

The Impact of Inhaled Corticosteroids on the Prognosis of Chronic Obstructive Pulmonary Disease

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Background: A comprehensive analysis of the effects of inhaled corticosteroids (ICS) on COPD in a real-world setting is required due to safety concerns regarding ICS in COPD. This study aimed to explore the impact of ICS on the prognosis of Asian COPD patients in the real-life world.

Methods: We examined 978 COPD patients registered in the Korean National Health and Nutrition Examination Survey (KNHANES) database and with their data linked to Health Insurance and Review Assessment (HIRA) data. The outcome measures were ascertained by HIRA from January 1, 2009, to December 31, 2012. This study enrolled two arms; ICS users (N = 85, mean age = 66.7 ± 8.9 years) and non-ICS users (N = 893, mean age = 63.7 ± 9.7 years).

Results: Compared to the non-ICS users, the ICS users had a higher rate of pneumonia, tuberculosis, and acute exacerbations ($P < 0.05$). Hospitalization due to respiratory causes was also higher among ICS users ($P < 0.05$). Multivariate analysis showed that acute exacerbation was independently associated with the development of pneumonia ($P < 0.05$), whereas ICS therapy had a tendency to be associated with pneumonia. Another multivariate analysis demonstrated that old age, FEV₁, ICS therapy, and pneumonia were independently associated with the occurrence of acute exacerbation ($P < 0.05$). The concomitant pneumonia (HR = 3.353, $P = 0.004$) was independently associated with higher mortality ($P < 0.05$).

Conclusion: Our data demonstrated that the ICS users had a higher rate of pneumonia and tuberculosis and the concomitant pneumonia was independently associated with higher mortality, highlighting the importance of cautious and targeted administration of ICS in COPD.

Keywords: COPD, inhaled corticosteroids, pneumonia, mortality

Introduction

Although chronic obstructive pulmonary disease (COPD) has been a major public health concern and was expected to rank third among all the causes of death by 2030, there is still no therapeutic intervention that modifies the natural course of COPD.^{1,2} The pharmacological treatment of COPD comprises long-acting muscarinic antagonist (LAMA), long-acting beta-agonists (LABA), the combination of LAMA and LABA, the combination of LABA and inhaled corticosteroids (ICS), and triple therapy including LABA, LAMA, and ICS. The benefits of ICS in COPD reported by various studies include the reduction of frequency of COPD exacerbations, a lower rate of hospitalization, and a reduction of all-cause mortality in some COPD subgroups.³⁻⁶ However, the use of ICS in COPD is much debated because of the associated

safety concerns;^{7–10} there is a concern about the attendant side effects of ICS on COPD including pneumonia and tuberculosis.^{11,12} Consequently, the withdrawal of ICS in COPD patients is common due to ICS-related adverse events or treatment-related risks outweighing the expected benefits.^{13,14} In addition, ICS treatment is associated with several challenges; observational studies suggested that overprescription of ICS is common in patients with COPD and smoking can result in steroid resistance by decreasing the efficacy of ICS in COPD.^{13,15,16}

However, so far, there are few comprehensive analyses of the effects of ICS on COPD in a real-world setting. Hence, this study was conducted to investigate the impact of ICS on the prognosis of Asian COPD patients in the real world setting by analyzing the Korean National Health and Nutrition Examination Survey (KNHANES) merged with Health Insurance and Review Assessment (HIRA) data.

Methods

Study Population

This study analyzed the KNHANES data that was linked to HIRA data, from Jan 2007 to Dec 2012. KNHANES is a nationally representative cross-sectional complex survey that includes approximately 10,000 individuals each year, collecting information on socioeconomic status, health-related behaviors, quality of life, health-care utilization, anthropometric measures, biochemical and clinical profiles for non-communicable diseases, and dietary intakes with three component surveys: health interview, health examination and nutrition survey.¹⁷ HIRA contains comprehensive and rich information on health-care services such as treatments, pharmaceuticals, procedures, and diagnoses for almost 50 million South Korean beneficiaries.¹⁸

Data on baseline comorbidities were obtained through HIRA and analyzed further for future events. Spirometry data of 17,472 subjects whose aged 40 years or older were obtained out of the 43,864 subjects of KNHANES. Among them, 2,450 patients with COPD who met the inclusion criteria were enrolled in our study. Patients with missing smoking data (N = 34), smoking amount less than 10 pack years (N = 1,277), and detection of cancer (N = 161) during the screening period from Jan 2007 to Dec 2008 were excluded (Figure 1). Finally, 978 patients linked with NHIS were analyzed for the primary and secondary outcomes of this study.

Main Outcomes

The occurrences of events including primary and secondary outcomes were investigated during the observation period, from Jan 2009 to Dec 2012 (Figure 2). Primary outcomes included pneumonia, acute exacerbation, and mortality. Secondary outcomes comprised co-morbidities including tuberculosis, ischemic heart disease, cerebrovascular stroke, lung cancer, osteoporosis, diabetes mellitus, hypertension, arrhythmia, and heart failure. The outcome measures were ascertained by HIRA data from January 1, 2009, to December 31, 2012. The first incident event was only used in the analyses for participants with more than one event. International Classification of Disease, Tenth Revision (ICD-10) codes were used to identify outcomes as follows: lung cancer (C33, C34), osteoporosis (M80, M81, M82), diabetes (E10-E14), ischemic heart disease (I20-I25), cerebrovascular disease (I60-I69), arrhythmia (I44-I49), and heart failure (I50).

Definition and Covariates

The inclusion criteria for COPD patients were as follows: (1) age ≥ 40 years; (2) current or former smoker with a smoking history of ≥ 10 pack-years; (3) pre-bronchodilator ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity < 0.7 ; (4) no history of any cancer during the screening period.

Tuberculosis was defined if ICD-10 diagnoses of TB (A15–A19, U88.0–U88.1) were met and two or more of following anti-tuberculosis medications were prescribed in 90 days: simultaneously prescribed isoniazid and rifampicin (considered as one anti-tuberculosis medicine), ethambutol, pyrazinamide, prothionamide, para-aminosalicylate, and cycloserine.¹⁹ Pneumonia was defined via the presence of ICD codes ranging from J12.x to J18.x, and prescription of antibiotics.²⁰

An eligible 85 ICS users (13 patients on ICS, 42 patients with ICS/LABA, and 30 patients with ICS/LABA/LAMA) were identified from all the patients treated by ICS in the cohort who had a prescription for an inhaled respiratory

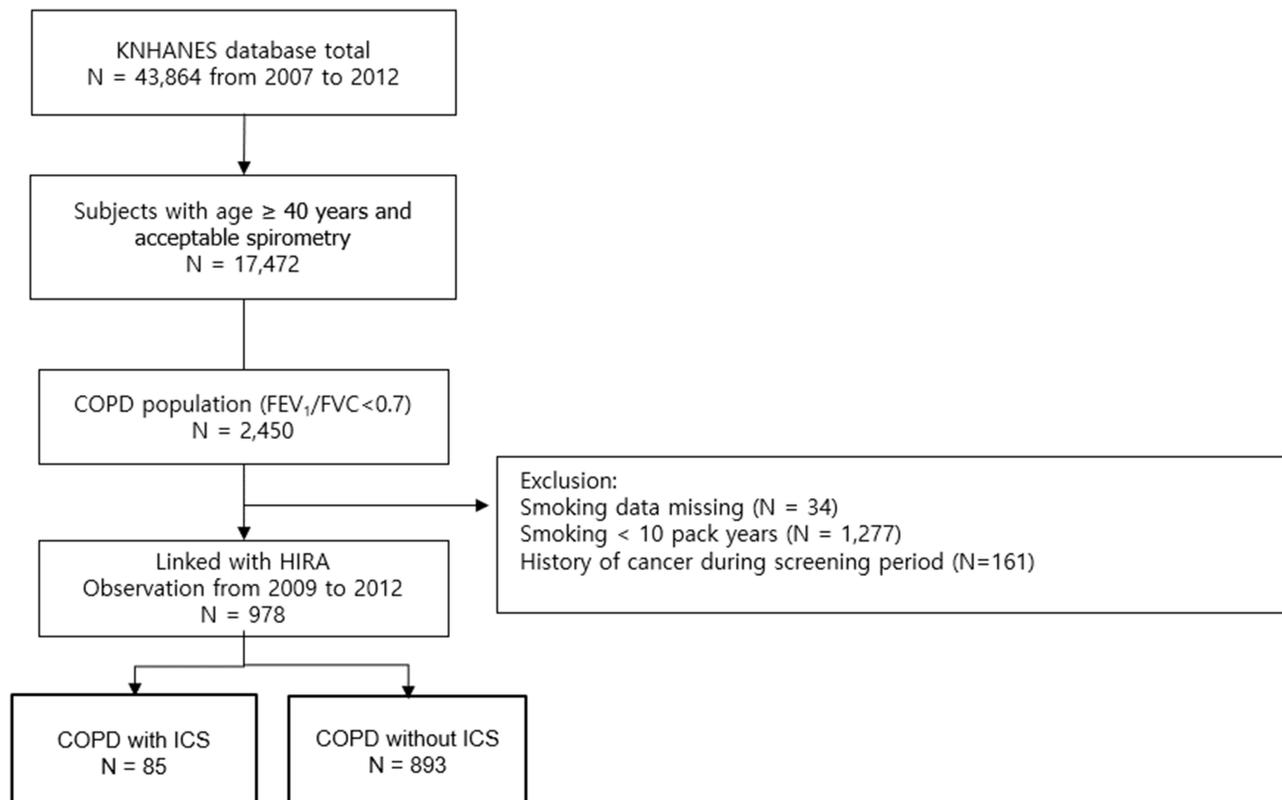


Figure 1 Flow diagram of this study.

Screening period

→ Exclusion : Patients with previous history of any cancer from Jan 1 2007 to Dec 31 2008

Observation for the development of co-morbidities for 4 years

→ COPD with ICS
→ COPD without ICS

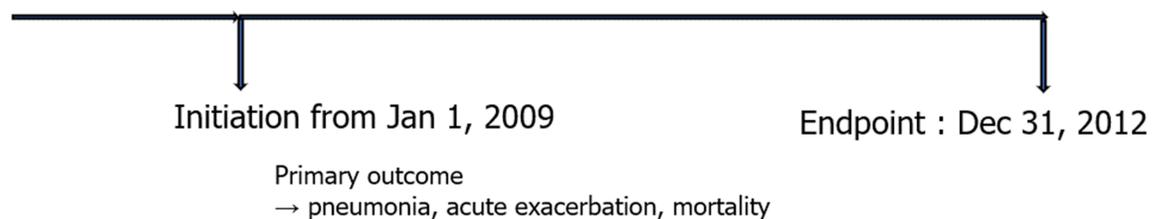


Figure 2 Study design.

medication for 120 days or longer during the observation period ([Supplement Table 1](#)). The ICS users consisted of all individuals who were dispensed at least one of the following inhaled respiratory medications: beclomethasone, budesonide, triamcinolone, ciclesonide, fluticasone, or flunisolide.¹⁹ A detailed history of smoking (smoking amount, duration, and non-smoking period) was evaluated by self-administered questionnaires at baseline. Former smokers were defined as smokers whose smoking cessation period was one year or more at enrollment.²¹ Data on body mass index (body weight in kilograms divided by height in meters squared; kg/m²), systolic and diastolic blood pressure, fasting serum glucose, and fasting total cholesterol level measured at baseline were obtained.

Measurements

According to the guidelines of the American Thoracic Society and European Respiratory Society, spirometry (Elite-DX or CPFS; Medgraphics, St Paul, MN, USA) was performed, and the acceptability and repeatability criteria of the spirometry were established.²² Normal predictive values of spirometry in the Korean population were obtained based on the second KNHANES data.²³

HRQL Assessed Using the EQ-5D Instrument

The EuroQol five-dimensions five-level (EQ-5D) includes a descriptive module (two pages) and the EuroQol Visual Analogue Scale (three pages). The descriptive module explores mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has a five-level response corresponding to no problem, slight problems, moderate problems, severe problems, and extreme problems.²⁴

Statistical Analyses

All values were expressed as mean \pm standard deviation for continuous data and number (percent) for categorical data. Student's *t*-test, one-way ANOVA test, or Kruskal–Wallis test was performed for continuous variables. χ^2 test or Fisher's exact test was used for categorical data. A *P* < 0.05 was considered to be significant. A Cox proportional hazard regression analysis was performed to find the significant variables associated with the development of pneumonia, the occurrence of acute exacerbation, and mortality. A *P*-value of less than 0.05 was deemed significant. All statistical analyses were performed using SAS version 9.2 software (SAS Institute Inc., Cary, NC, USA).

Ethics Statement

The current study was approved by the institutional review board of Konkuk University Medical Center (Approval Number = 177 KHH1010338). The data accessed complied with relevant data protection and privacy regulations. The requirement for informed consent was waived by the ethics review board due to the retrospective nature of the study.

Results

Baseline Characteristics of the Patients with COPD

Baseline characteristics (*n* = 978) are presented in Table 1; the mean age was 64.0 \pm 9.6 years, mean FEV₁ was 76.0 \pm 15.6% (pre-bronchodilator), 52.6% were current smokers, and 95.9% were males. Co-morbidities at the time of enrollment were diabetes mellitus (12.2%), hypertension (33.2%), coronary artery disease (3.8%), myocardial infarction

Table 1 Baseline Characteristics of the Patients with Chronic Obstructive Pulmonary Disease

Variable	Number (Percent)
Total number	978
Age (years)	64.0 \pm 9.6
Male	938 (95.9)
Current smoker	514 (52.6)
Smoking history (pack-years)	36.2 \pm 21.2
Systolic blood pressure (mmHg)	127.2 \pm 16.5
Diastolic blood pressure (mmHg)	78.6 \pm 10.8

(Continued)

Table 1 (Continued).

Variable	Number (Percent)
Cardiovascular comorbidities	
Coronary artery disease	37 (3.8)
Myocardial infarction	16 (1.6)
Cerebrovascular stroke	8 (0.8)
Diabetes mellitus	119 (12.2)
Hypertension	325 (33.2)
Hypercholesterolemia	64 (6.5)
BMI (kg/m ²)	23.3 ± 2.8
EQ-5D	0.92 ± 0.13
Leukocyte (×10 ³ /μL)	6.95 ± 2.37
Hemoglobin (g/dL)	4.87 ± 1.28
Platelet (×10 ³ /μL)	240.5 ± 58.3
Pre-bronchodilator pulmonary function	
FVC (%)	89.9 ± 4.2
FEV ₁ (%)	76.0 ± 15.6
FEV ₁ /FVC	0.62 ± 0.08

Abbreviations: BMI, body mass index; EQ-5D, EuroQol five-dimensions five-level; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, Long-acting muscarinic antagonist; mMRC, modified Medical Research Council.

(1.6%), and cerebrovascular stroke (0.8%). At the time of enrollment, the ICS users had a higher smoking amount, lower EQ-5D score, lower FEV₁, and FEV₁/FVC than non-ICS users ($P < 0.05$) ([Supplement Table 2](#)).

Adverse Events Based on ICS Usage and the Severity of COPD

Compared to non-ICS users, the ICS users had a higher rate of pneumonia, tuberculosis, acute exacerbation, and lung cancer. Hospitalization due to respiratory causes was higher among the ICS users ($P < 0.05$) ([Table 2](#)). The incidence of lung cancer was higher among ICS users in moderate COPD subgroup, although the number of cases was small ($P < 0.05$) ([Table 3](#)). Hospital admissions due to respiratory causes were higher among the ICS users in mild and moderate COPD subgroups ([Table 3](#)) ($P < 0.05$). However, there was no difference in the mortality rate between ICS users and non-ICS users in all the COPD subgroups ([Table 3](#)). The rate of pneumonia infection was higher among ICS users in all the mild, moderate, and severe COPD subgroups, whereas the rate of pulmonary tuberculosis was higher among ICS users in moderate COPD subgroup ([Table 3](#), [Supplement Table 3](#)) ($P < 0.05$).

Risk factors associated with primary outcomes include the development of pneumonia, acute exacerbation, and mortality.

Multi-variable Cox regression analyses were performed in two models: Model 1 (adjusted for age, sex, smoking, FEV₁ and significant factors in the univariate analysis), Model 2 (including all factors). Variables included in the primary outcomes by univariate Cox regression analysis are presented in [Table 4–6](#). The multivariable Cox regression analysis revealed that the development of pneumonia was significantly associated with acute exacerbation (model 1, Hazard ratio (HR) = 17.016, $P < 0.001$; model 2, HR = 16.860, $P < 0.001$) and had a tendency to be associated with ICS therapy (model 1, HR = 1.554, $P = 0.074$; model 2, HR = 1.574, $P = 0.067$) ([Table 4](#)). Another multivariable Cox regression

Table 2 Adverse Events Based on ICS Usage from 2009 to 2012

Variable	ICS User (n = 85)		Non-ICS User (n = 893)		p-value
	No. of Patients (Percent)	Rate Per 1000 Patients-Year (No. of Events)	No. of Patients (Percent)	Rate Per 1000 Patients-Year (No. of Events)	
Acute exacerbation					
Moderate	49 (57.7)	1388 (472)	68 (7.6)	73 (259)	<0.001
Severe	28 (32.9)	232 (79)	58 (6.5)	27 (98)	<0.001
Pneumonia	30 (35.3)	276 (94)	67 (7.5)	29 (102)	<0.001
Tuberculosis	12 (14.1)	76 (26)	31 (3.5)	8 (28)	<0.001
Diabetes mellitus	28 (32.9)	1850 (629)	300 (33.6)	2304 (8229)	0.903
Cardiovascular events					
Hypertension	54 (63.5)	5024 (1708)	463 (51.9)	4504 (16,089)	0.039
Arrhythmia	9 (10.6)	206 (70)	78 (8.7)	251 (896)	0.566
Heart failure	8 (9.4)	165 (56)	33 (3.7)	89 (318)	0.012
Ischemic heart disease	20 (23.5)	859 (292)	185 (20.7)	701 (2504)	0.543
Cerebral hemorrhage	0 (0.0)	0 (0.0)	7 (0.8)	10 (36)	NA
Cerebral ischemia	4 (4.7)	94 (32)	68 (7.6)	266 (949)	0.326
Osteoporosis	11 (12.9)	503 (171)	94 (10.5)	190 (680)	0.492
Lung cancer	6 (7.1)	412 (140)	17 (1.9)	79 (283)	0.003
Admission (All causes)	49 (57.7)	650 (221)	419 (46.9)	341 (1217)	0.059
Admission (Respiratory causes)	32 (37.7)	297 (101)	125 (14.0)	71 (253)	<0.001
Mortality	5 (5.9)	15 (5)	46 (5.2)	13 (46)	0.772

Abbreviations: ICS, inhaled corticosteroid; NA, not available; No., number.

analysis (model 2) showed that old age (HR = 1.043, $P < 0.001$), FEV₁ (HR = 0.972, $P < 0.001$), ICS therapy (HR = 4.040, $P < 0.001$), and pneumonia (HR = 6.610, $P < 0.001$) were independently associated with the occurrence of acute exacerbation (Table 5). The concomitant pneumonia (model 1, HR = 3.113, $P = 0.001$; model 2, HR = 3.353, $P = 0.004$) was independently associated with higher mortality (Table 6).

Discussion

Our study aimed to explore the impact of ICS on the prognosis of Asian COPD patients in the real-world setting. Our study also provides a comprehensive analysis of the clinical course of COPD in the light of the development of comorbidities according to ICS intervention.

Our Study Presents Some Interesting Findings

First, our data demonstrated that ICS therapy was associated with the development of pneumonia in univariate analysis along with a tendency to have an association with pneumonia through multivariate analysis. Also, ICS users in COPD of this study had a higher rate of tuberculosis and were accompanied by more frequent hospitalization due to respiratory diseases. However, the number of subjects enrolled in our study is not big enough to conclude the harmful side effects of ICS in subgroups of COPD. The study was also limited by its nature of not being a randomized controlled trial and lower baseline pulmonary function in the ICS group. Therefore, the subgroup analysis based on COPD severity was performed

Table 3 Adverse Events According to the Severity of COPD

Variable	Mild FEV ₁ ≥ 80%		p-value	Moderate FEV ₁ 80–50%		p-value	Severe FEV ₁ <50%		p-value
	ICS	Non ICS		ICS	Non ICS		ICS	Non ICS	
	No. (Per.)	No. (Per.)	No. (Per.)	No. (Per.)	No. (Per.)	No. (Per.)			
Total number	15	400		46	457		24	36	
Acute exacerbation									
Moderate	7 (46.7)	25 (6.3)	<0.001	23 (50.0)	32 (7.0)	<0.001	19 (79.2)	11 (30.6)	<0.001
Severe	7 (46.7)	21 (5.3)	<0.001	11 (23.9)	30 (6.6)	<0.001	10 (41.7)	7 (19.4)	0.061
Pneumonia	6 (40.0)	29 (7.3)	<0.001	6 (34.8)	34 (7.4)	<0.001	8 (33.3)	4 (11.1)	0.035
Tuberculosis	1 (6.7)	12 (3.0)	0.424	6 (13.0)	16 (3.5)	0.003	5 (20.8)	3 (8.3)	0.163
Diabetes mellitus	8 (53.3)	132 (33.0)	0.102	14 (30.4)	155 (33.9)	0.634	6 (25.0)	13 (36.1)	0.365
Osteoporosis	3 (20.0)	41 (10.3)	0.229	5 (10.9)	50 (10.9)	0.988	3 (12.5)	3 (8.3)	0.598
Cardiovascular events									
Hypertension	8 (53.3)	213 (53.3)	0.995	30 (65.2)	228 (49.9)	0.047	6 (66.7)	22 (61.1)	0.662
Arrhythmia	4 (26.7)	32 (8.0)	0.012	2 (4.4)	44 (9.6)	0.236	3 (12.5)	2 (5.6)	0.340
Heart failure	2 (13.3)	16 (4.0)	0.082	4 (8.7)	16 (3.5)	0.086	2 (8.3)	1 (2.8)	0.333
Ischemic heart disease	6 (40.0)	91 (22.8)	0.121	8 (17.4)	83 (18.2)	0.897	6 (25.0)	11 (30.6)	0.640
Cerebral hemorrhage	0 (0.0)	2 (0.5)	NA	0 (0.0)	5 (1.1)	NA	0 (0.0)	0 (0.0)	NA
Cerebral ischemia	3 (20.0)	30 (7.5)	0.079	1 (2.2)	37 (8.1)	0.147	0 (0.0)	1 (2.8)	NA
Lung cancer	1 (6.7)	8 (2.0)	0.223	5 (10.9)	8 (1.8)	<0.001	0 (0.0)	1 (2.8)	NA
Admission (All causes)	12 (80.0)	187 (46.8)	0.011	23 (50.0)	210 (46.0)	0.600	14 (58.3)	22 (61.1)	0.830
Admission (Respiratory causes)	6 (40.0)	52 (13.0)	0.003	15 (32.6)	60 (13.1)	<0.001	11 (45.8)	13 (36.1)	0.451
Mortality	0 (0.0)	19 (4.8)	NA	3 (6.5)	24 (5.3)	0.716	2 (8.3)	3 (8.3)	0.999

Abbreviations: FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; NA, not available; No., number; Per., percent.

considering the lower baseline FEV₁ in ICS users. This subgroup analysis also showed that ICS users had a higher rate of pneumonia in all COPD subgroups and had a higher admission rate due to respiratory causes in mild and moderate COPD subgroups. These data are supported by a recent study in a real-world setting where the incidence of severe pneumonia requiring hospitalization was higher with the use of a triple combination of LAMA, LABA, and ICS compared to a combination of LAMA and LABA.⁹ A meta-analysis in COPD treatment showed that the incidence of adverse events including pneumonia was lower in LABA/LAMA versus LABA/ICS, and LABA/LAMA presented a lower risk for withdrawals due to lack of efficacy versus LAMA and adverse events versus LABA/ICS.¹⁰

Recent randomized controlled trials provided some bodies of evidence on the benefits of ICS in the COPD subtype with high blood eosinophil count and frequent exacerbation.^{3,4} However, other observational studies reported that overprescription of ICS in COPD is widespread and clinicians should consider the potential harm even when appropriately prescribed in COPD.^{13,25} Previous studies supporting withdrawal of ICS in a group of COPD patients for whom the risk of ICS-related adverse effects outweigh the expected benefits or the clinical benefits are unproven.^{25,26} Potential negative health consequences related to inappropriate prescribing of ICS include a high incidence of respiratory infection, hoarseness, skin bruising, decreased bone density, fracture, increased risk of diabetes, and cataract.^{7,26} ICS therapy can increase the risk of respiratory infections including not only pneumonia but also oropharyngeal candidiasis, tuberculosis, and nontuberculous mycobacterial pulmonary infection through the impairment of bactericidal activity,

Table 4 Risk Factors Associated with the Development of Pneumonia

	Uni-Variate		Multi-Variable Model 1		Multi-Variable Model 2	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)	1.036 (1.013–1.059)	0.002	0.993 (0.969–1.016)	0.538	0.995 (0.970–1.020)	0.693
Male	0.763 (0.310–1.878)	0.557	0.673 (0.271–1.672)	0.394	0.700 (0.278–1.765)	0.450
Current smoker	0.736 (0.494–1.098)	0.133	0.816 (0.539–1.234)	0.335	0.847 (0.550–1.305)	0.452
BMI (kg/m ²)	0.945 (0.880–1.015)	0.121			1.020 (0.941–1.104)	0.634
FEV ₁ (% predicted)	0.975 (0.963–0.987)	<0.001	1.003 (0.991–1.015)	0.667	1.002 (0.989–1.014)	0.768
Diabetes mellitus	1.336 (0.890–2.005)	0.162			1.112 (0.710–1.742)	0.642
Hypertension	1.348 (0.899–2.024)	0.149			0.979 (0.621–1.543)	0.927
Cerebral ischemia	2.267 (1.287–3.993)	0.005	1.477 (0.805–2.710)	0.208	1.413 (0.758–2.631)	0.276
Heart failure	3.566 (1.948–6.529)	<0.001	1.602 (0.838–3.065)	0.154	1.667 (0.849–3.274)	0.138
Ischemic heart disease	1.478 (0.948–2.304)	0.085			1.019 (0.645–1.612)	0.934
ICS therapy	5.696 (3.701–8.766)	<0.001	1.554 (0.958–2.519)	0.074	1.574 (0.969–2.556)	0.067
Acute exacerbation (none vs ≥ 1)	19.458 (12.332–30.704)	<0.001	17.016 (10.255–28.234)	<0.001	16.860 (10.138–28.040)	<0.001

Notes: Multi-variable Cox regression analyses were performed in two models: Model 1 (adjusted for age, sex, smoking, FEV₁ and significant factors in the univariate analysis), Model 2 (including all factors).

Abbreviations: BMI, body mass index; CI, confidential interval; FEV₁, forced expiratory volume in 1 second; HR, Hazard ratio; ICS, inhaled corticosteroid.

Table 5 Risk Factors Associated with the Development of Acute Exacerbation (None Vs ≥1)

	Uni-Variate		Multi-Variable Model 1		Multi-Variable Model 2	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)	1.058 (1.039–1.077)	<0.001	1.044 (1.023–1.065)	<0.001	1.043 (1.023–1.064)	<0.001
Male	0.908 (0.426–1.938)	0.804	0.928 (0.431–1.998)	0.849	0.915 (0.424–1.974)	0.821
Current smoker	0.800 (0.587–1.092)	0.160	1.055 (0.759–1.467)	0.748	1.061 (0.763–1.477)	0.724
BMI (kg/m ²)	0.894 (0.845–0.946)	<0.001	0.968 (0.914–1.025)	0.271	0.970 (0.915–1.027)	0.292
FEV ₁ (% predicted)	0.957 (0.948–0.966)	<0.001	0.971 (0.962–0.981)	<0.001	0.972 (0.962–0.982)	<0.001
Diabetes mellitus	1.126 (0.816–1.554)	0.471			0.920 (0.648–1.307)	0.641
Hypertension	1.376 (1.003–1.888)	0.048	0.703 (0.487–1.016)	0.061	0.715 (0.492–1.039)	0.079
Cerebral ischemia	1.894 (1.185–3.025)	0.008	1.548 (0.922–2.599)	0.099	1.568 (0.931–2.641)	0.091
Heart failure	2.871 (1.712–4.813)	<0.001	1.116 (0.642–1.940)	0.698	1.095 (0.626–1.916)	0.751
Ischemic heart disease	1.510 (1.070–2.131)	0.019	1.239 (0.852–1.803)	0.262	1.250 (0.857–1.822)	0.246
ICS therapy	8.437 (6.064–11.739)	<0.001	4.011 (2.742–5.867)	<0.001	4.040 (2.758–5.916)	<0.001
Pneumonia	11.735 (8.559–16.089)	<0.001	6.535 (4.591–9.301)	<0.001	6.610 (4.629–9.438)	<0.001

Notes: Multi-variable Cox regression analyses were performed in two models: Model 1 (adjusted for age, sex, smoking, FEV₁ and significant factors in the univariate analysis), Model 2 (including all factors).

Abbreviations: BMI, body mass index; CI, confidential interval; FEV₁, forced expiratory volume in 1 second; HR, Hazard ratio; ICS, inhaled corticosteroid.

Table 6 Risk Factors Associated with Mortality

	Uni-Variate		Multi-Variable Model 1		Multi-Variable Model 2	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)	0.985 (0.958–1.013)	0.295	0.984 (0.956–1.014)	0.300	0.987 (0.957–1.018)	0.404
Male	1.041 (0.253–4.278)	0.956	1.063 (0.255–4.423)	0.933	1.064 (0.255–4.443)	0.932
Current smoker	1.407 (0.802–2.468)	0.234	1.372 (0.764–2.465)	0.290	1.315 (0.717–2.412)	0.377
BMI (kg/m ²)	0.965 (0.875–1.064)	0.473			0.980 (0.882–1.090)	0.712
FEV ₁ (% predicted)	0.995 (0.978–1.012)	0.545	0.999 (0.981–1.016)	0.884	0.998 (0.980–1.017)	0.832
Cerebral ischemia	0.790 (0.246–2.537)	0.692			0.893 (0.266–2.994)	0.854
Heart failure	0.933 (0.227–3.835)	0.923			0.899 (0.208–3.891)	0.886
Ischemic heart disease	0.496 (0.212–1.162)	0.106			0.503 (0.209–1.208)	0.124
ICS therapy	1.158 (0.460–2.914)	0.755			0.761 (0.263–2.199)	0.614
Pneumonia	2.908 (1.523–5.554)	0.001	3.113 (1.601–6.053)	0.001	3.353 (1.463–7.685)	0.004
Acute exacerbation (none vs ≥ 1)	1.603 (0.840–3.062)	0.153			1.031 (0.425–2.498)	0.947

Notes: Multi-variable Cox regression analyses were performed in two models: Model 1 (adjusted for age, sex, smoking, FEV₁ and significant factors in the univariate analysis), Model 2 (including all factors).

Abbreviations: BMI, body mass index; CI, confidential interval; FEV₁, forced expiratory volume in 1 second; HR, Hazard ratio; ICS, inhaled corticosteroid.

interleukin-1, tumor necrosis factor α production, and T-cell activation.^{11,12,19,27–30} In addition, Suissa et al reported that weaning of ICS in COPD has decreased the rate of serious pneumonia by 20% in the first month and to 50% by the fourth month after discontinuation.⁸ Therefore, targeted ICS therapy is required in COPD where the clinical benefits can outweigh the harmful risks.

Second, the current study revealed that the concomitant pneumonia was independently associated with a higher rate of exacerbation and higher mortality. Therefore, this study suggests that the development of pneumonia in COPD functioning as a predictor of acute exacerbation and mortality should be deemed an important clinical outcome. Although COPD patients were at increased risk for pneumonia, it remained controversial whether a concomitant pneumonia in COPD is associated with higher mortality.^{31–33} It was reported that a pneumonia during hospitalization due to acute exacerbations of COPD increased in-hospital morbidity comprising increased length of hospital stay and more frequent ICU admissions.^{33–36} Some studies showed that community acquired pneumonia in COPD was associated with higher mortality, in addition to other worse outcomes including longer hospital stay and more ICU admissions.^{33,36} On the other hand, a few studies reported otherwise that the mortality during hospitalization is not affected by pneumonia in COPD, although pneumonia can increase in-hospital morbidity in COPD.^{34,35} Hence, this topic merits further verification.

Third, the occurrence of acute exacerbation in this cohort was independently associated with pneumonia and ICS therapy, along with older age and lower FEV₁. Our finding that ICS therapy was associated with exacerbations should be interpreted with caution considering the observational study design. Since ICS therapy is indicated in COPD patients with frequent exacerbations, the frequent exacerbations associated with ICS therapy may simply reflect a clinical practice of prescribing ICS therapy in COPD exacerbators in South Korea and cannot explain the causal link without a randomized control design study. While big randomized controlled trials including Wisdom and FLAME supported a safe withdrawal of ICS in COPD, a recent IMPACT trial reported that triple therapy including ICS, LAMA, and LABA resulted in a lower rate of COPD exacerbations and hospitalization and even improved the survival rate.^{3,37,38} Therefore, further validation seems to be required in this area.

We Acknowledge Several Limitations of This Study

First, analysis on blood eosinophil was not performed due to a lack of data in the KNAHES. Second, post-bronchodilator values were not obtained due to the lack of information in the KNHANES data, and the definition of COPD by less than

70% of prebronchodilator FEV₁/FVC can harbor the potential risk of overdiagnosis. Third, the small number of ICS users (85 out of 978, 8.7%) is a limitation in the interpretation of our analysis, therefore this study cannot determine the causal link between ICS therapy and adverse events. Fourth, we cannot rule out the influence of unmeasured confounders despite subgroup analysis of our data. Fifth, COPD patients of this cohort were not treated by current therapeutic strategies because observation period is not up-to-date. Sixth, a higher rate of lung cancer in ICS users cannot be generalized because of lower FEV₁ and higher smoking amount in ICS users.

In conclusion, our data demonstrated that the ICS users had a higher rate of pneumonia and tuberculosis and the concomitant pneumonia was independently associated with higher mortality, highlighting the importance of cautious and targeted administration of ICS in COPD.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors report no potential conflicts of interest in this work.

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