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Coexisting COPD Increases Mortality in Patients With Corticosteroid-Dependent Asthma: A Nationwide Population-Based Study

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ABSTRACT

Purpose: Chronic corticosteroid (CS) use is a risk factor for long-term mortality in asthmatic patients, and the presence of coexisting chronic obstructive pulmonary disease (COPD) is associated with a severe presentation and poor prognosis. However, the impact of coexisting COPD on long-term mortality in patients with CS-dependent asthma has not been well elucidated. This study aimed to determine the impact of coexisting COPD on long-term mortality in patients with CS-dependent asthma.

Methods: A retrospective cohort of patients with CS-dependent asthma aged 40 years or older was established using records from the Korean National Health Insurance Service database for 2005 to 2015. We classified the subjects into 2 groups according to the presence of COPD and evaluated the hazard ratio (HR) for all-cause mortality in patients with COPD relative to those without COPD.

Results: Of 8,021 patients with CS-dependent asthma, 3,121 (38.9%) had COPD. All-cause mortality was significantly greater in patients with CS-dependent asthma and COPD than in those without COPD (9,955/100,000 person-years vs. 5,585/100,100 person-years, $P < 0.001$). The adjusted HRs were 1.29 (95% confidence interval [CI], 1.21-1.38), and the associations were especially significant for chronic lower respiratory diseases (subdistribution HR, 2.30; 95% CI, 2.06-2.57) and lung cancer (subdistribution HR, 1.34; 95% CI, 1.02–1.78).

Conclusions: In this population-based retrospective cohort study, the presence of physician-recognized COPD was associated with greater all-cause mortality and greater risk of mortality due to chronic lower respiratory diseases and lung cancer in patients with CS-dependent asthma. Early recognition and appropriate management of COPD can improve treatment outcomes in patients with CS-dependent asthma.

Keywords: Mortality; chronic obstructive pulmonary disease; steroids; asthma; treatment; population

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INTRODUCTION

The asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) is a common condition that shares features of both asthma and COPD.[1] The proportion of COPD among asthmatic patients has been reported to be up to 50%,[2] and coexisting COPD has a substantial impact on the natural course of asthma. Previous reports have found that coexisting COPD is associated with frequent exacerbations of asthma, reduced quality of life, and increased use of healthcare resources in patients with asthma.[3-6] COPD, in conjunction with asthma, is also associated with increased mortality compared to patients with only asthma and no other respiratory conditions.[7]

Severe asthma is diagnosed in 5%-10% of asthma patients,[8] and 20%-60% of patients with severe asthma regularly use systemic corticosteroids (CSs)[9-11] and are defined as patients with CS-dependent asthma. This condition is one of the most serious forms of severe asthma and has an increased risk of CS-related comorbidities, exacerbations, healthcare use, and most importantly, mortality in asthmatic patients.[12]

A significant proportion of patients with severe asthma are considered to have COPD. A survey of asthma experts has reported that about 38% of severe asthmatic patients are expected to have ACO.[13] Another study using a severe asthma registry to evaluate the proportion of asthmatic patients with COPD found that about one-fourth of patients with severe asthma were diagnosed with ACO based on clinical features such as smoking history and persistent airflow limitations.[14] This study also found that ACO patients used more oral CS medication than those with only severe asthma and had more frequent emergency department (ED) visits in the previous year, suggesting poor asthma control and, perhaps, poor prognoses in this population. However, there are few longitudinal follow-up data addressing the prognosis of ACO in the context of patients with CS-dependent severe asthma.

We recently established a retrospective cohort of CS-dependent asthmatic patients using the Korea National Health Insurance Service (NHIS) database.[12] Using this database, we evaluated the impact of coexisting COPD on mortality and healthcare use in patients with CS-dependent asthma.

MATERIALS AND METHODS

Study design and study population
In Korea, mandatory health care for almost all Korean citizens (nearly 50 million subjects) is provided by the NHIS. Accordingly, the NHIS collects the following health data for its insured subjects: 1) outpatient visit and admission records, 2) major and minor diagnoses, 3) drug prescriptions, 4) national health examination data, and 5) death.[15]

In our previous study, we constructed a retrospective CS-dependent asthma cohort composed of 8,334 patients aged 18 years or older for whom patient records were available for the period between January 1, 2005 to December 31, 2005.[12] Using this dataset and subjects, we enrolled 8,021 patients aged 40 years or older in the study. Patients were followed until the date of death or December 31, 2015, whichever was sooner.

This study was approved by the Institutional Review Board (IRB) of our institution (IRB number: HYUH 2017-09-051). The requirement for informed consent from the participants was waived because the NHIS database was constructed after anonymization.

Definitions

We defined adult asthma according to the following criteria: 1) age ≥ 18 years, 2) ≥ 2 claims under the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes J45–J46, and 3) ≥ 1 claim for the use of asthma-related drugs, which include inhaled or systemic CS medication, bronchodilators, leukotriene receptor antagonists, and xanthine derivatives (*e.g.,* theophylline) during the baseline period (12 months after the diagnosis of asthma between January 1 and December 31 of 2005).[12,16,17] CS-dependent asthma was defined as the presence of asthma and prescription of systemic CS under codes ICD-10 J45–J46 for at least 6 months in the baseline period.[18-20] COPD was defined according to the following criteria: 1) aged 40 or older[21] and 2) at least one claim under a major diagnosis of COPD during the baseline period.

We defined the baseline comorbidities as comorbidities with ≥ 1 claim under ICD-10 codes as a major diagnosis during the baseline period as follows: diabetes mellitus (E10–E14), Cushing's disease (E24), adrenal insufficiency (E27.3–E27.4), bone necrosis (M87), osteoporosis (M80–M82), vertebral or pelvic fracture (S22.0–S22.1, S32.0, and M48.4), pneumonia (J12–J18), tuberculosis (A15–A19), hypertension (I10–I15), angina (I20), myocardial infarction (I21), heart failure (I50), peptic ulcer (K25–K27), gastrointestinal bleeding (K92.0–K92.2), glaucoma (H40 and H42), and cataract (H25, H26, and H28).

Regarding the mortality date and cause of mortality, we used data provided by the Statistics Korea, an initiative of the Ministry of Strategy and Finance of Korea.[15] We classified the causes of deaths according to the following 10 categories: 1) respiratory diseases (J00–J99), 2) cardiovascular diseases (I00–I99), 3) malignant neoplasms (C00–C97), 4) injury, poisoning, and external causes (S00–T98), 5) endocrine diseases (E00–E90), 6) gastrointestinal diseases (K00–K93), 7) neurologic diseases (G00–G99), 8) mental and behavioral disorders (F00–F99), 9) musculoskeletal and connective tissue diseases (M00–M99), and 10) miscellaneous.

Regarding healthcare use, we defined an asthma-related ED visit and hospitalization as a visit to an ED and admission to a hospital under ICD-10 codes J45–J46 as a major or minor diagnosis during the follow-up period, respectively.

Main outcomes and measures

The primary outcome was to evaluate the impact of coexisting COPD on all-cause mortality in patients with CS-dependent asthma during the follow-up period. The secondary outcome was to evaluate the cause of mortality in patients with CS-dependent asthma with COPD.

Statistical analysis

We used the McNemar test to compare the baseline characteristics (age group, sex, type of insurances, Charlson comorbidity index [CCI],[22] comorbidities, and asthma-related medications) of patients with CS-dependent asthma according to the presence or absence of COPD. We used Kaplan-Meier survival analysis to estimate survival curves and used the log-rank test to compare survival between the groups. Cox proportional hazard regression modeling was used to determine hazard ratios (HRs) and 95% confidence intervals (CIs) for the main outcomes in patients with CS-dependent asthma and COPD relative to those

without COPD. We further adjusted for the effect of age, sex, type of insurance, and CCI using the multivariable Cox proportional regression model.

To assess the effect of coexisting COPD on mortality and healthcare use, we compared the incidence rates (per 100,000 person-years [PY]) of mortality and healthcare use in patients with COPD vs. those without COPD by the normal approximation test for binomials.

We also determined the HRs for each cause of mortality. We used a cause-specific and subdistribution proportional hazards regression model to account for competing risks caused by mortality due to other causes.[23] We considered 2-sided *P* values < 0.05 statistically significant.

As the baseline characteristics of patients with CS-dependent asthma and COPD and those without COPD were significantly different, propensity score matching was used to reduce selection bias, and patients with COPD were matched 1:1 with patients without COPD with regard to age, sex, and CCI (**Supplementary Fig. S1** and **Supplementary Table S1**). Using the matched population, we undertook the same analyses as those performed in the unmatched population. The characteristics of the 2 populations were compared using standardized mean differences. Standardized mean differences > 0.10 were considered unbalanced.[24]

All analyses in our study were performed using SAS® 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Population
The baseline cohort comprised 8,021 patients at least of 40 years of age with CS-dependent asthma, of whom 3,121 (38.9%) also had COPD. Patients with COPD were older (mean 69.2 years vs. 66.0 years, *P* < 0.001) and were predominantly male (68.9% vs. 48.2%, *P* < 0.001), were more likely to use medical aid as their insurance (7.7% vs. 3.1%, *P* < 0.001), and had higher CCI values (mean 3.9 vs. 3.7, *P* < 0.001) (**Table 1**). Regarding comorbidities, there were no significant differences in comorbidities, including diabetes mellitus, adrenal insufficiency, bone necrosis, osteoporosis, gastrointestinal bleeding, glaucoma, or cataract. While vertebral or pelvic fracture (6.3% vs. 4.3%, *P* < 0.001), previous history of pneumonia (46.3% vs. 21.2%, *P* < 0.001), tuberculosis (11.5% vs. 4.5%, *P* < 0.001), myocardial infarction (3.8% vs. 2.5%, *P* < 0.001), congestive heart failure (15.6% vs. 10.5%, *P* < 0.001), and peptic ulcer disease (48.0% vs. 39.8%, *P* < 0.001) were more frequent among patients with COPD compared to those without in our cohort, Cushing's syndrome (3.2% vs. 2.0%, *P* = 0.002) and hypertension (57.8% vs. 54.4%, *P* = 0.003) were more frequent among patients without COPD compared to those with.

The proportion of patients who used inhalers, including any inhaled CS (82.8% vs. 70.0%, *P* < 0.001), long-acting β_2 agonist (LABA) (72.3% vs. 60.6%, *P* < 0.001), long-acting muscarinic antagonist (LAMA) (35.5% vs. 14.7%, *P* < 0.001), or short-acting β_2 agonist (91.3% vs. 76.2%, *P* < 0.001), were significantly greater in patients with COPD than in those without. There was no significant difference in the use of leukotriene receptor antagonists between the 2 groups.

Mortality
As shown in the survival analyses (**Figure**), all-cause mortality was significantly greater in patients with COPD than in those without (9,955/100,000 PY vs. 5,585/100,100 PY, *P* < 0.001). As shown in **Table 2**, in univariable Cox regression analyses, patients with COPD were 1.77-

Table 1. Baseline demographics

| Variables	CS-dependent asthma		P value
	With COPD (n = 3,121)	Without COPD (n = 4,900)	
Age (yr)	69.2 ± 9.6	66.0 ± 11.3	< 0.001
Forties	115 (3.7)	465 (9.5)	
Fifties	373 (12.0)	928 (18.9)	
Sixties	981 (31.4)	1,486 (30.3)	
≥ Seventies	1,652 (52.9)	2,021 (41.2)	
Sex			< 0.001
Male	2,149 (68.9)	2,361 (48.2)	
Female	972 (31.1)	2,539 (51.8)	
Type of insurance			< 0.001
Self-employed health insurance	1,206 (38.6)	2,023 (41.3)	
Employee health insurance	1,675 (53.7)	2,723 (55.6)	
Medical aid	240 (7.7)	154 (3.1)	
Charlson comorbidities index	3.9 ± 2.4	3.7 ± 2.3	< 0.001
Comorbidities			
Metabolic disease	1,057 (33.9)	1,593 (32.5)	0.208
Diabetes mellitus	1,008 (32.3)	1,520 (31.0)	0.230
Cushing's syndrome	63 (2.0)	157 (3.2)	0.002
Adrenal insufficiency	51 (1.6)	89 (1.8)	0.543
Bone disease	650 (20.8)	1,041 (21.2)	0.654
Bone necrosis	17 (0.5)	16 (0.3)	0.137
Osteoporosis	588 (18.8)	967 (19.7)	0.323
Vertebral or pelvic fracture	195 (6.3)	210 (4.3)	< 0.001
Infectious disease	1,525 (48.9)	1,133 (23.1)	< 0.001
Pneumonia	1,445 (46.3)	1,040 (21.2)	< 0.001
Tuberculosis	359 (11.5)	222 (4.5)	< 0.001
Cardiovascular disease	1,907 (61.1)	3,006 (61.4)	0.826
Hypertension	1,697 (54.4)	2,831 (57.8)	0.003
Angina	439 (14.1)	620 (12.7)	0.068
Myocardial infarction	118 (3.8)	120 (2.5)	0.001
Congestive heart failure	487 (15.6)	512 (10.5)	< 0.001
Gastrointestinal disease	1,508 (48.3)	1,964 (40.1)	< 0.001
Peptic ulcer disease	1,498 (48.0)	1,950 (39.8)	< 0.001
Gastrointestinal bleeding	28 (0.9)	49 (1.0)	0.645
Ophthalmologic disease	155 (5.0)	223 (4.6)	0.392
Glaucoma	22 (0.7)	31 (0.6)	0.697
Cataract	140 (4.5)	196 (4.0)	0.290
Medication during follow-up*			< 0.001
Any ICS	2,583 (82.8)	3,430 (70.0)	< 0.001
Any LABA	2,257 (72.3)	2,968 (60.6)	< 0.001
Any LAMA	1,109 (35.5)	722 (14.7)	< 0.001
SABA	2,848 (91.3)	3,735 (76.2)	< 0.001
LTRA	1,836 (58.8)	2,894 (59.1)	0.836

Data are presented as frequency (%) and mean ± standard deviation.
COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β_2 agonist; LTRA, leukotriene receptor antagonist.
*Some patients received more than one medication.

fold (95% CI, 1.66–1.88) were more likely to die during the follow-up period. Regardless of the adjustment for covariables, the HRs remained significantly increased: the HRs in model 1 for which age and sex were adjusted were 1.32 (95% CI, 1.24-1.41), while the HR in model 2 in which type of insurance was further adjusted was 1.30 (95% CI, 1.22-1.39), and was 1.29 (95% CI, 1.21-1.38) in model 3 for which CCI was further adjusted. Subgroup analyses performed by the sex and age groups produced similar results.

After matching (**Supplementary Table S1**), in the survival analyses, patients with COPD had an increased risk of mortality compared to those without (HR, 1.37; 95% CI, 1.26-1.49).
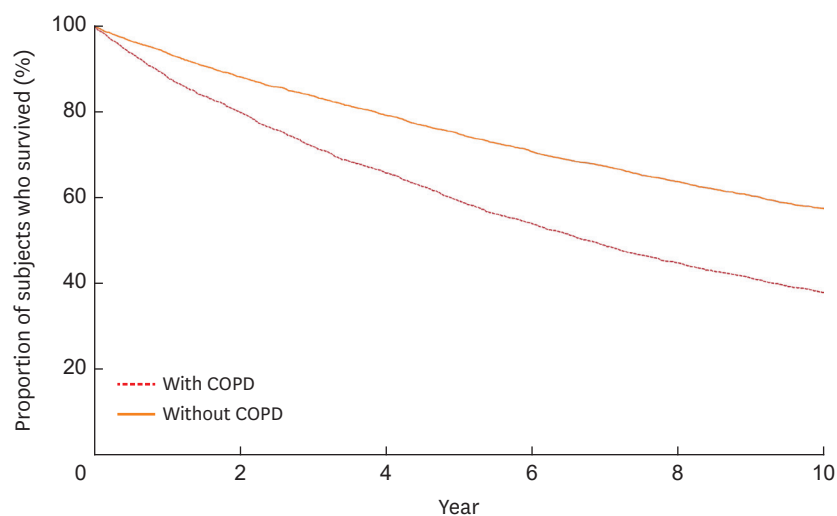
Subjects at risk						
With COPD	4,900	4,326	3,889	3,474	3,133	27
Without COPD	3,121	2,498	2,057	1,689	1,404	17

Figure. Kaplan-Meier survival plot of time to death.
COPD, chronic obstructive pulmonary disease.

Cause of mortality

The most common etiology of mortality in CS-dependent asthma patients was respiratory diseases (44.1%), followed by cardiovascular diseases (16.8%), malignancy (13.5%), injury, poisoning, and external causes (4.5%), and endocrine diseases (3.3%) (**Table 3**).

The cause-specific mortality risks associated with respiratory diseases (HR, 1.91; 95% CI, 1.73–2.11), including chronic lower respiratory diseases such as asthma, bronchiectasis, or COPD itself (HR, 2.23; 95% CI, 2.00–2.49) and lung cancer (HR, 1.46; 95% CI, 1.11–1.92), were greater in patients with COPD compared with those without COPD, which was consistent with the analyses

Table 2. The effects of COPD on mortality in patients with CS-dependent asthma

Variables	Mortality (/100,000 PY)	HR for mortality (95% CI)			
		Unadjusted model	Adjusted model		
			Model 1	Model 2	Model 3
Overall population[*]	7,085				
CS-independent asthma without COPD	9,955	Reference	Reference	Reference	Reference
CS-independent asthma with COPD	5,585	1.77 (1.66–1.88)	1.32 (1.24–1.41)	1.30 (1.22–1.39)	1.29 (1.21–1.38)
Male[†]	8,223				
CS-independent asthma without COPD	6,207	Reference	Reference	Reference	Reference
CS-independent asthma with COPD	10,964	1.75 (1.61–1.89)	1.36 (1.25–1.47)	1.33 (1.23–1.45)	1.33 (1.23–1.44)
Female[†]	5,776				
CS-independent asthma without COPD	5,036	Reference	Reference	Reference	Reference
CS-independent asthma with COPD	7,992	1.58 (1.42–1.76)	1.27 (1.14–1.41)	1.25 (1.12–1.39)	1.23 (1.11–1.37)
Age < 60[‡]	1,937				
CS-independent asthma without COPD	1,407	Reference	Reference	Reference	Reference
CS-independent asthma with COPD	3,653	2.60 (2.09–3.23)	2.26 (1.81–2.82)	2.13 (1.70–2.67)	2.09 (1.66–2.62)
Age ≥ 60[‡]	9,292				
CS-independent asthma without COPD	7,826	Reference	Reference	Reference	Reference
CS-independent asthma with COPD	11,593	1.47 (1.38–1.57)	1.26 (1.18–1.35)	1.24 (1.16–1.33)	1.24 (1.16–1.32)

COPD, chronic obstructive pulmonary disease; CS, corticosteroid; HR, hazard ratio; CI, confidence interval.
[*]Age and sex were adjusted in model 1. Age, sex, and type of insurance were adjusted in model 2. Age, sex, type of insurance, and Charlson comorbidities index were adjusted in model 3; [†]In subgroup analyses by sex, the above-mentioned variables (except sex) were adjusted in each model; [‡]In subgroup analyses by age, the above-mentioned variables (except age) were adjusted in each model.

Table 3. HRs (95% CIs) for mortality in patients with CS-dependent asthma and COPD relative to those without COPD

Variables	Total* (n = 3,939)	Without COPD (n = 2,042)	With COPD (n = 1,897)	Cause-specific HR (95% CI)	Cause-specific subdistribution HR (95% CI)[†]
Respiratory diseases	1,736 (44.1)	712/1,736 (41.0)	1,024/1,736 (59.0)	1.91 (1.73–2.11)	1.96 (1.77–2.17)
Chronic lower respiratory diseases	1,463 (37.1)	542/1,463 (37.0)	921/1,463 (63.0)	2.23 (2.00–2.49)	2.30 (2.06–2.57)
Pneumonia	132 (3.4)	85/132 (64.4)	47/132 (35.6)	0.73 (0.51–1.06)	0.68 (0.47–0.99)
Cardiovascular diseases	661 (16.8)	423/661 (64.0)	238/661 (36.0)	0.84 (0.71–0.99)	0.79 (0.67–0.93)
Hypertension	73 (1.9)	49/73 (67.1)	24/73 (32.9)	0.74 (0.44–1.22)	0.73 (0.45–1.19)
Ischemic heart disease	196 (5.0)	125/196 (63.8)	71/196 (36.2)	0.83 (0.61–1.12)	0.80 (0.59–1.09)
Heart failure	77 (2.0)	53/77 (68.8)	24/77 (31.2)	0.70 (0.43–1.15)	0.68 (0.41–1.12)
Cerebrovascular disease	199 (5.1)	132/199 (66.3)	67/199 (33.7)	0.74 (0.55–1.00)	0.70 (0.51–0.96)
Malignant neoplasms	532 (13.5)	284/532 (53.4)	248/532 (46.6)	1.19 (1.00–1.42)	1.10 (0.92–1.31)
Lung cancer	217 (5.5)	102/217 (47.0)	115/217 (53.0)	1.46 (1.11–1.92)	1.34 (1.02–1.78)
Other cancer	315 (8.0)	182/315 (57.8)	133/315 (42.2)	1.03 (0.82–1.30)	0.94 (0.75–1.19)
Injury, poisoning, and external causes	179 (4.5)	100/179 (55.9)	79/179 (44.1)	1.07 (0.79–1.46)	0.99 (0.73–1.35)
Endocrine diseases	130 (3.3)	102/130 (78.5)	28/130 (21.5)	0.39 (0.25–0.60)	0.38 (0.24–0.59)
Diabetes mellitus	121 (3.1)	95/121 (78.5)	26/121 (21.5)	0.39 (0.25–0.61)	0.37 (0.23–0.60)
Gastrointestinal diseases	75 (1.9)	49/75 (65.3)	26/75 (34.7)	0.83 (0.51–1.35)	0.78 (0.47–1.28)
Neurologic diseases	48 (1.2)	35/48 (72.9)	13/48 (27.1)	0.51 (0.26–0.98)	0.47 (0.24–0.90)
Mental and behavioral disorders	31 (0.8)	18/31 (58.1)	13/31 (41.9)	1.22 (0.59–2.54)	1.22 (0.58–2.58)
Musculoskeletal and connective tissue diseases	21 (0.5)	13/21 (61.9)	8/21 (38.1)	1.15 (0.46–2.88)	1.11 (0.46–2.65)
Osteoporosis	11 (0.3)	7/11 (63.6)	4/11 (36.4)	0.84 (0.24–3.01)	0.83 (0.25–2.81)
Other	526 (13.4)	306/526 (58.2)	220/526 (41.8)	1.02 (0.86–1.23)	0.97 (0.80–1.16)

Data are presented as number (%) and risk ratios (95% CI).
CS, corticosteroid; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.
*Thirty-five patients who did not have information regarding cause of mortality were excluded; [†]Subdistribution HR of the disease-specific cause of mortality was calculated with other causes of mortality as competing risks.

considering competing risks caused by other diseases: respiratory diseases (subdistribution HR, 1.96; 95% CI, 1.77–2.17), including chronic lower respiratory diseases (subdistribution HR, 2.30; 95% CI, 2.06–2.57) and lung cancer (subdistribution HR, 1.34; 95% CI, 1.02–1.78).

Similarly, after propensity matching, the cause-specific HRs and subdistribution HRs for mortality related to respiratory diseases (HR, 1.88; 95% CI, 1.68–2.10 and subdistribution HR, 1.87; 95% CI, 1.67–2.08) and lung cancer (HR, 1.49; 95% CI, 1.10–2.00 and subdistribution HR, 1.35; 95% CI, 1.01–1.82) were significantly increased in patients with COPD relative to those without COPD (**Supplementary Table S2**).

Healthcare use
The rates of annual ED visits (per 100,000 PY; 32,328 vs. 24,248 PY; $P < 0.001$), including asthma-related ED visits (10,970 PY vs. 6,163 PY; $P < 0.001$) and annual hospitalizations (323,882 PY vs. 200,597 PY; $P < 0.001$), asthma-related hospitalizations (112,684 PY vs. 53,343 PY; $P < 0.001$), were greater in patients with COPD than in those without. Similar results were obtained in propensity-matching analyses (data not shown).

DISCUSSION

This study evaluated the impact of coexisting physician-diagnosed COPD on long-term outcomes in patients with CS-dependent asthma using a large-scale, nationwide population-based, longitudinal cohort study. We showed that coexisting COPD is associated with increased risks of mortality, ED visits, and hospitalization. In addition, we also showed that CS-dependent asthmatic patients with COPD had increased risks of death due to chronic lower respiratory disease and lung cancer.

Coexisting COPD has a negative impact on patients with severe asthma. Previous studies revealed that patients with severe asthma and COPD are more likely to be older, male, and ever-smokers and to have lower lung function and exacerbations needing ER visits.[14,25] Similarly, our study showed that patients with CS-dependent asthma and COPD were older and had a higher proportion of males, lower socioeconomic status estimated by type of insurance, and higher CCI values than those without COPD. The major advantage of our study was that the negative impact of coexisting COPD on treatment outcomes in patients with CS-dependent asthma, including mortality, ED visits, and hospitalization, remained even after adjusting for these factors. The findings are strengthened by our use of a large population-based longitudinal cohort study design and by the similarity of the results obtained with and without the use of propensity matching.

As patients with severe asthma display many of the features of COPD, and there is, therefore, a considerable overlap between the 2 conditions, it is often challenging to distinguish severe asthma from COPD. Surprisingly, in this study, about 40% of patients with CS-dependent asthma were diagnosed as also having COPD by their attending physicians. Although the reasons why these patients were classified as having COPD are unclear, our study results suggest that early recognition of COPD in patients with CS-dependent asthma is important in real-world clinics especially when considering the potential vulnerabilities (older age, high CCI, and lower socioeconomic status), substantial healthcare use, and increased mortality among these patients. However, it is not known whether early diagnosis and management of coexisting COPD might be helpful in preventing poor treatment outcomes in patients with severe asthma. Further studies on this issue are urgently needed.

In our study, patients with CS-dependent asthma and COPD were more likely to die due to respiratory diseases and due to lung cancer than those without. Recognizing the causes of deaths and determining appropriate preventive strategies on the basis of the study results using a large-population database remain essential considerations to improve treatment outcomes of disease. Accordingly, our results emphasize the importance of disease control in patients with CS-dependent asthma and COPD. In our study, despite systemic CS use due to uncontrolled disease and recognition of COPD, the attending physicians prescribed LAMA to only about one-third of their patients. Although there is no direct evidence that the additional use of LAMA can reduce mortality in CS-dependent patients with severe asthma and COPD, there is limited evidence supporting the use of LAMA in addition to inhaled corticosteroid/LABA in patients with severe asthma.[25,26] As our study population had COPD, we also need to consider the impact of inhaler treatment on mortality in the context of COPD. Recent studies showed that triple therapy (in a single inhaler) showed improved survival after 1 year of treatment in patients with moderate-to-severe COPD.[27,28] Our results, together with previous study findings, may indicate that we need to build a strategy to optimize the medical treatment of patients with severe asthma and COPD.

One of the most important causes of death in COPD patients is lung cancer. A previous study reported that patients with COPD were about 3.2-fold more likely to die due to lung cancer than those without.[29] In our study, the cause-specific HR of mortality due to lung cancer was significantly increased in patients with COPD compared to those without. These results may imply that the surveillance of lung cancer development after recognition of COPD in CS-dependent patients with asthma and COPD is important. Other efforts to reduce exposure to risk factors for lung cancer, such as smoking, may also need to be emphasized.

This study had several limitations. First, this study enrolled subjects from a single country. As the prevalence of asthma and COPD according to age and sex and the patterns of drug prescription differ by ethnicity and country, future studies considering the influence of those factors are needed. Secondly, the baseline characteristics of patients with and without COPD were quite different. Thus, we verified our results using 2 methods (*i.e.*, adjustment for covariables and propensity matching methods). Regardless of the statistical method used, our study results consistently showed that patients with COPD had a higher risk of mortality and increased healthcare use. Thirdly, we used only the ICD-10 codes to define COPD since spirometric data were not available. Accordingly, the severity of COPD (*i.e.*, Global Initiative for Chronic Obstructive Lung Disease severity) could not be taken into consideration in our analyses. However, it is notable that the recognition of COPD by attending physicians in real-world clinics have significantly reflected the outcomes in this population. Fourthly, we could not analyze the impact of important confounders, such as occupation, education, and smoking habits, as the claims data did not include these variables. However, we included the type of insurance which may have provided partial adjustment for socioeconomic exposure. Despite these limitations, our study was strengthened by the use of a large, nationwide study population.

In conlusion, in this population-based retrospective cohort study, the diagnosis of COPD was associated with a greater rate of mortality in patients with CS-dependent asthma. The main causes of mortality were chronic lower respiratory diseases and lung cancer. The findings suggest that early recognition and proper management of COPD may improve treatment outcomes in patients with CS-dependent asthma.

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SUPPLEMENTARY MATERIALS

Supplementary Table S1
Characteristics of patients with CS-dependent asthma COPD vs. those without COPD after propensity score matching

Click here to view

Supplementary Table S2
HRs (95% CIs) for mortality in patients with CS-dependent asthma and COPD relative to those without COPD after matching

Click here to view

Supplementary Fig. S1

Propensity score overlap between patients with corticosteroid-dependent asthma and COPD and those without COPD.

Click here to view

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