CHEST

Gastroesophageal Reflux Disease Increases Susceptibility to Nontuberculous Mycobacterial Pulmonary Disease

Youlim Kim, MD, PhD; Jai Hoon Yoon, MD, PhD; Jiin Ryu, MS; Bumhee Yang, MD; Sung Jun Chung, MD; Hyung Koo Kang, MD; Dong Won Park, MD, PhD; Tai Sun Park, MD, PhD; Ji-Yong Moon, MD, PhD; Tae-Hyung Kim, MD, PhD; Sang-Heon Kim, MD, PhD; Jang Won Sohn, MD, PhD; Ho Joo Yoon, MD, PhD; Hyun Lee, MD, PhD; and Hayoung Choi, MD, PhD

BACKGROUND: Gastroesophageal reflux disease (GERD) is a common comorbidity of nontuberculous mycobacteria (NTM) pulmonary disease (PD). Although GERD is associated with more symptoms and severe disease in patients with NTM PD, whether GERD is associated with an increased risk of NTM PD developing is unknown.

RESEARCH QUESTION: Does GERD influence the development of NTM PD? Are there any factors associated with an increased risk of NTM PD among patients with GERD? What is the impact of NTM PD on the health-care use of patients with GERD?

STUDY DESIGN AND METHODS: Data from the Korean National Health Insurance Service National Sample Cohort between 2002 and 2015 were used. The incidence and risk of NTM PD were compared between patients with GERD (GERD cohort; n = 17,424) and patients matched for age, sex, type of insurance, and Charlson Comorbidity Index (matched cohort; n = 69,696). Using the GERD cohort, the factors associated with incident NTM PD also were evaluated.

RESULTS: During a median follow-up duration of 5.1 years, the age- and sex-adjusted incidence of NTM PD was significantly higher in the GERD cohort (34.8 per 100,000 person-years [PY]) than in the matched cohort (10.5 per 100,000 PY; $P < .001$), with a subdistribution hazard ratio (HR) of 3.36 (95% CI, 2.10-5.37). Regarding risk factors associated with NTM PD, age of 60 years or older (adjusted HR, 3.57; 95% CI, 1.58-8.07) and bronchiectasis (adjusted HR, 18.69; 95% CI, 6.68-52.28) were associated with an increased risk of incident NTM PD in the GERD cohort. Compared with patients with GERD who did not demonstrate NTM PD, those with NTM PD showed higher all-cause (13,321 PY vs 5,932 PY; $P = .049$) and respiratory disease-related (5,403 vs 801; $P = .011$) ED visits or hospitalizations.

INTERPRETATION: GERD is associated with an increased incidence of NTM PD. Older age and bronchiectasis are risk factors for NTM PD in patients with GERD. NTM PD in patients with GERD is associated with increased health-care use. CHEST 2023; 163(2):270-280

KEY WORDS: epidemiology; gastroesophageal reflux; nontuberculosis mycobacterium; risk

ABBREVIATIONS: CCI = Charlson Comorbidity Index; GERD = gastroesophageal reflux disease; HR = hazard ratio; ICD-10 = International Classification of Diseases, 10th Revision; NTM = nontuberculous mycobacteria; PD = pulmonary disease; PPI = proton pump inhibitor; PPV = positive predictive value; PY = person-years

AFFILIATIONS: From the Division of Pulmonary, Allergy and Critical Care Medicine (Y. K.), Department of Internal Medicine, Konkuk University School of Medicine, the Division of Gastroenterology and Hepatology (J. H. Y.), the Division of Pulmonary Medicine and Allergy (S. J. C., D. W. P., T. S. P., J.-Y. M., T.-H. K., S.-H. K., J. W. S., H. J. Y., and H. L.), Department of Internal Medicine, Hanyang University College of Medicine, the Biostatistical Consulting and Research Lab (J. R.), Medical Research Collaborating Center, Hanyang University, the Division of Pulmonary, Allergy, and Critical Care Medicine (H. C.),

Take-home Points

Study Questions: Is gastroesophageal reflux disease (GERD) associated with an increased risk of nontuberculous mycobacteria (NTM) pulmonary disease (PD)? If so, which factors are associated with an increased risk of NTM PD in patients with GERD? What are the effects of NTM PD on health-care use in patients with GERD?

Results: We found that patients with GERD had an approximately 3.4-fold increased risk of NTM PD developing compared with those without GERD, and the former was associated positively with respiratory-related health-care use. In addition, older age and bronchiectasis were predictors of NTM PD developing in patients with GERD.

Interpretation: GERD is associated with an increased incidence of NTM PD. Older age and bronchiectasis are risk factors for NTM PD in patients with GERD. NTM PD in patients with GERD is associated with increased health-care use.

The prevalence of nontuberculous mycobacteria (NTM) pulmonary disease (PD) has increased worldwide, and the disease burden associated with NTM PD is substantial.[1-5] NTM PD is known to be associated with many comorbidities.[6] The proper management of these comorbidities is important because they affect the clinical presentation and prognosis of patients with NTM PD and can be attributable to the development or progression of NTM PD.[7]

Gastroesophageal reflux disease (GERD) is a common comorbidity of NTM PD.[6,8,9] In previous studies, up to 45% of patients with NTM PD were shown to have GERD, which is associated with more symptoms and severe disease in this population.[8,9] Although the association between GERD and NTM PD has been relatively well studied in terms of symptoms and disease presentation,[8,9] whether GERD predisposes a patient to NTM PD developing and, if so, which factors are associated with the development of NTM PD in patients with GERD, remains unknown. Because identifying modifiable risk factors is an important strategy to reduce the disease burden of NTM PD, solving these issues may be clinically relevant and important.

In the present study, the effects of GERD on the development of NTM PD were evaluated and factors associated with increased risk of NTM PD were elucidated in patients with GERD. In addition, the association between the development of NTM PD and health-care use was evaluated in patients with GERD.

Study Design and Methods

Study Population

Data from the National Health Insurance Service National Sample Cohort, which is a population-based retrospective cohort, including a 2.2% representative sample of Korean citizens, were used. In Korea, the National Health Insurance Service covers the health insurance of almost all Korean citizens. The National Health Insurance Service National Sample Cohort database collects health data regarding major and minor diagnoses using the International Classification of Diseases, 10th Revision (ICD-10), codes during the outpatient visit, ED visit, or hospitalization and drug prescriptions.[10]

As shown in Figure 1, 877,320 adult patients 20 years of age or older were identified between January 1, 2002, and December 31, 2014. We excluded 21,282 patients who received a diagnosis of GERD between January 1, 2002, and December 31, 2002. Among the remaining 856,038 patients, 17,659 patients had a new diagnosis of GERD and 838,379 patients were without GERD. Because baseline characteristics between patients with and without GERD differed significantly, we decided to match the two groups.

The enrollment period was between January 1, 2003, and December 31, 2014. To establish the NTM PD-naïve GERD cohort, patients with a diagnosis of NTM PD before enrollment (n = 7) and those who died within 1 year after enrollment (n = 228) also were excluded from the GERD cohort. Additionally, to establish an NTM PD-naïve control group, patients with a diagnosis of NTM PD (n = 314) were excluded. Each patient with GERD was matched exactly to four control participants without GERD based on age, sex, type of insurance, and Charlson Comorbidity Index (CCI).[11] Among the NTM PD-naïve control group, those who died within 1 year after matching were replaced with those who did not die within 1 year after matching in the process of matching. Finally, 17,424 NTM-naïve patients with GERD (GERD cohort) and 69,696 NTM-naïve matched patients (matched cohort) were included in the present

Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, the Division of Pulmonary and Critical Care Medicine (B. Y.), Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, and the Division of Pulmonary and Critical Care Medicine (H. K. K.), Department of Internal Medicine, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea.

Y. Kim, J. H. Yoon, and J. Ryu contributed equally to this manuscript as first authors.

H. Lee and H. Choi contributed equally to this manuscript as corresponding authors.

CORRESPONDENCE TO: Hayoung Choi, MD, PhD; email: hychoimd@gmail.com

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study. Both cohorts were followed up through December 31, 2015, to compare the incidence of NTM PD (Fig 1).

The study protocol was approved by the institutional review board of Hanyang University Hospital (application no. HYUH- 2021-06-009), and the need for informed consent was waived because anonymized National Health Insurance Service data were used for this study.

Exposure

GERD was defined based on ICD-10 codes for GERD (K20.8, K20.9, K21.0, or K21.9) as a major or minor diagnosis and the prescription of proton pump inhibitors (PPIs) for > 3 months within 1 year after the first diagnosis of GERD.[12] Because clinical guidelines recommend an empirical PPI treatment for GERD for at least 8 weeks,[13-15] we defined GERD as a > 3-month use of PPIs.

Outcomes

The main outcomes evaluated in this study were (1) comparison between the GERD cohort and the matched cohort regarding the incidence and risk of incident NTM PD, and (2) risk factors for NTM PD in the GERD cohort. An incident case of NTM PD was defined based on the presence of a new primary or secondary diagnostic code associated with NTM PD (A31.0, A31.8, or A31.9) plus claims data for acid-fast bacilli smears or mycobacterial culture.[4,16] The claims data for microbiological tests indicated only performance of the tests by attending physicians; they did not indicate positive results. For sensitivity analysis, we also defined NTM PD as follows: ICD-10 code only or ICD-10 code, claims for acid-fast bacilli smears or mycobacterial culture, plus macrolide prescription for more than one month (e-Table 1).

Other minor outcomes were comparing the rates of all-cause and respiratory disease-related health-care use (ED visit and hospitalization) between the patients with GERD with NTM PD and those without NTM PD. A respiratory-related health-care visit was defined as one with ICD-10 respiratory disease codes (J00-J99).[17,18]

Covariates

Comorbidities also were defined using the following ICD-10 diagnosis codes: COPD (J42-J44, except J43.0 [unilateral emphysema]), asthma (J45-J46), bronchiectasis (J47), cerebrovascular disease (I60-I69), angina or myocardial infarction (I20-I25), diabetes mellitus (E10-E14), chronic kidney disease (N18), and connective tissue disease (M05, M06, M32, M35, and M45).[16-19] CCI was calculated according to a previous report.[11]

Statistical Analysis

Data for the baseline characteristics were presented as numbers (percentages), and standardized differences between the GERD and matched cohorts were computed to assess whether the two groups had been well matched.[20] To evaluate the effects of GERD on NTM PD incidence, the incidence rate (per 100,000 person-years [PY]) of NTM PD was compared using the exact mid *P* test for binominals.[21] To compute the cumulative curves of incident NTM PD, we used the cumulative incidence function, which estimates the cumulative incidence accounting for competing risks. The cumulative incidence of NTM PD between the GERD and matched cohorts was compared using Gray's test, which was used to test the hypotheses of equality of cumulative incidence functions between the two groups.[22]

To determine the hazard ratio (HR) for incident NTM PD in the GERD cohort relative to the matched cohort, we performed a

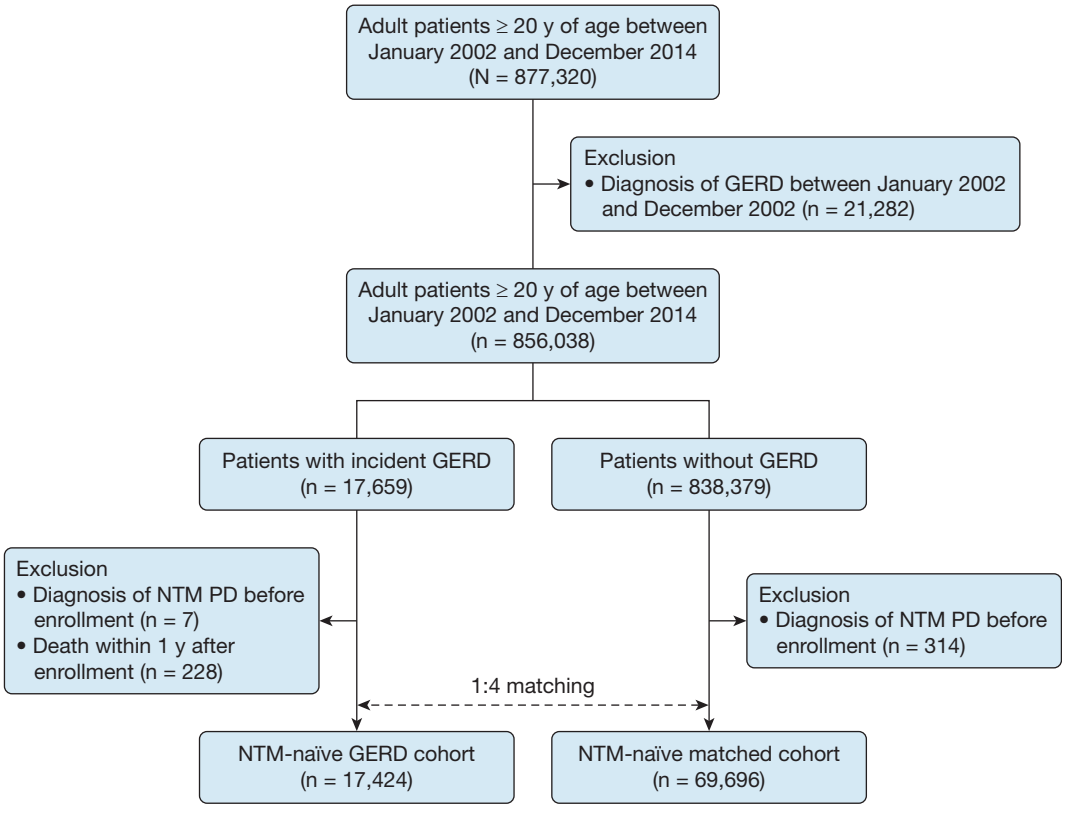

Figure 1 – *Flow chart showing the study population. GERD = gastroesophageal reflux disease; NTM = nontuberculous mycobacteria; PD = pulmonary disease.*

subdistribution Cox proportional hazards regression model to account for competing risks caused by mortality. Because all baseline variables were matched appropriately between the GERD and matched cohorts, adjustment for covariates was not performed. To validate the Cox proportional hazards regression model, sensitivity analyses excluding patients with a diagnosis of NTM PD early in the observation periods (1 year and 2 years) were performed (e-Table 1). To validate that 1 year was adequate to identify prevalent cases of NTM, sensitivity analyses using 2 years and 3 years to identify prevalent cases of NTM were performed (e-Table 1). We also performed propensity score-matching analyses on 12,162 patients with GERD and 12,162 without GERD matched for age, sex, insurance type, pulmonary and extrapulmonary comorbidities, and CCI (e-Tables 2, 3).

To analyze the risk factors associated with NTM PD in patients with GERD, a Cox proportional hazards regression model was performed, adjusting for age (< 60 years vs ≥ 60 years), sex, type of insurance, pulmonary and extrapulmonary comorbidities, and CCI using the GERD cohort. To evaluate health-care use in patients with GERD based on the development of NTM PD, annual health-care use (per 100,000 PY) was compared between patients with GERD who demonstrated NTM PD and those who did not. Wald test was used to calculate the 95% CIs for the Cox model.

All tests were two-sided and P values of $< .05$ were considered statistically significant. All statistical analyses were performed using SAS version 9.4 software (SAS Institute).

Results

Baseline Characteristics

The baseline characteristics of the study population are summarized in Table 1. Approximately 90% of patients were at least 40 years of age and 50% were men. Most patients received self-employed health insurance and employee health insurance. The GERD cohort and matched cohort were well balanced in terms of age, sex, type of insurance, pulmonary or extrapulmonary comorbidities, and CCI (standardized difference, 0.00 for most variables).

Incidence and Risk of NTM PD in GERD Cohort vs Matched Cohort

During the median follow-up duration of 5.1 years (interquartile range, 3.0-7.2 years), the age- and sex-adjusted incidence of NTM PD was significantly higher in the GERD cohort (34.8 per 100,000 PY) than in the matched cohort (10.5 per 100,000 PY; $P < .001$) (Fig 2). Similarly, the risk of incident NTM PD developing was significantly higher in the GERD cohort than in the matched cohort (subdistribution HR, 3.36; 95% CI, 2.10-5.37) (Table 2).

Regardless of age group and sex, the risk of incident NTM PD was significantly higher in the GERD cohort compared with the matched cohort (e-Fig 1). All sensitivity analyses of (1) excluding patients with a diagnosis of NTM PD within 2 years of enrollment, (2) using different periods (2 or 3 years) to identify prevalent cases of NTM PD, and (3) defining NTM PD showed similar results (e-Table 1). Furthermore, propensity score-matching analysis showed similar results (HR, 3.87; 95% CI, 1.58-9.47) (e-Table 3).

Risk Factors for Incident NTM PD in Patients With GERD

Table 3 summarizes the factors associated with incident NTM PD in the GERD cohort. In both univariate and multivariate analyses, age of 60 years or older (unadjusted HR, 3.37; 95% CI, 1.56-7.29; adjusted HR, 3.57; 95% CI, 1.58-8.07) and bronchiectasis (unadjusted HR, 19.80; 95% CI, 8.15-48.13; adjusted HR, 18.69; 95% CI, 6.68-52.28) were associated significantly with an increased risk of incident NTM PD in the GERD cohort. In addition, the same analysis was performed when a history of macrolide use was included (e-Table 4).

Effects of NTM PD Developing on Health-Care Outcomes in Patients With GERD

Compared with patients with GERD who did not demonstrate NTM PD, those who demonstrated NTM PD showed increased all-cause (13,321 per 100,000 PY vs 5,932 per 100,000 PY; $P = .049$) and respiratory disease-related (5,403 per 100,000 PY vs 801 per 100,000 PY; $P = .011$) ED visits or hospitalization (Fig 3).

Discussion

In the present study, whether GERD is a predisposing factor for the development of NTM PD was evaluated and which factors are associated with an increased risk of NTM PD among patients with GERD was investigated. The results showed that patients with GERD had approximately a 3.4-fold increased risk of NTM PD developing compared with those without GERD, and the former were associated positively with respiratory-related health-care use. In addition, older age and bronchiectasis were predictors of NTM PD developing in patients with GERD.

The incidence of NTM PD in patients with GERD in this study was 35 per 100,000 PY, an approximate 3.4-

TABLE 1] Baseline Characteristics of the Study Population

Variable	Total (N = 87,120)	GERD Cohort (n = 17,424)	Matched Cohort (n = 69,696)	Standardized Difference
Age group, y				
20-29	3,195 (3.7)	639 (3.7)	2,556 (3.7)	0.00
30-39	6,730 (7.7)	1,346 (7.7)	5,384 (7.7)	0.00
40-49	14,735 (16.9)	2,947 (16.9)	11,788 (16.9)	0.00
50-59	22,895 (26.3)	4,579 (26.3)	18,316 (26.3)	0.00
60-69	20,580 (23.6)	4,116 (23.6)	16,464 (23.6)	0.00
≥ 70	18,985 (21.8)	3,797 (21.8)	15,188 (21.8)	0.00
Sex				
Male	43,630 (50.1)	8,726 (50.1)	34,904 (50.1)	0.00
Female	43,490 (49.9)	8,698 (49.9)	34,792 (49.9)	0.00
Type of insurance				
Self-employed health insurance	29,425 (33.8)	5,885 (33.8)	23,540 (33.8)	0.00
Employee health insurance	50,280 (57.7)	10,056 (57.7)	40,224 (57.7)	0.00
Medical aid	7,415 (8.5)	1,483 (8.5)	5,932 (8.5)	0.00
Pulmonary comorbidities				
COPD	7,108 (8.2)	1,432 (8.2)	5,676 (8.1)	0.00
Asthma	12,762 (14.7)	2,405 (13.8)	10,357 (14.9)	−0.03
Bronchiectasis	912 (1.1)	186 (1.1)	726 (1.0)	0.00
Extrapulmonary comorbidities				
Cerebrovascular disease	10,541 (12.1)	2,008 (11.5)	8,533 (12.2)	−0.02
Angina or MI	8,196 (9.4)	2,135 (12.3)	6,061 (8.7)	0.12
Diabetes mellitus	24,609 (28.3)	4,446 (25.5)	20,163 (28.9)	−0.08
Chronic kidney disease	1,326 (1.5)	223 (1.3)	1,103 (1.6)	−0.03
Connective tissue disease	4,995 (5.7)	1,268 (7.3)	3,687 (5.3)	0.08
Charlson Comorbidity Index				
0	12,600 (14.5)	2,520 (14.5)	10,080 (14.5)	0.00
1	23,435 (26.9)	4,687 (26.9)	18,748 (26.9)	0.00
2	19,060 (21.9)	3,812 (21.9)	15,248 (21.9)	0.00
3	11,945 (13.7)	2,389 (13.7)	9,556 (13.7)	0.00
4	7,790 (8.9)	1,558 (8.9)	6,232 (8.9)	0.00
≥ 5	12,290 (14.1)	2,458 (14.1)	9,832 (14.1)	0.00

Data are presented as No. (%). Each patient with GERD was matched exactly with four patients without GERD as control participants based on age, sex, type of insurance, and Charlson Comorbidity Index. GERD = gastroesophageal reflux disease; MI = myocardial infarction.

fold increased risk of NTM PD compared with the risk for patients without GERD. Because the incidence of NTM PD in the Korean population ranged from 6 to 19 cases per 100,000 per year between 2008 and 2016 in a previous study,[4] the GERD-related disease burden of incident NTM PD seems to be substantial. Further evidence supports a close relationship between GERD and NTM PD in terms of prevalence and disease presentation in previous studies.[6,8,9] In addition to showing cross-sectional association between GERD and NTM PD, the temporal relationship between GERD and NTM PD was clarified in the present study. To the best of our knowledge, this is the first study in which GERD was shown as a predisposing factor for NTM PD using a longitudinal cohort.

The major effect of GERD on NTM PD is thought to be achieved through gastric-to-pulmonary microaspiration and, consequently, the continuous destruction of the protective barrier of the airways,[23] which may create a

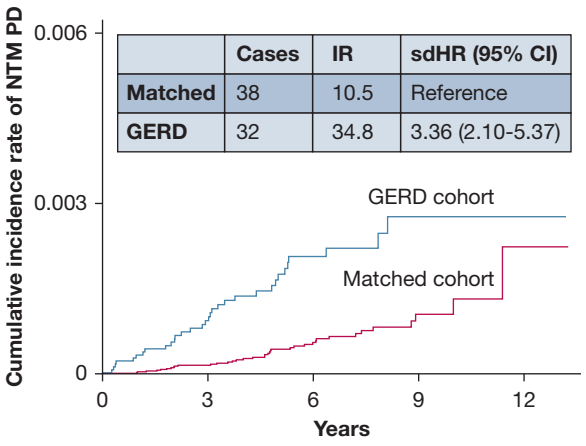

Figure 2 – *Line graph showing the cumulative incidence of NTM PD (per 100,000 person-years) in the GERD and matched cohorts. GERD = gastroesophageal reflux disease; IR = incidence rate; NTM = nontuberculous mycobacteria; PD = pulmonary disease; sdHR = subdistribution hazard ratio.*

predisposing condition to NTM infection. In addition, NTM could be ingested through contaminated water or food. During reflux, NTM can be microaspirated and deposited into the lung, causing infection in epithelial cells in which barriers are damaged during a gastroesophageal reflux microaspiration episode.[24] In a recent study, *Mycobacterium abscessus* was shown to survive in human airway cells in simulated acidic conditions.[24] Bile aspirated into the lung during GERD is another possible mechanism. In a previous study, bile was detected in sputum from patients with GERD.[25] Also, GERD-derived bile acids have been detected in BAL fluid. A predisposition to pulmonary infection has been associated with bile acid aspiration in several studies, including infection with *Pseudomonas aeruginosa*, an important pathogen associated with several respiratory diseases.[26-29] Therefore, even if acid secretion is suppressed by PPI treatment in patients with GERD, NTM PD may be induced or aggravated through mechanisms such as bile reflux. The authors showed that chenodeoxycholic acid, a bile component, significantly increased transforming growth factor β expression in airway epithelial cells,[25] which may be associated with a favorable environment for NTM PD. Transforming growth factor β levels were shown to increase in patients with NTM PD compared with control participants.[30] The PPIs frequently used in patients with GERD may have several roles. PPIs may reduce respiratory symptoms associated with GERD (such as cough) or damage of the lung caused by acidic contents. However, PPIs may increase the

TABLE 2] Age- and Sex-Specific Incidence Rates and HRs for Incident NTM PD in the GERD Cohort and Matched Cohort

Variable	Incident Case of NTM PD	Incidence Rate (per 100,000 PY)	Subdistribution HR (95% CI)[a]
Overall			
Matched cohort	38	10.5	Reference
GERD cohort	32	34.8	3.36 (2.10-5.37)
Age group, y			
< 60			
Matched cohort	13	6.2	Reference
GERD cohort	9	17.1	2.77 (1.18-6.47)
≥ 60			
Matched cohort	25	16.3	Reference
GERD cohort	23	58.3	3.65 (2.07-6.44)
Sex			
Male			
Matched cohort	22	12.3	Reference
GERD cohort	15	33.0	2.71 (1.41-5.23)
Female			
Matched cohort	16	8.7	Reference
GERD cohort	17	36.5	4.24 (2.14-8.40)

GERD = gastroesophageal reflux disease; HR = hazard ratio; NTM = nontuberculous mycobacteria; PD = pulmonary disease; PY = person-years.
[a]To determine the relative HR for incident NTM PD in the GERD cohort, an unadjusted Cox proportional hazards regression model was used because all baseline variables were matched appropriately between the GERD and matched cohorts. Competing risk of mortality was considered in the model.

TABLE 3] Risk Factors for the Development of NTM PD in Patients With GERD

Variable	No. at Risk (n = 17,424)	Incident Case of NTM PD (n = 32)	Univariate Analysis		Multivariate Analysis	
			Unadjusted HR	95% CI	Adjusted HR[a]	95% CI
Age group, y						
< 60	9,511 (54.6)	9 (0.1)	Reference	Reference	Reference	Reference
≥ 60	7,913 (45.4)	23 (0.3)	3.37	1.56-7.29	3.57	1.58-8.07
Sex						
Male	8,726 (50.1)	15 (0.2)	Reference	Reference	Reference	Reference
Female	8,698 (49.9)	17 (0.2)	1.10	0.55-2.20	0.93	0.45-1.88
Type of insurance						
Self-employed health insurance	5,885 (33.8)	7 (0.1)	Reference	Reference	Reference	Reference
Employee health insurance	10,056 (57.7)	22 (0.2)	1.92	0.82-4.49	1.71	0.73-4.01
Medical aid	1,483 (8.5)	3 (0.2)	1.72	0.45-6.65	1.34	0.34-5.31
Pulmonary comorbidities						
COPD	1,432 (8.2)	5 (0.3)	2.11	0.81-5.49	1.01	0.33-3.11
Asthma	2,405 (13.8)	6 (0.2)	1.46	0.60-3.56	0.90	0.33-2.45
Bronchiectasis	186 (1.1)	6 (3.2)	19.80	8.15-48.13	18.69	6.68-52.28
Extrapulmonary comorbidities						
Cerebrovascular disease	2,008 (11.5)	3 (0.1)	0.89	0.27-2.92	0.83	0.24-2.90
Angina or MI	2,135 (12.3)	3 (0.1)	0.76	0.23-2.50	0.59	0.17-2.00
Diabetes mellitus	4,446 (25.5)	6 (0.1)	0.73	0.30-1.78	0.72	0.26-1.97
Chronic kidney disease	223 (1.3)	1 (0.4)	3.31	0.45-24.29	5.55	0.67-45.98
Connective tissue disease	1,268 (7.3)	4 (0.3)	1.81	0.64-5.16	1.71	0.57-5.11
Charlson Comorbidity Index						
0	2,520 (14.5)	5 (0.2)	Reference	Reference	Reference	Reference
1	4,687 (26.9)	8 (0.2)	0.82	0.27-2.52	0.69	0.22-2.13
2	3,812 (21.9)	7 (0.2)	0.90	0.29-2.83	0.60	0.18-1.98
3	2,389 (13.7)	5 (0.2)	1.05	0.30-3.63	0.60	0.16-2.33
4	1,558 (8.9)	4 (0.3)	1.34	0.36-4.98	0.70	0.16-3.08
≥ 5	2,458 (14.1)	3 (0.1)	0.69	0.16-2.88	0.35	0.06-1.97

Data are presented as No. (%) or ratio (95% CI), unless otherwise indicated. GERD = gastroesophageal reflux disease; HR = hazard ratio; MI = myocardial infarction; NTM = nontuberculous mycobacteria; PD = pulmonary disease.

[a]Multivariate Cox regression analysis was adjusted for age (< 60 y vs ≥ 60 y), sex, type of insurance, pulmonary and extrapulmonary comorbidities, and Charlson Comorbidity Index in the GERD cohort.

susceptibility to NTM PD, as shown in other pulmonary infections. For example, several observational studies showed a positive association between the use of PPIs and the risk of community-acquired pneumonia.[31-34]

Notably, in the present study, the risk of NTM PD was increased significantly in patients with GERD who were older than 60 years. In previous studies, elderly patients were shown to have fewer typical GERD symptoms, but more severe GERD-related complications and esophageal lesions, compared with younger individuals.[35] In addition, a decrease in gastric emptying[36] and increased microaspiration or reflux associated with impaired swallowing[37,38] are more common in the elderly population. Accordingly, elderly

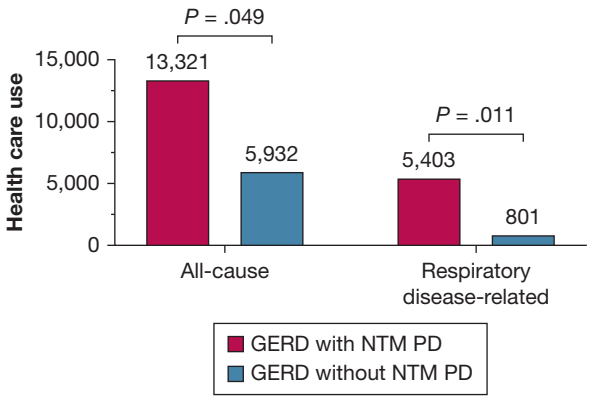

Figure 3 – *Bar graph showing a comparison of all-cause and respiratory disease-related health-care use (ED visits and hospitalizations per 100,000 person-years) during follow-up between patients with GERD who demonstrated NTM PD and those who did not demonstrate NTM PD. GERD = gastroesophageal reflux disease; NTM = nontuberculous mycobacteria; PD = pulmonary disease.*

patients with GERD are likely to experience a large amount of aspiration of acidic gastric contents compared with young patients with GERD, which consequently may lead to an increased risk of NTM. In this study, bronchiectasis also was shown as a risk factor for NTM PD in patients with GERD. Previous studies similarly have shown that the risk of NTM PD in patients with bronchiectasis is significantly higher than that in those without bronchiectasis,[16,39] indicating that bronchiectasis-related lung destruction can be a predisposing factor for NTM PD. Thus, GERD-induced aspiration of acidic gastric contents may aggravate bronchiectasis-related inflammation, which could facilitate NTM infection in patients with GERD.

Despite female sex being a well-known risk factor for NTM PD,[40] our findings and those of previous research surprisingly showed no association between female sex and an increased risk of NTM PD in patients with GERD.[8] The prevalence of GERD is higher in women than in men. However, men frequently have more pathologic diseases like reflux esophagitis and Barrett's esophagus, whereas women have more nonerosive reflux disease.[41] Accordingly, among patients with GERD, the increased risk of NTM PD developing in women may be attenuated by a higher susceptibility to NTM PD in men with more severe GERD.

Chronic airway diseases (COPD, asthma, or bronchiectasis) previously were shown to increase significantly the risk of NTM PD in the general population.[16,39,42,43] However, our study unexpectedly revealed that asthma or COPD were not related to the increased incidence of NTM PD among patients with GERD; only bronchiectasis was associated with a higher risk of NTM PD. A previous study similarly showed that patients with GERD and concomitant *Mycobacterium avium* complex PD showed a lower tendency of having COPD or asthma than age- and sex-matched patients with GERD but no *M avium* complex PD. The difference was statistically insignificant, however.[9] In contrast with our results, a similar rate of bronchiectasis was observed between the two groups.[9] Although the underlying mechanism of this phenomenon is unclear, one plausible explanation exists. GERD may have an additional effect on the risk of NTM PD in patients with more destructive and purulent airway disease (eg, bronchiectasis), but it may not have synergistic or additive effects on the development of NTM PD in patients with less destructive airway disease (eg, COPD or asthma).

The results of the present study have several potential clinical implications. First, because the risk of NTM PD in patients with GERD was significantly higher than in those without GERD, NTM PD should be suspected when new-onset or worsening of respiratory symptoms develop during regular follow-up in patients with GERD. Second, because the results indicate that older age and bronchiectasis significantly increased the risk of NTM PD, more active strategies (eg, screening of symptoms and regular chest radiography follow-up) may be helpful in patients with GERD and these risk factors. Third, patients with GERD who demonstrated NTM PD made more respiratory disease-related ED visits and were hospitalized more often than those who did not demonstrate NTM PD. Thus, when GERD and NTM PD are combined, clinicians should focus on the variations of respiratory symptoms.

Although an association was found between GERD and NTM PD using a population-based longitudinal cohort, several limitations should be acknowledged. First, this study was performed with the Korean population. Thus, studies in other countries and different ethnicities are needed to generalize the findings. Second, because the National Health Insurance Service National Sample Cohort database does not contain data on smoking history, BMI, pulmonary function test results, or types of NTM PD, these factors could not be evaluated in our analyses. Third, because ICD-10 codes were used, misclassification of GERD diagnosis may be an issue. The insurance claim-based definition of GERD studied in the Canadian context revealed a sensitivity, specificity, and positive predictive value (PPV) of 56.1%, 98.5%, and 94.8%, respectively.[44]

Although differences in study design make it impossible to compare the diagnostic accuracy directly between our study and previous studies, the PPV reported in our study may be higher than that reported in the previous study because we also incorporated information on PPI use in the definition of GERD. Fourth, a misclassification issue exists regarding NTM PD diagnosis. In a previous study, the insurance claim-based definition of NTM PD among US Medicare beneficiaries with bronchiectasis revealed a PPV of 63.2%.[45] Because we also considered claims data for acid-fast bacilli smears or mycobacterial cultures when defining NTM PD, the PPV may be higher than that of the previous study. Furthermore, we also performed sensitivity analyses with new definitions of NTM PD (ie, diagnosis code of NTM PD only or combination of diagnostic code of NTM PD, claims data for acid-fast bacilli smears or mycobacterial culture, and macrolide prescription for more than 1 month). Sensitivity analyses demonstrated that GERD increased the risk of NTM PD regardless of NTM PD definition used (e-Table 1). Fifth, misclassification also should be considered regarding the definition of comorbidities. Sixth, the presence of GERD could raise the clinical index of suspicion for NTM PD because GERD may increase respiratory symptoms, particularly in the setting of underlying lung diseases, such as bronchiectasis.

Interpretation

GERD was shown to be an important predisposing factor for the development of NTM PD, and older age and bronchiectasis were risk factors for incident NTM PD in patients with GERD. NTM PD developing in patients with GERD is associated with increased health-care use.

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References

1. Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. *Clin Chest Med*. 2015;36(1):13-34.
2. Donohue MJ, Wymer L. Increasing prevalence rate of nontuberculous mycobacteria infections in five states, 2008-2013. *Ann Am Thorac Soc*. 2016;13(12):2143-2150.
3. Park SC, Kang MJ, Han CH, et al. Prevalence, incidence, and mortality of nontuberculous mycobacterial infection in Korea: a nationwide population-based study. *BMC Pulm Med*. 2019;19(1):140.
4. Lee H, Myung W, Koh WJ, Moon SM, Jhun BW. Epidemiology of nontuberculous mycobacterial infection, South Korea. 2007-2016. *Emerg Infect Dis*. 2019;25(3):569-572.
5. Ratnatunga CN, Lutzky VP, Kupz A, et al. The rise of non-tuberculosis mycobacterial lung disease. *Front Immunol*. 2020;11:303.
6. Uno S, Asakura T, Morimoto K, et al. Comorbidities associated with nontuberculous mycobacterial disease in Japanese adults: a claims-data analysis. *BMC Pulm Med*. 2020;20(1):262.
7. Andrejak C, Thomsen VO, Johansen IS, et al. Nontuberculous pulmonary mycobacteriosis in Denmark: incidence and prognostic factors. *Am J Respir Crit Care Med*. 2010;181(5):514-521.
8. Koh WJ, Lee JH, Kwon YS, et al. Prevalence of gastroesophageal reflux disease in patients with nontuberculous mycobacterial lung disease. *Chest*. 2007;131(6):1825-1830.
9. Thomson RM, Armstrong JG, Looke DF. Gastroesophageal reflux disease, acid suppression, and Mycobacterium avium complex pulmonary disease. *Chest*. 2007;131(4):1166-1172.
10. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: the National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. *Int J Epidemiol*. 2017;46(2):e15.
11. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139.
12. Kim SY, Min C, Oh DJ, Choi HG. Bidirectional association between GERD and asthma: two longitudinal follow-up studies using a national sample cohort. *J Allergy Clin Immunol Pract*. 2020;8(3):1005-1013 e1009.
13. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol*. 2013;108(3):308-328.
14. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon Consensus. *Gut*. 2018;67(7):1351-1362.
15. Jung HK, Tae CH, Song KH, et al. 2020 Seoul consensus on the diagnosis and management of gastroesophageal reflux disease. *J Neurogastroenterol Motil*. 2021;27(4):453-481.
16. Yang B, Ryu J, Kim T, et al. Impact of bronchiectasis on incident nontuberculous mycobacterial pulmonary disease: a 10-year national cohort study. *Chest*. 2021;159(5):1807-1811.
17. Lee H, Ryu J, Nam E, et al. Increased mortality in patients with corticosteroid-dependent asthma: a nationwide population-based study. *Eur Respir J*. 2019;54(5):1900804.
18. Lee H, Ryu J, Chung SJ, et al. Coexisting COPD increases mortality in patients with corticosteroid-dependent asthma: a nationwide population-based study. *Allergy Asthma Immunol Res*. 2020;12(5):821-831.
19. Choi H, Yang B, Nam H, et al. Population-based prevalence of bronchiectasis and associated comorbidities in South Korea. *Eur Respir J*. 2019;54(2):1900194.
20. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107.
21. Martin DO, Austin H. Exact estimates for a rate ratio. *Epidemiology*. 1996;7(1):29-33.
22. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;16(3):1141-1154.
23. Lee AS, Ryu JH. Aspiration pneumonia and related syndromes. *Mayo Clin Proc*. 2018;93(6):752-762.
24. Dawrs SN, Kautz M, Chan ED, Honda JR. Mycobacterium abscessus and gastroesophageal reflux: an in vitro study. *Am J Respir Crit Care Med*. 2020;202(3):466-469.
25. Perng DW, Chang KT, Su KC, et al. Exposure of airway epithelium to bile acids associated with gastroesophageal reflux symptoms: a relation to transforming growth factor-beta1 production and fibroblast proliferation. *Chest*. 2007;132(5):1548-1556.
26. Hunt EB, Sullivan A, Galvin J, MacSharry J, Murphy DM. Gastric aspiration and its role in airway inflammation. *Open Respir Med J*. 2018;12:1-10.
27. D'Ovidio F, Mura M, Tsang M, et al. Bile acid aspiration and the development of bronchiolitis obliterans after lung transplantation. *J Thorac Cardiovasc Surg*. 2005;129(5):1144-1152.
28. Palm K, Sawicki G, Rosen R. The impact of reflux burden on Pseudomonas positivity in children with cystic fibrosis. *Pediatr Pulmonol*. 2012;47(6):582-587.
29. Reen FJ, Woods DF, Mooij MJ, Adams C, O'Gara F. Respiratory pathogens adopt a chronic lifestyle in response to bile. *PLoS One*. 2012;7(9):e45978.
30. Ovrutsky AR, Merkel PA, Schonteich E, et al. Patients with non-tuberculous mycobacterial lung disease have elevated transforming growth factor-beta following ex vivo stimulation of blood with live Mycobacterium intracellulare. *Scand J Infect Dis*. 2013;45(9):711-714.
31. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA*. 2004;292(16):1955-1960.
32. Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. *Arch Intern Med*. 2007;167(9):950-955.
33. Hsu WT, Lai CC, Wang YH, et al. Risk of pneumonia in patients with gastroesophageal reflux disease: a population-based cohort study. *PLoS One*. 2017;12(8):e0183808.
34. Lambert AA, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell TA. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. *PLoS One*. 2015;10(6):e0128004.
35. Scholten T. Long-term management of gastroesophageal reflux disease with pantoprazole. *Ther Clin Risk Manag*. 2007;3(2):231-243.
36. Soenen S, Rayner CK, Horowitz M, Jones KL. Gastric emptying in the elderly. *Clin Geriatr Med*. 2015;31(3):339-353.
37. Greenwald DA. Aging, the gastrointestinal tract, and risk of acid-related disease. *Am J Med*. 2004;117(suppl 5A):8S-13S.
38. Raiha I, Manner R, Hietanen E, Hartiala J, Sourander L. Radiographic pulmonary changes of gastro-oesophageal reflux disease in elderly patients. *Age Ageing*. 1992;21(4):250-255.
39. Shteinberg M, Stein N, Adir Y, et al. Prevalence, risk factors and prognosis of nontuberculous mycobacterial infection among people with bronchiectasis: a

population survey. *Eur Respir J*. 2018;51(5):1702469.

40. Mirsaeidi M, Sadikot RT. Gender susceptibility to mycobacterial infections in patients with non-CF bronchiectasis. *Int J Mycobacteriol*. 2015;4(2):92-96.
41. Kim YS, Kim N, Kim GH. Sex and gender differences in gastroesophageal reflux disease. *J Neurogastroenterol Motil*. 2016;22(4):575-588.
42. Marras TK, Campitelli MA, Kwong JC, et al. Risk of nontuberculous mycobacterial pulmonary disease with obstructive lung disease. *Eur Respir J*. 2016;48(3):928-931.
43. Andréjak C, Nielsen R, Thomsen V, Duhaut P, Sørensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. *Thorax*. 2013;68(3):256-262.
44. Lopushinsky SR, Covarrubia KA, Rabeneck L, Austin PC, Urbach DR. Accuracy of administrative health data for the diagnosis of upper gastrointestinal diseases. *Surg Endosc*. 2007;21(10):1733-1737.
45. Ku JH, Henkle EM, Carlson KF, Marino M, Winthrop KL. Validity of diagnosis code-based claims to identify pulmonary NTM disease in bronchiectasis patients. *Emerg Infect Dis*. 2021;27(3):982-985.