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Increased Risk of Incident Chronic Obstructive Pulmonary Disease and Related Hospitalizations in Tuberculosis Survivors: A Population-Based Matched Cohort Study

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ABSTRACT

Background: Tuberculosis (TB) survivors have an increased risk of developing chronic obstructive pulmonary disease (COPD). This study assessed the risk of COPD development and COPD-related hospitalization in TB survivors compared to controls.
Methods: We conducted a population-based cohort study of TB survivors and 1:1 age- and sex-matched controls using data from the Korean National Health Insurance Service database collected from 2010 to 2017. We compared the risk of COPD development and COPD-related hospitalization between TB survivors and controls.
Results: Of the subjects, 9.6% developed COPD, and 2.8% experienced COPD-related hospitalization. TB survivors had significantly higher COPD incidence rates (36.7/1,000 vs. 18.8/1,000 person-years, $P < 0.001$) and COPD-related hospitalization (10.7/1,000 vs. 4.3/1,000 person-years, $P < 0.001$) than controls. Multivariable Cox regression analyses revealed higher risks of COPD development (adjusted hazard ratio [aHR], 1.63; 95% confidence interval [CI], 1.54–1.73) and COPD-related hospitalization (aHR, 2.03; 95% CI, 1.81–2.27) in TB survivors. Among those who developed COPD, the hospitalization rate was higher in individuals with post-TB COPD compared to those with non-TB COPD (10.7/1,000 vs. 4.9/1,000 person-years, $P < 0.001$), showing an increased risk of COPD-related hospitalization (aHR, 1.84; 95% CI, 1.17–2.92).

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Conceptualization: Shin DW, Lee H. Formal analysis: Kim T, Choi H, Kim SH, Yang B, Han K, Jung JH, Kim BG, Park DW, Moon JY, Kim SH, Kim TH, Yoon HJ, Shin DW, Lee H. Writing - original draft: Kim T, Choi H, Kim SH, Yang B, Han K, Jung JH, Kim BG, Park DW, Moon JY, Kim SH, Kim TH, Yoon HJ, Shin DW, Lee H.

Conclusion: TB survivors had higher risks of incident COPD and COPD-related hospitalization compared to controls. These results suggest that previous TB is an important COPD etiology associated with COPD-related hospitalization.

Keywords: Pulmonary Tuberculosis; Chronic Obstructive Pulmonary Disease; Hospitalization; Observational Study

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is prevalent in 10% of the global population and is the third-most common cause of death worldwide.[1] Globally, the disease burden of COPD is expected to increase in the future due to continued exposure to COPD risk factors and world population aging.[2,3] Apart from smoking and air pollution, a history of respiratory infections is now recognized as an important but underrecognized etiology of COPD[4,5] that should be managed properly.

The concept that a previous pulmonary tuberculosis (TB) history is associated with the development of chronic airway obstruction is now well established.[3-9] Particularly, it has been reported that the risk of COPD is up to 3 times higher in patients with a previous TB diagnosis than in those without a previous TB diagnosis.[8,9] Even after successful TB treatment, a considerable proportion of survivors from TB (TB survivors) suffer from impairment of pulmonary function and persistent pulmonary inflammation. Accordingly, it is plausible to hypothesize that the risk of both COPD development and COPD-related hospitalization is higher in TB survivors than in those without a previous TB history. However, interestingly, while studies have focused on the impact of previous TB on the development of COPD, few studies have evaluated the impact of previous TB on COPD-related hospitalization,[10] which is an important predictor of mortality in the COPD population.[11] Accordingly, we hypothesized that the risk of COPD-related hospitalization is higher in TB survivors than in those without previous TB.

In this study, utilizing the unique context of South Korea, which has the highest burden of TB among the Organization for Economic Cooperation and Development countries,[12] we aimed to evaluate whether the risk of both incident COPD and COPD-related hospitalization is higher among TB survivors than among age- and sex-matched controls.

METHODS

Study design and database

In this study, we conducted a retrospective cohort analysis based on the population, utilizing the database of the Korean National Health Insurance Service (NHIS). The NHIS, a comprehensive single-payer healthcare system in South Korea, encompasses approximately 97% of the Korean population.[13,14] The database includes extensive details on patient interactions with healthcare services, with a focus on diagnostic coding following the International Classification of Diseases, 10th Revision (ICD-10). Additionally, it encompasses detailed socio-demographic information about its users, such as age, gender, and income levels.

The NHIS repository also integrates data derived from health screenings. These screenings, conducted either annually or every two years and sponsored by the Ministry of Health and

Welfare, are accessible at no cost to all individuals aged 40 and above, as well as to employees of any age. The participation rate for these screenings is approximately 72% of those eligible. The collected data from these screenings include responses from self-administered health behavior questionnaires, covering aspects like smoking habits, alcohol use, exercise frequency, and previous health history. They also measure various physical and biological metrics, such as body mass index (BMI), blood pressure, and a range of laboratory tests including hemoglobin, creatinine levels, and lipid profiles.[14]

Study population

The flowchart for this study is summarized in **Fig. 1**. We defined TB survivors as patients aged ≥ 20 years who completed treatment for active TB and survived for ≥ 1 year after the date of TB diagnosis. To establish groups of TB survivors and controls, respectively, we used information recorded in the NHIS claims database from 2010–2017. For TB survivors, there were 231,984 individuals newly diagnosed with active TB. We extracted a total of 83,009 individuals after excluding 1) those who were diagnosed with multidrug-resistance TB (n = 1,088), 2) those who received TB treatment with a duration of < 156 days (n = 24,862), 3) those who had only extra-pulmonary TB (n = 2,023), and 4) those who did not undergo health screening examination

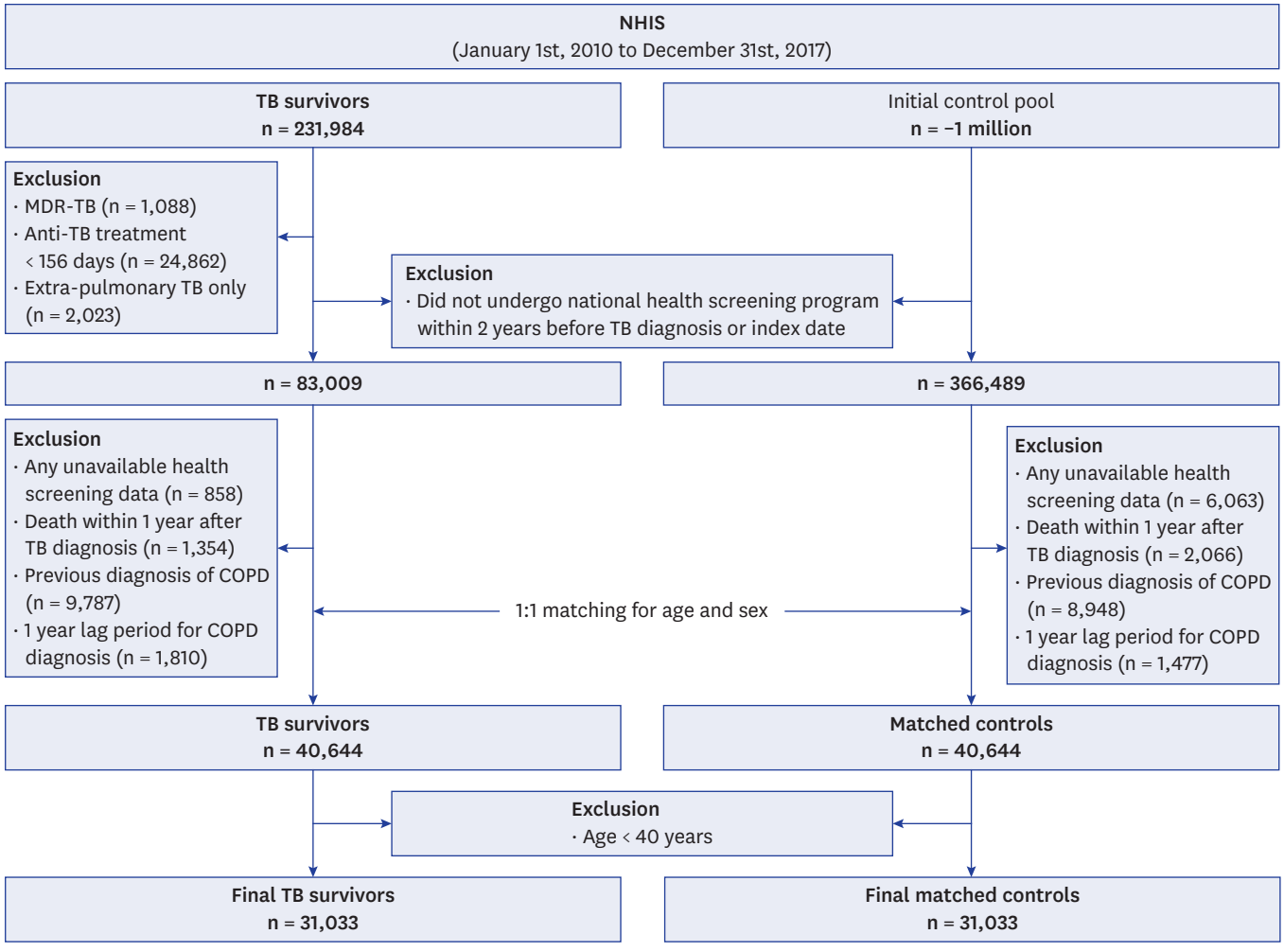

Fig. 1. Flowchart of study subject selection.
NHIS = Korean National Health Insurance Service, MDR = multi-drug resistant, TB = tuberculosis, COPD = chronic obstructive pulmonary disease.

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within 2 years before TB diagnosis (n = 121,002). After further excluding those with any missing baseline information (n = 858), deaths within 1 year after TB diagnosis (n = 1,354), those with a previous COPD diagnosis before TB diagnosis (n = 9,787), and those with a COPD diagnosis within 1 year after TB diagnosis (n = 1,810), a total of 40,644 TB survivors remained. The missing information indicates missing at least one of the variables, including age, sex, BMI, smoking status, alcohol consumption, physical activity, income, residential area, systolic and diastolic blood pressure, fasting blood glucose, and total cholesterol. Of the 40,644 TB survivors, 40,644 were available for 1:1 age- and sex-matching. Finally, 31,033 TB survivors aged ≥ 40 years were enrolled in this study.

For controls, using a pool of about 1 million non-TB individuals, we matched all individuals diagnosed with TB in a specific year with non-TB individuals based on age and sex. Matched non-TB individuals were assigned an index date that corresponded to the first date of TB diagnosis of the matched TB survivors. Among the about 1 million non-TB individuals, we excluded those who did not undergo a national health screening program within 2 years before the index date, and a total of 366,489 non-TB individuals were used for 1:1 age- and sex-matching. When matched non-TB individuals met the exclusion criteria (i.e., those who did not undergo a health screening program within 2 years before the index date, those with unavailable health screening data, those with a COPD diagnosis before the index date, and those who died or were diagnosed with COPD within 1 year after index date), new non-TB individuals were matched. Among 40,644 matched non-TB individuals, we finally enrolled 31,033 controls aged ≥ 40 years for this study.

Study exposure: prior pulmonary TB

Pulmonary TB was defined by ≥ 1 claims made under ICD-10 codes for TB (A15–A19) and the specific NHIS codes for TB (V000 and V246).[15-21] To decrease the burden of TB, Korean NHIS has provided a special co-payment reduction program for all patients diagnosed with active TB. Specific insurance codes (V000 and V246) are required for patients with active TB after confirmation of their diagnosis; TB patients then receive additional insurance coverage and ultimately only pay 0–10% of total TB-related medical care. Because the NHIS database contains complete information about insured medical services throughout the country, the claims database enabled us to review all patients with active TB in the nation using their unique insurance codes.[15-21]

Study outcomes: COPD incidence and COPD-related hospitalization

The primary outcomes of this study were COPD incidence and COPD-related hospitalization. The incidence of COPD was defined as follows: 1) ICD-10 codes for COPD or emphysema, J43–J44 (except J43.0 [unilateral emphysema]), and 2) ≥ 2 outpatient visits or ≥ 1 hospitalization claims. COPD-related hospitalization was defined as: 1) ICD-10 codes for COPD or emphysema, J43–J44 (except J43.0), and 2) hospitalization claims. Additionally, main causes of hospitalizations were determined by the major ICD-10 diagnostic codes claimed at hospitalizations. The COPD-related hospitalization was compared between TB survivors and controls as well as among individuals who developed COPD, i.e., individuals with non-TB COPD (COPD developer among TB survivors) and those with post-TB COPD (COPD developer among controls).

Covariates

Comorbidities (hypertension, diabetes mellitus [DM], dyslipidemia, chronic kidney disease, ischemic heart disease, asthma, bronchiectasis, and cancer) were defined based

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on a combination of past medical history, ICD-10 codes, or drug prescriptions (for DM, dyslipidemia, or hypertension).[22-26] The Charlson comorbidity index was calculated based on the ICD-10 codes and used to classify study participants into 4 groups (0, 1, 2, or ≥ 3 points).[27] Data regarding physical examinations and laboratory findings were derived from the health screening records maintained by the NHIS. The BMI was computed by dividing an individual's weight in kilograms by their height in meters squared. This calculation was then used to classify participants into four distinct categories based on the obesity definitions prevalent in the Asia-Pacific region. These categories are underweight, defined as a BMI less than 18.5 kg/m^2; normal weight, with a BMI ranging from 18.5 to 22.9 kg/m^2; overweight, categorized by a BMI of 23 to 24.9 kg/m^2; and obese, characterized by a BMI of 25 kg/m^2 or more.[28] Self-questionnaires were used to classify smoking status (never-smoker, ex-smoker, and current smoker), alcohol consumption habits (non-drinker, mild drinker [mean alcohol consumption of < 10 g/day], moderate drinker [mean alcohol consumption of 10–30 g/day], or heavy drinker [mean alcohol consumption of ≥ 30 g/day]), and regular physical activity. Participants were classified into 5 groups of physical activity according to the metabolic-equivalent task (MET) score recorded while measuring the energy cost, as follows: inactive, < 500, 500–999, 1,000–1,499, or ≥ 1,500 MET-min/week.[29,30] Residential area groups included urban and rural areas. Participants were classified into quartiles of household income based on insurance premium levels, which are determined by income levels in Korea; additionally, we placed individuals receiving medical aid (the poorest 3% of the population) into the lowest-income quartile.

Statistical analysis

Continuous variables are presented as mean ± standard deviation values and categorical variables are presented as numbers and percentages. The differences between TB survivors and controls were analyzed using Student's *t*-test for continuous variables or Pearson's χ^2 test for categorical variables. The incidence rate of the primary outcomes (COPD incidence and COPD-related hospitalization) was calculated by dividing the number of incident cases by the total follow-up duration; it is presented as events per 1,000 person-years. We used Cox proportional hazards regression modeling to evaluate the risk of both COPD incidence and COPD-related hospitalization in TB survivors vs. controls and the risk of COPD-related hospitalization in individuals with post-TB COPD vs. those with non-TB COPD. In an adjusted model, socio-demographic factors (age, sex, BMI, income level, residence type, personal behaviors [smoking, alcohol consumption, and physical activity]) and comorbidities (asthma and bronchiectasis), which potentially can be associated with the development of COPD and COPD-related hospitalization, were adjusted. A cumulative incidence plot was used to describe the incidence probability of COPD and COPD-related hospitalization between TB survivors vs. controls, and a log-rank test was used to evaluate the significant difference between the groups. All tests were 2-sided, and *P* values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Ethics statement

The research protocol for this study received approval from the Hallym University Kangnam Sacred Heart Hospital's Institutional Review Board (IRB application No. 2022-10-015). Considering the data being publicly available and anonymized in accordance with confidentiality standards, the IRB exempted the need for obtaining written informed consent from individual participants.

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RESULTS

Baseline characteristics

Table 1 presents the baseline characteristics of study participants while comparing TB survivors to controls. The mean age of participants was 57.2 ± 11.2 years, and 62.9% were

Table 1. Baseline characteristics of subjects

Characteristics	Total (N = 62,066)	Controls (n = 31,033)	TB survivors (n = 31,033)	*P* value
Age, yr	57.2 ± 11.2	57.2 ± 11.2	57.2 ± 11.2	1.000
40–49	18,438 (29.7)	9,219 (29.7)	9,219 (29.7)	1.000
50–59	19,364 (31.2)	9,682 (31.2)	9,682 (31.2)	
60–69	13,328 (21.5)	6,664 (21.5)	6,664 (21.5)	
70–79	9,480 (15.3)	4,740 (15.3)	4,740 (15.3)	
≥ 80	1,456 (2.4)	728 (2.4)	728 (2.4)	
Sex				1.000
Male	39,056 (62.9)	19,528 (62.9)	19,528 (62.9)	
Female	23,010 (37.1)	11,505 (37.1)	11,505 (37.1)	
Body mass index, kg/m^2	23.1 ± 3.2	24.1 ± 3.1	22.1 ± 2.9	< 0.001
< 18.5	3,481 (5.6)	688 (2.2)	2,793 (9.0)	
18.5–23.0	27,765 (44.7)	10,797 (34.8)	16,968 (54.7)	
23.0–25.0	14,640 (23.6)	8,390 (27.0)	6,250 (20.1)	
≥ 25.0	16,180 (26.1)	11,158 (36.0)	5,022 (16.2)	
Smoking, pack-years				< 0.001
Never-smoker	32,962 (53.1)	17,224 (55.5)	15,738 (50.7)	
Ex-smoker	12,238 (19.7)	6,814 (22.0)	5,424 (17.5)	
Current smoker	16,866 (27.2)	6,995 (22.5)	9,871 (31.8)	
Alcohol consumption				< 0.001
Never	32,463 (52.3)	16,318 (52.6)	16,145 (52.0)	
Mild	12,501 (20.1)	6,822 (22.0)	5,679 (18.3)	
Moderate	10,882 (17.5)	5,485 (17.7)	5,397 (17.4)	
Heavy	6,220 (10.0)	2,408 (7.8)	3,812 (12.3)	
Physical activity, METs	612.6 ± 623.6	648.2 ± 631.2	577.0 ± 613.9	< 0.001
Never	15,090 (24.3)	6,743 (21.7)	8,347 (26.9)	
< 500	17,416 (28.1)	8,738 (28.2)	8,678 (28.0)	
500–1,000	16,253 (26.2)	8,306 (26.8)	7,947 (25.6)	
1,000–1,500	7,094 (11.4)	3,875 (12.5)	3,219 (10.4)	
≥ 1,500	6,213 (10.0)	3,371 (10.9)	2,842 (9.2)	
Residential area				< 0.001
Urban	27,649 (44.6)	13,392 (43.2)	14,257 (45.9)	
Rural	34,417 (55.5)	17,641 (56.9)	16,776 (54.1)	
Income, quartile				< 0.001
Q1 (lowest)	13,378 (21.6)	6,316 (20.4)	7,062 (22.8)	
Q2	11,305 (18.2)	5,128 (16.5)	6,177 (19.9)	
Q3	15,014 (24.2)	7,324 (23.6)	7,690 (24.8)	
Q4	22,369 (36.0)	12,265 (39.5)	10,104 (32.6)	
Comorbidities				
Diabetes mellitus	11,680 (18.8)	4,580 (14.8)	7,100 (22.9)	< 0.001
Hypertension	18,810 (30.3)	9,731 (31.4)	9,079 (29.3)	< 0.001
Dyslipidemia	17,694 (28.5)	8,344 (26.9)	9,350 (30.1)	< 0.001
Chronic kidney disease	3,816 (6.2)	1,808 (5.8)	2,008 (6.5)	0.003
Ischemic heart disease	3,991 (6.4)	1,801 (5.8)	2,190 (7.1)	< 0.001
Asthma	7,546 (12.2)	2,224 (7.2)	5,322 (17.2)	< 0.001
Bronchiectasis	1,532 (2.5)	63 (0.2)	1,469 (4.7)	< 0.001
Cancer	2,583 (4.2)	871 (2.8)	1,712 (5.5)	< 0.001
Charlson comorbidity index	1.6 ± 1.7	1.2 ± 1.5	2.1 ± 1.8	< 0.001
0	20,911 (33.7)	14,047 (45.3)	6,864 (22.1)	
1	14,554 (23.5)	7,259 (23.4)	7,295 (23.5)	
2	10,945 (17.6)	4,733 (15.3)	6,212 (20.0)	
≥ 3	20,911 (33.7)	14,047 (45.3)	6,864 (22.1)	

Data are presented as number (percentage) values or mean ± standard deviation values.
TB = tuberculosis, MET = metabolic-equivalent task.

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male. TB survivors were more likely to include those with lower BMIs (22.1 ± 2.9 vs. 24.1 ± 3.1 kg/m^2), a higher proportion of current smokers (31.8% vs. 22.5%), a higher proportion of individuals who consumed alcohol heavily (12.8% vs. 7.8%), less physically active individuals (577.0 ± 613.9 vs. 648.2 ± 631.2 METs), and individuals with lower incomes (a proportion of the lowest quartile, 22.8% vs. 20.4%) than controls (P < 0.001 for all). TB survivors also tended to have more comorbidities, including DM, dyslipidemia, ischemic heart disease, asthma, bronchiectasis, and cancer, than controls (P < 0.001 for all). The clinical characteristics of the study population according to COPD and COPD-related hospitalization are summarized in **Supplementary Table 1**.

Risk for incidence of COPD

During a median follow-up period of 4.4 years, which included a 1-year lag period (interquartile range, 2.6–6.3 years), a total of 5,944 (9.6%) individuals developed COPD. The incidence rate of COPD was significantly higher among TB survivors than among controls (36.7/1,000 vs. 18.8/1,000 person-years, P < 0.001). Similarly, there was a significant intergroup difference in the cumulative incidence probability (%) for COPD development (log-rank test, P < 0.001) (**Fig. 2A**). The hazards for developing COPD were also higher among TB survivors than among controls (adjusted hazard ratio [aHR], 1.63; 95% confidence interval [CI], 1.54–1.73) (**Table 2**).

Risk for COPD-related hospitalization

During a median follow-up period of 4.6 years, which included a 1-year lag period (interquartile range, 2.8–6.5 years), a total of 1,707 (2.8%) individuals experienced COPD-related hospitalizations. The incidence rate of COPD-related hospitalization was significantly higher among TB survivors than among controls (10.7/1,000 vs. 4.3/1,000 person-years, P < 0.001), and there was a significant intergroup difference in the cumulative incidence probability (%)

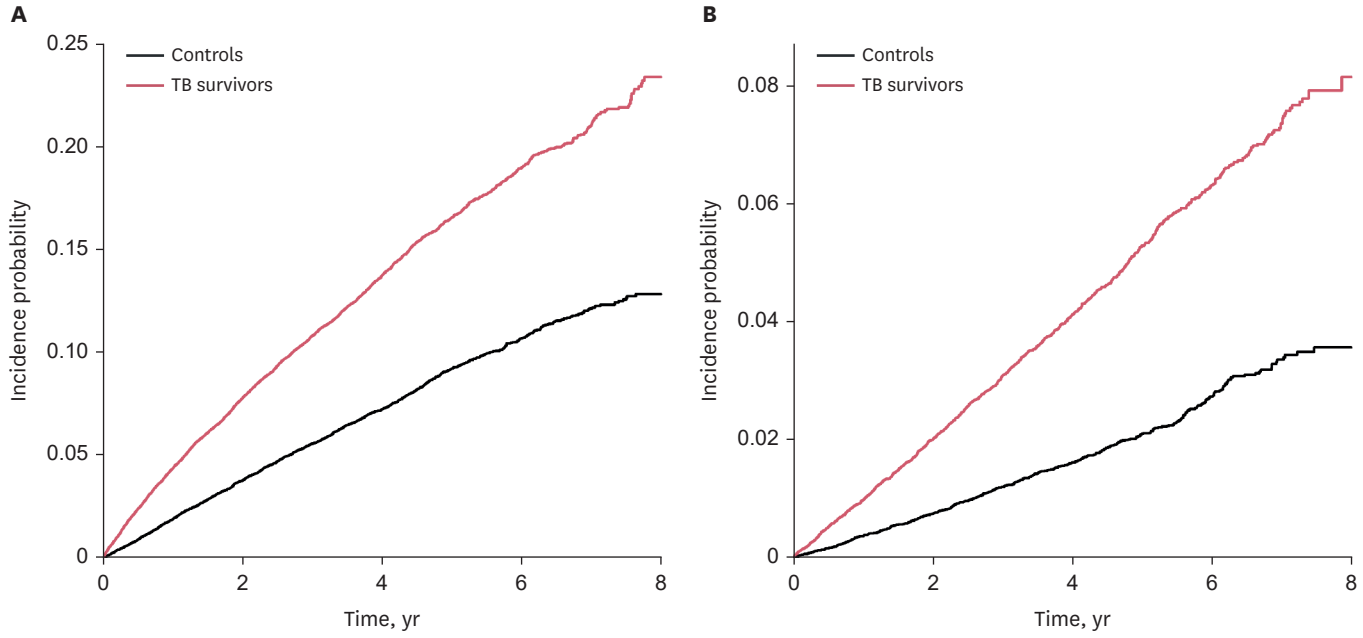

Fig. 2. Cumulative incidence probability (%) of COPD incidence (**A**) and COPD-related hospitalization (**B**) according to the presence or absence of a previous TB history.
TB = tuberculosis, COPD = chronic obstructive pulmonary disease.

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Table 2. Incidence and risk of COPD hospitalization in TB survivors vs. controls

Characteristics	TB survivors vs. Controls				Post-TB COPD vs. Non-TB COPD	
	COPD incidence		COPD-related hospitalization		COPD-related hospitalization	
	Controls (n = 31,033)	TB survivors (n = 31,033)	Controls (n = 31,033)	TB survivors (n = 31,033)	Non-TB COPD (n = 2,103)	Post-TB COPD (n = 3,841)
No. of events	2,103	3,841	504	1,203	26 (1.2%)	106 (2.8%)
Duration	111,687.33	104,798.97	116,117.89	112,707.29	5,349.44	9,922.44
IR (/1,000 PY)	18.83	36.65	4.34	10.67	4.86	10.68
Unadjusted HR (95% CI)	1 (Reference)	1.94 (4.84–2.05)	1 (Reference)	2.46 (2.22–2.73)	1 (Reference)	2.23 (1.45–3.41)
Adjusted HR[a] (95% CI)	1 (Reference)	1.63 (1.54–1.73)	1 (Reference)	2.03 (1.81–2.27)	1 (Reference)	1.84 (1.17–2.92)

COPD = chronic obstructive pulmonary disease, TB = tuberculosis, IR = incidence rate, PY = person-years, HR = hazard ratio, CI = confidence interval.
[a]Age, sex, body mass index, smoking, drinking, physical activity, residential area, income, Charlson comorbidity index, and comorbidities such as asthma and bronchiectasis were adjusted for.

for COPD-related hospitalization (log-rank test, $P < 0.001$) (**Fig. 2B**). The hazards for COPD-related hospitalization were also higher among TB survivors than among controls (aHR, 2.03; 95% CI, 1.81–2.27). Furthermore, among individuals who developed COPD, the hazards of COPD-related hospitalization were significantly higher among individuals with post-TB COPD than those with non-TB COPD (aHR, 1.84; 95% CI, 1.17–2.92) (**Table 2**).

The main causes of COPD-related hospitalization in TB survivors and controls, respectively, are presented in **Supplementary Table 2**. In both TB survivors and controls, respiratory diseases were the most common reason for hospitalization, followed by malignant neoplasms and cardiovascular diseases. However, the proportion of hospitalizations associated with respiratory diseases was higher among TB survivors than among controls ($P < 0.001$).

Stratified analysis

Table 3 presents stratified analyses for the risk of incident COPD in TB survivors and controls according to age, sex, BMI, smoking status, alcohol consumption, physical activity, residential area, and income level. Although smoking, alcohol consumption, physical activity, residence, and income level had no significant interaction on the association, age, sex, and BMI had a significant impact on the association. The risk of incident COPD in TB survivors vs. controls was more significant among younger individuals, men, and those with lower BMIs (*P* for

Table 3. Hazard ratios and 95% CIs for chronic obstructive pulmonary disease incidence according to prior TB history with stratification by age, sex, BMI, smoking, drinking, physical activity, residence, and income

Subgroups	Group	No. of events	IR (/1,000 PY)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Age, yr					
40–49	Controls (n = 9,219)	316	8.9	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 9,219)	623	18.1	2.03 (1.78–2.32)	1.74 (1.51–1.99)
50–59	Controls (n = 9,682)	541	15.3	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 9,682)	1,114	33.4	2.18 (1.96–2.41)	1.81 (1.62–2.01)
60–69	Controls (n = 6,664)	600	26.2	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 6,664)	1,099	52.5	1.20 (1.81–2.21)	1.65 (1.49–1.83)
70–79	Controls (n = 4,740)	571	35.8	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 4,740)	899	63.1	1.75 (1.58–1.95)	1.45 (1.31–1.62)
≥ 80	Controls (n = 728)	75	38.9	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 728)	106	57.8	1.48 (1.10–1.99)	1.23 (0.91–1.65)
P for interaction				0.017	0.013
Sex					
Male	Controls (n = 19,528)	1,228	17.7	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 19,528)	2,336	36.0	2.03 (1.89–2.17)	1.71 (1.59–1.85)
Female	Controls (n = 11,505)	875	20.7	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 11,505)	1,505	37.8	1.82 (1.67–1.97)	1.51 (1.39–1.65)
P for interaction				0.047	0.025

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Table 3. (Continued) Hazard ratios and 95% CIs for chronic obstructive pulmonary disease incidence according to prior TB history with stratification by age, sex, BMI, smoking, drinking, physical activity, residence, and income

Subgroups	Group	No. of events	IR (/1,000 PY)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
BMI, kg/m^2					
< 18.5	Controls (n = 688)	36	15.3	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 2,793)	414	45.9	2.99 (2.13–4.21)	2.76 (1.96–3.89)
18.5–23.0	Controls (n = 10,797)	724	18.4	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 16,968)	1,988	34.3	1.86 (1.71–2.03)	1.61 (1.47–1.75)
23.0–25.0	Controls (n = 8,390)	586	19.3	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 6,250)	795	37.6	1.94 (1.74–2.16)	1.63 (1.46–1.82)
≥ 25.0	Controls (n = 11,158)	757	19.1	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 5,022)	644	38.7	2.01 (1.81–2.24)	1.56 (1.40–1.73)
P for interaction				0.054	0.018
Smoking history					
Never-smoker	Controls (n = 17,224)	1,265	20.1	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 15,738)	2,087	38.7	1.92 (1.79–2.06)	1.56 (1.45–1.68)
Ex-smoker	Controls (n = 6,814)	437	18.8	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 5,424)	663	38.1	2.02 (1.79–2.28)	1.70 (1.50–1.92)
Current smoker	Controls (n = 6,995)	401	15.8	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 9,871)	1,091	32.7	2.06 (1.84–2.31)	1.79 (1.59–2.01)
P for interaction				0.496	0.111
Alcohol consumption					
Never	Controls (n = 16,318)	1,268	21.5	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 16,145)	2,244	41.0	1.90 (1.77–2.03)	1.58 (1.47–1.70)
Mild	Controls (n = 6,822)	380	15.6	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 5,679)	599	31.2	1.99 (1.75–2.27)	1.71 (1.50–1.95)
Moderate	Controls (n = 5,485)	299	15.3	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 5,397)	533	29.6	1.93 (1.68–2.23)	1.65 (1.43–1.91)
Heavy	Controls (n = 2,408)	156	17.9	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 3,812)	465	36.3	2.02 (1.69–2.43)	1.75 (1.46–2.11)
P for interaction				0.866	0.349
Physical activity, METs					
Never	Controls (n = 6,743)	527	20.9	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 8,347)	1,218	42.4	2.02 (1.82–2.23)	1.70 (1.53–1.89)
< 500	Controls (n = 8,738)	559	17.6	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 8,678)	1,000	33.4	1.89 (1.71–2.10)	1.59 (1.43–1.77)
500–1,000	Controls (n = 8,306)	535	18.2	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 7,947)	898	33.7	1.85 (1.66–2.06)	1.57 (1.40–1.75)
1,000–1,500	Controls (n = 3,875)	235	17.2	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 3,219)	365	35.0	2.02 (2.71–2.38)	1.72 (1.45–2.03)
≥ 1,500	Controls (n = 3,371)	247	21.1	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 2,842)	360	39.9	1.88 (1.60–2.21)	1.61 (1.37–1.90)
P for interaction				0.759	0.783
Residence					
Urban	Controls (n = 13,392)	878	18.2	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 14,257)	1,665	34.3	1.88 (1.73–2.04)	1.60 (1.47–1.74)
Rural	Controls (n = 17,641)	1,225	19.3	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 16,776)	2,176	38.7	2.00 (1.86–2.14)	1.65 (1.53–1.78)
P for interaction				0.268	0.570
Income, quartile					
Q1 (lowest)	Controls (n = 6,316)	471	20.2	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 7,062)	929	40.0	1.96 (1.76–2.20)	1.66 (1.48–1.86)
Q2	Controls (n = 5,1258)	340	18.4	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 6,177)	722	35.0	1.90 (1.67–2.16)	1.59 (1.40–1.82)
Q3	Controls (n = 7,324)	498	19.0	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 7,690)	915	35.0	1.84 (1.65–2.06)	1.55 (1.38–1.73)
Q4	Controls (n = 12,265)	794	18.2	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 10,104)	1,275	36.6	2.01 (1.84–2.20)	1.68 (1.54–1.85)
P for interaction				0.658	0.658

TB = tuberculosis, BMI = body mass index, IR = incidence rate, PY = person-years, HR = hazard ratio, CI = confidence interval, MET = metabolic-equivalent task.
[a]In the adjustment, age, sex, BMI, smoking, drinking, physical activity, residence, income, Charlson comorbidity index, and comorbidities such as asthma and bronchiectasis were considered.

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interaction = 0.013 for age, 0.025 for sex, and 0.018 for BMI). **Table 4** showed the risk of COPD-related hospitalization according to a previous TB history stratified by age, sex, BMI, smoking, alcohol consumption, physical activity, residence, and income level. Other than sex, these variables did not have a significant impact on the association between previous TB and the risk of COPD-related hospitalization; the risk of COPD-related hospitalization in TB survivors vs. controls was more significant in males (*P* for interaction = 0.008).

DISCUSSION

In this study, we evaluated the clinical impact of a previous history of TB on COPD development and COPD-related hospitalization. Our analyses showed that the risk of COPD development and COPD-related hospitalization was significantly higher among TB survivors than among controls; the impact of previous TB on COPD development was especially higher among younger individuals, males, and those with lower BMIs. In comparison, the impact of previous TB on COPD-related hospitalization was especially substantial in males.

Table 4. Hazard ratios and 95% CIs for COPD-related hospitalization according to prior TB history with stratification by age, sex, BMI, smoking, drinking, physical activity, residence, and income

Subgroups	Group	No. of events	IR (/1,000 PY)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Age, yr					
40–49	Controls (n = 9,219)	44	1.2	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 9,219)	119	3.3	2.74 (1.94–3.87)	2.23 (1.57–3.16)
50–59	Controls (n = 9,682)	93	2.5	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 9,682)	289	8.1	3.19 (2.53–4.03)	2.47 (1.94–3.14)
60–69	Controls (n = 6,664)	139	5.7	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 6,664)	348	15.0	2.63 (2.16–3.21)	2.14 (1.75–2.62)
70–79	Controls (n = 4,740)	185	10.9	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 4,740)	383	24.0	2.21 (1.86–2.64)	1.86 (1.55–2.22)
≥ 80	Controls (n = 728)	43	21.1	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 728)	64	32.1	1.53 (1.04–2.25)	1.30 (0.88–1.92)
P for interaction				0.012	0.054
Sex					
Male	Controls (n = 19,528)	320	4.5	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 19,528)	854	12.3	2.78 (2.44–3.16)	2.24 (1.96–2.57)
Female	Controls (n = 11,505)	184	4.2	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 11,505)	349	8.1	1.93 (1.62–2.31)	1.66 (1.38–2.00)
P for interaction				0.001	0.008
BMI, kg/m^2					
< 18.5	Controls (n = 688)	19	7.9	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 2,793)	154	15.7	2.00 (1.24–3.22)	1.95 (1.21–3.15)
18.5–23.0	Controls (n = 10,797)	187	4.6	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 16,968)	614	9.9	2.17 (1.84–2.56)	1.89 (1.60–2.24)
23.0–25.0	Controls (n = 8,390)	125	4.0	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 6,250)	228	10.0	2.53 (2.03–3.14)	2.18 (1.74–2.71)
≥ 25.0	Controls (n = 11,158)	173	4.2	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 5,022)	207	11.5	2.74 (2.24–3.35)	2.14 (1.75–2.63)
P for interaction				0.276	0.703
Smoking history					
Never-smoker	Controls (n = 17,224)	282	4.3	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 15,738)	563	9.6	2.24 (1.94–2.58)	1.87 (1.61–2.18)
Ex-smoker	Controls (n = 6,814)	94	3.9	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 5,424)	219	11.7	3.03 (2.38–3.86)	2.50 (1.96–3.20)
Current smoker	Controls (n = 6,995)	128	4.9	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 9,871)	421	11.9	2.44 (2.00–2.97)	2.07 (1.69–2.54)
P for interaction				0.108	0.129

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Table 4. (Continued) Hazard ratios and 95% CIs for COPD-related hospitalization according to prior TB history with stratification by age, sex, BMI, smoking, drinking, physical activity, residence, and income

Subgroups	Group	No. of events	IR (/1,000 PY)	Unadjusted HR (95% CI)	Adjusted HR[a] (95% CI)
Alcohol consumption					
Never	Controls (n = 16,318)	295	4.8	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 16,145)	676	11.3	2.37 (2.07–2.72)	2.00 (1.74–2.31)
Mild	Controls (n = 6,822)	95	3.8	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 5,679)	167	8.2	2.16 (1.68–2.78)	1.85 (1.43–2.38)
Moderate	Controls (n = 5,485)	63	3.1	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 5,397)	181	9.5	3.08 (2.31–4.10)	2.51 (1.88–3.36)
Heavy	Controls (n = 2,408)	51	5.6	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 3,812)	179	13.1	2.33 (1.71–3.18)	1.93 (1.41–2.64)
P for interaction				0.307	0.422
Physical activity, METs					
Never	Controls (n = 6,743)	6,743	6.1	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 8,347)	8,347	13.2	2.17 (1.81–2.60)	1.80 (1.49–2.18)
< 500	Controls (n = 8,738)	8,738	4.0	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 8,678)	8,678	9.9	2.50 (2.04–3.07)	2.10 (1.70–2.59)
500–1,000	Controls (n = 8,306)	8,306	3.6	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 7,947)	7,947	10.1	2.80 (2.25–3.49)	2.38 (1.90–2.98)
1,000–1,500	Controls (n = 3,875)	3,875	3.6	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 3,219)	3,219	8.2	2.28 (1.62–3.21)	1.92 (1.36–2.72)
≥ 1,500	Controls (n = 3,371)	3,371	4.3	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 2,842)	2,842	9.9	2.30 (1.64–3.21)	1.97 (1.41–2.76)
P for interaction				0.503	0.427
Residence					
Urban	Controls (n = 13,392)	184	3.7	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 14,257)	487	9.4	2.56 (2.16–3.03)	2.15 (1.80–2.57)
Rural	Controls (n = 17,641)	320	4.9	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 16,776)	716	11.8	2.44 (2.14–2.78)	1.96 (1.71–2.25)
P for interaction				0.666	0.393
Income, quartile					
Q1 (lowest)	Controls (n = 6,316)	110	4.5	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 7,062)	311	12.3	2.74 (2.20–3.40)	2.26 (1.81–2.83)
Q2	Controls (n = 51,258)	85	4.4	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 6,177)	238	10.8	2.45 (1.91–3.14)	2.02 (1.57–2.60)
Q3	Controls (n = 7,324)	130	4.8	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 7,690)	288	10.3	2.16 (1.76–2.66)	1.76 (1.42–2.18)
Q4	Controls (n = 12,265)	179	4.0	1.00 (Reference)	1.00 (Reference)
	TB survivors (n = 10,104)	366	9.8	2.47 (2.07–2.96)	2.09 (1.74–2.51)
P for interaction				0.495	0.413

CI = confidence interval, COPD = chronic obstructive pulmonary disease, TB = tuberculosis, BMI = body mass index, IR = incidence rate, PY = person-years, HR = hazard ratio, MET = metabolic-equivalent task.

[a]In the adjustment, age, sex, body mass index, smoking, drinking, physical activity, residence, income, Charlson comorbidity index, and comorbidities such as asthma and bronchiectasis were considered.

Previous studies have shown that there is a strong relationship between COPD and a previous history of TB.[3-9] For example, the prevalence or incidence of TB-associated COPD is strongly influenced by the TB burden where the research was performed[31-33]; the risk for COPD development was shown to be 3 times higher among patients with a previous TB history compared to those without a previous TB history in low- and middle-income countries, many of which have intermediate- or high-level TB burdens.[6,8,9] In this study, which was conducted using representative national data of South Korea, a country with an intermediate-level TB burden, the risk of COPD incidence in TB survivors was 1.63 higher than that in the control group.

Furthermore, a previous study has shown that COPD patients with previous TB diagnoses had more severe diseases than COPD patients without previous TB diagnoses.[10] Therefore, understanding clinical outcomes for this population—such as hospitalization, which is a

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predictor for mortality in COPD—is especially important in countries with intermediate- or high-level TB burdens. Despite its clinical relevance, however, information on this topic is very scarce.[34-36] Except for a single prospective study (n = 1,784) that reported worse outcomes, including more hospitalizations among COPD patients with a previous TB history than among those without a previous TB history,[10] other studies have been limited by their relatively small study populations and their study designs, such as a case-control study design[35] or a cross-sectional study design,[34] that make it difficult to confirm the causal inference between a previous TB history and COPD-related hospitalization. Overcoming these limitations by enrolling a larger population and using a longitudinal database, our study provides solid evidence that prior TB is a risk factor for COPD-related hospitalization, emphasizing the importance of TB prevention and management to mitigate TB-related COPD outcomes.

The increased number of COPD-associated hospitalizations in TB survivors may be explained by the presence of airway inflammation and remodeling in this population. The most common cause of COPD-related hospitalization is an acute exacerbation of COPD,[37] and COPD exacerbations are associated with increased airway inflammation that is caused mainly by respiratory viruses and bacteria.[38] Inflammatory cytokine levels are dynamic immediately after the initiation of pulmonary TB treatment,[39,40] moreover, in the late stage of TB treatment, levels of interleukin-1β, tumor necrosis factor-α, and interferon-γ are elevated.[41] Even after a microbiologic cure is achieved with pulmonary TB treatment, inflammation might persist.[42] Regarding airway remodeling, matrix metalloproteinases that degrade components of the extracellular matrix and are considered a key factor in TB-related lung damage[43] worsen airway damage and therefore render patients with COPD more vulnerable to COPD exacerbations. Taken together, more severe inflammation and airway remodeling after pulmonary TB infection probably play a major role in the greater number of COPD-related hospitalizations among TB survivors compared to controls.

In this study, the most common cause of COPD-related hospitalization was respiratory diseases in both TB survivors and controls. Furthermore, the contribution of chronic respiratory diseases, including COPD and asthma, to hospitalization was greater among individuals with post-TB COPD than those with non-TB COPD (data not shown). Possible explanations for this phenomenon might arise from previous findings showing that prior TB is related to more severe COPD presentations; results from the Burden of Obstructive Lung Disease[6] and PLATINO study,[7] together with those of other systematic reviews, have consistently demonstrated that previous TB is associated with more abnormal lung structure and reduced lung function.[8,44,45] These results suggest that clinicians need to actively screen for COPD and related lung damage when managing TB survivors, supporting the recent concept of the Global Initiative for Chronic Obstructive Lung Disease strategy mentioning TB-associated COPD as a distinct infectious etiotype of COPD. Since information on TB-related COPD is not widely available, future studies are needed to optimize the preventive and treatment strategies in this population.

There are some limitations to this study. First, the diagnosis of COPD was based on ICD-10 codes, and no data concerning the severity of the airflow limitation were available. As a result, the relationship between the severity of COPD and the risk of COPD-related hospitalization could not be evaluated. Additionally, the subset of study participants diagnosed with asthma may actually have COPD; that is because the Korean healthcare system requires pulmonary function tests for COPD but not for asthma, potentially leading to misclassification in our analysis. Second, the extent of lung damage due to TB sequelae, including cavity, could

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not be confirmed as the results of radiology were not available, although the extent of TB sequalae could influence the severity of COPD and the likelihood of hospitalizations. Third, as we aimed to assess a broader perspective on the healthcare burden among patients with COPD, causes of COPD-related hospitalizations were not confined to COPD exacerbations or pneumonia. Fourth, because our study was performed in a single country, our findings may not be generalizable to other regions with different TB incidence rates.

In conclusion, the risk of incident COPD as well as COPD-related hospitalization was higher among TB survivors than among age- and sex-matched controls. To reduce the global burden of TB-related COPD, early screening of COPD among TB survivors and new strategies to decrease the TB prevalence rate worldwide are needed.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline characteristics of the patients according to the incidence of COPD and COPD-related hospitalization

Supplementary Table 2

Causes of chronic obstructive pulmonary disease-related hospitalization in TB survivors and controls

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