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Original Article



# Long-Term Prognosis of Asthma-Bronchiectasis Overlapped Patients: A Nationwide Population-Based Cohort Study

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## ABSTRACT

**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

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## 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.[1] With recent advances in radiologic techniques, the identified prevalence, mortality, and medical burden of bronchiectasis are gradually increasing.[2-4] 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.[5]

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.[6] 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.[7,10]

The coexistence of asthma and bronchiectasis is frequently observed. In Korea, 17.2% of patients with bronchiectasis had comorbid asthma.[5] The bronchiectasis prevalence in severe asthma was even higher (24.8%–67.5%).[11,14] As asthma is presumed to be a possible predictor for the development of bronchiectasis, exploring their relationship is important.[15] 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.[16] 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


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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]).[17] 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$^2$).[18] 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.[19]

## 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.[20]

## 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.[21,22]

## 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.[23-25]

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.[26,27] The MPR was calculated as the sum of the day's supply for medication


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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 $\chi^2$ 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


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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),

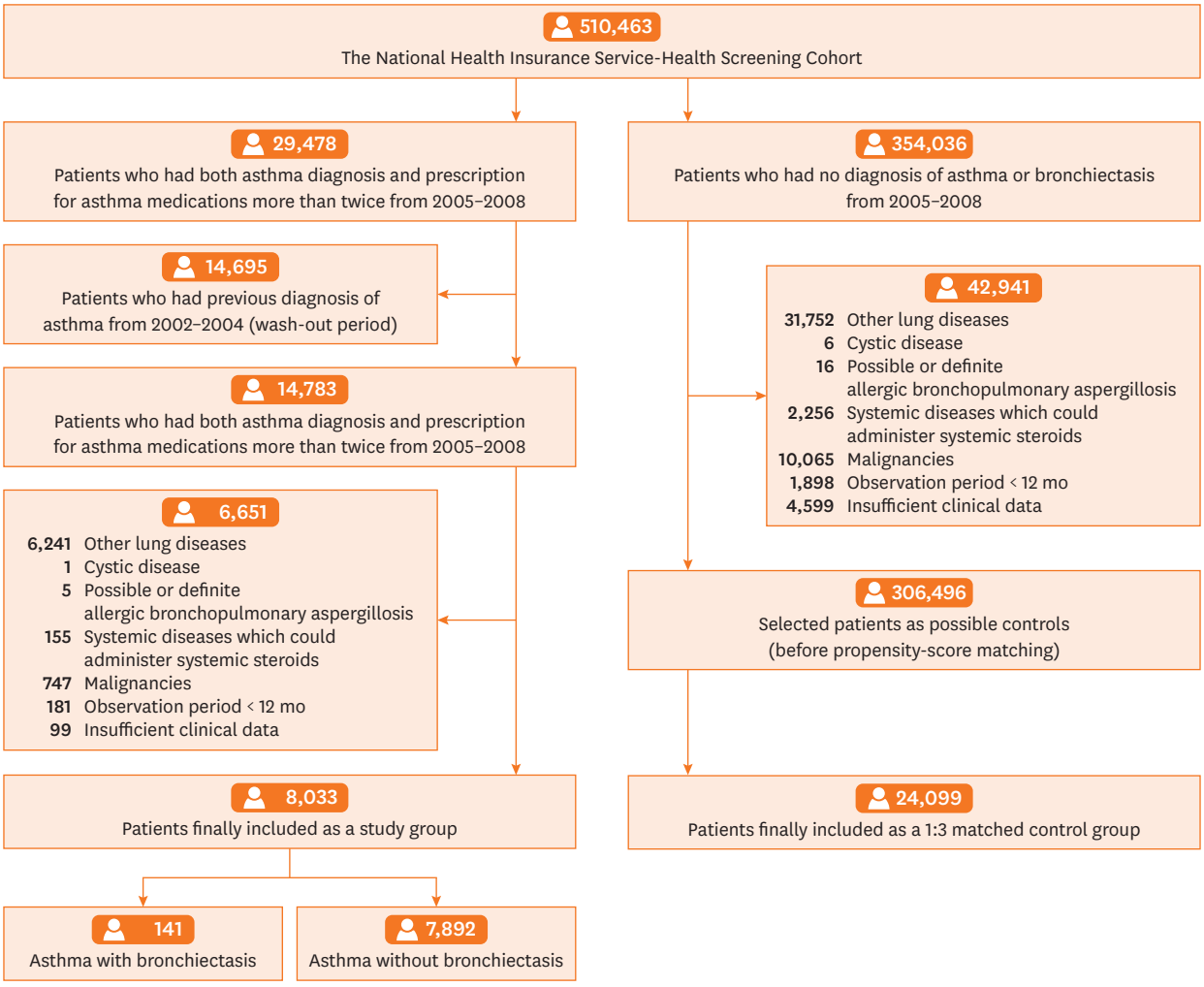


**Fig. 1.** Study scheme and measured time periods.


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**Table 1.** Baseline characteristics of the study population

| Characteristics | Asthmatics, total (n = 8,033) | Asthmatics with bronchiectasis (n = 141) | Asthmatics without bronchiectasis (n = 7,892) | *P* value* |
|---|---|---|---|---|
| Age (yr) | 58.1 ± 9.4 | 59.3 ± 9.4 | 58.1 ± 9.4 | 0.898 |
| Men | 3,445 (42.8) | 70 (49.6) | 3,375 (42.7) | 0.101 |
| Ever-smoker | 1,870 (23.2) | 41 (28.8) | 1,829 (23.1) | 0.100 |
| BMI status† | | | | 0.174 |
| Underweight | 142 (1.7) | 4 (2.8) | 138 (1.7) | |
| Normal | 2,596 (32.3) | 56 (39.7) | 2,540 (32.1) | |
| Overweight | 2,160 (26.8) | 32 (22.5) | 2,128 (26.9) | |
| Obese | 3,135 (39.0) | 49 (34.5) | 3,086 (39.1) | |
| Comorbidities | | | | |
| Previous MI | 73 (0.9) | 2 (1.4) | 71 (0.9) | 0.519 |
| CHF | 270 (3.3) | 4 (2.8) | 266 (3.3) | 0.727 |
| Previous vascular disease | 753 (9.3) | 16 (11.2) | 737 (9.3) | 0.417 |
| Previous CVD | 494 (6.1) | 12 (8.4) | 482 (6.1) | 0.239 |
| Dementia | 65 (0.8) | 1 (0.7) | 64 (0.8) | 0.893 |
| Rheumatologic disease | 321 (4.0) | 7 (4.9) | 314 (3.9) | 0.553 |
| Mild liver disease | 1,307 (16.2) | 30 (21.1) | 1,277 (16.1) | 0.104 |
| Diabetes | 889 (11.0) | 14 (9.9) | 875 (11.0) | 0.663 |
| Diabetes with chronic complications | 393 (4.8) | 9 (6.3) | 384 (4.8) | 0.407 |
| Hemi- or paraplegia | 32 (0.4) | 0 (0.0) | 32 (0.4) | 0.448 |
| Renal disease | 43 (0.5) | 1 (0.7) | 42 (0.5) | 0.775 |
| Moderate or severe liver disease | 30 (0.3) | 0 (0.0) | 30 (0.3) | 0.463 |
| CCI | | | | 0.077 |
| 0 | 3,840 (47.8) | 55 (38.7) | 3,785 (47.9) | |
| 1 | 2,351 (29.2) | 42 (29.2) | 2,309 (29.2) | |
| 2 | 1,015 (12.6) | 23 (16.2) | 992 (12.5) | |
| ≥ 3 | 827 (10.2) | 21 (14.7) | 806 (10.2) | |

Data are presented as numbers (%) or means ± standard deviations.
BMI, body mass index; MI, myocardial infarction; CHF, congestive heart failure; CVD, cerebrovascular disease; CCI, Charlson comorbidity score.
**P* value for comparison between asthmatics with bronchiectasis and those without; †Cut-off values for BMI categories were as follows: underweight (< 18.5 kg/m$^2$), normal (between 18.5 kg/m$^2$ and 22.9 kg/m$^2$), overweight (between 23.0 kg/m$^2$ and 24.9 kg/m$^2$), and obese (≥ 25 kg/m$^2$).

**Table 2.** Clinical outcomes of asthma exacerbations during follow-up period

| Variable | Asthma, total (n = 8,034) | Asthmatics with bronchiectasis (n = 141) | Asthmatics without bronchiectasis (n = 7,892) | *P* value* |
|---|---|---|---|---|
| Patients with acute exacerbation(s) | 481 (5.9) | 16 (11.3) | 465 (5.8) | 0.006 |
| Number of acute exacerbation(s) | | | | 0.009 |
| 1 | 302 (3.7) | 8 (5.6) | 294 (3.7) | |
| ≥ 2 | 179 (2.2) | 8 (5.6) | 171 (2.1) | |
| Time to first acute exacerbation | 2,478.0 ± 3.8 | 1,970.9 ± 33.3 | 2,479.7 ± 3.8 | 0.005 |
| Number of ER visit | 481 (5.9) | 16 (11.3) | 465 (5.8) | < 0.001 |
| Number of admission | 190 (2.3) | 9 (6.3) | 181 (2.2) | < 0.001 |
| Number of ICU care | 12 (0.0) | 0 (0.0) | 12 (0.1) | NA |
| Death | 55 (0.6) | 1 (0.7) | 54 (0.6) | 0.507 |

Data are presented as numbers (%) or means ± standard deviations.
ER, emergency room; ICU, intensive care unit; NA, not available.
**P* value for comparison between asthmatics with bronchiectasis and those without.

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%)


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**Table 3.** Multivariate analyses of risk factors for acute asthma exacerbation

| Variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | aHR (95% CI) | *P* value | aHR (95% CI) | *P* value |
| Age | 1.02 (1.01–1.03) | < 0.001 | 1.02 (1.01–1.03) | < 0.001 |
| Men | 1.02 (0.85–1.22) | 0.817 | | |
| Ever-smoking | 1.18 (0.96–1.45) | 0.107 | | |
| Obesity | 0.97 (0.51–1.82) | 0.924 | | |
| CCI | 1.09 (1.02–1.16) | < 0.001 | | |
| Bronchiectasis | 2.00 (1.21–3.29) | < 0.001 | 1.73 (1.05–2.86) | 0.030 |
| Moderate to severe asthma (reference: mild asthma) | 2.31 (1.86–2.86) | < 0.001 | 2.09 (1.67–2.61) | < 0.001 |
| MPR status (reference: low adherence) | | | | |
| Medium adherence | 0.57 (0.44–0.84) | < 0.001 | 0.57 (0.42–0.79) | < 0.001 |
| High adherence | 0.60 (0.55–0.88) | < 0.001 | 0.64 (0.51–0.81) | < 0.001 |
| Asthma medication (1-yr period after first diagnosis) | | | | |
| ICS alone | 2.15 (1.32–3.49) | 0.001 | 1.80 (1.11–2.94) | 0.017 |
| ICS-LABA | 2.31 (1.86–2.86) | < 0.001 | | |
| Oral LABA | 1.16 (0.96–1.39) | 0.107 | | |
| Patch LABA | NA | NA | | |
| Inhaled LABA | NA | NA | | |
| LTRA | 1.34 (1.09–1.65) | 0.020 | | |
| Inhaled SABA only | 5.58 (2.64–11.77) | < 0.001 | 3.64 (1.71–7.74) | < 0.001 |
| Oral SABA | 1.09 (0.89–1.35) | 0.389 | | |
| Xanthine | 1.32 (1.09–1.59) | 0.003 | 1.22 (1.01–1.47) | 0.039 |
| Inhaled LAMA | NA | NA | | |
| Oral corticosteroids (< 10 mg PL equivalent dose) | 0.84 (0.37–1.91) | 0.685 | | |

CI, confidence interval; aHR, adjusted hazard ratio; CCI, Charlson comorbidity index; MPR, medication possession ratio; ICS, inhaled corticosteroids; LABA, long-acting $\beta_2$ agonists; LTRA, leukotriene receptor antagonists; SABA, short-acting $\beta_2$ agonists; LAMA, long-acting muscarinic receptor antagonists; PL, prednisolone; NA, not available.

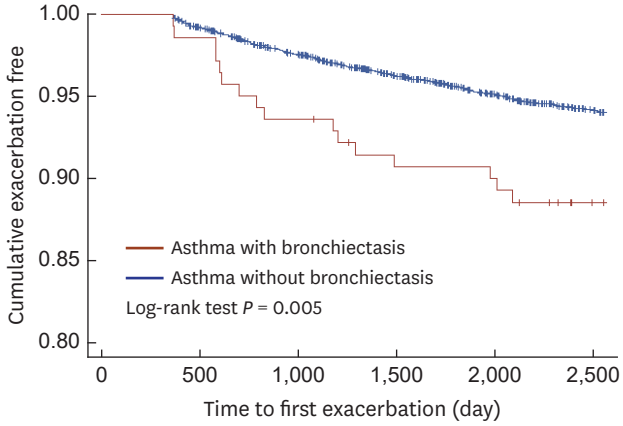


**Fig. 2.** Kaplan-Meier survival curves for the time to the first acute asthma exacerbation.

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,


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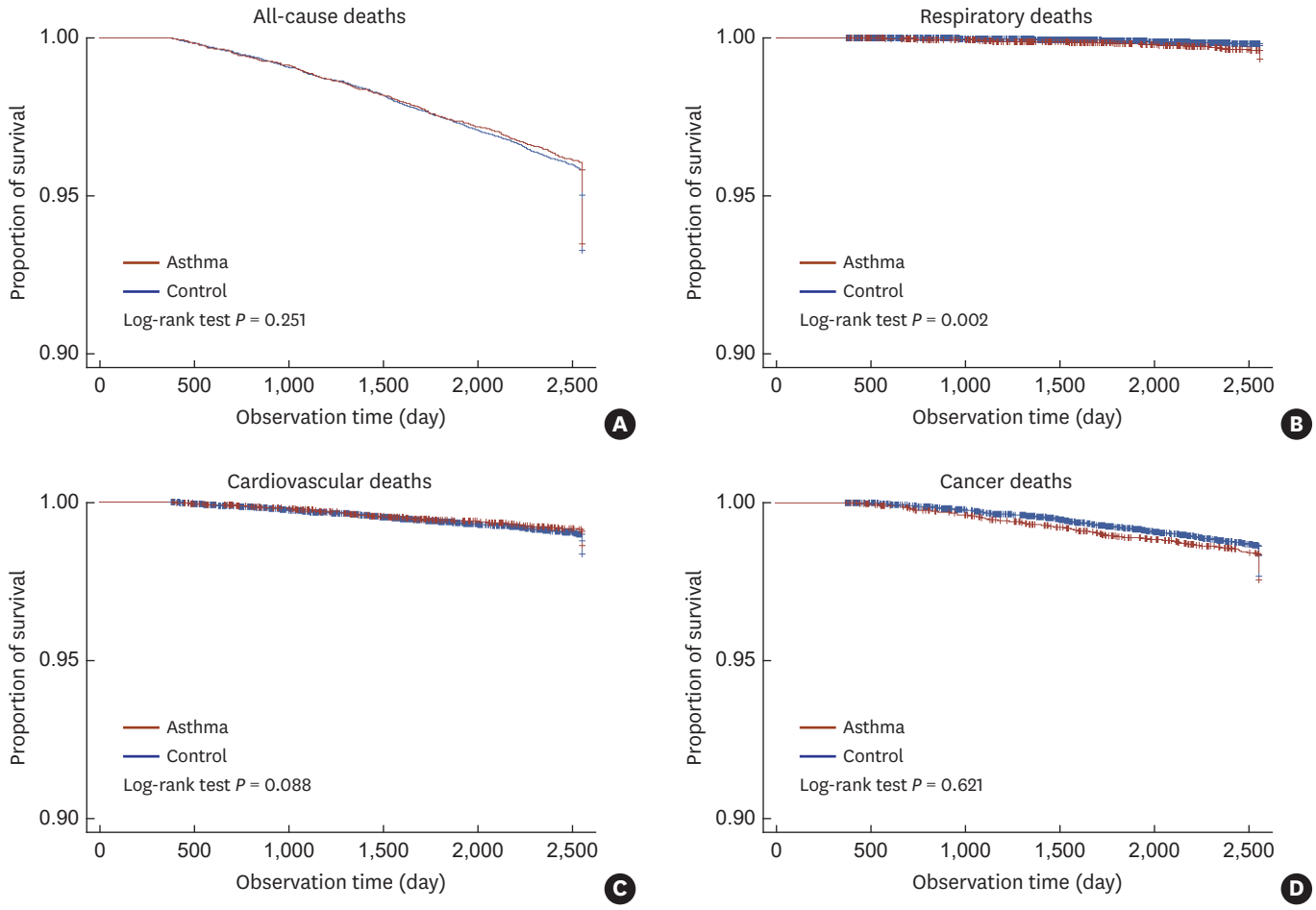


**Fig. 3.** Kaplan-Meier survival curve for the all-cause and cause-specific mortalities among total study population.

age (aHR, 1.12; 95% CI, 1.10–1.13), male sex (aHR, 1.90; 95% CI, 1.54–2.35), ever-smoking history (aHR, 1.79; 95% CI, 1.45–2.21), CCI (aHR, 1.16; 95% CI, 1.10–1.23), prior acute exacerbation history within 1 year (aHR, 1.60; 95% CI, 1.20–2.12), and underweight (aHR, 1.77; 95% CI, 1.16–2.70) were revealed as independent risk factors. Obesity was a negative risk factor for all-cause mortality (aHR, 0.80; 95% CI, 0.66–0.98). When using individual diseases as comorbidity variables instead of the CCI, no disease revealed a significant association with respiratory mortality. In the case of all-cause mortality, congestive heart failure was identified as an independent risk factor (aHR, 1.66; 95% CI, 1.23–2.24). In contrast, patients with previous cerebrovascular disease had a lower risk for all-cause mortality (aHR, 0.35; 95% CI, 1.03–1.76) (**Supplementary Table S5**).

## DISCUSSION

Non-cystic bronchiectasis is often accompanied by asthma. Although bronchiectasis occurs because of various long-term respiratory conditions and non-respiratory diseases,[28] 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.[5] This implies that there might be a causal relationship between the 2 distinct airway diseases.


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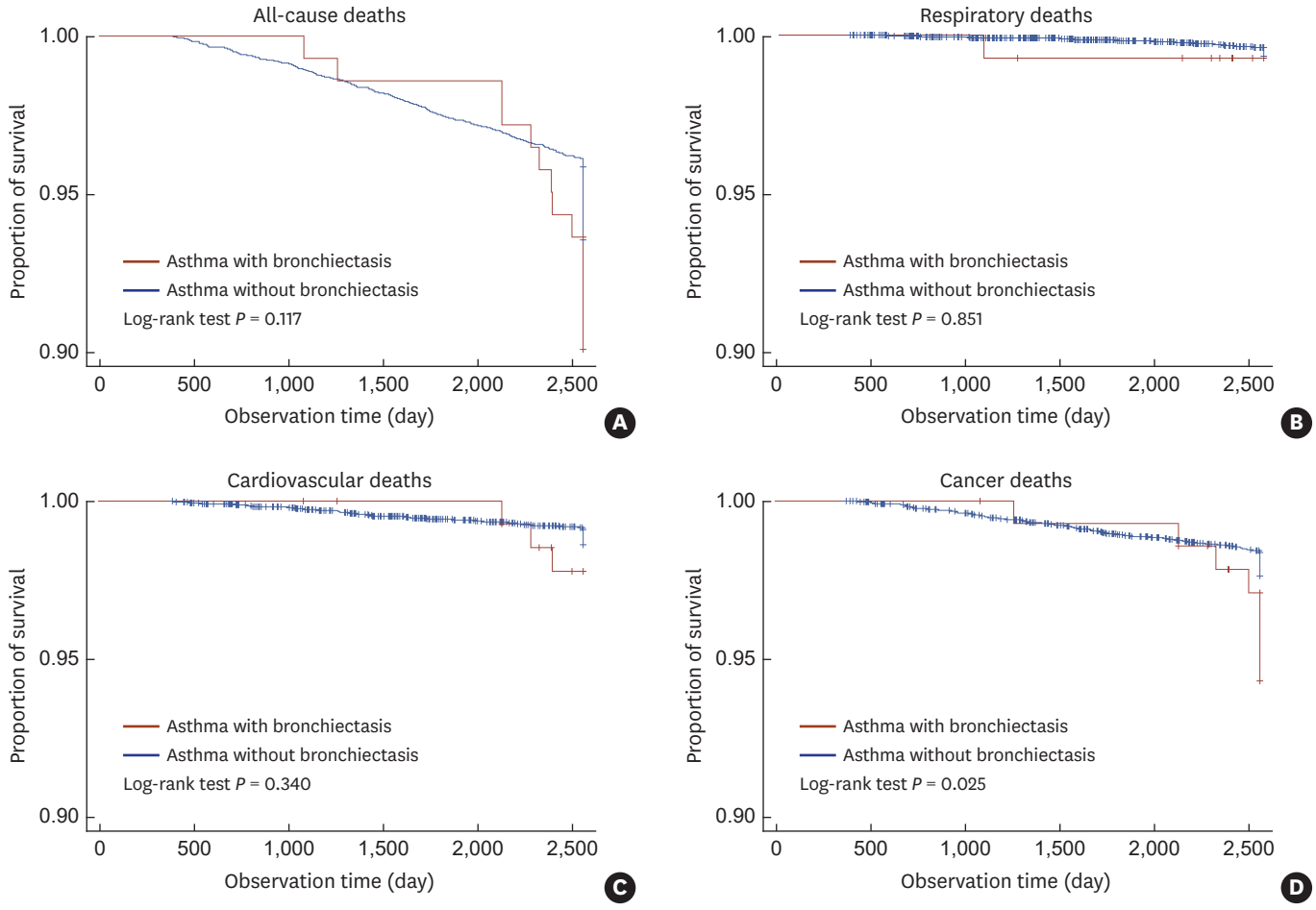


**Fig. 4.** Kaplan-Meier survival curve for the all-cause and cause-specific mortalities among asthmatics.

**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.

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.[29] Therefore, severe asthma with bronchiectasis is considered a distinct group in terms

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.[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.[31] Therefore, SABA-only treatment is no longer recommended in the recent Global Initiative for the Asthma (GINA) guideline.[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.[27,33]

In the mortality analysis, bronchiectasis was not an independent risk factor for all-cause or respiratory mortality. Recently, Choi *et al.*[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.[35] Nevertheless, mortality among patients hospitalized for acute exacerbations accounts for one-third of all deaths from asthma,[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.[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$^2$ 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.[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$^2$) for public health action would be necessary to reflect actual risks for type 2 diabetes and cardiovascular diseases as recommended by WHO experts.[42]


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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.[43] 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

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### 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*

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**Supplementary Table S5**

Multivariate analyses of risk factors for respiratory or all-cause mortality in asthmatics: Using separate diseases as comorbidity variable

Click here to view

**Supplementary Fig. S1**

Flowchart for the study population.

Click here to view

## REFERENCES

1. Chalmers JD, Chang AB, Chotirmall SH, Dhar R, McShane PJ. Bronchiectasis. Nat Rev Dis Primers 2018;4:45.
PUBMED | CROSSREF
2. Weycker D, Hansen GL, Seifer FD. Prevalence and incidence of noncystic fibrosis bronchiectasis among US adults in 2013. Chron Respir Dis 2017;14:377-84.
PUBMED | CROSSREF
3. Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. Eur Respir J 2016;47:186-93.
PUBMED | CROSSREF
4. Ringshausen FC, de Roux A, Diel R, Hohmann D, Welte T, Rademacher J. Bronchiectasis in Germany: a population-based estimation of disease prevalence. Eur Respir J 2015;46:1805-7.
PUBMED | CROSSREF
5. Choi H, Yang B, Nam H, Kyoung DS, Sim YS, Park HY, et al. Population-based prevalence of bronchiectasis and associated comorbidities in South Korea. Eur Respir J 2019;54:1900194.
PUBMED | CROSSREF
6. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, et al. GINA 2019: a fundamental change in asthma management: treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J 2019;53:1901046.
PUBMED | CROSSREF
7. Park SY, Kim JH, Kim HJ, Seo B, Kwon OY, Chang HS, et al. High prevalence of asthma in elderly women: findings from a Korean national health database and adult asthma cohort. Allergy Asthma Immunol Res 2018;10:387-96.
PUBMED | CROSSREF
8. Shin JY, Sohn KH, Shin JE, Park M, Lim J, Lee JY, et al. Changing patterns of adult asthma incidence: results from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database in Korea. Sci Rep 2018;8:15052.
PUBMED | CROSSREF
9. Kim BK, Kim JY, Kang MK, Yang MS, Park HW, Min KU, et al. Allergies are still on the rise? A 6-year nationwide population-based study in Korea. Allergol Int 2016;65:186-91.
PUBMED | CROSSREF
10. Lee EW, Kim HS, Kim W, Nam JY, Park JH. Socioeconomic burden of disease due to asthma in South Korea. Asia Pac J Public Health 2020;32:188-93.
PUBMED | CROSSREF
11. Menzies D, Holmes L, McCumesky G, Prys-Picard C, Niven R. Aspergillus sensitization is associated with airflow limitation and bronchiectasis in severe asthma. Allergy 2011;66:679-85.
PUBMED | CROSSREF
12. Dimakou K, Gousiou A, Toumbis M, Kaponi M, Chrysikos S, Thanos L, et al. Investigation of bronchiectasis in severe uncontrolled asthma. Clin Respir J 2018;12:1212-8.
PUBMED | CROSSREF
13. Bisaccioni C, Aun MV, Cajuela E, Kalil J, Agondi RC, Giavina-Bianchi P. Comorbidities in severe asthma: frequency of rhinitis, nasal polyposis, gastroesophageal reflux disease, vocal cord dysfunction and bronchiectasis. Clinics (Sao Paulo) 2009;64:769-73.
PUBMED | CROSSREF

14. Gupta S, Siddiqui S, Haldar P, Raj JV, Entwisle JJ, Wardlaw AJ, et al. Qualitative analysis of high-resolution CT scans in severe asthma. Chest 2009;136:1521-8.
PUBMED | CROSSREF

15. Lonni S, Chalmers JD, Goeminne PC, McDonnell MJ, Dimakou K, De Soyza A, et al. Etiology of non-cystic fibrosis bronchiectasis in adults and its correlation to disease severity. Ann Am Thorac Soc 2015;12:1764-70.
PUBMED | CROSSREF

16. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. BMJ Open 2017;7:e016640.
PUBMED | CROSSREF

17. Ekström M, Nwaru BI, Hasvold P, Wiklund F, Telg G, Janson C. Oral corticosteroid use, morbidity and mortality in asthma: a nationwide prospective cohort study in Sweden. Allergy 2019;74:2181-90.
PUBMED | CROSSREF

18. Pan WH, Yeh WT. How to define obesity? Evidence-based multiple action points for public awareness, screening, and treatment: an extension of Asian-Pacific recommendations. Asia Pac J Clin Nutr 2008;17:370-4.
PUBMED

19. Lee MH, Jo SH, Kwon S, Park BW, Bang DW, Hyon MS, et al. Impact of overweight/obesity on clinical outcomes of patient with vasospastic angina: from the vasospastic angina in Korea registry. Sci Rep 2020;10:4954.
PUBMED | CROSSREF

20. Franklin JM, Eddings W, Austin PC, Stuart EA, Schneeweiss S. Comparing the performance of propensity score methods in healthcare database studies with rare outcomes. Stat Med 2017;36:1946-63.
PUBMED

21. Bannay A, Chaignot C, Blotière PO, Basson M, Weill A, Ricordeau P, et al. The best use of the Charlson comorbidity index with electronic health care database to predict mortality. Med Care 2016;54:188-94.
PUBMED | CROSSREF

22. Stavem K, Hoel H, Skjaker SA, Haagensen R. Charlson comorbidity index derived from chart review or administrative data: agreement and prediction of mortality in intensive care patients. Clin Epidemiol 2017;9:311-20.
PUBMED | CROSSREF

23. Kang HR, Song HJ, Nam JH, Hong SH, Yang SY, Ju S, et al. Risk factors of asthma exacerbation based on asthma severity: a nationwide population-based observational study in South Korea. BMJ Open 2018;8:e020825.
PUBMED | CROSSREF

24. Lee YJ, Kwon SH, Hong SH, Nam JH, Song HJ, Lee JS, et al. Health care utilization and direct costs in mild, moderate, and severe adult asthma: a descriptive study using the 2014 South Korean Health Insurance Database. Clin Ther 2017;39:527-36.
PUBMED | CROSSREF

25. Lee SC, Son KJ, Han CH, Jung JY, Park SC. Impact of comorbid asthma on severity of coronavirus disease (COVID-19). Sci Rep 2020;10:21805.
PUBMED | CROSSREF

26. Lam WY, Fresco P. Medication adherence measures: an overview. BioMed Res Int 2015;2015:217047.
PUBMED | CROSSREF

27. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MCJM, Verhamme KMC. Medication adherence and the risk of severe asthma exacerbations: a systematic review. Eur Respir J 2015;45:396-407.
PUBMED | CROSSREF

28. Quint JK, Millett ERC, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. Eur Respir J 2016;47:186-93.
PUBMED | CROSSREF

29. Hill AT, Haworth CS, Aliberti S, Barker A, Blasi F, Boersma W, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. Eur Respir J 2017;49:1700051.
PUBMED | CROSSREF

30. Bendien SA, van Loon-Kooij S, Kramer G, Huijgen W, Altenburg J, Ten Brinke A, et al. Bronchiectasis in severe asthma: does it make a difference? Respiration 2020:1-9.
PUBMED | CROSSREF

31. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med 2019;380:2020-30.
PUBMED | CROSSREF

32. Global Initiative for Asthma. Global strategy for asthma management and prevention [Internet]. [place unknown]: Global Initiative for Asthma; 2020 [cited 2020 Dec]. Available from: https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf.
33. Sumino K, Cabana MD. Medication adherence in asthma patients. Curr Opin Pulm Med 2013;19:49-53.
PUBMED | CROSSREF
34. Choi H, Lee H, Ryu J, Chung SJ, Park DW, Sohn JW, et al. Bronchiectasis and increased mortality in patients with corticosteroid-dependent severe asthma: a nationwide population study. Ther Adv Respir Dis 2020;14:1753466620963030.
PUBMED | CROSSREF
35. D'Amato G, Vitale C, Molino A, Stanziola A, Sanduzzi A, Vatrella A, et al. Asthma-related deaths. Multidiscip Respir Med 2016;11:37.
PUBMED | CROSSREF
36. Krishnan V, Diette GB, Rand CS, Bilderback AL, Merriman B, Hansel NN, et al. Mortality in patients hospitalized for asthma exacerbations in the United States. Am J Respir Crit Care Med 2006;174:633-8.
PUBMED | CROSSREF
37. Santamaria F, Montella S, Pietrobelli A. Obesity and pulmonary disease: unanswered questions. Obes Rev 2012;13:822-33.
PUBMED | CROSSREF
38. Guenette JA, Jensen D, O'Donnell DE. Respiratory function and the obesity paradox. Curr Opin Clin Nutr Metab Care 2010;13:618-24.
PUBMED | CROSSREF
39. Hainer V, Aldhoon-Hainerová I. Obesity paradox does exist. Diabetes Care 2013;36 Suppl 2:S276-81.
PUBMED | CROSSREF
40. Lim J, Park HS. Trends in the prevalence of underweight, obesity, abdominal obesity and their related lifestyle factors in Korean young adults, 1998–2012. Obes Res Clin Pract 2018;12:358-64.
PUBMED | CROSSREF
41. Shin HY, Kang HT. Recent trends in the prevalence of underweight, overweight, and obesity in Korean adults: The Korean National Health and Nutrition Examination Survey from 1998 to 2014. J Epidemiol 2017;27:413-9.
PUBMED | CROSSREF
42. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.
PUBMED | CROSSREF
43. Kim L, Kim JA, Kim S. A guide for the utilization of Health Insurance Review and Assessment Service national patient samples. Epidemiol Health 2014;36:e2014008.
PUBMED | CROSSREF