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ORIGINAL RESEARCH

Risk of Pneumonia Associated with Inhaled Corticosteroid in Patients with Chronic Obstructive Pulmonary Disease: A Korean Population-Based Study

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Introduction: Inhaled corticosteroids (ICSs) are recommended for patients with frequent exacerbation of chronic obstructive pulmonary disease (COPD). However, accumulating evidence has indicated the risk of pneumonia from the use of ICS. This study aimed to investigate the association between ICS and pneumonia in the real-world clinical setting.

Methods: A retrospective cohort study was performed using nationwide population data from the Korea National Health Insurance Service. Subjects who had a new diagnosis of COPD and who received inhaled bronchodilators without a diagnosis of pneumonia before the initiation of bronchodilators were identified. Subjects were followed up until their first diagnosis of pneumonia. The risk of pneumonia in ICS users was compared to that in non-ICS users.

Results: A total of 87,594 subjects were identified and 1:1 matched to 22,161 ICS users and non-ICS users. More ICS users were diagnosed with pneumonia compared to non-ICS users (33.73% versus 24.51%, $P<0.0001$). The incidence rate per 100,000 person-years was 8904.98 for ICS users and 6206.79 for non-ICS users. The hazard ratio (HR) of pneumonia for ICS users was 1.62 (95% CI 1.54–1.70). The HR of subjects prescribed with the lowest ICS cumulative dose was 1.35 (1.27–1.43). The HR increased to 1.51 (1.42–1.60), 1.96 (1.85–2.09), and 2.03 (1.89–2.18) as the cumulative dose increased. Pneumonia was strongly associated with fluticasone propionate (1.79 (1.70–1.89)) and fluticasone furoate (1.80 (1.61–2.01)) use, compared to the use of other types of ICS.

Conclusion: ICS increases the risk of pneumonia in patients with COPD. Hence, ICS should be carefully prescribed in patients with risk factors for pneumonia while considering the cumulative doses and subtypes of ICS.

Keywords: inhaled corticosteroid, chronic obstructive pulmonary disease, pneumonia, fluticasone

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease characterized by irreversible airflow limitations. The principal treatment strategy includes the use of long-acting inhaled bronchodilators, such as long-acting muscarinic antagonists (LAMA) and long-acting β_2 agonists (LABA).[1] They can improve respiratory symptoms, lung function and physical activity, and notably decrease the exacerbation rate.[2] The use of inhaled corticosteroids (ICSs) is another

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therapeutic strategy for COPD. However, the role of ICS in the treatment of COPD remains controversial.[3,4] Therefore, ICS is recommended for specific target populations in the current COPD guidelines.[5]

Although ICS has been beneficial in terms of reducing the rate of acute exacerbation, it entails various adverse effects.[6] Respiratory adverse effects include pneumonia, tuberculosis, and non-tuberculous mycobacterial infection. Systemic adverse effects include diabetes, bone fractures, cataracts, and adrenal insufficiency.[7] Among these, pneumonia can cause potential damage to patients with COPD because it is closely linked with COPD exacerbation.[8] The association of ICS use with pneumonia has been reported in many studies including randomized controlled trials (RCTs) and meta-analyses.[9] However, there are still inconsistent results regarding which types of ICS are not associated with the likelihood of developing pneumonia.[10]

Real-life observational studies include a more heterogeneous population with broader inclusion criteria that could be excluded in RCTs.[11] They can support or strengthen the results of previous RCTs with narrow inclusion criteria. However, there is limited evidence of an association between ICS use and pneumonia in observational studies. Studies with long-term observational periods of more than 10 years are scarce, and almost all data are obtained from Western countries or their local communities, not from a nationwide population-based cohort. In addition, the risk of pneumonia for cumulative doses of ICS and ICS types other than fluticasone propionate and budesonide has not been addressed. This study aimed to determine whether the use of ICS elevates the risk of pneumonia in patients with COPD in a nationwide population cohort with an observation period of 13 years.

Methods

Data Source

In our retrospective cohort study, data from the Korea National Health Insurance Service (NHIS) were used. The NHIS is a unique health insurance program launched in 2002 by the government, covering approximately 97% of the Korean population. The remaining 3% of the population is insured by the Medical Assistance Program. Healthcare providers, including those from clinics, hospitals, and pharmacies in Korea, submit claims of their healthcare services to the NHIS electronically; these are then reimbursed. The claims data of the NHIS include healthcare utilization information for both inpatients and outpatients, such as patient demographics, diagnoses, procedures, surgical histories, and prescription drugs, which are provided for research purposes. The International Classification of Disease and Related Health Problems, 10th revision (ICD-10), was adopted in the NHIS to classify diseases according to diagnostic codes (Supplementary Table S1). Data on the diagnostic codes, diagnostic procedures, and prescription information including product names, dosages, prescription dates, and durations were collected.

Study Subjects

Among the entire nationwide population data, subjects with a diagnostic code of COPD (J42– J44, except J430) at least two times between January 01, 2005, and December 31, 2018, were included, and subjects with a diagnostic code of lung malignancy at least one time during the same period were excluded. In addition, subjects who did not undergo pulmonary function tests 1 year before or after the COPD diagnosis were excluded. Then, data were randomly 50% sampled by a revised NHIS policy for medical research related to medications. The subjects with COPD (n = 87,594) were included from the claims data if the following criteria were met: 1) age ≥40 years; 2) new COPD diagnostic code since January 01, 2005; 3) prescription of at least one type of inhaled bronchodilator such as LAMA, LABA, ICS, or short-acting β_2 agonist (SABA), after the COPD diagnosis; 4) no prescription with different components of ICS simultaneously; 5) no diagnosis of pneumonia before the index date; 6) no death before the index date; and 7) sufficient medication records. Study subjects were followed up until their initial diagnosis of pneumonia, their death, or to end of the follow-up period, whichever came first.

ICS users were defined as having prescribed ICS for at least 1 month, while non-ICS users were defined as those not prescribed ICS ever during the study period. Index date was calculated as the day of the first prescription of LAMA, LABA, and/or SABA for non-ICS users, and the day of the first prescription of ICS for ICS users. The bronchodilators prescribed during the 12 months after the index date were classified as SABA, LAMA, LABA, and LAMA + LABA combinations. Comorbidities were identified if at least two diagnostic codes were recorded during the study period, from the initial diagnosis of COPD to the final follow-up date. Asthma, interstitial lung disease, diabetes, hypertension, heart failure, chronic kidney disease, and chronic liver disease were considered as comorbidities. Severe exacerbation of COPD was defined as

a history of admission within 12 months prior to the index date where the main diagnosis was COPD. The proportion of subjects who received oral corticosteroids (OCSs) and OCS prescriptions day in the 12 months prior to the index date was analyzed. The intervals from the subjects' COPD diagnosis to the index date were also calculated. This study was approved by the Institutional Review Board of Wonju Severance Christian Hospital (CR318361). The requirement for informed consent was waived for the study as it retrospectively analyzed anonymous claim data.

Study Outcomes

The primary endpoint was the difference in the development of pneumonia between ICS users and non-ICS users. The secondary endpoint was the difference in the development of pneumonia derived from the subgroup analysis of ICS users: 1) cumulative dose of ICS, 2) daily dose of ICS, and 3) type of ICS. Cases of pneumonia were defined as cases with an initial claim date under the diagnostic code of pneumonia (J10–J18) in the time since the index date, regardless of whether they were claimed at inpatient or outpatient clinics.[12] The cumulative ICS dose was the summation of all prescribed doses of ICS, which was divided into four groups of quartiles according to 25%, 50%, and 75% of the population. The daily dose of ICS was calculated by dividing the total prescribed doses of ICS by the prescription period. The dosages of the various types of ICSs were converted into the equivalent doses of fluticasone propionate. Fluticasone propionate (50 μg) was equivalent to beclomethasone (100 μg), beclomethasone HFA (50 μg), budesonide (80 μg), ciclesonide (32 μg), and fluticasone furoate (10 μg).[13] Daily doses of ICS were classified into low (1–499 μg), medium (500–999 μg) and high doses (≥1000 μg) in reference to fluticasone propionate.

Statistical Analysis

ICS users and non-ICS users were chosen by applying propensity score matching to decrease selection bias. A 1:1 matching between ICS users and non-ICS users was performed using a logistic regression that included variables such as age, sex, comorbidities, history of COPD exacerbation, presence of OCS prescription, duration of OCS prescription, and interval period from COPD diagnosis to the index date. Baseline clinical characteristics of the ICS users and non-ICS users were compared using Student's *t*-test for continuous variables and the Chi-square test for categorical variables. Survival analysis over time was analyzed using Kaplan–Meier curves with a Log rank test. The types of ICSs were not included in the survival analysis because the durations of the prescriptions of some ICSs such as beclomethasone, ciclesonide, and fluticasone furoate were insufficient. Cox proportional hazards analyses were conducted to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the association between the prescription of ICS and the development of pneumonia. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). A *P*-value less than 0.05 was considered statistically significant.

Results

Demographics of the Study Subjects

The number of subjects diagnosed with COPD without lung cancer between 2005 and 2018 and who were receiving pulmonary function tests before or after 1 year since their COPD diagnosis was 1,545,246. The exclusion criteria were applied to half of the subjects through 50% sampling. As a result, 87,594 subjects with COPD were identified (59,694 ICS users and 27,900 non-ICS users). Both groups were finally matched to 22,161 ICS users and 22,161 non-ICS users (Figure 1).

Age distribution, sex, and comorbidities did not differ between ICS users and non-ICS users. Mean age was 65.4 ± 11.0 years for ICS users and 65.4 ± 11.0 years for non-ICS users ($P = 0.9281$). The proportion of male subjects was 72.40% for ICS users and 71.91% for non-ICS users ($P = 0.2435$). The history of COPD exacerbation and the proportion of OCS prescriptions 12 months prior to the index date were also comparable between the two groups. OCS prescription duration was 8.44 ± 13.56 days for ICS users, which was longer than the 7.79 ± 13.93 days for non-ICS users ($P < 0.0001$). There was a difference in the use of bronchodilators in addition to ICS use. SABA and LAMA were prescribed more frequently for non-ICS users compared to ICS users, while LABA was more frequently used for ICS users than for non-ICS users (Table 1).

Fluticasone propionate was the most frequently prescribed ICS (51.60%), followed by budesonide (22.80%), fluticasone furoate (11.37%), beclomethasone (9.73%), and ciclesonide (4.50%). The mean cumulative dose of ICSs was 132,315.7 ± 338,241.0 μg. The cumulative doses of ICS were divided into four quartiles: 1–15,000 μg (Q1), 15,000–30,720 μg (Q2), 30,721–107,160 μg (Q3), and >107,610 μg (Q4) according to the proportion

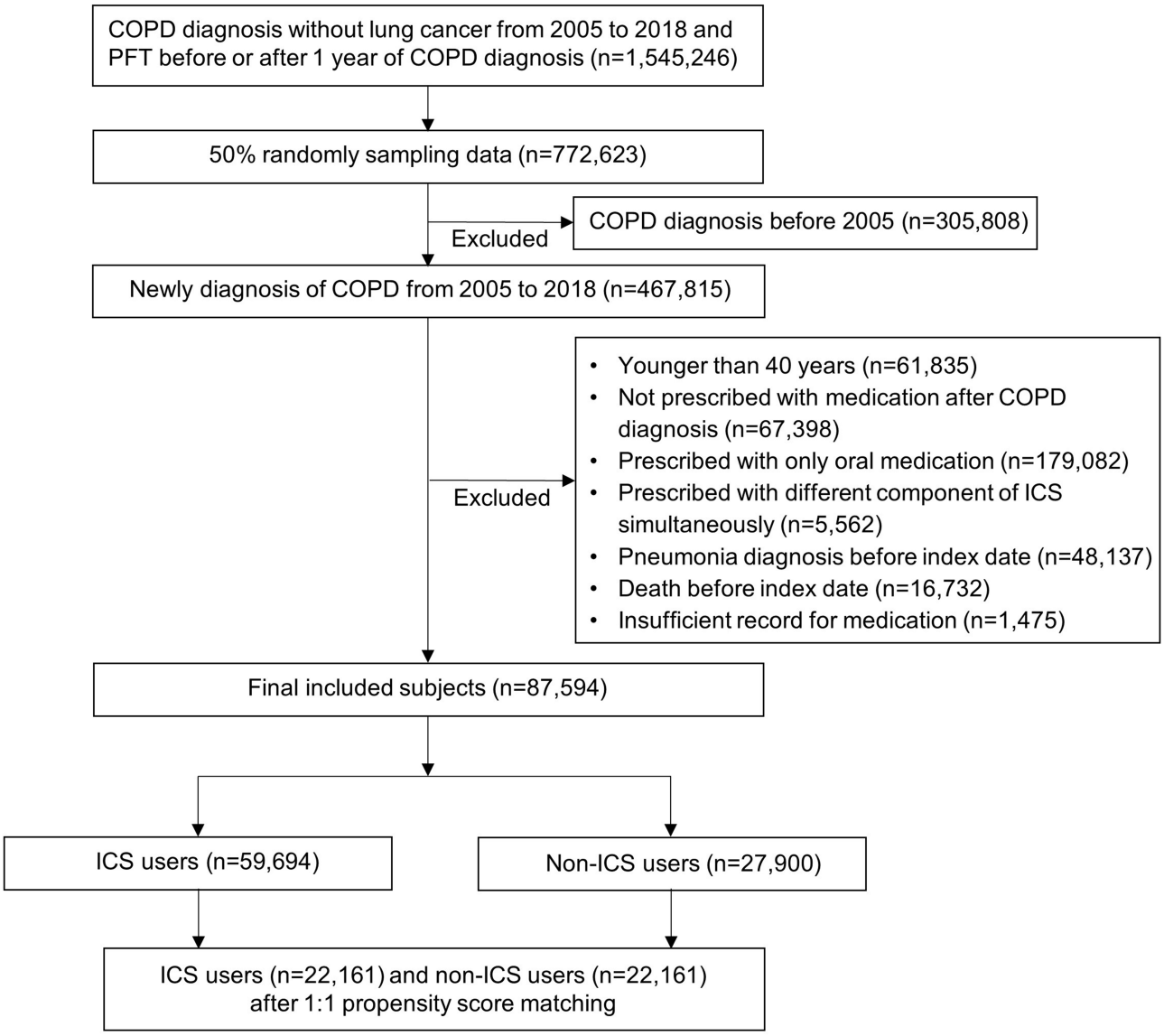

Figure 1 Patient selection flowchart.

of subjects. For the daily doses of ICS, 60.81% and 33.08% were classified as low and medium doses, respectively, while 6.11% were classified as on high doses (Table 2).

Incidence of Pneumonia in ICS Users

For ICS users, 7473 (33.73%) subjects were identified as having pneumonia during the study period, which was larger than the 5432 (24.51%) group of non-ICS users ($P < 0.0001$). The incidence rate per 100,000 person-years was 8904.98 for ICS users and 6206.79 for non-ICS users. The incidence of pneumonia increased with an increase in the cumulative ICS dose. Incidence rate was 7407.53 in Q1, 7502.87 in Q2, 9376.11 in Q3, and 11,096.63 in Q4. However, the incidence of pneumonia did not correlate with the daily ICS dose. The incidence rate was 8771.55 for low doses, 9126.64 for medium doses, and 8836.10 for high doses. The incidence of pneumonia varied according to the type of ICS. The incidence rate was 9434.95 for fluticasone propionate, 7614.98 for budesonide, 8388.57 for beclomethasone, 7252.61 for ciclesonide, and 12,278.90 for fluticasone furoate (Table 3). The cumulative proportion of patients who had a diagnosis of pneumonia over time was analyzed. In ICS users, pneumonia occurred more frequently than in non-ICS users (Figure 2A). Pneumonia occurred gradually over time rather than abruptly at a specific peak time. In addition, pneumonia occurred more frequently in those receiving higher cumulative

Table 1 Baseline Characteristics of the Study Subjects

	ICS Users (n=22,161)		Non-ICS Users (n=22,161)		*P* value
	n	%	n	%	
Age					
Mean (SD)	65.4 (11.0)		65.4 (11.0)		0.9281
40–49	1968	8.88	2021	9.12	0.4082
50–59	4590	20.71	4742	21.40	
60–69	7106	32.07	7059	31.85	
70–79	6329	28.56	6208	28.01	
≥ 80	2168	9.78	2131	9.62	
Sex					
Male	16,044	72.40	15,935	71.91	0.2435
Female	6117	27.60	6226	28.09	
Comorbidity					
Asthma	10,926	49.30	11,318	51.07	0.0060
Interstitial lung disease	325	1.47	344	1.55	0.3115
Diabetes	5623	25.37	5665	25.56	0.5779
Hypertension	10,105	45.60	10,242	46.22	0.0859
Heart failure	3746	16.90	3792	17.11	0.5436
Chronic kidney disease	839	3.79	881	3.98	0.3247
Chronic liver disease	6609	29.82	6716	30.31	0.1557
CCI					
Mean (SD)	2.78 (1.94)		2.83 (1.98)		0.0375
< 2	12,195	55.03	0.0050	53.96	0.0050
≥ 2	9966	44.97	10,203	46.04	
Bronchodilator					
SABA	1261	5.69	6166	27.82	<0.0001
LAMA	119	0.54	8761	39.53	
LABA	15,054	67.93	1037	4.68	
LAMA + LABA	5727	25.84	6197	27.96	
Severe exacerbation of COPD					
Yes	990	4.47	1045	4.72	0.1880
No	21,171	95.53	16,729	95.28	
OCS prescription					
Yes	17,186	77.55	17,322	78.16	0.1336
No	4975	22.45	4839	21.84	
OCS prescription day					
Mean (SD)	8.44 (13.56)		7.79 (13.93)		<0.0001
Interval from COPD diagnosis to index date					
Mean (SD)	315.3 (711.7)		344.6 (801.5)		<0.0001

Abbreviations: ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LABA, long-acting β_2 agonist.

doses of ICS (Figure 2B). The daily dose of ICS did not influence the occurrence of pneumonia (Figure 2C).

Risk of Pneumonia in ICS Users

The risk of pneumonia in ICS users and their subgroup was compared to that of non-ICS users. HR for the development of pneumonia in ICS users was 1.62 (95% CI 1.54–1.70) ($P < 0.0001$). The HR of Q1 subjects prescribed with the lowest ICS cumulative dose was 1.35 (1.27–1.43) ($P < 0.0001$). HR increased to 1.51 (1.42–1.60) in Q2 subjects, 1.96 (1.85–2.09) in Q3 subjects, and 2.03 (1.89–2.18) in Q4 subjects prescribed with the highest ICS cumulative doses (all $P < 0.0001$). The risk of pneumonia did not correlate with the daily ICS dose. HR was 1.59 (1.51–1.68) in low-dose ICS users, 1.67 (1.59–1.77) in medium-dose ICS users, and 1.55 (1.40–1.71) in high-dose ICS users (all $P < 0.0001$). The risk of pneumonia varied according to the type of ICS. The HRs of fluticasone propionate and fluticasone furoate were 1.79 (1.70–1.89) and 1.80 (1.61–2.01), respectively (all $P < 0.0001$). However, HR of other types of ICS decreased to 1.44 (1.35–1.54) in budesonide, 1.52 (1.38–1.68) in beclomethasone, and 1.29 (1.14–1.45) in ciclesonide (all $P < 0.0001$) (Figure 3 and Supplementary Table S2).

Discussion

In this study, the use of ICS was significantly associated with the development of pneumonia in COPD patients. The risk of pneumonia increased with an increase in the cumulative ICS cumulative dose, while it was not correlated with the daily dose of ICS. In addition, the risk of

Table 2 Characteristics of Inhaled Corticosteroid Users

	ICS User (Total 22,261)	
	n	%
ICS cumulative dose		
Mean (SD)	132,315.7 (338,241.0)	
Medium (Q1, Q3)	30,720 (15,000, 107,160)	
1–15,000 μg	5542	25.01
15,001–30,720 μg	5925	26.73
30,721–107,160 μg	5156	23.27
> 107,610 μg	5538	24.99
ICS dose		
Low	13,477	60.81
Medium	7330	33.08
High	1354	6.11
Type of ICS		
Fluticasone propionate	11,436	51.60
Budesonide	5062	22.80
Beclomethasone	2156	9.73
Ciclesonide	997	4.50
Fluticasone furoate	2520	11.37

Abbreviation: ICS, inhaled corticosteroid.

Table 3 Crude Incidence Rate of Pneumonia According to the ICS Type and Dose

Variables	Person Year	Pneumonia Patients	Incidence Rate (per 100,000)
Non-ICS user	87,517.00	5432	6206.79
ICS user	83,919.32	7473	8904.98
ICS cumulative dose (μg)			
1–15,000	22,396.12	1659	7407.53
15,000–30,720	18,486.25	1387	7502.87
30,721–107,160	20,264.26	1900	9376.11
> 107,610	22,772.68	2527	11,096.63
ICS dose			
Low	48,189.90	4227	8771.55
Medium	30,602.72	2793	9126.64
High	5126.70	453	8836.10
Type of ICS			
Fluticasone propionate	49,698.20	4689	9434.95
Budesonide	21,076.88	1605	7614.98
Beclomethasone	6139.31	515	8388.57
Ciclesonide	3902.04	283	7252.61
Fluticasone furoate	3102.88	381	12,278.90

Abbreviation: ICS, inhaled corticosteroid.

pneumonia differed according to the types of ICS; fluticasone propionate and fluticasone furoate were highly associated with pneumonia compared to other ICS types.

The risk of pneumonia due to ICS use was first reported in the TORCH study.[14] In that study, the relative risk of pneumonia in ICS users compared to non-ICS users was 1.52 (1.32–1.76) and the incidence rate of pneumonia per 100,000 persons was 5200 for non-ICS users and 8800 for ICS users, which is similar to our study results. Subsequent RCTs and meta-analyses also raised concerns about the risk of pneumonia from the use of ICS in COPD.[15,16] However, some RCTs reported that ICS use did not increase the risk of pneumonia.[17–19] These contradictory results in clinical trials might be attributable to the differences in study protocols and populations, the severity of COPD, risk factors of pneumonia, and misdiagnosis of pneumonia.[20]

RCTs can demonstrate a direct causal relationship through strict inclusion criteria. However, approximately 90% of COPD patients do not meet the inclusion criteria of these clinical trials.[11] However, observational studies have a wide spectrum of inclusion criteria and can represent the actual population, including primary care settings. Previous observational studies using the health administrative databases of local communities or nations also showed an elevated risk of pneumonia from the use of ICSs in COPD.[21–26] The relative risk of pneumonia in ICS users was 1.11–1.70. The present study also showed an increased risk of pneumonia in this patient population. Although additional evidence with rigorous criteria is necessary, the association between the risk of pneumonia and ICS use has been found in most observational studies, consolidating the positive results seen in the RCTs and meta-analyses.

The HR of 1.62 in the present study ranges within the risk seen in previous observational studies (1.11–1.70).[21–26] However, this figure is relatively higher than that in other studies. The reason for the higher risk of pneumonia might be attributable to the characteristics of Korean patients with COPD as well as the study duration. Low body mass index

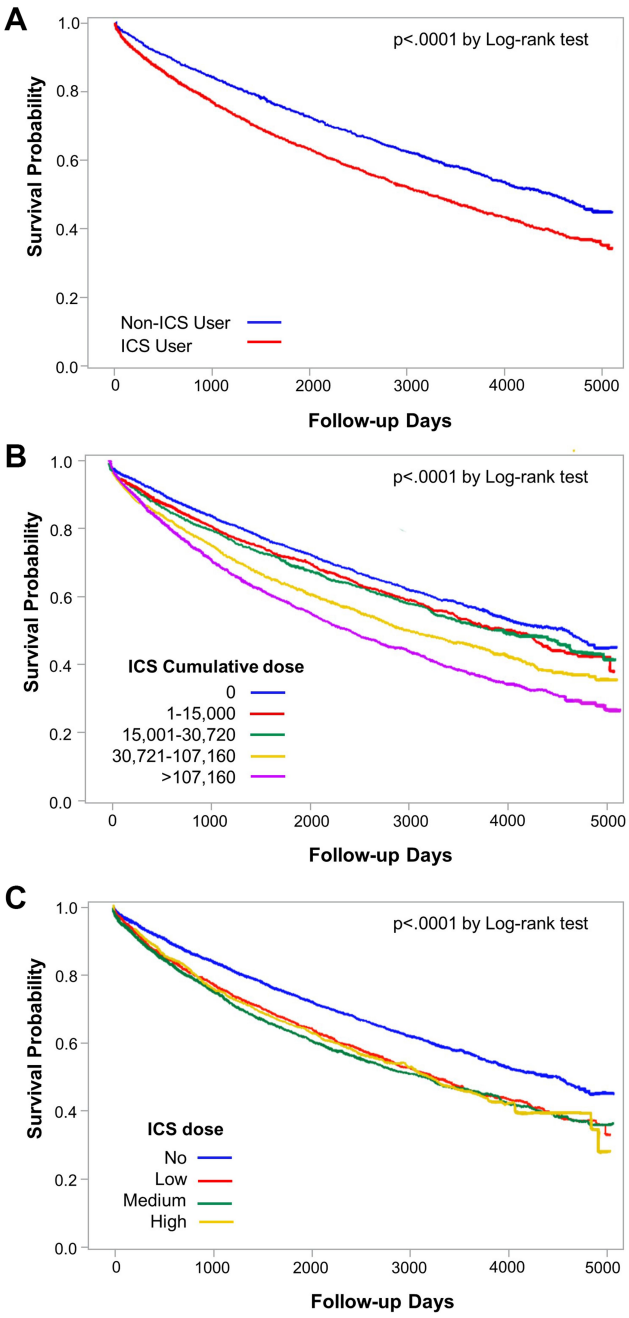

Figure 2 Survival analysis of the development of pneumonia using Kaplan–Meier curve according to the use of inhaled corticosteroid (ICS) (**A**), cumulative dose of ICS (**B**), and daily dose of ICS (**C**).

(BMI) is an independent risk factor of pneumonia in COPD.[27] The mean BMI of patients enrolled in the Korean COPD cohort was 23 ± 3 kg/m^2, which is lower than 27 ± 6 kg/m^2 observed in the Western COPD cohort in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study.[28] Another characteristic was lung function. Lung function, such as FEV_1 and FVC, is usually presented as a predictive value (%). However, the absolute value of lung function from healthy adults presented in liters was significantly lower in Asians than in whites.[29] In this regard, although COPD patients from different races have the same airflow limitations determined via predictive values, their absolute lung functions might be significantly different. Lower lung function was found to be an independent risk factor for pneumonia, and the recommended dosage of ICS is consistent regardless of ethnic differences.[5,27] Therefore, the risk of pneumonia could be increased in the Korean population. The present study had

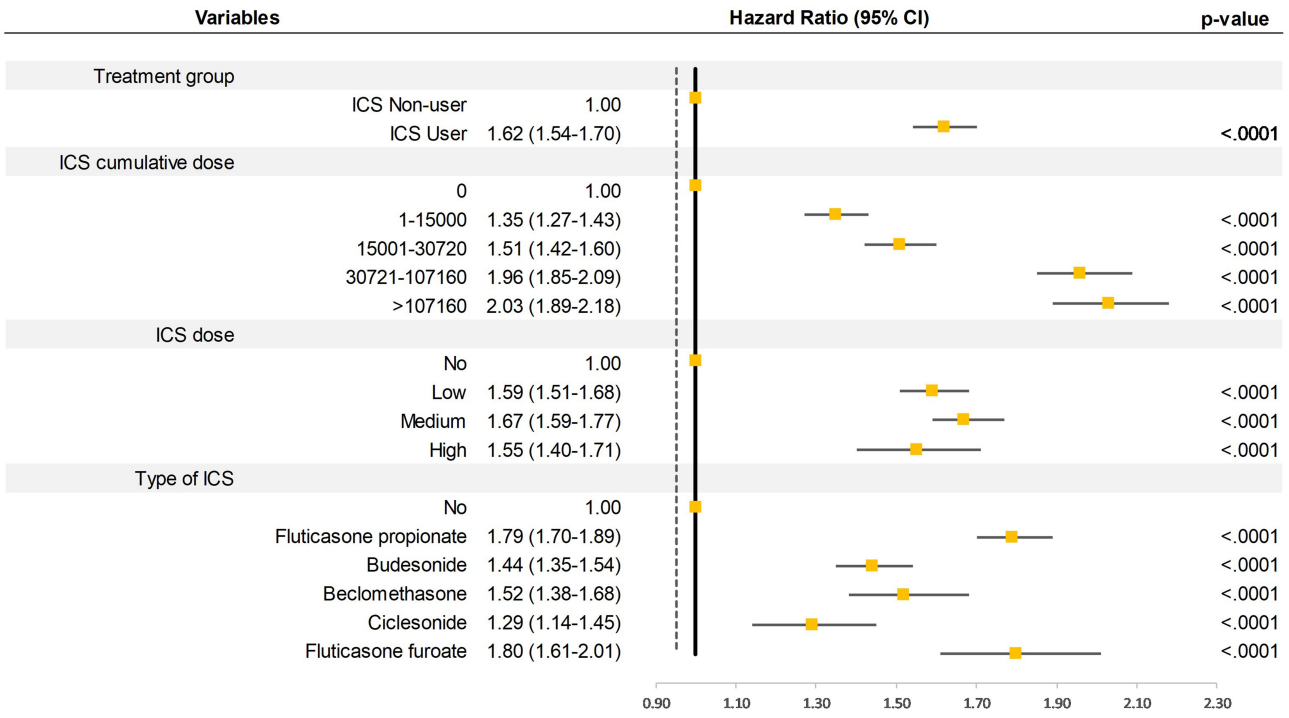

Figure 3 Hazard ratios of pneumonia according to the use of inhaled corticosteroid (ICS) and subtype of ICS users.

a long observational period of 13 years, while the observational period of other studies was usually 5 years.[20] Therefore, differences in the incidence of pneumonia between ICS users and non-ICS users might become prominent during longer observation periods.

Cumulative doses of ICSs were rarely taken into account when considering the risk of pneumonia. Instead, the daily doses of ICS, classified into low, medium and high doses, were regarded as significant factors associated with pneumonia. An observational study examining the commercial healthcare database of an American population reported that the HR of pneumonia increased as the daily ICS doses increased: 1.38 (1.27–1.49), 1.69 (1.52–1.88), and 2.57 (1.98–3.33) for low, medium, and high doses of ICS, respectively.[25] Another observational study analyzing Taiwan's nationwide, population-based database also showed that the odds ratio of pneumonia increased with an increment in the daily ICS dose: 1.10 (1.04–1.16), 1.33 (1.26–1.39), and 1.63 (1.50–1.78) for low, medium, and high doses of ICS, respectively.[26] Side effects from the cumulative dose of ICS in COPD patients, particularly elderly patients, include tuberculosis, risk of fractures, and cataracts.[13,30] The reason for the link between the risk of pneumonia and the cumulative dose of ICS in the present study seems inexplicable. Although ICS use is an effective treatment strategy, its overuse has been increasingly recognized. Almost 70% of COPD patients were reported to receive ICSs when enrolled in RCTs and market surveys.[31] In the present Korea NHIS data, 59,694/87,594 (68.15%) COPD patients were treated with ICS. Therefore, ICSs may be overly prescribed in the actual clinical setting for the treatment of COPD. Given that the cumulative dose of ICS is another risk factor for pneumonia, we need to follow the recommendation of COPD guidelines that recommend that ICSs should be discontinued if pneumonia or a lack of response to ICSs is present.[5] In the observational study by Suissa., et al, the risk of pneumonia gradually decreased after discontinuation of ICS and disappeared after 6months.[21]

It remains to be confirmed whether some types of ICS result in a higher risk of pneumonia, since most study results were derived from indirect comparisons between fluticasone propionate and budesonide in the meta-analyses and observational studies. In the meta-analyses, fluticasone propionate was consistently associated with an increased risk of pneumonia (odds ratio, 1.43–1.75), while budesonide was not associated with pneumonia (odds ratio of 0.84–1.19).[32–36] In the observational study by Suissa et al, the relative risk of pneumonia was 2.01 (1.93–2.10) for fluticasone propionate compared to 1.17 (1.09–1.26) for budesonide.[21] In the study using Swedish registry medical records, the rate ratio of pneumonia in subjects treated with fluticasone propionate in comparison to those treated with budesonide was 1.73 (1.57–1.90).[37] A Taiwan's population-based study showed a significantly increased risk

of pneumonia in subjects treated with a fluticasone propionate-containing regimen (odds ratio, 1.22–1.35), but no statistically significant risk of pneumonia in those treated with a budesonide-containing regimen.[26] The present study results are consistent with those of previous studies that a higher risk of pneumonia was associated with fluticasone propionate use than with budesonide (HR, 1.79 (1.70–1.89) versus 1.44 (1.35–1.54)). In addition, fluticasone furoate was highly associated with pneumonia (1.80 (1.61–2.01)). Therefore, the type of ICS should be carefully determined when prescribing ICSs to patients with risk factors for pneumonia, and subsequent observational studies are needed to confirm the different risks of pneumonia according to ICS subtypes.

The strength of the present study is its study design: we performed a nationwide population-based cohort study with a long-term observational period. Almost all Korean populations were included in the NHIS so that it could be the representative data of our country. While other observational studies adopted a case-control design,[21–24] the present study was conducted by using a cohort design to clarify the causal relationship between ICS use and the risk of pneumonia. In addition, daily doses of ICS and some type of ICS, such as fluticasone propionate and budesonide, were mainly reported as risk factors for pneumonia in other observational studies.[20] However, the cumulative dose of the ICS and every type of ICS prescribed for COPD in real-world clinical settings were compared in the present study.

There are limitations to this study. First, although we performed 1:1 propensity score matching, the severity of COPD might not match for ICS users and non-ICS users without the available clinical information of COPD in the claims database. Instead, COPD admission, OCS prescription, and OCS prescription duration were used as surrogates for COPD severity in the propensity score matching. Second, diagnosis of pneumonia was only based on diagnostic codes and was not radiologically confirmed. However, this is an inherent issue in most studies related to pneumonia, regardless of the study design. Third, the proportion of asthma as a comorbidity was approximately 50% in both groups. Although some proportion of subjects with asthma as a comorbidity had asthma-COPD overlap features, this might be due to the definition of comorbidities, which was solely based on the diagnostic codes. Because at least two diagnostic codes were recorded during the entire study period, these were defined as comorbidities. A population-based study from Taiwan, which has a healthcare system similar to Korea, also reported a high proportion of asthma as a comorbidity (approximately 50%).[26]

Conclusion

The use of ICS increases the risk of pneumonia in patients with COPD. Therefore, ICSs should be carefully prescribed in patients with risk factors for pneumonia, considering the cumulative doses and subtypes of ICS.

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