > 1,000 mg	33,987 (24.4)

Values are presented as number (%), mean ± standard deviation, or median [interquartile range].

GERD = gastroesophageal reflux disease, LAMA = long-acting muscarinic antagonists, LABA = long-acting β_2 -agonists, ICS = inhaled corticosteroids, CCI = Charlson Comorbidity Index, OCS = oral corticosteroid.

Statistical analysis

Baseline characteristics and medication prescriptions were summarized using descriptive statistics, including mean (standard deviation) or median [interquartile range] for continuous variables and number with percentage for categorical variables. A univariate Cox proportional hazards regression model was used to identify significant risk factors for the development of TB. Subsequently, a multivariate model was constructed, incorporating covariates that were significant in the univariate analysis at two significance levels of *P* value: Model 1 at 0.1 and Model 2 at 0.05. The proportional hazard assumption was assessed using Schoenfeld residuals, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. The analysis was performed only on cases with complete data, and a threshold of *P* value < 0.05 was deemed statistically significant. All the analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics statement

This study was approved by the Institutional Review Board of the Ajou University Hospital (AJOUIRB-EXP-2021-582). The requirement for informed consent was waived by the ethical review board.

RESULTS

Baseline characteristics

This cohort included 139,589 patients with a mean age of 68.9 years, of whom 75.5% were male (**Table 1**). The inhaler treatment regimens included LAMA or LAMA/LABA in 77,505 (55.5%), LAMA/ICS in 30,417 (21.8%), triple therapy (LAMA/LABA/ICS) in 3,913 (2.8%), and LABA alone in 27,754 (19.9%) patients (**Table 1**). A history of TB was reported in 2,696 patients (1.9%), and 23,865 patients (17.1%) had diabetes mellitus, 2,509 (1.8%) had osteoporosis, 4,293 (3.1%) had chronic renal disease, and 7,304 (5.2%) had bronchiectasis (**Table 1**).

Hospital visits

During the screening period, 53,231 patients (38.1%) were hospitalized at least once for respiratory or cardiovascular conditions (**Supplementary Table 1**). Among them, 18,113 (13.0%) were hospitalized for respiratory conditions (**Supplementary Table 1**).

Prevalence of newly developed TB

While 2,399 patients (1.72%) developed TB, 2,276 (1.63%) were newly diagnosed with pulmonary TB during the study period, and 1,326 patients (0.95%) were bacteriologically and histologically confirmed (**Supplementary Table 2**). The remaining 128 patients (0.09%) were diagnosed with extrapulmonary TB, including those with nervous system involvement (A17), TB in other organs (A18), and miliary TB (A19) (**Supplementary Table 2**).

Risk factors, including inhaler prescription & comorbidities, for the development of pulmonary TB through univariate analyses

Significant risk factors for pulmonary TB identified in univariate analysis included age, sex, prior TB history, bronchiectasis, chronic renal disease, OCS use, Charlson Comorbidity Index (CCI) score, and hospitalization (**Table 2**). In contrast, ICS prescription was not associated with TB development (HR, 1.00; 95% CI, 0.78–1.29) and was therefore excluded in the multivariate analysis. Among the comorbidities, only bronchiectasis showed a statistically significant association with TB risk (HR, 1.28; 95% CI, 1.08–1.51) and was therefore included in the multivariate model (**Table 2**).

Risk factors for pulmonary TB identified through multivariate analyses

In multivariate analysis (Model 1) adjusted for factors with P value < 0.10 in the univariate analysis, the following factors were independently associated with an increased risk of developing pulmonary TB: previous history of TB (HR, 18.11; 95% CI, 16.42–19.99), age ≥ 80 years (HR, 1.92; 95% CI, 1.53–2.40), male sex (HR, 1.40; 95% CI, 1.26–1.55), and hospitalization for any reason (HR for ≥ 2 during screening, 1.55; 95% CI, 1.40–1.72) (**Table 2**). In multivariate analysis (Model 2) adjusted for factors with P value < 0.05, the same factors remained significant: previous TB history (HR, 18.14; 95% CI, 16.44–20.02), age ≥ 80 years (HR, 1.92; 95% CI, 1.53–2.39), male sex (HR, 1.40; 95% CI, 1.26–1.56), and hospitalization for any reason (HR for ≥ 2 during screening, 1.54; 95% CI, 1.39–1.70) (**Table 2**).

Table 2. Risk factors for the development of pulmonary tuberculosis (A15, A16) in chronic obstructive pulmonary disease

Variables	Cox regression analysis					
	Univariate		Multivariate model 1		Multivariate model 2	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Therapy (observational period)						
ICS (ICS/LABA or triple)	1.00 (0.78–1.29)	0.984	-	-	-	-
Non-ICS (LABA/LAMA or LAMA)	Ref.					
Age group, yr						
40–49	Ref.		Ref.		Ref.	
50–59	1.05 (0.83–1.33)	0.670	1.03 (0.81–1.30)	0.836	1.03 (0.81–1.30)	0.833
60–69	1.06 (0.85–1.32)	0.637	1.11 (0.89–1.39)	0.346	1.11 (0.89–1.39)	0.353
70–79	1.23 (0.99–1.52)	0.067	1.31 (1.05–1.63)	0.016	1.30 (1.05–1.62)	0.017
80–	1.84 (1.47–2.30)	< 0.001	1.92 (1.53–2.40)	< 0.001	1.92 (1.53–2.39)	< 0.001
Sex, male	1.37 (1.24–1.52)	< 0.001	1.40 (1.26–1.55)	< 0.001	1.40 (1.26–1.56)	< 0.001
Previous history of tuberculosis	19.21 (17.45–21.16)	< 0.001	18.11 (16.42–19.99)	< 0.001	18.14 (16.44–20.02)	< 0.001
GERD	1.02 (0.94–1.11)	0.590	-	-	-	-
Asthma	1.04 (0.96–1.14)	0.306	-	-	-	-
Heart failure	0.99 (0.85–1.15)	0.849	-	-	-	-
Diabetes mellitus	0.96 (0.86–1.08)	0.514	-	-	-	-
Osteoporosis	1.18 (0.89–1.57)	0.242	-	-	-	-
Bronchiectasis	1.28 (1.08–1.51)	0.004	1.05 (0.89–1.24)	0.559	1.05 (0.89–1.24)	0.578
Diffuse interstitial lung disease	1.25 (0.81–1.92)	0.309	-	-	-	-
Chronic liver diseases	1.15 (0.92–1.45)	0.221	-	-	-	-
Chronic renal diseases	1.25 (1.00–1.56)	0.052	0.97 (0.85–1.01)	0.765	-	-
OCS use (prednisolone $\geq$ 420 mg)	0.93 (0.86–1.01)	0.081	0.93 (0.84–1.02)	0.072	-	-
Cerebrovascular stroke	1.00 (0.86–1.16)	0.955	-	-	-	-
CCI score						
0 (CCI score = 0)	Ref.		-	-	-	-
1 (CCI score = 1)	0.96 (0.81–1.15)	0.677	-	-	-	-
2 (CCI score = 2)	1.05 (0.88–1.25)	0.585				
3 (CCI score $\geq$ 3)	1.19 (1.01–1.40)	0.042				
Hospitalization, any reason (screening period)						
0	Ref.		Ref.		Ref.	
1	1.46 (1.32–1.62)	< 0.001	1.31 (1.18–1.45)	< 0.001	1.30 (1.17–1.44)	< 0.001
$\geq$ 2	1.97 (1.78–2.17)	< 0.001	1.55 (1.40–1.72)	< 0.001	1.54 (1.39–1.70)	< 0.001

Multivariate cox regression analyses were performed in two models: Model 1 (adjusted for age, sex, and factors with $P < 0.10$ in the univariate analysis), Model 2 (adjusted for age, sex, and significant factors with $P < 0.05$ in the univariate analysis).

CI = confidence interval, ICS = inhaled corticosteroids, LABA = long-acting β_2 -agonists, LAMA = long-acting muscarinic antagonists, Ref = reference, GERD = gastroesophageal reflux disease, OCS = oral corticosteroids, CCI = Charlson Comorbidity Index.

Risk factors for overall TB infections

In the univariate analysis, the risk factors for the development of overall TB included age, sex, previous history of TB, bronchiectasis, chronic renal disease, OCS use, CCI score, and hospitalization, consistent with the findings for pulmonary TB (Supplementary Table 3). The multivariate analysis (Model 1) adjusted for factors with P value < 0.10 in the univariate analysis identified the following independent risk factors: a history of TB (HR, 18.31; 95% CI, 16.51–20.31), age ≥ 80 years (HR, 1.92; 95% CI, 1.53–2.40), and hospitalization for any reason (HR for ≥ 2 during screening, 1.63; 95% CI, 1.46–1.82) (Supplementary Table 3). In the multivariate analysis (Model 2) adjusted for factors with P value < 0.05 , the same factors were confirmed as significant: history of TB (HR, 18.35; 95% CI, 16.54–20.35), age ≥ 80 years (HR, 1.62; 95% CI, 1.27–2.05), and hospitalization for any reason (HR for ≥ 2 during screening, 1.62; 95% CI, 1.45–1.80) (Supplementary Table 3).

DISCUSSION

This study aimed to evaluate the risk factors for the development of TB in patients with COPD, with a particular focus on inhaler prescriptions and comorbidities. Our findings demonstrate that a history of TB, advanced age, and hospitalization during the screening period were significant independent risk factors. However, inhaler therapy, including ICS, was not independently associated with the development of TB in patients with COPD. To minimize selection bias, we used a nationwide claims database. Moreover, we addressed the methodological limitations of previous studies by implementing a study design based on the initiation of a new inhaler therapy to avoid time-related biases. To the best of our knowledge, this is the largest cohort study to investigate a comprehensive range of risk factors for the development of TB, including ICS therapy, in patients with COPD.

Our analyses demonstrated that inhaler prescription was not an independent risk factor for the development of TB in patients with COPD. Several studies have reported an association between ICS and an increased incidence of TB owing to the immunosuppressive effects of corticosteroids.^{12,13} A nested case-control study in Korea that matched 4,139 patients on ICS with 20,583 controls identified a dose-dependent relationship between ICS use and TB risk.¹² Another nested case-control study conducted in Quebec reported an increased risk of TB among ICS users who were not receiving OCSs.¹⁶ However, these studies often did not adequately adjust for key confounding factors such as TB history, underlying airway diseases, and comorbid conditions. In contrast, other studies found no association between ICS therapy and TB risk, consistent with our findings.^{12,17} A large case-control study in Taiwan reported no increase in the incidence of TB among patients with COPD receiving ICS therapy, with no observed relationship between the duration or dosage of ICS and TB risk.¹² The authors of that study highlighted the importance of addressing methodological issues and suggested that incorporating time-dependent covariates provides a more accurate representation of drug exposure.¹² Therefore, our study included a history of TB, comorbidities of COPD, and hospitalization in the multivariate analysis to account for potential confounders.

Notably, our study found a significant association between a history of TB and the development of TB in patients with COPD. While a history of TB has been recognized as a risk factor for recurrent TB in high-prevalence regions, our study underscores its significance as a major risk factor for TB in COPD.^{18,19} Survivors of TB often develop post-TB lung disease despite successful treatment, primarily due to residual structural lung damage and persistent respiratory abnormalities.^{9,20} Early studies have demonstrated that residual cavitation significantly increases the risk of TB relapse.^{19,21} Moreover, immune dysregulation in COPD may further exacerbate the susceptibility to TB reactivation.²²

The present finding of increased susceptibility to recurrent TB suggests that certain individuals may be intrinsically vulnerable to TB. For instance, the natural resistance-associated macrophage protein 1 (*NRAMP1*) gene, which regulates mycobacterial clearance by maintaining phagosome acidity, has been extensively studied as a key genetic determinant.^{23,24} *NRAMP1* variants have been linked to more severe manifestations of TB, including increased cavity formation and TB pleurisy.²⁵ In addition, polymorphisms in the tumor necrosis factor- α gene have been implicated in both COPD pathogenesis and TB susceptibility.^{27,28} These genetic factors may predispose patients with TB to severe post-TB lung damage, further increasing the risk of disease recurrence.²³⁻²⁷

In our COPD cohort, older patients were found to be at a greater risk of TB. Although TB is highly prevalent among younger adults, numerous studies have emphasized increased susceptibility to TB in the older population.^{28,29} This heightened vulnerability is largely attributable to immunosenescence, and the presence of comorbidities can further compromise immune function.³⁰ As the global life expectancy continues to increase, TB in the older population is expected to become an increasingly significant public health concern. Moreover, TB in the older population often presents with atypical symptoms, and pre-existing chronic respiratory conditions such as COPD can obscure the diagnosis of TB due to overlapping clinical manifestations.³¹ This underscores the critical importance of maintaining a high index of suspicion of TB in older patients with COPD. However, further research on the incidence of TB in relation to a history of TB in patients with COPD stratified by ICS therapy appears to be both necessary and meaningful.

This study identified male sex as an independent risk factor for TB in patients with COPD. This association is particularly relevant in Korea, where the smoking rate among men is three times higher than that among women.³² However, smoking status was not adjusted for in our analysis because of the lack of available data. Given that smoking is a well-established risk factor for TB, it is essential to determine whether the observed association between male sex and TB is influenced by differences in smoking rates.³³

Our study demonstrated that patients with a higher frequency of hospitalization during the screening period had an increased risk of developing TB. This finding suggests that more severe COPD is associated with a higher risk of TB activation because hospitalizations in COPD, representing the overall burden of severe illness, are closely linked to severe acute exacerbations.⁵ Our analysis was limited to all-cause hospitalization; however, hospitalization due to respiratory diseases can serve as a more precise indicator of severe acute exacerbations of COPD. Although limited research exists on the relationship between COPD severity and TB activation, Benfield et al.⁷ reported that patients with moderate to severe COPD experienced more frequent hospitalizations due to infections, including TB. The authors attributed this vulnerability to impaired lung immunity, characterized by mucus hypersecretion and ciliary dysfunction, which predisposes patients to a higher incidence of respiratory infections.⁷ Moreover, a prolonged hospital stay may increase the risk of nosocomial infections, including TB transmission, further reinforcing this association.³⁴

This study has important public health implications, underscoring the need for targeted TB screening and preventive measures in patients with COPD and a history of TB.³⁵ Early identification and intervention among high-risk individuals can substantially reduce the burden of active TB, particularly in settings with limited healthcare resources. This issue is even more pressing in countries with a high prevalence of TB, where the combined burden of COPD and TB poses a major healthcare challenge.

This study had several limitations. First, this was not a prospective study, although the observational design reflects real-world clinical practice. Second, hospitalization for any cause was used as a covariate and interpreted as a proxy for COPD exacerbation; however, hospital admissions may have been attributed to non-COPD conditions. Consequently, the lack of data on the specific reasons for hospitalization limits the accurate assessment of exacerbation-related risks. Third, a history of TB was defined as any diagnosis before the index date, but stratification by treatment outcome was not possible. Fourth, the HIRA database does not include pulmonary function test results, which are essential for

the accurate assessment of COPD severity. Fifth, smoking status and family history were not investigated because of a lack of information. Sixth, the precise ICS dosage was not measured. Finally, data on medication adherence and socioeconomic factors, both of which can influence TB risk, were excluded from the analysis.

In conclusion, our data demonstrated that older age, male sex, history of TB, and hospitalization during the screening period were independent risk factors for the development of pulmonary TB in patients with COPD, whereas ICS prescription was not. This study underscores the significant risk of TB reactivation in patients with COPD and a history of TB or frequent hospitalizations indicative of severe exacerbation of COPD. These findings emphasize the need for targeted screening and preventive measures to mitigate the risk of TB development in this vulnerable population.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Hospital visit during screening period in this COPD cohort

Supplementary Table 2

Prevalence of tuberculosis

Supplementary Table 3

Risk factors for the development of all types of tuberculosis (A15-19, U84.30, U84.31) in COPD

REFERENCES

1. Park JH. Clinical characteristics of chronic obstructive pulmonary disease according to smoking status. *Tuberc Respir Dis* 2025;88(1):14-25. [PUBMED](#) | [CROSSREF](#)
2. Stolz D, Mkorombindo T, Schumann DM, Agusti A, Ash SY, Bafadhel M, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *Lancet* 2022;400(10356):921-72. [PUBMED](#) | [CROSSREF](#)
3. Al Wachami N, Guennouni M, Iderdar Y, Boumendil K, Arraji M, Mourajid Y, et al. Estimating the global prevalence of chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *BMC Public Health* 2024;24(1):297. [PUBMED](#) | [CROSSREF](#)
4. Hwang YI, Park YB, Yoo KH. Recent trends in the prevalence of chronic obstructive pulmonary disease in Korea. *Tuberc Respir Dis* 2017;80(3):226-9. [PUBMED](#) | [CROSSREF](#)
5. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet* 2007;370(9589):786-96. [PUBMED](#) | [CROSSREF](#)
6. Kim SH, Moon JY, Min KH, Lee H. Proposed etiotypes for chronic obstructive pulmonary disease: controversial issues. *Tuberc Respir Dis* 2024;87(3):221-33. [PUBMED](#) | [CROSSREF](#)
7. Benfield T, Lange P, Vestbo J. COPD stage and risk of hospitalization for infectious disease. *Chest* 2008;134(1):46-53. [PUBMED](#) | [CROSSREF](#)
8. Menezes AM, Hallal PC, Perez-Padilla R, Jardim JR, Muiño A, Lopez MV, et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. *Eur Respir J* 2007;30(6):1180-5. [PUBMED](#) | [CROSSREF](#)
9. Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. *Thorax* 2000;55(1):32-8. [PUBMED](#) | [CROSSREF](#)
10. Inghammar M, Löfdahl CG, Winqvist N, Ljungberg B, Eggesten A, Engström G. Impaired pulmonary function and the risk of tuberculosis: a population-based cohort study. *Eur Respir J* 2011;37(5):1285-7. [PUBMED](#) | [CROSSREF](#)

11. Inghammar M, Ekblom A, Engström G, Ljungberg B, Romanus V, Löfdahl CG, et al. COPD and the risk of tuberculosis - a population-based cohort study. *PLoS One* 2010;5(4):e10138. [PUBMED](#) | [CROSSREF](#)
12. Lee CH, Kim K, Hyun MK, Jang EJ, Lee NR, Yim JJ. Use of inhaled corticosteroids and the risk of tuberculosis. *Thorax* 2013;68(12):1105-13. [PUBMED](#) | [CROSSREF](#)
13. 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(4):1018-24. [PUBMED](#) | [CROSSREF](#)
14. Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea Health Insurance Review and Assessment (HIRA) data as a resource for health research: strengths, limitations, applications, and strategies for optimal use of HIRA data. *J Korean Med Sci* 2017;32(5):718-28. [PUBMED](#) | [CROSSREF](#)
15. Park JE, Lee E, Singh D, Kim EK, Park B, Park JH. The effect of inhaler prescription on the development of lung cancer in COPD: a nationwide population-based study. *Respir Res* 2024;25(1):229. [PUBMED](#) | [CROSSREF](#)
16. Brassard P, Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and risk of tuberculosis in patients with respiratory diseases. *Am J Respir Crit Care Med* 2011;183(5):675-8. [PUBMED](#) | [CROSSREF](#)
17. Brode SK, Campitelli MA, Kwong JC, Lu H, Marchand-Austin A, Gershon AS, et al. The risk of mycobacterial infections associated with inhaled corticosteroid use. *Eur Respir J* 2017;50(3):1700037. [PUBMED](#) | [CROSSREF](#)
18. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet* 2001;358(9294):1687-93. [PUBMED](#) | [CROSSREF](#)
19. Verver S, Warren RM, Beyers N, Richardson M, van der Spuy GD, Borgdorff MW, et al. Rate of reinfection tuberculosis after successful treatment is higher than rate of new tuberculosis. *Am J Respir Crit Care Med* 2005;171(12):1430-5. [PUBMED](#) | [CROSSREF](#)
20. Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: from epidemiology to pathophysiology. *Eur Respir Rev* 2018;27(147):170077. [PUBMED](#) | [CROSSREF](#)
21. Panjabi R, Comstock GW, Golub JE. Recurrent tuberculosis and its risk factors: adequately treated patients are still at high risk. *Int J Tuberc Lung Dis* 2007;11(8):828-37. [PUBMED](#)
22. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008;359(22):2355-65. [PUBMED](#) | [CROSSREF](#)
23. Bellamy R, Ruwende C, Corrah T, McAdam KP, Whittle HC, Hill AV. Variations in the NRAMP1 gene and susceptibility to tuberculosis in West Africans. *N Engl J Med* 1998;338(10):640-4. [PUBMED](#) | [CROSSREF](#)
24. Cervino AC, Lakiss S, Sow O, Hill AV. Allelic association between the NRAMP1 gene and susceptibility to tuberculosis in Guinea-Conakry. *Ann Hum Genet* 2000;64(6):507-12. [PUBMED](#) | [CROSSREF](#)
25. Abe T, Iinuma Y, Ando M, Yokoyama T, Yamamoto T, Nakashima K, et al. NRAMP1 polymorphisms, susceptibility and clinical features of tuberculosis. *J Infect* 2003;46(4):215-20. [PUBMED](#) | [CROSSREF](#)
26. Gingo MR, Silveira LJ, Miller YE, Friedlander AL, Cosgrove GP, Chan ED, et al. Tumour necrosis factor gene polymorphisms are associated with COPD. *Eur Respir J* 2008;31(5):1005-12. [PUBMED](#) | [CROSSREF](#)
27. Sakao S, Tatsumi K, Igari H, Shino Y, Shirasawa H, Kuriyama T. Association of tumor necrosis factor α gene promoter polymorphism with the presence of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;163(2):420-2. [PUBMED](#) | [CROSSREF](#)
28. Byng-Maddick R, Noursadeghi M. Does tuberculosis threaten our ageing populations? *BMC Infect Dis* 2016;16(1):119. [PUBMED](#) | [CROSSREF](#)
29. Caraux-Paz P, Diamantis S, de Wazières B, Gallien S. Tuberculosis in the elderly. *J Clin Med* 2021;10(24):5888. [PUBMED](#) | [CROSSREF](#)
30. Negin J, Abimbola S, Marais BJ. Tuberculosis among older adults—time to take notice. *Int J Infect Dis* 2015;32:135-7. [PUBMED](#) | [CROSSREF](#)
31. Abbara A, Collin SM, Kon OM, Buell K, Sullivan A, Barrett J, et al. Time to diagnosis of tuberculosis is greater in older patients: a retrospective cohort review. *ERJ Open Res* 2019;5(4):00228-2018. [PUBMED](#) | [CROSSREF](#)
32. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980–2012. *JAMA* 2014;311(2):183-92. [PUBMED](#) | [CROSSREF](#)
33. Leung CC, Li T, Lam TH, Yew WW, Law WS, Tam CM, et al. Smoking and tuberculosis among the elderly in Hong Kong. *Am J Respir Crit Care Med* 2004;170(9):1027-33. [PUBMED](#) | [CROSSREF](#)
34. Pearson ML, Jereb JA, Frieden TR, Crawford JT, Davis BJ, Dooley SW, et al. Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis. A risk to patients and health care workers. *Ann Intern Med* 1992;117(3):191-6. [PUBMED](#) | [CROSSREF](#)
35. Alsdurf H, Empringham B, Miller C, Zwerling A. Tuberculosis screening costs and cost-effectiveness in high-risk groups: a systematic review. *BMC Infect Dis* 2021;21(1):935. [PUBMED](#) | [CROSSREF](#)