Respiratory Research

RESEARCH

Open Access

Risk of incident chronic obstructive pulmonary disease during longitudinal follow-up in patients with nontuberculous mycobacterial pulmonary disease

Bo-Guen Kim[1,2†], Sun Hye Shin[3†], Sun-Kyung Lee[1,4], Sang-Heon Kim[1] and Hyun Lee[1*]

Abstract

Background The Global Initiative for Chronic Obstructive Lung Disease 2023 revision proposed that chronic obstructive pulmonary disease (COPD) has various etiologies including infections (COPD-I), such as tuberculosis and human immunodeficiency virus. While nontuberculous mycobacterial pulmonary disease (NTM-PD) and pulmonary tuberculosis share similar clinical manifestations, research on COPD development during longitudinal follow-up in patients with NTM-PD is limited. In this study, we aimed to evaluate the incidence and risk of COPD development in patients with NTM-PD.

Methods We retrospectively enrolled patients with NTM-PD with normal lung function and 1:4 age-, sex-, body mass index-, and smoking status-matched controls between November 1994 and January 2022. We compared the risks of spirometry-defined COPD between the NTM-PD and control groups (study 1). A nationwide cohort study using the health insurance claims database was conducted to validate the findings (study 2).

Results In study 1, during a mean follow-up of 3.3 years, COPD occurred in 14.0% (241/1,715) and 4.3% (293/6,860) of individuals in the NTM-PD and matched control cohorts, respectively. The NTM-PD cohort exhibited a higher risk of incident COPD (adjusted hazard ratio [aHR], 2.57; 95% CI, 2.15–3.09) compared to matched controls. In study 2, COPD occurred in 6.2% (24/386) and 2.5% (28/1,133) of individuals with and without NTM-PD, respectively. The NTM-PD cohort had a higher risk of incident COPD (aHR, 2.04; 95% CI, 1.21–3.42) compared to matched controls.

Conclusion These findings suggest that NTM-PD could be considered a new etiotype of COPD-I and emphasize the importance of monitoring lung function in individuals with NTM-PD.

Keywords Nontuberculous mycobacterial pulmonary disease, Chronic obstructive pulmonary disease

†Bo-Guen Kim and Sun Hye Shin contributed equally to this work.

*Correspondence:
Hyun Lee
namuhanayeyo@hanyang.ac.kr
[1]Division of Pulmonary Medicine and Allergy, Department of Internal Medicine, Hanyang University College of Medicine, 222-1, Wangsimni-ro, Seongdong-gu, Seoul 04763, Republic of Korea
[2]Division of Pulmonary Medicine, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[3]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[4]Department of Mathematics, College of Natural Sciences, Hanyang University, Seoul, Republic of Korea

Background

Chronic obstructive pulmonary disease (COPD) is the third leading cause of mortality worldwide, with more than 3 million deaths per year [1, 2]. To reduce its global burden, the recently revised Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 have proposed a new taxonomy (etiotype) to emphasize early recognition of various COPD etiologies. Among them, COPD due to infections (COPD-I) includes childhood infections, tuberculosis-associated COPD, and human immunodeficiency virus-associated COPD [3]. However, other studies have suggested that infections other than these diseases are also associated with obstructive lung disease [4, 5]. The GOLD committee has recommended increased attention to these other infections linked to COPD [6, 7].

Nontuberculous mycobacterial pulmonary disease (NTM-PD) is a chronic and progressing infectious respiratory disease caused by various NTM species, with an increasing incidence worldwide [8]. Airflow obstruction or physician-diagnosed COPD is common in patients with NTM-PD [9]. However, since COPD is a common risk factor for NTM-PD, [10] whether NTM-PD precedes COPD or vice versa remains unclear. Although previous studies have suggested that patients with NTM-PD experience a faster decline in forced expiratory volume in 1 s (FEV_1) than that of the general population, [11–14] and coexisting NTM-PD is associated with the faster decline in FEV_1 in patients with established COPD, [15, 16] only a few studies have explored whether NTM-PD can serve as an infectious etiotype for COPD [4].

Therefore, the present study aimed to investigate the incidence and risk of developing COPD in patients with NTM-PD with normal lung function. To achieve this, we conducted a retrospective single-center cohort involving a large number of patients with NTM-PD and matched controls and compared the incidences of spirometry-defined COPD between them. To validate the main outcomes, we conducted a nationwide population-based cohort study using the health insurance claim database.

Materials and methods

Data source

Two study designs were developed to investigate the incidence and risk of developing COPD. Study 1 aimed to compare the incidence of COPD between patients with NTM-PD and matched controls, who had undergone a comprehensive health screening examination at the Samsung Medical Center (1,960-bed university-affiliated, tertiary referral hospital). Data were extracted from the Clinical Data Warehouse (CDW) Darwin-C at the Samsung Medical Center [17].

Study 2 aimed to validate the findings of study 1 by evaluating the incidence and risk of newly diagnosed and treated COPD among individuals with and without NTM-PD. We used a nationwide representative dataset of approximately 1,000,000 individuals, the Korean National Health Insurance Service National Sample Cohort (NHIS-NSC), which contains information on demographics, healthcare utilization, health screening examinations, disease diagnosis, drug prescription, and death [18]. **Supplementary Method** details the methodology of study 2.

Study 1 was approved by the Institutional Review Board of the Samsung Medical Center (IRB no.: SMC 2023-08-084). Study 2 was approved by the Institutional Review Board of the Hanyang University Hospital (IRB no.: HYUH 2023-06-007). The requirement for obtaining informed consent was waived because the CDW and NHIS databases had been constructed after anonymization. These studies were conducted in accordance with the principles of the Declaration of Helsinki.

Study population

In study 1, the NTM-PD group initially included 8,184 patients with NTM-PD who had undergone a spirometry test between November 1994 and January 2022. Exclusion criteria were as follows: (1) an abnormal baseline spirometry result, defined as an FEV_1/forced vital capacity (FVC) ratio < 0.7 or a predicted percentage value (%pred) of FEV_1 < 80 (n = 5,009); (2) no follow-up spirometry test for at least 1 year after the baseline spirometry (n = 274); and (3) a previous diagnosis of COPD (n = 869). Additionally, exclusion criteria from the NTM-PD group included a history of lung resection surgery (n = 61) and missing data on smoking status (n = 256).

The control group initially included 323,862 participants who underwent a health screening examination with a baseline spirometry test during the same period. After applying the same exclusion criteria and excluding those with an established diagnosis of NTM-PD (n = 687), 90,088 participants were enrolled in this study. We performed propensity score-matching at a ratio of 1:4 based on age, sex, body mass index (BMI), and smoking status, resulting in 1,715 patients in the NTM-PD group and 6,860 participants in the matched control groups (Fig. 1). In study 1, both patients with NTM-PD and controls were followed up from the date of the baseline spirometry until COPD diagnosis, death, or December 31, 2022, whichever occurred first.

In study 2, patients with NTM-PD who were free from COPD at baseline and within 1 year after enrollment (n = 386) and 1:3 age- and sex-matched controls without NTM-PD or COPD (n = 1,133) were included (**Supplementary Method** and Supplementary Fig. 1). To minimize the risk of reverse causality, we implemented a 12-month COPD-free washout period; consequently, patients were followed up from 12 months after the

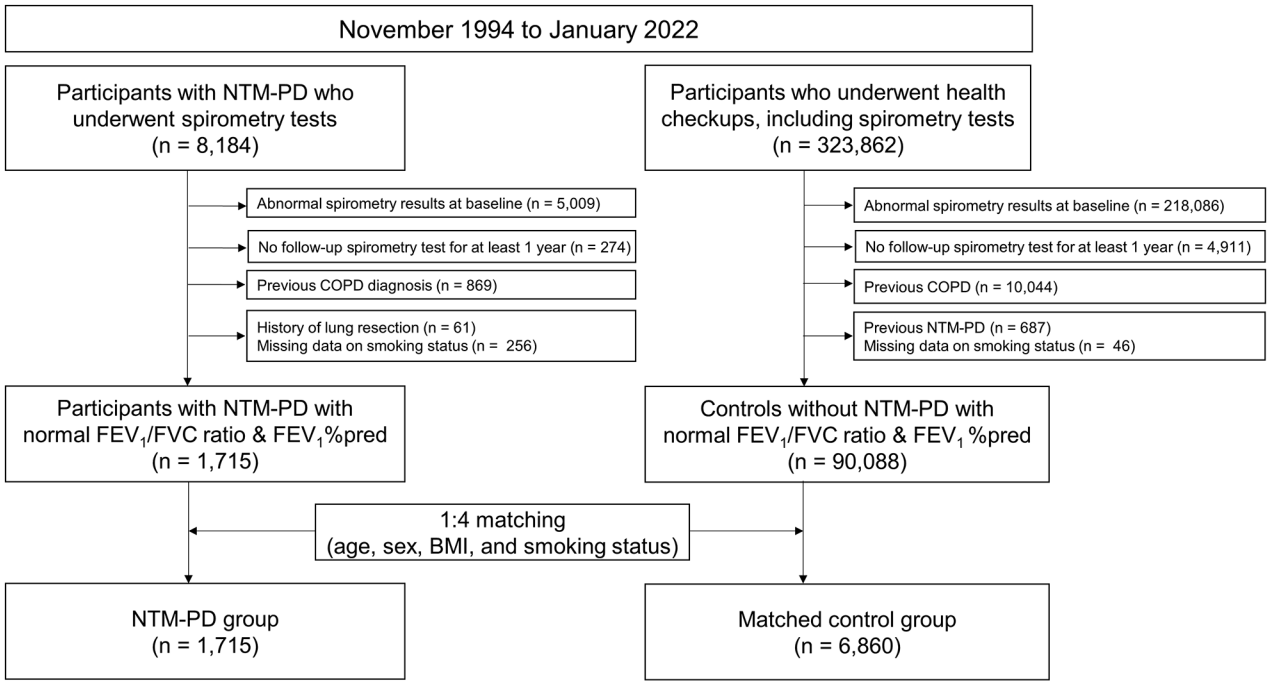

Fig. 1 Flowchart of the study population. **Abbreviations:** NTM-PD, nontuberculous mycobacterial pulmonary disease; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; BMI, body mass index

enrollment with the endpoint being death, a COPD diagnosis, or December 31, 2019, whichever occurred first.

Exposure

The exposure variable was NTM-PD. In study 1, we defined NTM-PD as the presence of both International Classification of Disease Codes-10th Revision (ICD-10) codes of A31.0, A31.8, or A31.9 and microbiological findings (≥2 positive culture results from separately expectorated sputum samples with the same species, or ≥1 positive culture result from bronchial washing, bronchoalveolar lavage, or lung biopsy with species identification) [17]. NTM species were identified using a nested multiplex polymerase chain reaction and reverse hybridization assay of the internal transcribed spacer region of *rpoB* [19]. In study 2, NTM-PD was defined as a case in which the diagnostic code A31.0, A31.8, or A31.9 was assigned for the main- or sub-diagnosis, and specific medical practice codes (e.g., microbial culture or identification codes) were entered together (**Supplementary Method**).

Study outcome

The primary outcome was newly diagnosed COPD during the follow-up period. In study 1, COPD was defined as a pre-bronchodilator FEV_1/FVC ratio < 0.7. When multiple spirometry results were present, the first date of reporting pre-bronchodilator FEV_1/FVC ratio < 0.7 was considered the newly diagnosed COPD date. In study 2, COPD was defined as the presence of ICD-10 codes J43–J44, except J43.0, and COPD medication prescribed at least twice within 1 year [20, 21].

Spirometry and annual lung function decline

The baseline spirometry was defined as the first spirometry taken between 6 months before and 6 months after the date of NTM-PD diagnosis for patients with NTM-PD and as the spirometry taken on the same day as the health screening exam for controls.

Spirometry was performed using the Vmax 22 system (SensorMedics, Yorba Linda, CA, USA) according to the American Thoracic Society/European Respiratory Society guidelines [22]. The absolute values of FEV_1 and FVC were obtained, and %pred FEV_1 and FVC were calculated using the equation obtained by analyzing the representative values of the Korean population [23]. Lung function decline was calculated as follows: [(last FEV_1 or FVC) – (FEV_1 or FVC at baseline)]/follow-up duration (years) [11, 24]. Rapid FEV_1 decline was defined as a loss in FEV_1 of > 60 mL/year [25].

Covariates

In study 1, covariate data were extracted from the CDW including age, sex, BMI, smoking status, and comorbidities (pulmonary tuberculosis, diabetes mellitus, hypertension, ischemic heart disease, and cerebrovascular disease), defined using ICD-10 codes [26–30].

Supplementary Method outlines the definitions of the covariates for study 2.

Statistical analysis

Baseline characteristics were expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. We compared the two groups using the χ^2 test for categorical variables and *t*-tests for continuous variables.

In study 1, we performed a 1:4 propensity score-matching between the NTM-PD and control cohorts based on age, sex, BMI, and smoking status. In study 2, we performed a 1:3 matching between the two cohorts based on age and sex. Standardized mean difference (SMD) was used to examine the balance of covariate distributions between the groups, and an SMD > 0.1 was considered to indicate an imbalance [31].

The cumulative incidence of COPD was determined using the Kaplan–Meier curve. Cox proportional-hazards regression analyses were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the comparison of incident COPD between the NTM-PD and matched control cohorts, adjusted for age, sex, BMI, smoking status, and comorbidities (tuberculosis, hypertension, diabetes mellitus, ischemic heart disease, and cerebrovascular disease).

In study 2, the Kaplan–Meier curve and multivariable Cox proportional-hazards regression analyses were used to estimate the comparative risks of incident COPD in the NTM-PD and matched control cohorts. Detailed descriptions of statistical analyses are provided in **Supplementary Method**. Statistical significance was defined as a two-sided *p*-value < 0.05, and all analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software version 4.2.1 (Vienna, Austria).

Results

Baseline characteristics

Table 1 presents the baseline characteristics of the patients from study 1. Patients with NTM-PD were more likely to be older, women, or had a lower BMI than those without NTM-PD. Most (85.0%) of the patients had never smoked, with no significant difference in the smoking status between the two groups. All comorbidities, except cerebrovascular disease, were more common in the NTM-PD group than in the control group (all $p < 0.001$). Despite matching, variables including age and sex continued to exhibit differences between the two groups (SMD > 0.1). However, the SMDs markedly decreased (Supplementary Fig. 2), and the SMD for the smoking status was < 0.1.

Lung function decline

At baseline, FEV_1, and FEV_1/FVC ratio were significantly lower in patients with NTM-PD than in those without NTM-PD (NTM-PD vs. matched control; FEV_1, 2.6 vs. 2.7 L, $p = 0.017$; FEV_1/FVC, 0.79 vs. 0.81, $p < 0.001$), although all patients had normal range of spirometry results. During a mean spirometry follow-up of 3.3 years, the annual decline in FEV_1 was greater in patients with NTM-PD than in those without NTM-PD (NTM-PD vs. matched control, −77.6 vs. −47.3 mL, $p < 0.001$). Patients with NTM-PD exhibited a higher proportion of rapid FEV_1 decline than that of matched controls (45.3% vs. 37.9%, $p < 0.001$; Table 2).

Table 1 Baseline characteristics of propensity score-matched cohorts

	Before matching				After matching*			
	Total (*n* = 91,803)	Control group (*n* = 90,088)	NTM-PD group (*n* = 1,715)	*p*	Total (*n* = 8,575)	Matched control group (*n* = 6,860)	NTM-PD group (*n* = 1,715)	SMD
Age, years	47 ± 10	47 ± 9	62 ± 11	< 0.001	60 ± 10	60 ± 10	62 ± 11	0.207
Male sex, n (%)	52,344 (57.0)	51,609 (57.3)	735 (42.9)	< 0.001	3,295 (38.4)	2,560 (37.3)	735 (42.9)	0.113
BMI, kg/m²	23.6 ± 3.0	23.6 ± 3.0	21.5 ± 3.0	< 0.001	22.9 ± 2.7	22.0 ± 2.7	21.5 ± 3.0	0.161
Smoking status, n (%)				0.383				0.099
Never-smoker	74,595 (81.3)	73,187 (81.2)	1,408 (82.1)		7,289 (85.0)	5,881 (85.7)	1,408 (82.1)	
Ever-smoker	17,208 (18.7)	16,901 (18.8)	307 (17.9)		1,286 (15.0)	979 (14.3)	307 (17.9)	
Comorbidity								
Pulmonary tuberculosis	590 (0.6)	515 (0.6)	75 (4.4)	< 0.001	122 (1.4)	47 (0.7)	75 (4.4)	0.237
Diabetes mellitus	601 (0.7)	502 (0.6)	99 (5.8)	< 0.001	148 (1.7)	49 (0.7)	99 (5.8)	0.288
Hypertension	4,182 (4.6)	4,024 (4.5)	158 (9.2)	< 0.001	698 (7.1)	540 (7.9)	158 (9.2)	0.048
Ischemic heart disease	530 (0.6)	501 (0.6)	29 (1.7)	< 0.001	75 (0.8)	46 (0.7)	29 (1.7)	0.095
Cerebrovascular disease	564 (0.6)	563 (0.6)	1 (0.1)	< 0.001	57 (0.6)	56 (0.8)	1 (0.1)	0.115

Data are expressed as mean ± standard deviation or number (%)

*Matched with age, sex, BMI, and smoking status

Abbreviations: NTM-PD, nontuberculous mycobacterial pulmonary disease; SMD, standardized mean difference; BMI, body mass index

Table 2 Result of pulmonary function test in the study population

Variables	Total (*n* = 91,803)	Control group (*n* = 90,088)	NTM-PD group (*n* = 1,715)	*p*	Matched control group (*n* = 6,860)	NTM-PD group (*n* = 1,715)	*p*
Interval between baseline and follow-up spirometry tests, years	3.3 ± 3.0	3.3 ± 3.0	3.3 ± 2.6	0.394	3.2 ± 2.7	3.3 ± 2.6	0.053
Baseline spirometry							
FVC, L	3.8 ± 0.8	3.8 ± 0.8	3.3 ± 0.8	< 0.001	3.2 ± 0.7	3.3 ± 0.8	0.011
FVC, % predicted	94.9 ± 10.9	95.0 ± 10.8	92.7 ± 12.2	< 0.001	95.5 ± 12.2	92.7 ± 12.2	< 0.001
FEV_1, L	3.2 ± 0.7	3.2 ± 0.7	2.6 ± 0.6	< 0.001	2.7 ± 0.6	2.6 ± 0.6	0.017
FEV_1, % predicted	102.3 ± 13.5	102.4 ± 13.4	97.5 ± 12.9	< 0.001	105.4 ± 15.0	97.5 ± 12.9	< 0.001
FEV_1/FVC (%)	82.9 ± 5.5	83.0 ± 5.4	79.0 ± 6.3	< 0.001	81.4 ± 5.8	79.0 ± 6.3	< 0.001
Follow-up spirometry							
FVC, L	3.7 ± 0.8	3.8 ± 0.8	3.1 ± 0.8	< 0.001	3.2 ± 0.7	3.1 ± 0.8	0.001
FVC, % predicted	93.8 ± 11.5	93.9 ± 11.3	86.3 ± 14.6	< 0.001	93.6 ± 13.7	86.3 ± 14.6	< 0.001
FEV_1, L	3.0 ± 0.7	3.0 ± 0.7	2.4 ± 0.6	< 0.001	2.5 ± 0.6	2.4 ± 0.6	< 0.001
FEV_1, % predicted	99.10 ± 14.3	99.1 ± 14.2	88.2 ± 15.2	< 0.001	98.5 ± 17.3	88.2 ± 15.2	< 0.001
FEV_1/FVC (%)	81.1 ± 6.3	81.2 ± 6.3	77.2 ± 8.5	< 0.001	79.0 ± 7.1	77.2 ± 8.5	< 0.001
COPD development	2,272 (2.5)	2,031 (2.3)	241 (14.0)	< 0.001	293 (4.3)	241 (14.0)	< 0.001
Change in lung function							
FEV_1 decline, mL/year	38.4 ± 132.9	37.7 ± 131.8	77.6 ± 176.0	< 0.001	47.3 ± 126.6	77.6 ± 176.0	< 0.001
Rapid FEV_1 decline*	34,794 (37.9)	34,017 (37.8)	777 (45.3)	< 0.001	2,598 (37.9)	777 (45.3)	< 0.001

Data are expressed as mean ± standard deviation or number (%)

*Decline in FEV_1 > 60 mL/year is defined as a rapid FEV_1 decline

Abbreviations: NTM-PD, nontuberculous mycobacterial pulmonary disease; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; COPD, chronic obstructive pulmonary disease

Incidence and risk of COPD

In study 1, during a mean follow-up of 3.3 years, 14.0% of patients in the NTM-PD group (241/1,1715) and 4.3% of patients in the matched control group (293/6,860) developed COPD. In the multivariable-adjusted model, the adjusted HR (aHR) was 2.57 (95% CI: 2.15–3.09) for the comparison of incident COPD between the NTM-PD and matched control groups. In the subgroup analysis, the risk of incident COPD was more evident in women (aHR = 5.44; 95% CI: 4.11–7.23) than in men, and in the age group < 60 years (aHR = 6.94; 95% CI: 4.84–9.94) compared to the other group (Table 3). Kaplan–Meier curves also demonstrated a significant difference in the cumulative incidence rate of COPD between the two groups (log-rank $p < 0.001$, Fig. 2 and Supplementary Fig. 3A).

Validation with NHIS-NSC data (study 2)

Supplementary Table 1 presents the baseline characteristics of the patients with NTM-PD and 1:3 age- and sex-matched controls of study 2. Although the smoking status did not differ significantly, patients with NTM-PD exhibited a lower BMI and higher Charlson comorbidity index than those of the matched controls. Furthermore, 6.2% (24/386) and 2.5% (28/1,133) of the patients with and without NTM-PD, respectively, developed COPD with respective incidence rates of 14.8 and 5.3 per 100,000 person-years (Table 4). The NTM-PD cohort exhibited a higher risk of COPD (aHR = 2.04; 95% CI: 1.21–3.42) than that of the matched control cohort. Similarly, the cumulative incidence rate of COPD differed significantly between the two groups (log-rank $p < 0.001$, Supplementary Fig. 3B). In the subgroup analysis, the risk of incident COPD was more evident in women (aHR = 3.55; 95% CI: 1.65–7.62) than in men.

Discussion

The present study provided longitudinal evidence for the association between NTM-PD and the development of COPD, utilizing a single-center database with a large number of patients with NTM-PD. Patients with NTM-PD exhibited a greater decline in lung function and approximately 2.5-fold higher risk of COPD incidence than those of the matched controls without NTM-PD. These findings were validated using a nationally representative cohort with similar hazard magnitudes. Notably, most (74–85%) patients in both cohorts were never-smokers, underscoring the potential role of NTM-PD as a major etiological factor in COPD-I.

Previous studies have reported lung function decline in patients with NTM-PD based on clinical outcomes or disease severity [11–14]. In a previous study where patients with NTM-PD ($n = 358$) were categorized into treatment-failure ($n = 68$), observation ($n = 118$), and treatment-success ($n = 172$) groups, FEV_1 decline was faster in the treatment-failure group compared to other groups (52.2, 30.8, and 28.2 mL/year, respectively) [11].

Table 3 Association between NTM-PD and COPD development

	n	Incident cases of COPD (*n* [%])	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Before matching				
Control cohort	90,088	2,031 (2.3)	Reference	Reference
NTM-PD cohort	1,715	241 (14.0)	5.46 (4.78–6.24)	1.81 (1.54–2.13)
After matching				
Matched control cohort	6,860	293 (4.3)	Reference	Reference
NTM-PD cohort	1,715	241 (14.0)	3.02 (2.54–3.58)	2.57 (2.15–3.09)
Sex				
Male				
Matched control cohort	2,560	209 (8.2)	Reference	Reference
NTM-PD cohort	735	120 (16.3)	1.84 (1.47–2.30)	1.56 (1.23–1.97)
Female				
Matched control cohort	4,300	84 (2.0)	Reference	Reference
NTM-PD cohort	980	121 (12.3)	5.75 (4.36–7.61)	5.44 (4.11–7.23)
Age				
< 60 years				
Matched control cohort	3,111	48 (1.5)	Reference	Reference
NTM-PD cohort	686	80 (11.7)	7.18 (5.02–10.26)	6.94 (4.84–9.94)
≥ 60 years				
Matched control cohort	3,749	245 (6.5)	Reference	Reference
NTM-PD cohort	1,029	161 (15.6)	2.17 (1.78–2.65)	2.01 (1.63–2.47)

*Adjusted for age, sex, BMI, smoking status, and comorbidities (tuberculosis, hypertension, diabetes mellitus, ischemic heart disease, and cerebrovascular disease)

Abbreviations: NTM-PD, nontuberculous mycobacterial pulmonary disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval; BMI, body mass index

Even after adjusting for multiple confounders, NTM-PD treatment failure was significantly associated with a greater decline in lung function. Additionally, in the treatment failure group, approximately 16% (5/31) of patients with normal spirometry results at baseline transitioned to obstructive spirometry. A recent study in South Korea categorized patients with NTM-PD ($n=354$) into mild, moderate, and severe groups based on the BMI, age, cavity, erythrocyte sedimentation rate, and sex (BACES) severity score system [32] and reported that the annual declines in FEV_1, FVC, and diffusing capacity for carbon monoxide increased with increasing disease severity of NTM-PD [13]. FEV_1 decreased by 26.4, 31.3, and 35.7 mL/year in mild, moderate, and severe groups, respectively [13]. By demonstrating that treatment failure and severe NTM-PD were associated with a faster FEV_1 decline, these studies supported the notion that NTM-PD is a risk factor for COPD development. However, these studies focused on lung function decline among patients with NTM-PD and did not compare them with healthy controls. A comparative study from Japan included 22 never-smokers with NTM-PD and 9 healthy never-smokers. Although the sample size was small, the FEV_1 decline was significantly greater in the NTM-PD group than in the control group (−70 vs. 20 mL/year) [12]. Our present study, which included a large number of patients with NTM-PD and matched controls, confirmed a greater lung function decline in patients with NTM-PD than in those without NTM-PD. Notably, we excluded patients with abnormal lung function or the diagnosis of COPD at baseline.

Regarding the association between NTM-PD and COPD development, a previous study using Taiwanese National Health Insurance data reported that the incidence of COPD was approximately 3.0-fold higher in the NTM cohort than in the non-NTM cohort [4]. However, this study did not include information on the smoking status and BMI. Since smoking exposure is a major risk factor for COPD, the lack of smoking status data was a notable limitation of this study. The present study overcomes these limitations and is the first to report a higher incidence of COPD in patients with NTM-PD than in smoking status-matched controls. An important strength of the present study was its longitudinal cohort design, which utilized a relatively large-scale and comprehensive dataset from a tertiary referral center and validation with a nationwide dataset. In study 1, the NTM-PD diagnosis was objectively defined using ICD-10 codes and microbiological findings. Using spirometry data, we objectively measured COPD development and excluded those with abnormal spirometry results at baseline. In study 2, we demonstrated the association between NTM-PD and COPD treatment, extending beyond spirometry-defined COPD in real-world clinical settings. These findings suggest that, akin to pulmonary tuberculosis, NTM-PD serves as a risk factor for COPD.

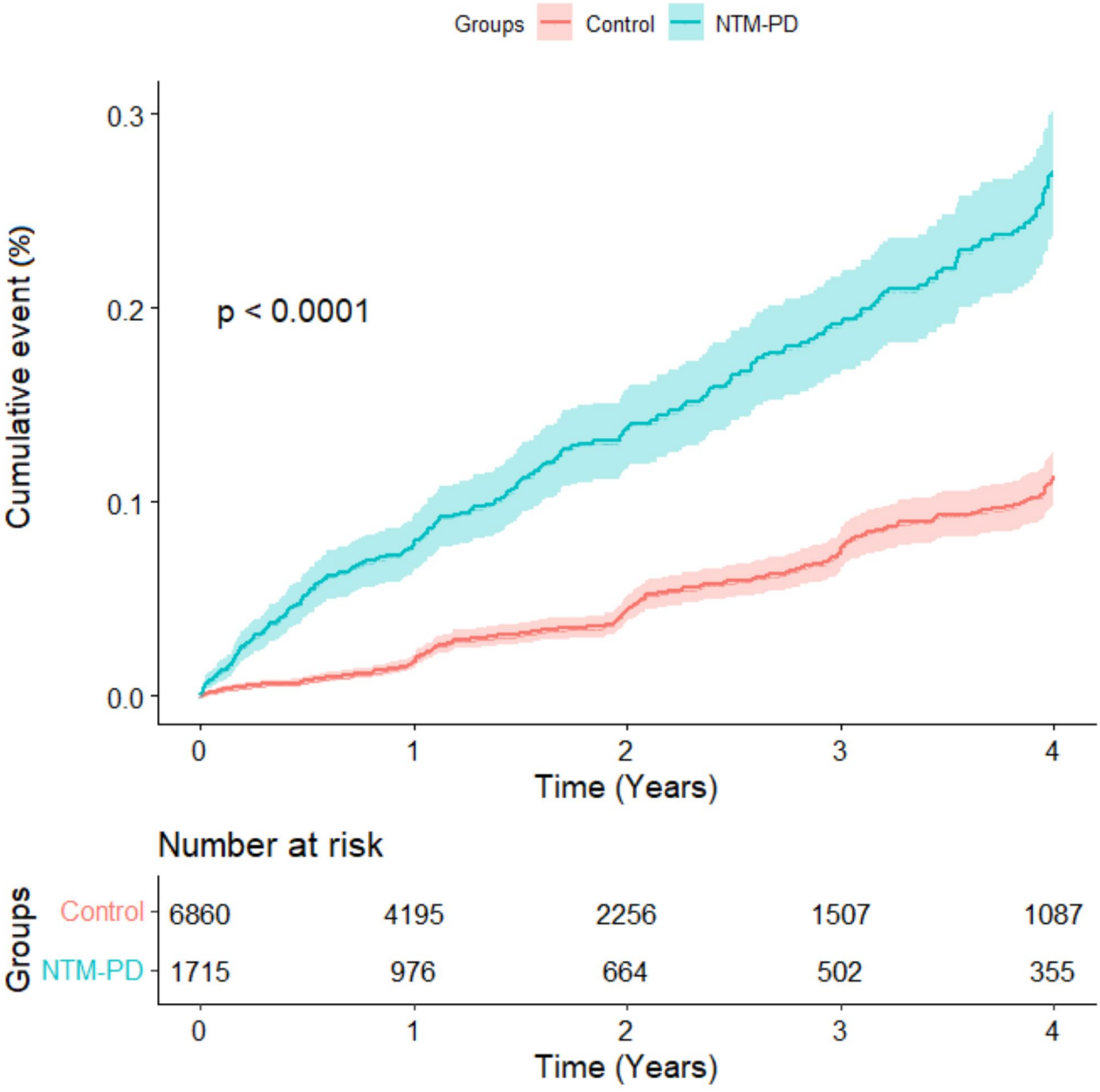

Fig. 2 Cumulative incidence of COPD according to the presence or absence of NTM-PD in study 1 (NTM-PD cohort versus matched control cohort). **Abbreviations**: NTM-PD, nontuberculous mycobacterial pulmonary disease; COPD, chronic obstructive pulmonary disease

Considering the substantial incidence of radiographic airway involvement, including bronchiolitis and parenchymal destruction involving the alveoli [33], an association between NTM-PD and airflow obstruction is predictable. In patients with NTM-PD whose spirometry test is apparently "normal," a mild obstructive pattern and gas trapping may be present [14]. Although the pathogenesis of NTM-PD has not been fully investigated, recurrent and persistent NTM infections are related to impaired mucociliary clearance and Th1 immune deficiency in the host [34]. Moreover, NTM species can damage the airway cilia, creating a vicious cycle that further impairs mucociliary clearance [35]. NTM infection induces airway inflammation and excessive neutrophilic response, which can compromise the airways, leading to pathological remodeling similar to that in tuberculosis (e.g., bronchiolitis, bronchiectasis, or cavity formation), [36] which is now recognized as a major etiotype of COPD-I. Therefore, persistent NTM infection and NTM-related inflammation may be responsible for COPD development.

Table 4 Overall and sex- and age-specific incidence rates and HR for COPD in the NTM-PD and matched control cohorts using a nationwide cohort dataset

	Cases	Incidence rate (/100,000 PY)	Sub-distribution hazard ratio (95% CI)	
			Unadjusted HR	Adjusted HR*
Overall				
Matched control cohort	28	5.3	Reference	Reference
NTM-PD cohort	24	14.8	2.10 (1.30–3.38)	2.04 (1.21–3.42)
Sex				
Male				
Matched control cohort	16	8.0	Reference	Reference
NTM-PD cohort	6	10.6	1.05 (0.48–2.30)	0.94 (0.41–2.13)
Female				
Matched control cohort	12	3.7	Reference	Reference
NTM-PD cohort	18	17.1	3.50 (1.84–6.67)	3.55 (1.65–7.62)
Age				
< 60 years				
Matched control cohort	8	2.8	Reference	Reference
NTM-PD cohort	14	15.9	3.71 (1.64–8.37)	1.93 (0.73–5.07)
≥ 60 years				
Matched control cohort	20	8.1	Reference	Reference
NTM-PD cohort	10	13.5	1.49 (0.80–2.75)	1.68 (0.86–3.27)

*Adjusted for BMI and Charlson comorbidity index

The smoking status was not adjusted for because it did not differ significantly between the two groups

Abbreviations: HR, hazard ratio; COPD, chronic obstructive pulmonary disease; NTM-PD, nontuberculous mycobacterial pulmonary disease; PY, per year; CI, confidence interval

This study has several clinical implications. First, it highlights the need for healthcare workers, patients, and local communities to recognize that NTM-PD can be associated with the development of COPD. Considering the increasing global prevalence of NTM-PD, COPD related to this disease might have been on the rise; however, without awareness of this association, its burden is likely to remain under-recognized. We suggest two strategies to ameliorate COPD progression in patients with NTM-PD. The first involves regular measurement of lung function in this population. Although the current guidelines for the NTM-PD diagnosis and treatment focus on identification and eradication of the causative microorganism, they do not mention lung function measurement or COPD development in patients with NTM-PD [7]. Close monitoring of symptoms, radiologic progression, and lung function could aid in the early detection of COPD. The second strategy entails the appropriate treatment of NTM-PD, as inappropriate treatment of NTM-PD is relatively common in real-world settings [37]. Because treatment failure could more rapidly decline lung function, which might lead to the COPD development, emphasizing appropriate NTM-PD treatment is crucial. Second, this study suggests the requirement for more basic research to elucidate the underlying mechanisms of COPD development in patients with NTM-PD. Unveiling specific molecular signaling pathways may help identify early biomarkers predicting COPD development and potential treatment-targeting molecules for this specific phenotype of COPD in patients with NTM-PD.

Despite its strengths, this study had several limitations. First, NTM-PD was diagnosed based on the presence of ICD-10 codes and microbiological findings. Therefore, patients with mild or asymptomatic NTM-PD or undiagnosed NTM-PD, such as cases where NTM species were isolated from only one sputum specimen, might not have been included in this study. Second, the incidence of COPD was higher in study 1 than in study 2. The potential reasons for overestimation in study 1 are as follows: (1) Study 1 was conducted at a tertiary referral hospital with a large number of patients with NTM-PD. The patients with NTM-PD in the present study were likely to experience more severe disease (and were more prone to developing COPD) compared to those with NTM-PD in general. (2) We defined newly diagnosed COPD as the first detected airflow obstruction using pre-bronchodilator spirometry results. Thus, a transient airflow obstruction could have been captured as COPD, and pre-bronchodilator airflow obstruction could have overestimated COPD. (3) Study 2 defined COPD as the ICD-10 codes for COPD and use of bronchodilators [20, 21, 38]. Since patients with ICD-10 codes for COPD who were not under treatment were not considered as having COPD, this could also lead to the discrepancy in the prevalence of COPD between the studies [39]. Fourth, as this study utilized data extracted from the CDW and NHIS-NSC, we lacked information on the presence and

extent of coexisting bronchiectasis, pulmonary fibrosis, clinical phenotype of NTM-PD (nodular bronchiectasis or fibrocavitary), and severity of NTM-PD. In evaluating the association between NTM-PD and COPD risk, we were unable to consider some important variables, such as bronchiectasis and pulmonary fibrosis [40, 41] due to the following reasons: Our study relied on formal interpretations of chest CT findings by radiologists, who sometimes omit detailed descriptions of bronchiectasis and/or fibrosis when interpreting CT findings of patients with NTM-PD. Consequently, the presence of bronchiectasis and/or fibrosis may be underreported. Additionally, clinicians often record the ICD-10 code for NTM-PD while omitting codes for bronchiectasis or fibrosis. Given these constraints, bronchiectasis and pulmonary fibrosis were not included in our study. Further studies with more detailed information are required to explore the association between NTM-PD and COPD. Fifth, our study spans a considerable period during which both the prevalence and awareness of NTM-PD have increased substantially. This could have influenced the timing of diagnosis and initiation of antibiotic treatment for NTM-PD, potentially affecting the observed association between NTM-PD and the development of COPD. Future studies are warranted to address these remaining questions. Finally, as this study was conducted in South Korea, the generalizability of the results to other ethnic groups or countries may be limited.

Conclusion

In conclusion, patients with NTM-PD experienced a greater decline in lung function and a significantly higher incidence rate of COPD compared to those without NTM-PD. These findings emphasize the importance of monitoring lung function in patients with NTM-PD to improve their clinical prognosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-024-02963-3.

Supplementary Material 1: Supplementary Text. Supplementary Methods, Supplementary Figure Legends, Supplementary Table 1

Supplementary Material 2: Supplementary Figure 1. Flowchart of the study population using the nationwide dataset. *Abbreviations*: NTM-PD, nontuberculous mycobacterial pulmonary disease; COPD, chronic obstructive pulmonary disease

Supplementary Material 3: **Supplementary Figure 2.** Graph illustrating the change in standardized mean difference. *Abbreviations*: BMI, body mass index

Supplementary Material 4: **Supplementary Figure 3.** (A) Cumulative incidence of COPD according to the presence of NTM-PD in study 1 (NTM-PD cohort versus whole control). *Abbreviations*: NTM-PD, nontuberculous mycobacterial pulmonary disease; COPD, chronic obstructive pulmonary disease

Supplementary Material 5: **Supplementary Figure 3.** (B) Cumulative incidence of COPD (/100,000 person-years) in the NTM-PD and matched cohorts using the nationwide dataset. Abbreviations: NTM-PD, nontuberculous mycobacterial pulmonary disease; COPD, chronic obstructive pulmonary disease

Acknowledgements
We express our heartfelt gratitude and respect to Won-Jung Koh for constructing the comprehensive patient dataset for study 1. Won-Jung Koh passed away in August 2019. We dedicate this work to his memory.

Author contributions
H.L. is the guarantors of the manuscript and take responsibility for its content, including the data and analysis. B.-G.K., S.H.S. and H.L. contributed to the conception and design of the study. B.-G.K., S.H.S., S.-K., L. and H.L. were involved in the collection and interpretation of the data. B.-G.K. and S.-K.L. were involved in the statistical analyses. B.-G.K. and S.H.S. were a major contributor in writing the manuscript. All authors have read and approved the final manuscript.

Funding
None.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Study 1 was approved by the Institutional Review Board of the Samsung Medical Center (IRB no.: SMC 2023-08-084). Study 2 was approved by the Institutional Review Board of the Hanyang University Hospital (IRB no.: HYUH 2023-06-007). The requirement for obtaining informed consent was waived because the CDW and NHIS databases were constructed after anonymization. These studies were conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 27 March 2024 / Accepted: 27 August 2024
Published online: 09 September 2024

References

1. Prevalence and attributable health burden of chronic respiratory diseases. 1990–2017: a systematic analysis for the global burden of Disease Study 2017. Lancet Respir Med. 2020;8:585–96.
2. World Health Organization. 2019. Leading Causes of Death Globally. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death
3. The Global Strategy for Diagnosis. Management and Prevention of COPD (updated 2023), http://www.goldcopd.org. [Accessed Feb 7 2023].
4. Yeh JJ, Wang YC, Sung FC, Chou CY, Kao CH. Nontuberculosis mycobacterium disease is a risk factor for chronic obstructive pulmonary disease: a nationwide cohort study. Lung. 2014;192:403–11.
5. Lee MK, Kim SB, Shin B. Differences in the clinical characteristics of chronic pulmonary aspergillosis according to spirometric impairment. PLoS ONE. 2021;16:e0260274.
6. Alvar A, Antonio A, Bartolome RC, Kevin M, Sundeep S, Claus FV. GOLD 2023 executive Summary: responses from the GOLD Scientific Committee. Eur Respir J. 2023;61:2300616.
7. Lee H, Shin SH, Park HY, Lim SY. Can we call all obstructive lung diseases COPD? Eur Respir J 2023; 61(6).
8. Daley CL, Iaccarino JM, Lange C, Cambau E, Wallace RJ Jr., Andrejak C, Böttger EC, Brozek J, Griffith DE, Guglielmetti L, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Eur Respir J. 2020;56:2000535.

9. Lee SW, Park Y, Kim S, Chung EK, Kang YA. Comorbidities of nontuberculous mycobacteria infection in Korean adults: results from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database. BMC Pulm Med. 2022;22:283.
10. Loebinger MR, Quint JK, van der Laan R, Obradovic M, Chawla R, Kishore A, van Ingen J. Risk Factors for Nontuberculous Mycobacterial Pulmonary Disease: A Systematic Literature Review and Meta-Analysis. *Chest* 2023.
11. Lee MR, Yang CY, Chang KP, Keng LT, Yen DH, Wang JY, Wu HD, Lee LN, Yu CJ. Factors associated with lung function decline in patients with non-tuberculous mycobacterial pulmonary disease. PLoS ONE. 2013;8:e58214.
12. Park HY, Jeong BH, Chon HR, Jeon K, Daley CL, Koh WJ. Lung function decline according to clinical course in Nontuberculous Mycobacterial Lung Disease. Chest. 2016;150:1222–32.
13. Kobayashi T, Tsuyuguchi K, Arai T, Tsuji T, Maekura T, Kurahara Y, Sugimoto C, Minomo S, Nakao K, Tokura S, et al. Change in lung function in never-smokers with nontuberculous mycobacterial lung disease: a retrospective study. J Clin Tuberc Other Mycobact Dis. 2018;11:17–21.
14. Park HJ, Kim JY, Kim HJ, Yim JJ, Kwak N. Lung function decline in non-tuberculous mycobacterial pulmonary disease according to disease severity. Int J Tuberc Lung Dis. 2023;27:465–70.
15. Mehta M, Chapman KR, Heffer M, Marras TK. Impact of pulmonary nontuberculous mycobacterial treatment on pulmonary function tests in patients with and without established obstructive lung disease. Respirology. 2015;20:987–93.
16. Huang CT, Tsai YJ, Wu HD, Wang JY, Yu CJ, Lee LN, Yang PC. Impact of non-tuberculous mycobacteria on pulmonary function decline in chronic obstructive pulmonary disease. Int J Tuberc Lung Dis. 2012;16:539–45.
17. Kim SH, Jhun BW, Jeong BH, Park HY, Kim H, Kwon OJ, Shin SH. The higher incidence of COVID-19 in patients with Non-tuberculous Mycobacterial Pulmonary Disease: a single Center experience in Korea. J Korean Med Sci. 2022;37:e250.
18. Shin DW, Cho B, Guallar E. Korean National Health Insurance Database. JAMA Intern Med. 2016;176:138.
19. Lee H, Park HJ, Cho SN, Bai GH, Kim SJ. Species identification of mycobacteria by PCR-restriction fragment length polymorphism of the rpoB gene. J Clin Microbiol. 2000;38:2966–71.
20. Park HY, Kang D, Shin SH, Yoo KH, Rhee CK, Suh GY, Kim H, Shim YM, Guallar E, Cho J, Kwon OJ. Chronic obstructive pulmonary disease and lung cancer incidence in never smokers: a cohort study. Thorax. 2020;75:506–9.
21. Park HY, Kang D, Shin SH, Choi H, Jang SH, Lee CH, Kim H, Kwon OJ, Rhee CK, Cho J. Pulmonary tuberculosis and the incidence of Lung Cancer among patients with chronic obstructive Pulmonary Disease. Ann Am Thorac Soc. 2022;19:640–8.
22. Miller M. ATS/ERS task force: standardisation of spirometry. Eur Respir J. 2005;26:319–38.
23. Choi JK, Paek D, Lee JO. Normal predictive values of Spirometry in Korean Population. Tuberc Respir Dis. 2005;58:230–42.
24. Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, Guerra S, Marott JL, Martinez FD, Martinez-Camblor P, et al. Lung-function trajectories leading to Chronic Obstructive Pulmonary Disease. N Engl J Med. 2015;373:111–22.
25. Martinez FJ, Han MK, Allinson JP, Barr RG, Boucher RC, Calverley PMA, Celli BR, Christenson SA, Crystal RG, Fagerås M, et al. At the Root: defining and halting progression of early chronic obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2018;197:1540–51.
26. Choi H, Lee H, Lee SK, Yang B, Chung SJ, Yeo Y, Park TS, Park DW, Moon JY, Kim TH, et al. Impact of bronchiectasis on susceptibility to and severity of COVID-19: a nationwide cohort study. Ther Adv Respir Dis. 2021;15:1753466621995043.
27. Choi H, Yang B, Kim YJ, Sin S, Jo YS, Kim Y, Park HY, Ra SW, Oh YM, Chung SJ, et al. Increased mortality in patients with non cystic fibrosis bronchiectasis with respiratory comorbidities. Sci Rep. 2021;11:7126.
28. Lee H, Choi H, Yang B, Lee SK, Park TS, Park DW, Moon JY, Kim TH, Sohn JW, Yoon HJ, Kim SH. Interstitial lung disease increases susceptibility to and severity of COVID-19. Eur Respir J 2021, 58.
29. Yang B, Ryu J, Kim T, Jo YS, Kim Y, Park HY, Kang YA, Lee SJ, Lee OJ, Moon JY, et al. Impact of Bronchiectasis on Incident Nontuberculous Mycobacterial Pulmonary Disease: a 10-Year National Cohort Study. Chest. 2021;159:1807–11.
30. Yoo JE, Kim D, Han K, Rhee SY, Shin DW, Lee H. Diabetes Status and Association with risk of tuberculosis among Korean adults. JAMA Netw Open. 2021;4:e2126099.
31. Zhang Z, Kim HJ, Lonjon G, Zhu Y. Balance diagnostics after propensity score matching. Ann Transl Med. 2019;7:16.
32. Kim HJ, Kwak N, Hong H, Kang N, Im Y, Jhun BW, Yim JJ. BACES score for Predicting Mortality in Nontuberculous Mycobacterial Pulmonary Disease. Am J Respir Crit Care Med. 2021;203:230–6.
33. Fujita J, Ohtsuki Y, Suemitsu I, Shigeto E, Yamadori I, Obayashi Y, Miyawaki H, Dobashi N, Matsushima T, Takahara J. Pathological and radiological changes in resected lung specimens in Mycobacterium avium intracellulare complex disease. Eur Respir J. 1999;13:535–40.
34. Matsuyama M, Ishii Y, Yageta Y, Ohtsuka S, Ano S, Matsuno Y, Morishima Y, Yoh K, Takahashi S, Ogawa K, et al. Role of Th1/Th17 balance regulated by T-bet in a mouse model of Mycobacterium avium complex disease. J Immunol. 2014;192:1707–17.
35. Middleton AM, Chadwick MV, Nicholson AG, Dewar A, Groger RK, Brown EJ, Wilson R. The role of Mycobacterium avium complex fibronectin attachment protein in adherence to the human respiratory mucosa. Mol Microbiol. 2000;38:381–91.
36. Matsuyama M, Matsumura S, Nonaka M, Nakajima M, Sakai C, Arai N, Ueda K, Hizawa N. Pathophysiology of pulmonary nontuberculous mycobacterial (NTM) disease. Respir Investig. 2023;61:135–48.
37. van Jakko I, Dirk W, Jack G, Kozo M, Christoph L, Charles SH, Floto RA, Jennifer A, Prevots DR. David EG: poor adherence to management guidelines in nontuberculous mycobacterial pulmonary diseases. Eur Respir J. 2017;49:1601855.
38. Kim BG, Lee H, Kang MG, Kim JS, Moon JY. Risk of Ischemic Heart Disease in Chronic Obstructive Pulmonary Disease: a Nationwide Cohort Study. J Korean Med Sci. 2023;38:e344.
39. Kim T, Choi H, Kim SH, Yang B, Han K, Jung JH, Kim BG, Park DW, Moon JY, Kim SH, et al. Increased risk of Incident Chronic Obstructive Pulmonary Disease and related hospitalizations in tuberculosis survivors: a Population-based Matched Cohort Study. J Korean Med Sci. 2024;39:e105.
40. Faverio P, Stainer A, Bonaiti G, Zucchetti SC, Simonetta E, Lapadula G, Marruchella A, Gori A, Blasi F, Codecasa L et al. Characterizing non-tuberculous mycobacteria infection in Bronchiectasis. Int J Mol Sci 2016, 17.
41. Odashima K, Kagiyama N, Kanauchi T, Ishiguro T, Takayanagi N. Incidence and etiology of chronic pulmonary infections in patients with idiopathic pulmonary fibrosis. PLoS ONE. 2020;15:e0230746.

Publisher's note