Purpose: Asthma and bronchiectasis are common chronic respiratory diseases, and their coexistence is frequently observed but not well investigated. Our aim was to study the effect of comorbid bronchiectasis on asthma.

Methods: A propensity score-matched cohort study was conducted using the National Health Insurance Service-Health Screening Cohort database. From 2005 to 2008, 8,034 participants with asthma were weighted based on propensity scores in a 1:3 ratio with 24,099 participants without asthma. From the asthma group, 141 participants with overlapped bronchiectasis were identified, and 7,892 participants had only asthma. Clinical outcomes of acute asthma exacerbation(s) and mortality rates were compared among the study groups.

Results: The prevalence of bronchiectasis (1.7%) was 3 times higher in asthmatics than in the general population of Korea. Patients who had asthma comorbid with bronchiectasis experienced acute exacerbation(s) more frequently than non-comorbid patients (11.3% vs. 5.8%, \( P = 0.007 \)). Time to the first acute exacerbation was also shorter in the asthmatics with bronchiectasis group (1,970.9 days vs. 2,479.7 days, \( P = 0.005 \)). Although bronchiectasis was identified as a risk factor for acute exacerbation (adjusted odds ratio, 1.73; 95% confidence interval [CI], 1.05–2.86), there was no significant relationship between bronchiectasis and all-cause or respiratory mortality (adjusted hazard ratio [aHR], 1.17; 95% CI, 0.67–2.04 and aHR, 0.81; 95% CI, 0.11–6.08).

Conclusions: Comorbid bronchiectasis increases asthma-related acute exacerbation, but it does not raise the risk of all-cause or respiratory mortality. Close monitoring and accurate diagnosis of bronchiectasis are required for patients with frequent exacerbations of asthma.

Keywords: Asthma; bronchiectasis; prognosis; comorbidity; mortality; morbidity; symptom flare up
INTRODUCTION

Non-cystic fibrosis bronchiectasis (hereafter, “bronchiectasis”), characterized by irreversible bronchial dilation and bronchial inflammation, is usually associated with chronic sputum production, bacterial colonization of the lower respiratory tract, inflammation, and frequent exacerbations. With recent advances in radiologic techniques, the identified prevalence, mortality, and medical burden of bronchiectasis are gradually increasing. A nationwide cohort study in South Korea revealed that the estimated bronchiectasis prevalence during 2012–2017 was 464 per 100,000 individuals, implying that bronchiectasis is not a rare disease.

Asthma, a heterogeneous disease characterized by airway obstruction, hyper-reactivity, and chronic inflammation, is provoked or exacerbated by exercise, allergen or chemical irritant exposure, weather changes, or viral infections. In Korea, the adult asthma incidence was 6.07 per 1,000 person-years in 2008–2012, and the prevalence was 36.3 per 1,000 people in 2014. Asthma prevalence is increasing, and its economic burden has reached 645.8 million United States dollars.

The coexistence of asthma and bronchiectasis is frequently observed. In Korea, 17.2% of patients with bronchiectasis had comorbid asthma. The bronchiectasis prevalence in severe asthma was even higher (24.8%–67.5%). As asthma is presumed to be a possible predictor for the development of bronchiectasis, exploring their relationship is important. However, studies on the long-term prognosis of Asian patients with co-existing bronchiectasis and asthma are lacking. Therefore, we analyzed the effect of bronchiectasis on long-term prognosis in asthma patients.

MATERIALS AND METHODS

Data source and study design
This retrospective cohort study evaluated nationwide data using the National Health Insurance Service-Health Screening Cohort. This cohort comprised a 10% random sample from all health-screened participants aged 40–79 years from 2002 to 2003. This database contains fully adjudicated medical and pharmacy claims in South Korea, including general demographic data, the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes, medical institution type, medications prescribed, medical cost, and mortality information. We identified all outpatient visitors or hospitalized individuals with asthma diagnoses (ICD-10 codes: asthma [J45]; status asthmaticus [J46]) during 2005–2008. The study period was divided into the index, measurement, and follow-up periods (Supplementary Fig. S1).

Case identification
Asthma cases were included only when both the diagnostic and medication codes were simultaneously identified more than twice within 1-year period during the index period. Medication codes for inhaled corticosteroids (ICS), inhaled long-acting β2-agonists (LABA), inhaled long-acting muscarinic antagonists, fixed-dose combinations like ICS/LABA, inhaled short-acting β2-agonists (SABA), oral or patch LABAs, oral SABA, leukotriene antagonists, xanthine derivatives, and systemic corticosteroids were used to evaluate the pharmacotherapy for asthma patients. Patients with an asthma diagnosis during the wash-out period from 2003 to 2005, or those with an observation period < 1 year, were excluded. We also excluded...
patients with other diseases for which systemic corticosteroids may be prescribed (Crohn’s disease [K50], ulcerative colitis [K51], rheumatoid arthritis [M05], emphysema [J43], chronic obstructive pulmonary disease [J44], cystic fibrosis [E84], and current malignancy [C00-97]). In addition, other respiratory ailments were excluded to better identify the effect of bronchiectasis on asthma. Finally, allergic bronchopulmonary aspergillosis (ABPA) is a distinct disease, which could accompany severe asthma. Because ABPA’s disease nature is distinguishable with general bronchiectasis’s, possible or definite ABPA with diagnostic codes of aspergillosis or aspergilloma (B44), tonsillar aspergillosis (B44.2), and ABPA (B44.81) were excluded. (Supplementary Table S1).

**Body mass index (BMI) criteria and categorization**

BMI is calculated as weight in kilograms divided by the square of the height in meters (kg/m\(^2\)) and is categorized into 4 groups according to the Asian-Pacific cut-off points: underweight (< 18.5 kg/m\(^2\)), normal weight (18.5–22.9 kg/m\(^2\)), overweight (23–24.9 kg/m\(^2\)), and obese (≥ 25 kg/m\(^2\)). Because almost all Korean people are composed of Korean origin, baseline BMI was ascertained at the time of enrollment, and patients were classified into the “overweight/obese group (≥ 23 kg/m\(^2\))” or the “normal weight group (18.5–22.9 kg/m\(^2\))” according to the Asian-Pacific cut-off points.

**Propensity score-matched cohort**

To reduce potential confounders and balance the baseline covariates, propensity scores were derived from the predicted probability of subjects with, versus without, asthma using a logistic regression model with adjustment for enrolled year, age, sex, BMI, smoking status, and Charlson comorbidity index (CCI). A “greedy nearest-neighbor” algorithm was used to match patients in the 2 groups in a 1:3 ratio.

**CCI**

The CCI is a widely used prognostic model that predicts 1-year mortality risk depending on individual comorbidities. Each comorbidity was scored, and the CCI was calculated by summing the comorbidity scores (Supplementary Table S2). Because of usefulness for measuring the effect of comorbidities on mortality using the administrative database including ICD-10 codes, we adopted it as a variable.

**Assessment of asthma severity and drug adherence**

Asthma severities and drug adherence were evaluated during 2 measurement periods: 1 year after the first asthma diagnosis and 1 year before the first acute exacerbation. Using the claims database, as it is difficult to distinguish the precise ICS or ICS/LABA dosage, an operational definition of asthma severity was used as in the previous studies.

Asthma severity was classified as mild, moderate, or severe. Patients prescribed at least one asthma medication, excluding ICS/LABA inhalers, low-dose systemic corticosteroids (defined as a prednisolone equivalent < 10 mg/day for at least 2 weeks), and tiotropium, were defined as “mild.” Patients prescribed a low-dose or high-dose ICS/LABA inhaler, but not tiotropium or a low-dose oral corticosteroids (OCS), were defined as “moderate.” Patients administered both an ICS/LABA inhaler and at least one prescription of tiotropium or a low-dose OCS were defined as “severe.”

Drug adherence was measured with the medication possession ratio (MPR) for asthma medications. The MPR was calculated as the sum of the day’s supply for medication...
fills divided by the time from the first fill until the end of the measurement period. Each
MPR ratio was categorized into the low adherence (MPR < 0.5), medium adherence (MPR,
0.5–0.79), or high adherence (MPR ≥ 0.8) group.

Clinical outcomes
The primary outcome was the all-cause or cause-specific mortality rate among the study
groups. Other clinical outcomes related to acute asthma exacerbation were also evaluated.
Acute asthma exacerbation was defined as the presence of an asthma diagnostic code, plus
any of the following: high-dose systemic corticosteroid use (prednisolone equivalent ≥ 30 mg,
over 3 days consecutively), hospitalization, or emergency department visit. The time to the
first acute exacerbation was measured as the duration from the date of initial diagnosis to the
first exacerbation.

Ethical approval
The study was approved by the Institutional Review Board of National Health Insurance
Service Ilsan Hospital and adhered to the tenets of the Declaration of Helsinki (NHIMC 2020-
07-010). Because this study was based on anonymous health claims data, the requirement for
patient consent was waived. This article does not contain any studies with human or animal
subjects performed by any of the authors.

Statistical analysis
Variables of each group were compared using the paired t-test and χ² test. After the
proportional hazard assumption was tested, Cox proportional hazard models were fit to
estimate the all-cause and cause-specific adjusted hazard ratio (aHR) and 95% confidence
interval (CI). Subsequently, multivariate logistic regression analysis was performed to
evaluate the association between risk factors and outcomes related to the first acute asthma
exacerbation. The results are reported as the adjusted odds ratio (aOR) with 95% CI. All
statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA)
at a significance level of 5%.

RESULTS

Study population
During the index period, 8,033 asthma patients and 311,095 unmatched controls were
extracted. Among the controls, 24,099 patients, matched based on propensity scores
with asthma patients in a 1:3 ratio, were included as the final control group. Among the
asthmatics, 141 (1.7%) had comorbid bronchiectasis (Fig. 1, Supplementary Table S3). The
baseline characteristics of asthmatics are demonstrated in Table 1.

Asthma severity and drug adherence
Asthma severity and drug adherence between asthmatics with and without bronchiectasis
were compared during the 2 measurement periods (Supplementary Table S4). During
the 1-year period after the first asthma diagnosis, 112 (79.4%), 29 (20.5%), and 1 (0.7%)
cases were classified as “mild,” “moderate,” and “severe,” respectively, in the asthma-with-
bronchiectasis group, and the proportion of mild cases in this group was significantly lower
than that in the asthmatics without bronchiectasis group (79.4% vs. 88.7%, P < 0.001).
Regarding drug adherence, the proportion of high adherence was higher in asthmatics
without bronchiectasis than in those with (25.5% vs. 20.5%, P = 0.032). However, no
significant difference was observed during the 1-year period before the first asthma exacerbation between the 2 groups.

**Clinical outcomes of acute asthma exacerbation**
Among all asthma patients, 481 (5.9%) had acute exacerbation(s). The proportion of cases with frequent exacerbations (≥ 2 times) was higher in asthmatics with bronchiectasis (5.6% vs 2.1%, \( P = 0.009 \)) (Table 2). They exhibited a shorter time interval from the first diagnosis to the first acute exacerbation than those without bronchiectasis (1,970.9 days vs. 2,479.7 days, \( P = 0.005 \)) (Fig. 2). The proportions of emergency department visits (11.3% vs. 5.8%, \( P < 0.001 \)) and admissions (4.7% vs. 2.2%, \( P < 0.001 \)) were also significantly higher.

**Risk factors for acute asthma exacerbation**
Age (aOR, 1.02; 95% CI, 1.01–1.03), bronchiectasis (aOR, 1.73; 95% CI, 1.05–2.86), and moderate to severe asthma (aOR, 2.09; 95% CI, 1.67–2.61) were identified as the independent risk factors for acute exacerbation of asthma. Asthmatics who used more pharmacotherapy during 1-year period after asthma diagnosis were likely to experience acute exacerbation: ICS alone (aOR, 1.80; 95% CI, 1.11–2.94), inhaled SABA only (aOR, 3.64; 95% CI, 1.71–7.74),

Fig. 1. Study scheme and measured time periods.
and xanthine (aOR, 1.22; 95% CI, 1.01–1.47). Contrarily, patients with medium-to-high drug adherence had a lower risk of asthma exacerbation than those with low adherence (aOR, 0.57; 95% CI, 0.42–0.79 and aOR, 0.64; 95% CI, 0.51–0.81) (Table 3).

All-cause or cause-specific mortality rate
During the follow-up period, 471 of 8,034 (5.8%) asthma patients died (respiratory-related causes [9.7%], cardiovascular causes [20.8%], cancer-related [36.9%], and miscellaneous causes [32.4%]). Among the asthmatics with bronchiectasis, 13 of 141 (9.1%) patients died because of respiratory (7.6%), cardiovascular (23.0%), cancer-related (53.8%), and miscellaneous (15.3%)
causes. In the survival analysis for the total study population, the cumulative respiratory mortality of asthmatics was significantly higher than that of healthy controls \((P=0.002)\) (Fig. 3B). However, all-cause mortality was not significantly different between asthma and healthy groups \((P=0.251)\) (Fig. 3A). There was also no significant difference in all-cause death between the asthma-with- and -without-bronchiectasis groups \((P=0.117)\) (Fig. 4A). Only cumulative cancer mortality was significantly higher in asthmatics with bronchiectasis than in those without \((P=0.025)\) (Fig. 4D).

### Risk factors for respiratory or all-cause mortality

Age (aHR, 1.21; 95% CI, 1.16–1.27), male sex (aHR, 3.02; 95% CI, 1.54–5.90), and prior acute exacerbation history within 1 year (aHR, 4.89; 95% CI, 2.55–9.37) were significantly associated with increased risk of respiratory death (Table 4). Regarding all-cause mortality,
Non-cystic bronchiectasis is often accompanied by asthma. Although bronchiectasis occurs because of various long-term respiratory conditions and non-respiratory diseases, whether asthma causes bronchiectasis is controversial. Nevertheless, herein, the bronchiectasis comorbidity rate in asthmatics was 1.7%, which was 3 times higher than its prevalence in the general population of Korea. This implies that there might be a causal relationship between the 2 distinct airway diseases.

DISCUSSION

Fig. 3. Kaplan-Meier survival curve for the all-cause and cause-specific mortalities among total study population.
Regarding acute exacerbation, poor clinical outcomes were observed in asthma-bronchiectasis overlapped patients. Because more frequent exacerbations and shorter time to first exacerbation were identified in comorbid patients, they required more attention for proper asthma control. However, it is difficult to clearly distinguish which of the 2 diseases has developed an acute exacerbation in asthma-bronchiectasis overlapped patients. Therefore, severe asthma with bronchiectasis is considered a distinct group in terms

Fig. 4. Kaplan-Meier survival curve for the all-cause and cause-specific mortalities among asthmatics.

Table 4. Multivariate analyses of risk factors for respiratory or all-cause mortality in asthmatics

| Variable                              | Respiratory mortality | All-cause mortality |
|---------------------------------------|-----------------------|---------------------|
|                                       | aHR (95% CI)          | P value             | aHR (95% CI)      | P value             |
| Model 1                               |                       |                     |                    |                     |
| Age                                   | 1.21 (1.16–1.26)      | < 0.001             | 1.12 (1.10–1.13)  | < 0.001             |
| Men                                   | 3.02 (1.54–5.90)      | < 0.001             | 1.90 (1.54–2.35)  | < 0.001             |
| Ever-smoking                          | 1.36 (0.70–2.63)      | 0.351               | 1.79 (1.45–2.21)  | < 0.001             |
| Obesity                               | 0.57 (0.28–1.14)      | 0.116               | 0.80 (0.66–0.98)  | 0.032               |
| CCI                                   | 1.04 (0.86–1.25)      | 0.674               | 1.16 (1.10–1.23)  | < 0.001             |
| Bronchiectasis                        | 0.81 (0.11–6.08)      | 0.844               | 1.17 (0.67–2.04)  | 0.575               |
| Moderate to severe asthma at diagnosis| 1.21 (0.47–3.13)      | 0.682               | 1.16 (0.87–1.54)  | 0.297               |
| Presence of acute exacerbation history within 1 yr | 4.89 (2.55–9.37)      | < 0.001             | 1.60 (1.20–2.12)  | 0.001               |
| Model 2*                              |                       |                     |                    |                     |
| Underweight                           | 1.81 (0.55–5.88)      | 0.322               | 1.77 (1.16–2.70)  | 0.007               |

CCI, Charlson comorbidity index; aHR, adjusted hazard ratio; CI, confidence interval.
*Adjusted for age, men, ever-smoking, CCI, bronchiectasis, moderate to severe asthma at diagnosis, presence of acute exacerbation within 1 year.

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of disease severity, microbiology, and asthma phenotype on high-resolution computed tomography; sputum cultures are recommended for uncontrolled asthma to recognize bronchiectasis early and start targeted treatment.\textsuperscript{30}

The use of certain asthma medications demonstrated a significant relationship with acute exacerbation. Surprisingly, inhaled SABA use only revealed 3.64 times higher risk of acute exacerbation. The latest open-label-designed clinical trial in mild asthma patients reported the increased risk of severe exacerbations and asthma-related death in patients treated with inhaled SABA only.\textsuperscript{31} Therefore, SABA-only treatment is no longer recommended in the recent Global Initiative for the Asthma (GINA) guideline.\textsuperscript{32} Hence, this could constitute additional evidence that prescription of inhaled SABA only for asthma patients should be avoided.

Conversely, better adherence to medical treatment was a negative risk factor for asthma exacerbation. Compared to patients with low adherence, 0.57–0.64 times lower risk of acute exacerbation was observed in patients with medium-to-high adherence. Previously, the relationship between good adherence and lower risk of severe asthma exacerbation was demonstrated, and it should be emphasized when educating asthmatics.\textsuperscript{27,33}

In the mortality analysis, bronchiectasis was not an independent risk factor for all-cause or respiratory mortality. Recently, Choi \textit{et al.}\textsuperscript{34} demonstrated that bronchiectasis is associated with increased mortality in patients with corticosteroid-dependent severe asthma. However, our study indicated that bronchiectasis itself does not increase respiratory mortality among asthmatics without considering systemic corticosteroid use.

Recent history of acute asthma exacerbation should be addressed; the hazard risk of respiratory death was 4.89 times higher in those with than without acute exacerbation. Death from asthma is a complex phenomenon and is, in most cases, preventable.\textsuperscript{35} Nevertheless, mortality among patients hospitalized for acute exacerbations accounts for one-third of all deaths from asthma,\textsuperscript{36} which is consistent with our findings. Hence, proper control of usual asthma symptoms to avoid acute exacerbation should be highlighted.

Herein, we also observed a relationship between BMI and death rate. Obesity was associated with decreased risk of death; contrarily, being underweight increased the hazard risk of all-cause mortality. Our result was consistent with the ‘obesity paradox’ theory reported by studies on the relationship between obesity and improved survival rate.\textsuperscript{37–39} Although the specific mechanism for this paradox remains unclear, our results indicated a negative association between BMI and survival rate. Thus, proper nutritional support for individuals with a BMI < 25 kg/m\textsuperscript{2} is needed to improve the survival rate. However, it is early to presume that obesity has a protective effect on mortality. Because the specific obesity categories were not classified in this study, further subgroup analysis depending on the obesity class I to III is needed to determine the actual effect on the mortality risk. Moreover, the number of overweight and obese patients accounts for more than half of the study population, indicating that current BMI cut-off points for determining overweightness and obesity in Korea might not be appropriate. Westernized diets and obesity-related lifestyles have gradually raised the prevalence of overweightness and obesity in the Korean population.\textsuperscript{40,41} Therefore, redefining cut-off points for obesity or adding new indicator points (23.0, 27.5, 32.5, and 37.5 kg/m\textsuperscript{2}) for public health action would be necessary to reflect actual risks for type 2 diabetes and cardiovascular diseases as recommended by WHO experts.\textsuperscript{42}
This study has several strengths and limitations. To our knowledge, this is the first large-scale study to investigate the effect of comorbid bronchiectasis on clinical outcomes of asthma patients in Korea, including acute exacerbation and death. Additionally, it was conducted with a large-scale nationwide health insurance database representing the whole South Korean population. Conversely, because all variables were extracted based on the diagnostic codes, there could be bias due to missing data. Additionally, we did not have access to the results of pulmonary function and laboratory tests, which are essential to diagnose asthma, severity, and atopic status. Moreover, as the operational definition for asthma severity was only measured based on the medications used, it did not fully reflect the detailed asthma control status depending on individual symptoms, such as daytime symptoms, night waking, and activity limitations. These might contribute to misclassification of the asthma control status. Since we could not fully reflect GINA grade in the classification of asthma severity, further mortality analyses using pulmonary function test results and precise measurement of symptomatic scales, such as asthma control test or asthma control questionnaire, should be considered in the future study. Also, given the observational nature of this study, possible confounding variables, such as detailed smoking status, proper use of inhalers, education, or socioeconomic status, were not fully collected in the database. Finally, due to a small number of severe asthma cases, the relationship between severe asthma and bronchiectasis could not be evaluated.

In conclusion, we found that asthma-bronchiectasis overlapped patients had worse clinical outcomes with respect to acute exacerbation than did patients with only asthma. However, bronchiectasis itself was not associated with an increased risk of all-cause or respiratory mortality. These results suggest that the early appropriate diagnosis of bronchiectasis may be required for asthma patients who experience frequent exacerbations.

**SUPPLEMENTARY MATERIALS**

**Supplementary Table S1**  
ICD-10 codes for the selection of the study population

Click here to view

**Supplementary Table S2**  
ICD-10 codes for the Charlson comorbidity index

Click here to view

**Supplementary Table S3**  
Patient characteristics of the study subjects before and after propensity score matching

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**Supplementary Table S4**  
Comparison of asthma severity and drug adherence during measurement periods’

Click here to view
Supplementary Table S5
Multivariate analyses of risk factors for respiratory or all-cause mortality in asthmatics: Using separate diseases as comorbidity variable

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Supplementary Fig. S1
Flowchart for the study population.

Click here to view

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