Ther Adv Respir Dis
2020, Vol. 14: 1–11
DOI: 10.1177/1753466620963030
© The Author(s), 2020.
Article reuse guidelines: sagepub.com/journals-permissions

Bronchiectasis and increased mortality in patients with corticosteroid-dependent severe asthma: a nationwide population study

Hayoung Choi*, Hyun Lee*, Jiin Ryu, Sung Jun Chung, Dong Won Park, Jang Won Sohn, Ho Joo Yoon and Sang-Heon Kim

Abstract

Background: Long-term corticosteroid (CS) use is associated with increased mortality in patients with asthma, and comorbid bronchiectasis is also associated with frequent asthma exacerbation and increased healthcare use. However, there is limited information on whether bronchiectasis further increases mortality in patients with CS-dependent asthma. This study examined the impact of bronchiectasis on mortality in patients with CS-dependent asthma.

Methods: A retrospective cohort of patients with CS-dependent asthma ⩾18 years old was established using records from the Korean National Health Insurance Service database from 2005 to 2015. Patients with CS-dependent asthma with and without bronchiectasis were matched by age, sex, type of insurance, and Charlson comorbidity index. We evaluated the hazard ratio (HR) for all-cause mortality in patients with bronchiectasis compared with those without bronchiectasis.

Results: The study cohort included 754 patients with CS-dependent asthma with bronchiectasis and 3016 patients with CS-dependent asthma without bronchiectasis. Patients with CS-dependent asthma with bronchiectasis had a higher all-cause mortality than those without bronchiectasis (8429/100,000 *versus* 6962/100,000 person-years, $p < 0.001$). The adjusted HR for mortality in patients with CS-dependent asthma with bronchiectasis relative to those without bronchiectasis was 1.33 (95% confidence interval, 1.18–1.50), and the association was primarily significant for respiratory diseases (subdistribution HR = 1.65, 95% confidence interval, 1.42–1.92).

Conclusions: Bronchiectasis further increases all-cause mortality in patients with CS-dependent asthma, a trend that was especially associated with respiratory diseases including chronic obstructive pulmonary disease. Strategies to improve treatment outcomes in patients with CS-dependent asthma with bronchiectasis are urgently needed to improve long-term survival.

The reviews of this paper are available via the supplemental material section.

Keywords: asthma, bronchiectasis, corticosteroid, epidemiology, mortality

Received: 5 May 2020; revised manuscript accepted: 2 September 2020.

Correspondence to:
Sang-Heon Kim
Department of Internal Medicine, Hanyang University College of Medicine, 222 Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea
sangheonkim@hanyang.ac.kr

Hayoung Choi
Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Seoul, Korea;

Lung Research Institute, Hallym University College of Medicine, Chuncheon, Korea

Hyun Lee
Sung Jun Chung
Dong Won Park
Jang Won Sohn
Ho Joo Yoon
Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea

Jiin Ryu
Biostatistical Consulting and Research Lab, Medical Research Collaborating Center, Hanyang University, Seoul, Korea

*These authors contributed equally.

Introduction

Severe asthma comprises approximately 4–10% of patients with asthma,[1–4] and 20–60% of patients with severe asthma need regular use of a systemic corticosteroid (CS) due to uncontrolled asthma-related symptoms or frequent exacerbations.[5–7] Patients with CS-dependent asthma show an increased use of healthcare resources and higher mortality than other patients with asthma.[8] Because it causes a substantial burden on public health,[9–11] identifying and modifying factors associated with poor outcomes in patients with CS-dependent asthma may be the cornerstone to improving treatment outcomes in this population.

Comorbid bronchiectasis is one of the important factors that make the treatment of severe asthma difficult; bronchiectasis leads to poor symptom control with frequent exacerbation in patients with asthma.[12–14] In reverse, the existence of asthma is

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

associated with an independent increase in the risk of bronchiectasis exacerbation.[15–17] Considering the compounding effect of bronchiectasis on the prognosis of asthma, it might be postulated that a comorbidity of bronchiectasis may increase the consumption of healthcare resources and mortality in patients with CS-dependent asthma. However, there has been no study investigating the impact of bronchiectasis on mortality in patients with CS-dependent asthma.

We recently established a retrospective cohort of patients with CS-dependent asthma using a large population-based database, the Korea National Health Insurance Service (NHIS) database.[8] Using this cohort, we investigated the impact of bronchiectasis on mortality and health care use in patients with CS-dependent asthma.

Patients and methods

Data source and study cohort

This study used the NHIS database, which provides mandatory healthcare for almost all 50 million Korean citizens. The NHIS collects health data for its insured subjects, including admission and outpatient visit records, diagnoses, drug prescriptions, national health examination data, and death. The NHIS provides all above-mentioned information for research purposes.[18]

For this study, adult patients with asthma were defined as those 18 years or older who had two or more claims under International Classification of Diseases 10th revision (ICD-10) codes J45–46, and who had one or more claim in the baseline period for prescription of asthma medications, which included inhaled or systemic CSs, short-acting or long-acting bronchodilators, leukotriene receptor antagonists, and xanthine derivatives.[19–21] The CS-dependent asthma cohort was further restricted to those with the following criteria: (1) presence of asthma and (2) prescription of systemic CS under ICD-10 codes J45–46 for at least 6 months in the baseline period.[8,22,23] Bronchiectasis was defined using the ICD-10 diagnosis code J47 (bronchiectasis).[24] Subjects with cystic fibrosis (ICD-10 diagnosis code E84) were excluded.

From 1 January 2005 to 31 December 2005, there were 751,180 adult patients with asthma. Of those potential participants, we excluded 1277 patients with only one visit associated with ICD-10 codes J45–J46 as a major or minor diagnosis. Of the remaining 749,903 patients, we further excluded 50,623 who had rheumatoid arthritis (M05–M06), systemic lupus erythematous (M32) or systemic sclerosis (L94) ($n = 29,300$), inflammatory bowel disease (K50–K51) ($n = 2053$), or malignancy (C00–C99) ($n = 24,377$) and those with no claims for asthma-related medications ($n = 232,330$). Among the remaining 232,330, 8334 were compatible with CS-dependent asthma (definition was mentioned above).[8]

The index date was defined as 12 months from the first prescription of asthma-related medications with ICD-10 codes J45–J46 as a major or minor diagnosis between 1 January 2005 and 31 December 2005. The baseline period was defined as 12 months before the index date. The follow-up period was from the index date to the date of death or 31 December 2015, whichever was sooner (see Supplemental Figure 1).

Outcomes

The primary outcome of interest was all-cause mortality, and secondary outcomes were all-cause (with or without asthma) hospitalizations, all-cause (with or without asthma) emergency department (ED) visits, and causes of mortality. In terms of the causes of mortality, we collected information on malignant neoplasms (lung cancer and other cancers), endocrine diseases (diabetes mellitus), neurologic diseases, cardiovascular diseases (hypertension, ischemic heart diseases, heart failure, and cerebrovascular diseases), respiratory diseases [asthma, chronic obstructive pulmonary disease (COPD), and pneumonia], and gastrointestinal diseases.

Ethical approval

This study was approved by the Institutional Review Board of Hanyang University Hospital (application number: HYUH 2017-09-051). The requirement for informed consent from the participants was waived because the NHIS database was constructed after anonymization of all subjects.

Statistical analysis

Controls (patients with CS-dependent asthma without bronchiectasis) were identified through 1:4 matching. The propensity score for age, sex, type of insurance, and Charlson comorbidity index (CCI) was matched for each patient with

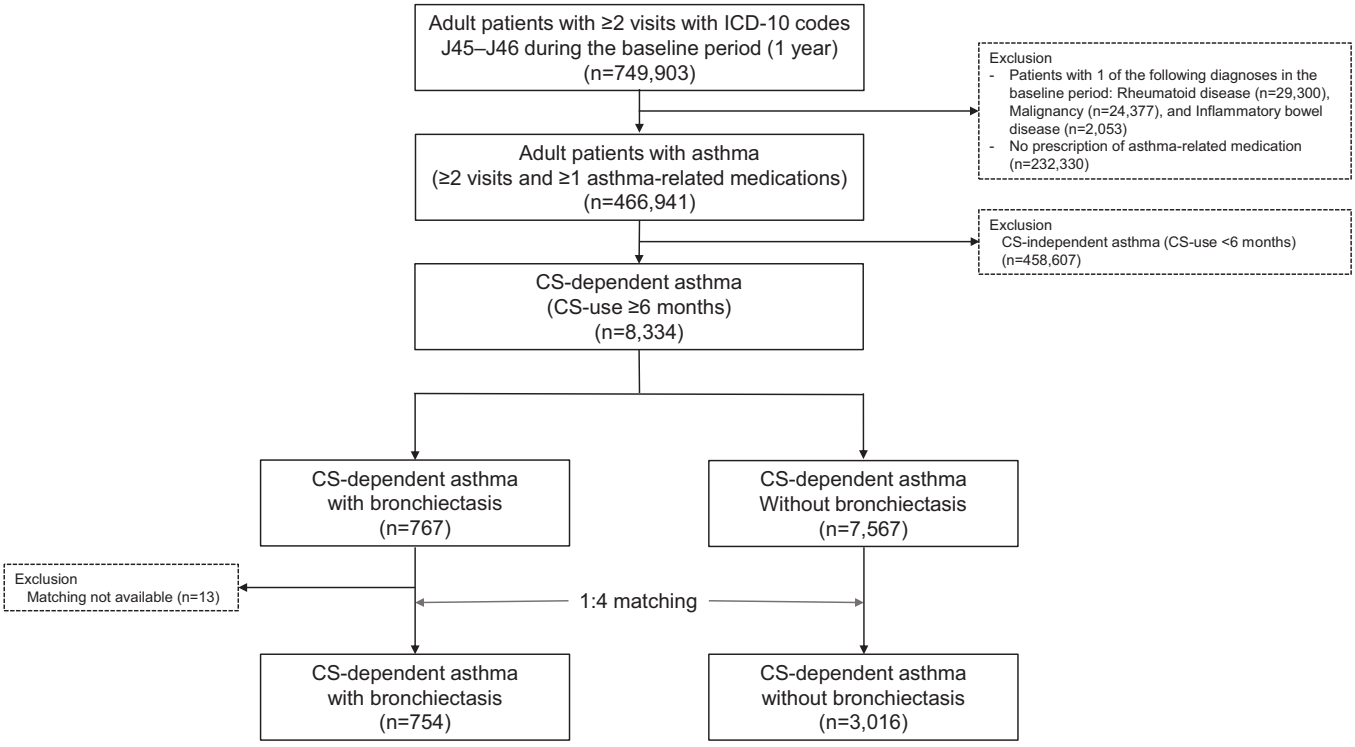

Figure 1. Flow chart of the study population.

CS-dependent asthma with bronchiectasis.[25] Standardized mean differences (SMDs) were identified to assess the balance of covariates after matching. SMDs >0.10 were considered imbalanced.[26] Comorbidities and respiratory medications were compared using the Chi-squared test.

To assess the effect of bronchiectasis on the main outcomes of mortality and healthcare use (ED visits and hospital admissions), the incidence rate of each outcome was calculated per 100,000 person-years (PYs) and compared between the two patient groups by the normal approximation test for binomials.

The Kaplan–Meier method was used to estimate survival curves during the follow-up period, and survival was compared among groups using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were evaluated for the main outcomes using the Cox proportional hazard regression model, comparing patients with bronchiectasis to the reference group of patients without bronchiectasis.

We also determined HRs for each cause of mortality. We used two competing risk regression models using cumulative incidence functions to account for competing risks caused by mortality from other causes. Among the two models, the first model used a subdistribution hazard model that included death from other causes in the risk set, and the second one used a cause-specific hazard model that included risks for all causes.[27] All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). All tests were two-tailed, and p-values <0.05 were considered statistically significant.

Results

Population

The baseline cohort comprised 8334 patients with CS-dependent asthma (see Methods).[8] Of these, 767 patients with CS-dependent asthma had bronchiectasis. After 1:4 matching, the study cohort included 754 patients with CS-dependent asthma with bronchiectasis matched with controls (3016 CS-dependent asthma patients without bronchiectasis). Overall, 13 patients with CS-dependent asthma with bronchiectasis were excluded as there were no appropriately matched controls in the cohort of patients with

Table 1. Baseline characteristics of the study population.

	CS-dependent asthma with bronchiectasis (*n* = 754)	CS-dependent asthma without bronchiectasis (*n* = 3016)	Standardized difference
Age (years)	66.0 ± 11.2	66.5 ± 11.5	−0.04
Age group			
20–29	4 (0.5)	14 (0.5)	0.00
30–39	14 (1.9)	56 (1.9)	0.00
40–49	46 (6.1)	184 (6.1)	0.00
50–59	115 (15.3)	449 (14.9)	0.01
60–69	256 (34.0)	989 (32.8)	0.03
70+	319 (42.3)	1324 (43.9)	−0.03
Sex			
Male	459 (60.9)	1892 (62.7)	−0.04
Female	295 (39.1)	1124 (37.3)	0.04
Type of insurance			
Self-employed health insurance	300 (39.8)	1216 (40.3)	−0.01
Employee health insurance	408 (54.1)	1628 (54.0)	0.00
Medical aid	46 (6.1)	172 (5.7)	0.02
Charlson comorbidity index	4.0 ± 2.3	3.9 ± 2.3	0.09

Values are presented as either *n* (%) or mean (standard deviation).
CS, corticosteroid.

CS-dependent asthma without bronchiectasis (Figure 1). As shown in Table 1, the two cohorts were well balanced according to the baseline characteristics of age, sex, type of insurance, and CCI. Supplemental Figure 2 also demonstrates the distribution for matching. Detailed information regarding comorbid profiles and respiratory medication is provided in Supplemental Table 1.

Mortality

The overall mortality was 7240/100,000 PY during a mean (±SD) of 7.0 years (±3.5 years) of follow up. All-cause mortality was significantly higher in patients with CS-dependent asthma with bronchiectasis than in those without bronchiectasis (8429/100,000 PY *versus* 6962/100,000 PY, $p < 0.001$). As shown in Figure 2, the cumulative survival rate was significantly lower in patients with CS-dependent asthma with bronchiectasis compared with those without bronchiectasis (log-rank $p < 0.001$).

The detailed information regarding the impact of bronchiectasis on mortality in patients with CS-dependent asthma by age and sex are summarized in Table 2. In univariable Cox regression analysis, patients with CS-dependent asthma with bronchiectasis were 1.27-times more likely to die (unadjusted HR = 1.27, 95% CI = 1.13–1.42) compared with those without bronchiectasis. The statistical significance was persisted after further adjustment of potential confounding factors including, age, sex, type of insurance, COPD, pneumonia, and the number of inhalers (adjusted HR in model 4 = 1.19, 95% CI = 1.05–1.35).

In subgroup analyses, regardless of age group and sex, patients with CS-dependent asthma with bronchiectasis had a higher risk of mortality

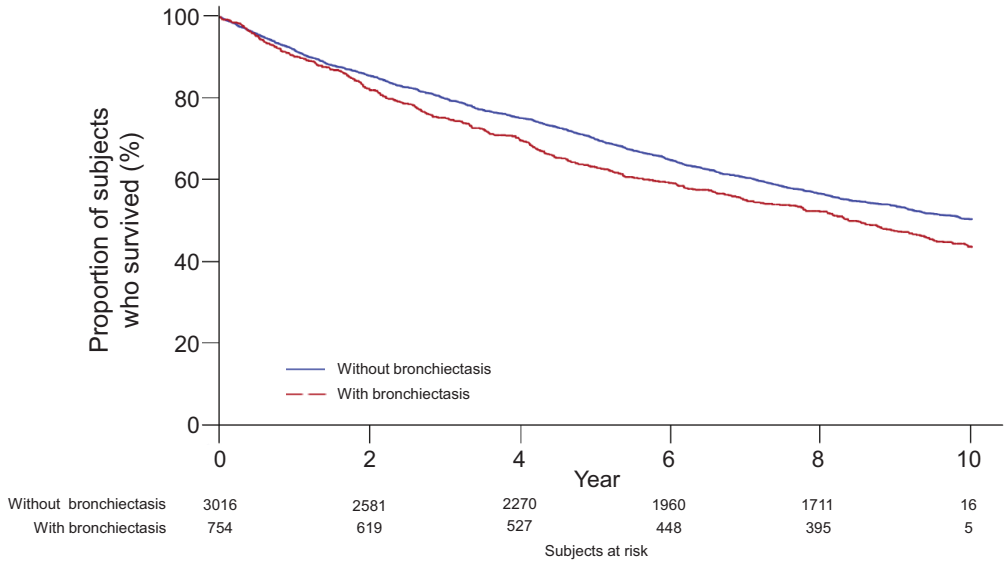

Figure 2. Kaplan–Meier survival analysis of time to death.

Table 2. The effect of bronchiectasis on mortality in patients who are CS-dependent.

	PY (/100,000)	HR for mortality (95% CI)				
		Unadjusted model	Adjusted model			
			Model 1	Model 2	Model 3	Model 4
All	7240					
Without bronchiectasis	6962	Reference	Reference	Reference	Reference	Reference
With bronchiectasis	8429	1.27 (1.13–1.42)	1.32 (1.17–1.49)	1.32 (1.17–1.49)	1.33 (1.18–1.50)	1.19 (1.05–1.35)
Male	8207					
Without bronchiectasis	7943	Reference	Reference	Reference	Reference	Reference
With bronchiectasis	9359	1.19 (1.03–1.38)	1.22 (1.04–1.41)	1.21 (1.04–1.41)	1.22 (1.04–1.42)	1.10 (0.94–1.29)
Female	5802					
Without bronchiectasis	5491	Reference	Reference	Reference	Reference	Reference
With bronchiectasis	7097	1.50 (1.21–1.86)	1.63 (1.31–2.04)	1.64 (1.31–2.05)	1.65 (1.32–2.06)	1.46 (1.15–1.86)
Age < 60	2032					
Without bronchiectasis	1621	Reference	Reference	Reference	Reference	Reference
With bronchiectasis	3835	2.45 (1.65–3.63)	2.46 (1.65–3.67)	2.53 (1.68–3.79)	2.60 (1.72–3.93)	1.53 (0.94–2.49)
Age ⩾ 60	9475					
Without bronchiectasis	9270	Reference	Reference	Reference	Reference	Reference
With bronchiectasis	10,340	1.20 (1.05–1.36)	1.22 (1.07–1.39)	1.22 (1.07–1.39)	1.22 (1.07–1.39)	1.12 (0.98–1.28)

Model 1, adjusted for age and sex; model 2, adjusted for age, sex, and type of insurance; model 3, adjusted for age, sex, type of insurance, and CCI; model 4, adjusted for age, sex, type of insurance, CCI, COPD, pneumonia, and number of inhalers (0–2 *versus* 3 or more).
CCI, Charlson comorbidity index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CS, corticosteroid; HR, hazard ratio.

Table 3. Common major causes* of mortality rate in patients with CS-dependent asthma according to bronchiectasis.

	Total (n = 1880)	CS-dependent asthma with bronchiectasis (n = 412)	CS-dependent asthma without bronchiectasis (n = 1468)	p-value
Respiratory diseases	868 (46.2)	240 (58.3)	628 (42.8)	<0.01
Chronic lower respiratory diseases	749 (39.8)	218 (52.9)	531 (36.2)	<0.01
Asthma	204 (10.9)	43 (10.4)	161 (11.0)	0.76
COPD	521 (27.7)	153 (37.1)	368 (25.1)	<0.01
Pneumonia	54 (2.9)	8 (1.9)	46 (3.1)	0.20
Malignant neoplasms	262 (13.9)	47 (11.4)	215 (14.6)	0.09
Lung cancer	107 (5.7)	22 (5.3)	85 (5.8)	0.73
Other cancers	155 (8.2)	25 (6.1)	130 (8.9)	0.07
Endocrine diseases	57 (3.0)	5 (1.2)	52 (3.5)	0.01
Diabetes mellitus	54 (2.9)	5 (1.2)	49 (3.3)	0.02
Mental and behavioral disorders	14 (0.7)	2 (0.5)	12 (0.8)	0.75
Neurologic diseases	22 (1.2)	5 (1.2)	17 (1.2)	>0.99
Cardiovascular diseases	301 (16.0)	47 (11.4)	254 (17.3)	<0.01
Hypertension	27 (1.4)	3 (0.7)	24 (1.6)	0.17
Ischemic heart disease	93 (4.9)	10 (2.4)	83 (5.7)	0.01
Heart failure	35 (1.9)	10 (2.4)	25 (1.7)	0.34
Cerebrovascular disease	90 (4.8)	14 (3.4)	76 (5.2)	0.14
Gastrointestinal diseases	27 (1.4)	5 (1.2)	22 (1.5)	0.67
Musculoskeletal and connective tissue diseases	8 (0.4)	1 (0.2)	7 (0.5)	>0.99
Osteoporosis	4 (0.2)	1 (0.2)	3 (0.2)	>0.99
Injury, poisoning, and external causes	84 (4.5)	8 (1.9)	76 (5.2)	<0.01
Others	237 (12.6)	52 (12.6)	185 (12.6)	0.99

Data are presented as the number (%).
*When a patient died, only one direct cause of mortality was determined by the attending physician.
COPD, chronic obstructive pulmonary disease; CS, corticosteroid.

compared with those without bronchiectasis in both the crude model and models 1–3 (adjusted for age and sex in model 1; adjusted for variables in model 1 and type of insurance in model 2; adjusted for variables in model 2 and CCI in model 3). Notably, the HR was highest in patients <60 years (adjusted HR in model 3 = 2.60, 95% CI = 1.72–3.93). However, when COPD, pneumonia, and the number of inhalers (0–2 *versus* 3 or more) were further adjusted, the statistical significance persisted only in females (adjusted HR = 1.46, 95% CI = 1.15–1.86). Particularly, in patients with CS-dependent asthma with COPD, patients with CS-dependent

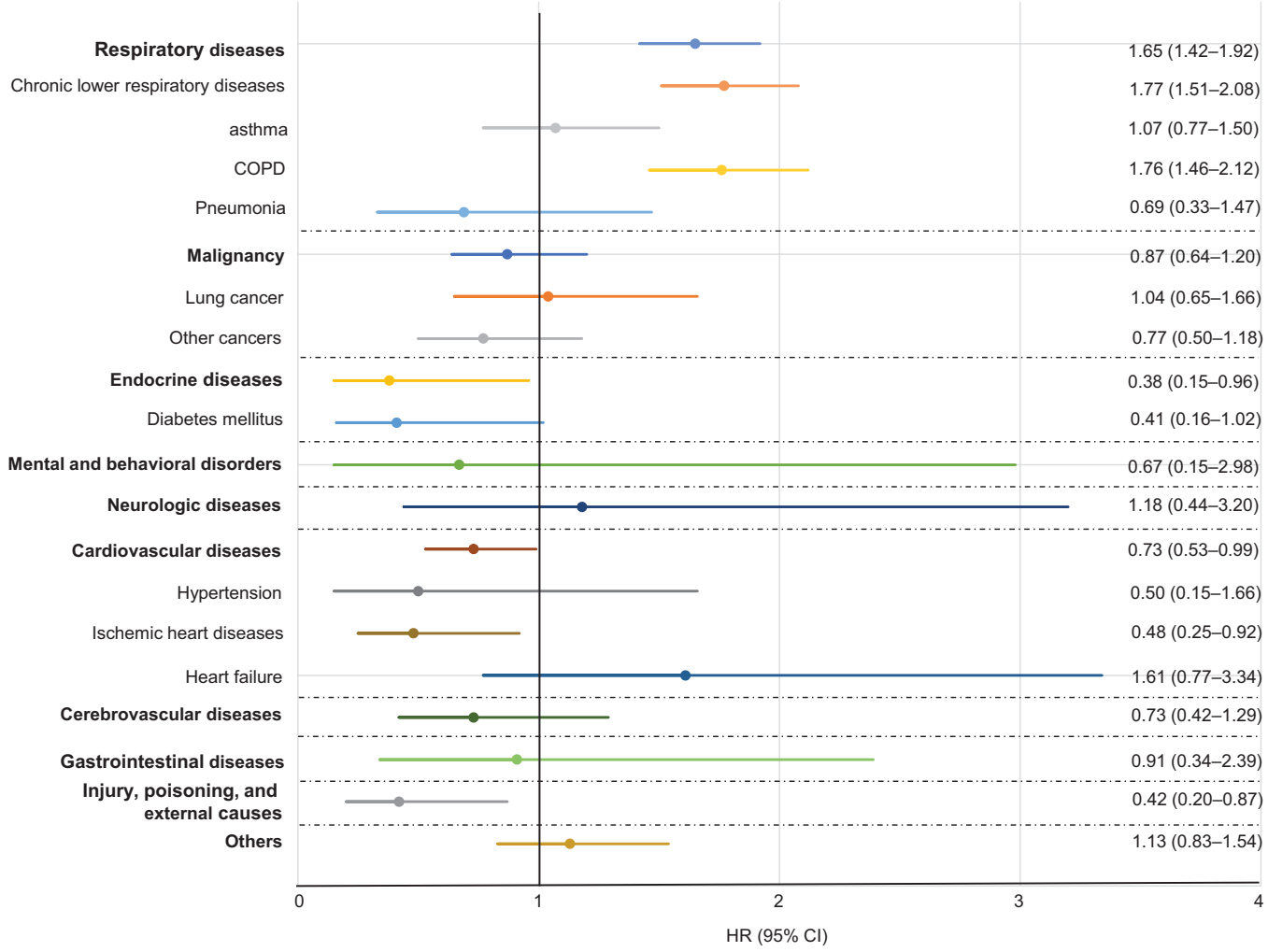

Figure 3. Forest plot of cause-specific hazard ratios representing mortality in CS-dependent asthma patients with bronchiectasis compared with those without bronchiectasis.
CS, corticosteroid.

asthma with bronchiectasis had a higher risk of mortality compared with those without bronchiectasis in models 1–3 but not in the crude model. However, in patients with CS-dependent asthma without COPD, patients with CS-dependent asthma with bronchiectasis did not have a higher risk of mortality than those without bronchiectasis (Supplemental Table 2).

Causes of mortality

As shown in Table 3, the most common cause of mortality was respiratory diseases in both patient groups: 58.3% in patients with CS-dependent asthma with bronchiectasis and 42.8% in those without bronchiectasis. The proportion of patients who died of COPD was higher in patients with CS-dependent asthma with bronchiectasis compared with those without bronchiectasis (37.1% *versus* 25.1%, $p < 0.01$). However, there was no significant intergroup difference in the proportion of patients who died of asthma ($p = 0.76$). The proportion of patients who died of malignant neoplasms and cardiovascular diseases was 11.4% for each group of disorders. In comparison, common causes of mortality in patients with CS-dependent asthma without bronchiectasis were respiratory diseases (42.8%), cardiovascular diseases (17.3%), and malignant neoplasms (14.6%).

The cause-specific HRs for mortality are summarized in Figure 3. The following diseases had a statistically significant cause-specific mortality

risk for patients with CS-dependent asthma with bronchiectasis relative to those without bronchiectasis: respiratory diseases (HR = 1.62, 95% CI = 1.40–1.88), chronic lower respiratory diseases (HR = 1.74, 95% CI = 1.49–2.04), and COPD (HR = 1.77, 95% CI = 1.46–2.13). A further analysis which considered competing risks caused by mortality due to other diseases revealed that subdistribution cause-specific mortality risks associated with respiratory diseases (subdistribution HR = 1.65, 95% CI = 1.42–1.92), chronic lower respiratory diseases (subdistribution HR = 1.77, 95% CI = 1.51–2.08), and COPD (subdistribution HR = 1.76, 95% CI = 1.46–2.12) were significant.

Healthcare use

The rates of asthma-related hospitalization (97,511/100,000 PY *versus* 68,734/100,000 PY) and all-cause hospitalization (321,188/100,000 PY *versus* 236,304/100,000 PY) were significantly higher in patients with CS-dependent asthma with bronchiectasis than in those without bronchiectasis ($p < 0.001$ for both). Though there was no significant intergroup difference in the rates of asthma-related ED visits (7908/100,000 PY *versus* 7862/100,000 PY, $p = 0.9182$), the rate of all-cause ED visits was significantly higher in patients with CS-dependent asthma with bronchiectasis than in those without bronchiectasis (30,422/100,000 PY *versus* 26,804/100,000 PY, $p < 0.001$).

Discussion

This study evaluated the impact of coexisting bronchiectasis on all-cause mortality in patients with CS-dependent asthma using a large, nationwide population database. Our study demonstrated that all-cause mortality and healthcare use were significantly higher in patients with CS-dependent asthma with bronchiectasis compared with those without bronchiectasis. The mortality in patients with CS-dependent asthma with bronchiectasis was primarily related to COPD.

The most important finding of this study is that physician-diagnosed bronchiectasis further increased the mortality risk for CS-dependent asthma patients in a longitudinal nationwide population-based cohort. Although the prevalence of bronchiectasis is generally low in all patients with asthma, the prevalence increases by up to 25–51% in those with severe asthma.[13,28,29] Several studies reported a significant association between asthma exacerbation risk and bronchiectasis.[13,30] However, increased mortality in severe asthma due to bronchiectasis has not previously been published and is the novel finding of this study. We highlighted that bronchiectasis further increased mortality in patients with CS-dependent asthma whose mortality is higher than general asthma patients.[8] Hence, clinicians should manage patients with severe asthma with bronchiectasis more cautiously, as they have higher long-term mortality risk as well as increased exacerbation risk.

Several potential reasons exist for the increased mortality seen in patients with CS-dependent asthma with bronchiectasis. First, bronchiectasis may cause recurrent respiratory infections in patients with CS-dependent asthma. The airway in bronchiectasis is predisposed to bacterial colonization due to mucus thickening and impaired mucociliary clearance.[31] The bacterial colonization is followed by a vicious cycle of inflammation and recurrent infection,[32,33] which results in a low quality of life and increased mortality.[34] Second, bronchiectasis may reduce lung function to a greater extent in patients with CS-dependent asthma than in those without bronchiectasis. Since bronchiectasis can result in obstructive as well as mixed obstructive–restrictive spirometry profiles,[34,35] patients with CS-dependent with bronchiectasis may experience a greater decline in lung function compared with those without bronchiectasis. In agreement with this suggestion, the COPD-related mortality was more significant in patients with CS-dependent asthma with bronchiectasis than in those without bronchiectasis. Our two hypotheses are also in line with the study finding that asthma-related healthcare use and respiratory diseases-related mortality were significantly higher in patients with CS-dependent with bronchiectasis than in those without bronchiectasis.

However, as the optimal treatment strategy for patients with CS-dependent asthma with bronchiectasis has not been established, an integrated treatment guideline is urgently needed. Interestingly, a recent preliminary study showed that mepolizumab, a potent biologic agent for CS-dependent asthma, may also be beneficial to the treatment of eosinophilic bronchiectasis.[36] Thus, we expect that coexisting bronchiectasis may not alter the effect of biologics on the treatment of CS-dependent asthma, as shown in the previous study.[37]

Another notable finding of this study is that the cause-specific mortality associated with respiratory diseases (HR = 1.62) was higher in patients with CS-dependent asthma with bronchiectasis than in those without bronchiectasis. The cause-specific mortality associated with respiratory diseases was significantly driven by COPD (HR = 1.77), however, there was no significant difference in the cause-specific mortality associated with asthma between the two groups. In our previous study, the cause-specific mortality associated with respiratory diseases, cardiovascular disease, malignant neoplasms, and endocrine diseases was higher in patients with CS-dependent asthma than in patients with CS-independent asthma.[8] Our study added a novel finding that bronchiectasis further increases the risk of mortality due specifically to respiratory diseases in patients with CS-dependent asthma.

Unexpectedly, patients with CS-dependent asthma with bronchiectasis aged <60 years showed higher HR for mortality than those aged $\geqslant 60$ years, although statistical significance disappeared in the fully adjusted model. As for the reasons why younger patients showed an unusually high HR, we carefully suggest that the impact of bronchiectasis on mortality gradually decreases as patients become older. Since older patients have other comorbidities that affect mortality in addition to bronchiectasis, the impact of bronchiectasis on mortality may be attenuated in older patients with CS-dependent asthma.

The major strength of our research is that, to the best of our knowledge, this is the first study to comprehensively investigate the impact of bronchiectasis on mortality in patients with CS-dependent asthma using a longitudinal population-based national cohort. However, the present study also had some limitations that should be acknowledged. First, we did not have clinical information on smoking history, pulmonary function test results, microbiologic test results, and detailed information on asthma (e.g. the onset and duration) and bronchiectasis (e.g. onset, duration, and extent). Thus, we could not adjust for some important confounding factors. Second, all diagnoses were based on ICD-10 codes and medications. Thus, there might be some errors in diagnosing diseases. Third, this study was performed in Korea. As epidemiology may differ by ethnicity and socioeconomic factors, our findings might not be generalizable to patients in other countries. However, despite the limitations above, we would like to emphasize that our approaches have the advantage of reflecting real-world practice.

In conclusion, bronchiectasis further increases all-cause mortality in patients with CS-dependent asthma. The cause-specific mortality in patients with bronchiectasis was more related to chronic respiratory diseases such as COPD than in those without bronchiectasis. Our results suggest that strategies to treat both severe asthma and bronchiectasis appropriately are urgently needed to improve long-term survival.

Acknowledgements

We thank the Biostatistical Consulting and Research Lab, Hanyang University, for assistance with statistical analysis.

Author contribution(s)

Hayoung Choi: Conceptualization; Formal analysis; Investigation; Writing-original draft; Writing-review & editing.

Hyun Lee: Conceptualization; Data curation; Formal analysis; Investigation; Writing-original draft; Writing-review & editing.

Jiin Ryu: Data curation; Formal analysis; Investigation; Methodology; Writing-original draft; Writing-review & editing.

Sung Jun Chung: Data curation; Formal analysis; Writing-review & editing.

Dong Won Park: Data curation; Formal analysis; Writing-review & editing.

Jang Won Sohn: Formal analysis; Investigation; Writing-review & editing.

Ho Joo Yoon: Investigation; Supervision; Writing-review & editing.

Sang-Heon Kim: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Writing-original draft; Writing-review & editing.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was

supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant no. HC19C0218), and the Korea Ministry of Environment (MOE) as "the Environmental Health Action Program" (2016001360003).

ORCID iD

Sang-Heon Kim https://orcid.org/0000-0001-8398-4444

Supplemental material

The reviews of this paper are available via the supplemental material section.

References

1. Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343–373.
2. Hekking PP, Wener RR, Amelink M, *et al.* The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015; 135: 896–902.
3. Larsson K, Stallberg B, Lisspers K, *et al.* Prevalence and management of severe asthma in primary care: an observational cohort study in Sweden (PACEHR). *Respir Res* 2018; 19: 12.
4. Kim B-K, Park S-Y, Ban G-Y, *et al.* Evaluation and management of difficult-to-treat and severe asthma: an expert opinion from the Korean academy of asthma, allergy and clinical immunology, the working group on severe asthma. *Allergy Asthma Immunol Res* 2020; 12: e61.
5. Kim MH, Kim SH, Park SY, *et al.* Characteristics of adult severe refractory asthma in Korea analyzed from the severe asthma registry. *Allergy Asthma Immunol Res* 2019; 11: 43–54.
6. Kim SH, Moon JY, Lee JH, *et al.* Perceptions of severe asthma and asthma-COPD overlap syndrome among specialists: a questionnaire survey. *Allergy Asthma Immunol Res* 2018; 10: 225–235.
7. van Bragt JJMH, Adcock IM, Bel EHD, *et al.* Characteristics and treatment regimens across ERS SHARP severe asthma registries. *Eur Respir J* 2020; 55: 1901163.
8. 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: 1900804.
9. McDonald VM and Gibson PG. Exacerbations of severe asthma. *Clin Exp Allergy* 2012; 42: 670–677.
10. Sadatsafavi M, Lynd L, Marra C, *et al.* Direct health care costs associated with asthma in British Columbia. *Can Respir J* 2010; 17: 74–80.
11. Sullivan PW, Campbell JD, Ghushchyan VH, *et al.* Characterizing the severe asthma population in the United States: claims-based analysis of three treatment cohorts in the year prior to treatment escalation. *J Asthma* 2015; 52: 669–680.
12. Crimi C, Ferri S and Crimi N. Bronchiectasis and asthma: a dangerous liaison? *Curr Opin Allergy Clin Immunol* 2019; 19: 46–52.
13. Coman I, Pola-Bibián B, Barranco P, *et al.* Bronchiectasis in severe asthma: clinical features and outcomes. *Ann Allergy Asthma Immunol* 2018; 120: 409–413.
14. García-Clemente M, Enríquez-Rodríguez AI, Iscar-Urrutia M, *et al.* Severe asthma and bronchiectasis. *J Asthma*. Epub ahead of print 20 February 2019. DOI: 10.1080/02770903.2019.1579832.
15. Mao B, Yang J-W, Lu H-W, *et al.* Asthma and bronchiectasis exacerbation. *Eur Respir J* 2016; 47: 1680–1686.
16. Mantyla J, Mazur W, Torola T, *et al.* Asthma as aetiology of bronchiectasis in Finland. *Respir Med* 2019; 152: 105–111.
17. Liu B-C, Huang T-X, Yang D, *et al.* Asthma-associated bronchiectasis: more attention needed! *Respir Med*. Epub ahead of print 12 September 2019. DOI: 10.1016/j.rmed.2019.09.009.
18. Cheol Seong S, Kim YY, Khang YH, *et al.* Data resource profile: the national health information database of the national health insurance service in South Korea. *Int J Epidemiol* 2017; 46: 799–800.
19. Cho EY, Oh KJ, Rhee CK, *et al.* Comparison of clinical characteristics and management of asthma by types of health care in South Korea. *J Thorac Dis* 2018; 10: 3269–3276.
20. Choi JY, Yoon HK, Lee JH, *et al.* Nationwide use of inhaled corticosteroids by South Korean asthma patients: an examination of the Health Insurance Review and Service database. *J Thorac Dis* 2018; 10: 5405–5413.
21. Kim S, Kim J, Kim K, *et al.* Healthcare use and prescription patterns associated with adult asthma in Korea: analysis of the NHI claims database. *Allergy* 2013; 68: 1435–1442.

22. Lefebvre P, Duh MS, Lafeuille MH, *et al.* Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol* 2015; 136: 1488–1495.

23. Wysocki K, Park SY, Bleecker E, *et al.* Characterization of factors associated with systemic corticosteroid use in severe asthma: data from the Severe Asthma Research Program. *J Allergy Clin Immunol* 2014; 133: 915–918.

24. Choi H, Yang B, Nam H, *et al.* Population-based prevalence of bronchiectasis and associated comorbidities in South Korea. *Eur Respir J* 2019; 54: 1900194.

25. Bergstralh E and Konsanke J. *Technical report series no. 56, computerized matching of cases to controls*. Rochester, MN: Department of Health Science Research, Mayo Clinic, 1995.

26. Sullivan GM and Feinn R. Using effect size-or why the p-value is not enough. *J Grad Med Educ* 2012; 4: 279–282.

27. Fine JP and Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94: 496–509.

28. Bisaccioni C, Aun MV, Cajuela E, *et al.* Comorbidities in severe asthma: frequency of rhinitis, nasal polyposis, gastroesophageal reflux disease, vocal cord dysfunction and bronchiectasis. *Clinics (Sao Paulo)* 2009; 64: 769–773.

29. Wang D, Luo J, Du W, *et al.* A morphologic study of the airway structure abnormalities in patients with asthma by high-resolution computed tomography. *J Thorac Dis* 2016; 8: 2697–2708.

30. Dimakou K, Gousiou A, Toumbis M, *et al.* Investigation of bronchiectasis in severe uncontrolled asthma. *Clin Respir J* 2018; 12: 1212–1218.

31. Chalmers JD, Chang AB, Chotirmall SH, *et al.* Bronchiectasis. *Nat Rev Dis Primers* 2018; 4: 45.

32. Mandal P and Hill AT. Bronchiectasis: breaking the cycle of inflammation and infection. *Lancet Respir Med* 2013; 1: e5–e6.

33. Polverino E, Goeminne PC, McDonnell MJ, *et al.* European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J* 2017; 50: 1700629.

34. Chalmers JD, Goeminne P, Aliberti S, *et al.* The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med* 2014; 189: 576–585.

35. Colom AJ, Maffey A, Garcia Bournissen F, *et al.* Pulmonary function of a paediatric cohort of patients with postinfectious bronchiolitis obliterans. A long term follow-up. *Thorax* 2015; 70: 169–174.

36. Rademacher J, Konwert S, Fuge J, *et al.* Anti-IL5 and anti-IL5Rα therapy for clinically significant bronchiectasis with eosinophilic endotype: a case series. *Eur Respir J* 2020; 55: 1901333.

37. Carpagnano GE, Scioscia G, Lacedonia D, *et al.* Severe uncontrolled asthma with bronchiectasis: a pilot study of an emerging phenotype that responds to mepolizumab. *J Asthma Allergy* 2019; 12: 83–90.

Visit SAGE journals online
journals.sagepub.com/
home/tar

SAGE journals