

Inhaled Corticosteroids Increase the Risk of Pneumonia in Patients With Chronic Obstructive Pulmonary Disease

A Nationwide Cohort Study

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Abstract: The association of inhaled corticosteroids (ICS) and pneumonia in patients with chronic obstructive pulmonary disease (COPD) is still controversial.

From the National Health Insurance Database of Taiwan, COPD cases with history of acute exacerbation (AE) were identified (COPD cohort). Time-dependent Cox regression analysis was applied to investigate the risk factors for pneumonia with COPD severity controlled by surrogate variables. Among the COPD cohort, those who continuously used ICS for more than 360 days without interruption were selected (ICS cohort). The incidence rate of pneumonia during ICS use was compared with those before ICS use and after ICS discontinuation by using pair *t* test.

A total of 6034 and 842 cases were identified as the COPD and ICS cohorts, respectively. In the COPD cohort, recent ICS use was independently associated with pneumonia (hazard ratio: 1.06 [1.02–1.11] for per 80 mg of budesonide). Other independent risk factors included age, male, diabetes mellitus, malignancy, low income, baseline pneumonia event, and recent use of oral corticosteroids and aminophylline. In the ICS cohort, while AE rate gradually decreased, the incidence rate

of pneumonia significantly increased after ICS use (from 0.10 to 0.21 event/person-year, $P = 0.001$).

This study demonstrates the association between ICS use and pneumonia in patients with COPD and history of AE. ICS should be judiciously used in indicated COPD patients.

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Abbreviations: AE = acute exacerbation, AIDS = acquired immunodeficiency syndrome, CI = confidence interval, COPD = chronic obstructive pulmonary disease, DDDs = defined daily doses, ESRD = end-stage renal disease, GOLD = Chronic Obstructive Lung Disease, ICD-9-CM = International Classification of Diseases, 9th revision, clinical modification, ICS = inhaled corticosteroids, INSPIRE = Investigating New Standards for Prophylaxis in Reducing Exacerbations, LABA = long-acting β_2 agonists, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, OR = odds ratio, TORCH = Towards a Revolution in COPD Health.

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INTRODUCTION

Combination therapy with inhaled corticosteroids (ICS)/long-acting β_2 agonists (LABA) is a cornerstone in the treatment of chronic obstructive pulmonary disease (COPD), which is characterized by both airway and systemic inflammation.¹ Two recent large clinical trials have demonstrated that ICS plus LABA can improve lung function and health status, and possibly reduce the frequency of acute exacerbation (AE) and mortality.^{2,3}

Long-term ICS therapy, however, is reported to increase the risk of pneumonia among COPD patients.^{4–7} A recent meta-analysis reports an odds ratio (OR) of 1.78 (95% confidence interval [CI]: 1.50–2.12) and 1.62 (95% CI: 1.00–2.62) for fluticasone and budesonide, respectively.⁴ Another meta-analysis using individual patient data from 7 clinical trials has a different conclusion and that budesonide is not associated with increased risk of pneumonia.⁸ The discrepancy may be due to differences in study designs and definitions of pneumonia among individual clinical trial. Moreover, pneumonia is simply an adverse event rather than the primary endpoint in these trials. Thus, a large cohort study with specific focus may be more suitable than currently available meta-analyses to understand the impact of ICS on the risk of pneumonia among COPD patients.

Recent cohort studies using health insurance claims data have shown an association between ICS use and increased risk of pneumonia.^{9,10} However, due to the built-in shortness of the symptoms and lung function results, none of these studies can control the confounding effect of COPD severity. This may have serious implications since COPD patients who require ICS

therapy are usually those with severely impaired lung function and an increased risk of respiratory tract infection.¹⁷ Other potential bias that has not yet been addressed in previous studies is that in real-world clinical practice, the severity of COPD and the dose of each drug may vary with time. For that, a time-dependent approach is a more suitable statistical method.

The National Health Insurance (NHI) of Taiwan is a mandatory universal health insurance program offering comprehensive medical care coverage to nearly 100% of the residents in Taiwan since 1996.¹² The Longitudinal Health Insurance Database (LHID) 2005, a subset database of the NHI program, contains the entire original claims data from 1996 to 2007 of 1,000,000 beneficiaries randomly sampled from the year 2005 Registry for Beneficiaries. This study used surrogate variables to control COPD severity and applied time-dependent Cox proportional hazards analysis to identify the risk factors of pneumonia among COPD patients identified in the LHID 2005, with special emphasis on the impact of ICS. The incidence rates of pneumonia before and during ICS use, and after discontinuation of ICS in the same patients were compared.

MATERIALS AND METHODS

The Institutional Review Board of the Taipei Medical University approved the study and waived the need for informed consent due to the retrospective design using an encrypted database (TMU REC: 201503024).

The study was divided into 2 parts (Figure 1). In the first part, COPD cases with history of AE were selected from the LHID 2005 to study the effect of its treatments and co-morbidities on the risk of developing pneumonia (COPD cohort). All selected cases were followed-up until pneumonia developed, December 31, 2007, or until the patient was lost to follow-up.

In the second part of the study, patients in the COPD cohort who continuously used ICS for more than 360 days were identified (ICS cohort), in which continuous use was defined as no interruption for more than 30 days. The incidence rates of pneumonia before and during ICS use, as well as after discontinuation of ICS, were compared.

Selection Criteria of COPD Patients With AE

In this study, COPD was defined as more than 2 out-patient or in-patient records <365 days apart with the compatible

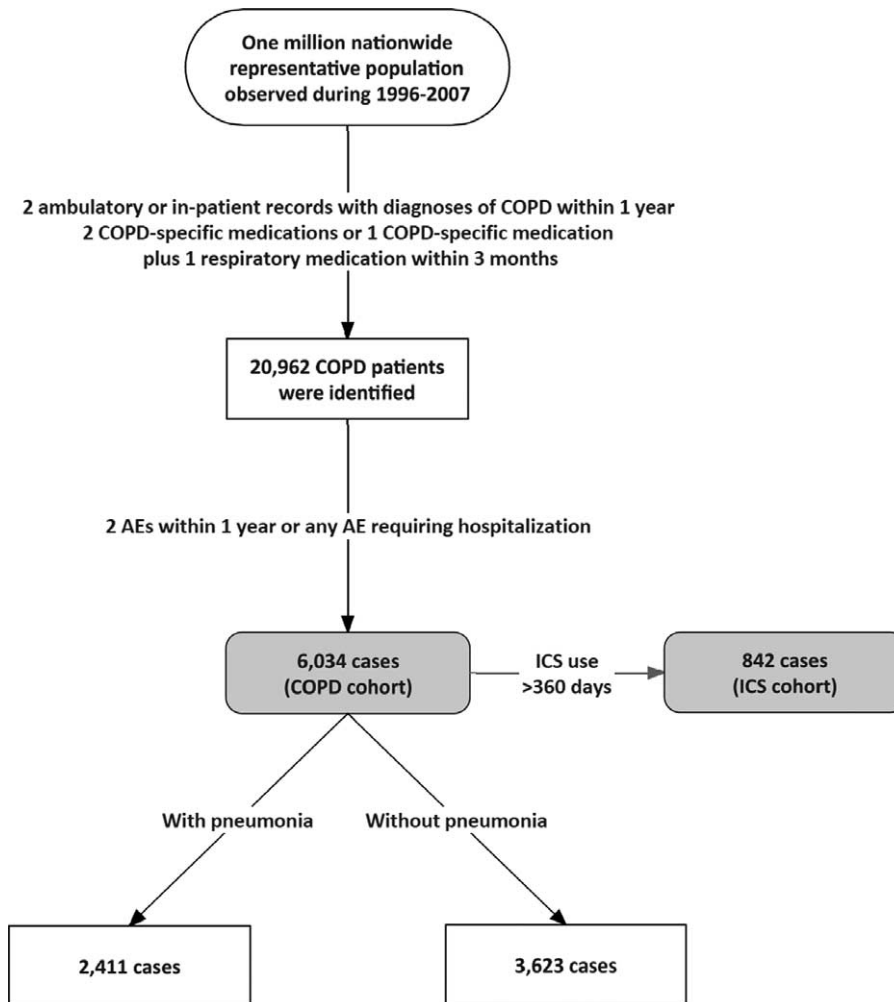


FIGURE 1. Flow chart of case selection from the Longitudinal Health Insurance Database 2005 of Taiwan. AE = acute exacerbation; COPD = chronic obstructive pulmonary disease.

diagnoses between 1996 and 2007, and prescription of more than 2 COPD-specific medications or 1 COPD-specific medication plus at least 1 airway medication(s) in 3 months.¹³ The compatible diagnoses of COPD included the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) codes 491, 492, 496, and A-code A325. Corticosteroids (inhaled, oral, or parenteral), beta-agonists (long-acting or short-acting; inhaled, oral, or parenteral), anti-cholinergics (ipratropium or tiotropium), aminophylline, and theophylline were considered COPD-specific medications.

Among patients who fulfilled the selection criteria of COPD, those with 2 episodes of AE within 1 year or 1 episode of AE requiring hospitalization were identified, with the first AE date defined as the enrollment date. In this study, AE was defined as emergency department visits or admissions with the ICD-9-CM codes 491, 492, 496, and A-code A325, plus prescription of systemic corticosteroids. The index date was noted as 365 days after the enrollment date. The baseline frequency of AE was calculated during the 1-year period from the enrollment to the index date.

Definition of Pneumonia

The diagnostic criteria of pneumonia consisted of a compatible diagnosis (ICD-9-CM codes 480–486 and A-codes A321) in the out-patient or in-patient discharge records, and prescriptions of pneumonia-specific antibiotics and chest radiography. Pneumonia-specific antibiotics included systemic beta-lactams and/or beta-lactamase inhibitors, fluoroquinolones, macrolides, and carbapenems. The presence of pneumonia events between the enrollment and index dates were also recorded.

Co-Morbidities

Underlying co-morbidities present before the index date were recorded, including malignancy, diabetes mellitus, end-

stage renal disease (ESRD), liver cirrhosis, autoimmune diseases, pneumoconiosis, and acquired immunodeficiency syndrome. Organ transplantation and low-income status were identified according to a previous publication.¹⁴

Statistical Analysis

The prescription duration of individual drugs were converted from claims data according to the defined daily doses (DDDs)¹⁵ and grouped according to their pharmacologic categories. Inhaled and systemic corticosteroids were converted to an equivalent dose of budesonide 800 µg and prednisolone in milligrams, respectively.¹⁶

In the first part of the study, variables potentially associated with the development of pneumonia within 180 days after the index date in the COPD cohort were analyzed using a time-dependent Cox proportional hazards model. The presence of baseline pneumonia event, baseline frequency of AE, and a time-dependent variable for the frequency of AE after the index date were used as surrogates for COPD severity in the statistical model.¹⁷ Other variables included age, sex, co-morbidities, and the time-dependent variables for the prescribed medications. All time-dependent variables were determined as the total prescribed dose of each specific class of medication and the total number of AE from 120 to 30 days prior to the end of each period. Significance for entry and stay were set at 0.15. Statistical significance was set at a 2-sided *P* < 0.05.

In order to ensure patients in a relatively stable condition either before or after treatment modification, and to avoid the potential confounding effects lasting from previous status, a 6-month period being 3 months prior to ICS use, 3 months before and 3 months after ICS discontinuation were selected to calculate the incidence rate of pneumonia in the ICS cohort in the second part of the study and compared using paired *t* test. All analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA).

TABLE 1. Characteristics of the COPD Patients With AE

	Not Developing Pneumonia (N = 3623)	Developing Pneumonia (n = 2411)	<i>P</i>
Age, yr	67.2 ± 11.4	69.6 ± 10.6	<0.001*
Male	2307 (63.7)	1641 (68.1)	<0.001†
Follow-up duration, yr	6.6 ± 3.1	4.1 ± 2.3	<0.001*
Co-morbidity			
Diabetes mellitus	777 (21.4)	600 (24.9)	0.002‡
Malignancy	132 (3.6)	103 (4.3)	0.216‡
Autoimmune disease	18 (0.5)	16 (0.7)	0.483‡
ESRD	17 (0.5)	11 (0.5)	0.942‡
Liver cirrhosis	7 (0.2)	0 (0)	0.047‡
Transplantation	1 (0)	0 (0)	>0.999‡
Pneumoconiosis	0 (0)	1 (0)	0.400‡
HIV/AIDS	0 (0)	0 (0)	–
Low income	79 (2.2)	62 (2.5)	0.325‡
Baseline condition			
Frequency of AE (event/person-yr)	2.4 ± 3.5	3.3 ± 4.9	<0.001*
With pneumonia event	441 (12.2)	532 (22.1)	<0.001†

Data were mean ± standard deviation or n (%) unless otherwise indicated. AE = acute exacerbation, AIDS = acquired immunodeficiency syndrome, COPD = chronic obstructive pulmonary disease, ESRD = end-stage renal disease, HIV = human immunodeficiency virus.

* Calculated by using independent-samples *t* test.

† Calculated by using chi-squared test.

‡ Calculated by using Fisher's exact test.

RESULTS

The COPD Cohort

Among the 1,000,000 beneficiaries in LHID 2005, 995,549 sought medical help at least once between 1996 and 2007. Based on criteria of COPD with AE, 6034 cases (males, 65.4%) were identified (COPD cohort). Their mean age was 68.2 ± 11.2 years. During follow-up, pneumonia developed in 2411 (40.0%) cases. Their clinical characteristics were summarized in Table 1 and their mean age (69.6 ± 10.6 years) was older than that of the nonpneumonia cases (67.2 ± 11.4 years). The pneumonia cases also had more male predominance (68.1% vs 63.7%) and had a higher prevalence of diabetes mellitus (24.9% vs 21.4%), but less prevalence of liver cirrhosis (0% vs 0.2%). Patients who developed pneumonia during the study period also had higher frequency of AE (3.3 ± 4.9 vs 2.4 ± 3.5 event/person-year) and were more likely to have pneumonia (22.1% vs 12.2%) in baseline condition. Other baseline characteristics listed in Table 1 were not significantly different between the 2 groups.

Factors Predicting the Development of Pneumonia

Time-dependent Cox proportional hazards regression analysis of the COPD cohort to identify independent risk factors of developing pneumonia revealed that ICS use (per 80 mg budesonide) from prior 120 to 30 days was an independent risk factor (hazard ratio [HR]: 1.06; 95% CI: 1.02–1.11) (Table 2). Other independent risk factors included age (every 10-year increment) (HR: 1.31; 95% CI: 1.26–1.37), male sex (HR: 1.17; 95% CI: 1.08–1.28), presence of diabetes mellitus (HR: 1.36; 95% CI: 1.25–1.48) or malignancy (HR: 1.46; 95% CI: 1.25–1.71), and low income (HR: 1.42; 95% CI: 1.12–1.78).

In addition, the use of oral corticosteroids (per gram of prednisolone) (HR: 1.21; 95% CI: 1.18–1.24) and aminophylline (each increment of 30 DDDs) (HR: 1.11; 95% CI: 1.08–1.13) from prior 120 to 30 days were also associated with increased risk of pneumonia. The number of AE (HR: 1.09; 95% CI: 1.05–1.12) from prior 120 to 30 days and presence of baseline pneumonia event (HR: 1.87; 95% CI: 1.70–2.06) were associated with increased risk of pneumonia.

The ICS Cohort and the Impact of ICS Use on Pneumonia Events

There were 842 COPD patients in the ICS cohort. Their clinical characteristics were summarized in Table 3. Their mean age was 65.9 ± 12.4 years and there was 74.3% male predominance. Like the COPD cohort, the presence of diabetes mellitus (19.0%) and malignancy (3.7%) were the most common co-morbidities. The baseline frequency of AE was 1.7 ± 4.0 event/person-year and 150 (17.8%) had pneumonia at baseline.

In the ICS cohort, 37 (4.4%), 64 (7.6%), and 46 (5.5%) patients developed pneumonia in the selected 6-month period before ICS use, during ICS use, and after ICS discontinuation, respectively. The rate of pneumonia events during ICS use (0.21 event/person-year) was significantly higher than that before ICS use (0.10 events/person-years) ($P = 0.001$, by paired t test) and not significantly different from that after ICS discontinuation (0.22 event/person-year) ($P = 0.192$, by paired t test) (Figure 2A). The rate of AE events before (1.51 events/person-year), during ICS use (1.22 events/person-year), and after ICS discontinuation (0.98 events/person-year) showed a decreasing trend (Figure 2B). On average, prescribing ICS for 9.1 [1/[0.21–0.10]] person-years increased 1 pneumonia event.

DISCUSSION

By analyzing longitudinal data from a nationwide cohort, this study has 2 important findings. First, using time-dependent analysis and controlling for COPD severity, the use of ICS has an independent and dose-dependent effect of increasing the risk of pneumonia. Second, while the incidence rate of AE continues to decrease, the incidence rate of pneumonia increases during ICS use and has a decreasing trend after ICS discontinuation.

Both airway and systemic inflammation characterize COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that a fixed combination of ICS/LABA should be considered for group C or D patients, who are highly symptomatic or have high risk of complications.¹ Although helpful in reducing inflammation, ICS has many potential short- and long-term side effects.¹ A higher risk of pneumonia while using ICS has been observed in several clinical trials,^{18–20} including the TOwards a Revolution

TABLE 2. Time-Dependent Cox Regression Analysis for Factors Predicting the Development of Pneumonia in the COPD Cohort

Variables	Estimate	Standard Error	P Value	Hazard Ratio	95% Confidence Interval	
					Lower	Upper
Age (10 yr)	0.271	0.021	<0.001	1.31	1.26	1.37
Male	0.159	0.044	<0.001	1.17	1.08	1.28
Diabetes mellitus	0.307	0.043	<0.001	1.36	1.25	1.48
Malignancy	0.379	0.080	<0.001	1.46	1.25	1.71
Low income	0.347	0.118	0.003	1.42	1.12	1.78
With baseline pneumonia	0.625	0.049	<0.001	1.87	1.70	2.06
Frequency of AE*	0.458	0.086	<0.001	1.09	1.05	1.12
Oral corticosteroid, g*	0.188	0.013	<0.001	1.21	1.18	1.24
Oral aminophylline (30 DDDs)*	0.099	0.009	<0.001	1.11	1.08	1.13
Inhaled corticosteroid (80 mg budesonide)*	0.061	0.021	0.005	1.06	1.02	1.11

AE = acute exacerbation, COPD = chronic obstructive pulmonary disease, DDD = defined daily dose.

* Time-dependent variables were calculated as the total doses of drugs or numbers of AE from 120 to 30 days prior to the end of each period.

TABLE 3. Characteristics of the ICS Cohort

	All Cohort (N = 6034)	ICS Cohort (n = 842)
Age, yr	68.2 ± 11.2	65.9 ± 12.4
Male	3948 (65.4)	626 (74.3)
Follow-up duration, yr	5.6 ± 3.0	
Co-morbidity		
Diabetes mellitus	1377 (22.8)	160 (19.0)
Malignancy	235 (3.9)	31 (3.7)
Autoimmune disease	34 (0.6)	6 (0.7)
ESRD	28 (0.5)	1 (0.1)
Liver cirrhosis	7 (0.1)	0 (0)
Transplantation	1 (0)	1 (0.1)
Pneumoconiosis	1 (0)	2 (0.2)
HIV/AIDS	0 (0)	0 (0)
Low income	141 (2.3)	8 (0.9)
Baseline condition		
Frequency of AE (event/person-yr)	2.8 ± 4.1	1.7 ± 4.0
With pneumonia event	973 (16.1)	150 (17.8)

Data were mean ± standard deviation or n (%) unless otherwise indicated. AE = acute exacerbation, AIDS = acquired immunodeficiency syndrome, ICS = inhaled corticosteroids, ESRD = end-stage renal disease, HIV = human immunodeficiency virus.

in COPD Health (TORCH) and Investigating New Standards for Prophylaxis in Reducing Exacerbations (INSPIRE) studies.^{2,3} Yet, some studies demonstrate the opposite.^{21–23}

Similarly, not all meta-analyses have the same conclusions on whether ICS use increase the risk of pneumonia.^{4,8} The recently published meta-analysis of 43 randomized controlled trials indicated that budesonide and fluticasone, delivered alone or in combination with a LABA, are associated with increased risk of pneumonia (budesonide: OR 1.62, 95% CI 1.00–2.62; fluticasone: OR 1.78, 95% CI 1.50–2.12).⁴ One explanation for the discrepancy is that the incidence rate of pneumonia in these clinical trials has been calculated from adverse event report, in which not every single pneumonia event is confirmed by chest

radiography and microbiologic data. Chest radiography was done in 72% and 58% of the reported pneumonia events in the TORCH and INSPIRE studies, respectively.^{2,3} Furthermore, the study design and treatment protocols were heterogeneous among these clinical trials.

Despite the lack of randomization, retrospective cohort studies may enroll much larger patient numbers than clinical trials. Patients with underlying co-morbidities are also more likely to develop certain complications but are always excluded in clinical trials. Thus, retrospective cohort studies, but not clinical trials, are more likely to represent the real-world situation. Several observational studies conducted to investigate the impact of ICS on the risk of pneumonia in COPD patients show an estimated relative risk of 1.11 to 3.26.^{7,9,10,24–26} Some even demonstrate a positive dose–response relationship between ICS and risk of pneumonia.^{7,9,10,24,25} However, these studies have 2 major limitations. First, without judicious control of the severity of COPD, the impact of ICS on the risk of pneumonia may be overestimated since COPD patients who require ICS therapy are usually those with severely impaired lung function, which in turn is associated with increased risk of respiratory tract infection.¹¹ Second, the dose of ICS is averaged in a certain period and arbitrarily categorized into 2 or 3 levels, in contrast to the real-world situation where it almost always varies with time.

This is the first study investigating the impact of ICS on the risk of pneumonia by applying time-dependent variables to represent the dynamic characteristics of COPD severity and medications. The presence of baseline pneumonia event, and baseline and recent frequency of AE were used as surrogates for controlling COPD severity.¹⁷ Because this study only includes COPD patients with more than 2 AEs or any AE requiring hospitalization within the 1-year period between enrollment and index date, the enrolled subjects are likely to represent those who really need ICS therapy.¹ The results provide evidence showing that ICS can increase the risk of pneumonia among COPD patients. In time-dependent multivariate Cox regression analysis, recent ICS use is independently associated with an increased risk for developing pneumonia.

This is also the first study providing longitudinal data on the incidence rate of pneumonia and AE before, during, and after ICS use. While the incidence rate of AE decreases gradually, the incidence rate of pneumonia increases significantly during ICS use. The findings are consistent with current knowledge that ICS plus LABA can prevent AE of COPD while rendering patients more susceptible to pneumonia.^{2,3}

The finding that baseline pneumonia event, recent frequency of AE, and oral aminophylline use are independently associated with increased risk of pneumonia is not surprising. All of the 3 variables may correlate with the severity of COPD, which in turn correlates with the risk of pneumonia.^{11,27} All of the other independent risk factors of pneumonia, including aging, co-morbid diabetes mellitus or malignancy, low income, and oral corticosteroid use, are well associated with immunosuppression,^{28–32} therefore increasing the possibility of developing pneumonia. Past evidence also supports the finding that men have a higher incidence of pneumonia than women, probably because of smoking and other lifestyle factors.³³

There are some limitations in this study. Due to the built-in shortage of claims data and retrospective design, the diagnoses of COPD and its severity, as well as pneumonia, are not confirmed. Though baseline frequency of AE and pneumonia event, and a time-dependent variable for the AE frequency were used as surrogate indicators in this study, they may not correlate

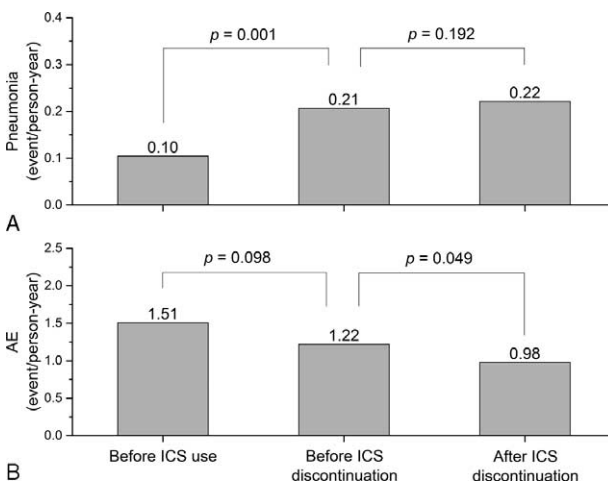


FIGURE 2. The incidence rates of pneumonia and acute exacerbations within the selected 6-month period before use of inhaled corticosteroids (ICS), before and after ICS discontinuation.

100% with COPD severity. Second, data on many possible confounding factors like nutritional status are not available. However, this study reports real-world findings and the results can therefore be applied to the majority of COPD patients.

In conclusion, using a nationwide cohort in Taiwan, this study demonstrates the association between ICS use and pneumonia in COPD patients. Hence, ICS should be used judiciously in indicated COPD patients.

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REFERENCES

- Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2013;187:347–365.
- Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med.* 2007;356:775–789.
- Wedzicha JA, Calverley PM, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med.* 2008;177:19–26.
- Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2014;3:CD010115.
- Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. *Arch Intern Med.* 2009;169:219–229.
- Drummond MB, Dasenbrook EC, Pitz MW, et al. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA.* 2008;300:2407–2416.
- Ernst P, Gonzalez AV, Brassard P, et al. Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. *Am J Respir Crit Care Med.* 2007;176:162–166.
- Sin DD, Tashkin D, Zhang X, et al. Budesonide and the risk of pneumonia: a meta-analysis of individual patient data. *Lancet.* 2009;374:712–719.
- DiSantostefano RL, Sampson T, Le HV, et al. Risk of pneumonia with inhaled corticosteroid versus long-acting bronchodilator regimens in chronic obstructive pulmonary disease: a new-user cohort study. *PLoS ONE.* 2014;9:e97149.
- Suissa S, Patenaude V, Lapi F, et al. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax.* 2013;68:1029–1036.
- Benfield T, Lange P, Vestbo J. COPD stage and risk of hospitalization for infectious disease. *Chest.* 2008;134:46–53.
- Bureau of National Health Insurance. The National Health Insurance Statistics 2015. http://www.nhi.gov.tw/English/webdata/webdata.aspx?menu=11&menu_id=296&webdata_id=1942&WD_ID=296
- Lee CH, Lee MC, Lin HH, et al. Pulmonary tuberculosis and delay in anti-tuberculous treatment are important risk factors for chronic obstructive pulmonary disease. *PLoS ONE.* 2012;7:e37978.
- Wang JY, Lee MC, Shu CC, et al. Optimal duration of anti-TB treatment in patients with diabetes: nine or six months? *Chest.* 2015;147:520–528.
- WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2015. Oslo; 2014
- Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J.* 2008;31:143–178.
- Gershon AS, Campitelli MA, Croxford R, et al. Combination long-acting beta-agonists and inhaled corticosteroids compared with long-acting beta-agonists alone in older adults with chronic obstructive pulmonary disease. *JAMA.* 2014;312:1114–1121.
- Kardos P, Wencker M, Glaab T, et al. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2007;175:144–149.
- Anzueto A, Ferguson GT, Feldman G, et al. Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. *COPD.* 2009;6:320–329.
- Ferguson GT, Anzueto A, Fei R, et al. Effect of fluticasone propionate/salmeterol (250/50 microg) or salmeterol (50 microg) on COPD exacerbations. *Respir Med.* 2008;102:1099–1108.
- Tashkin DP, Rennard SI, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. *Drugs.* 2008;68:1975–2000.
- Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs.* 2009;69:549–565.
- Welte T, Miravittles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2009;180:741–750.
- Thornton Snider J, Luna Y, Wong KS, et al. Inhaled corticosteroids and the risk of pneumonia in Medicare patients with COPD. *Curr Med Res Opin.* 2012;28:1959–1967.
- Yawn BP, Li Y, Tian H, et al. Inhaled corticosteroid use in patients with chronic obstructive pulmonary disease and the risk of pneumonia: a retrospective claims data analysis. *Int J Chron Obstruct Pulmon Dis.* 2013;8:295–304.
- Joo MJ, Au DH, Fitzgibbon ML, et al. Inhaled corticosteroids and risk of pneumonia in newly diagnosed COPD. *Respir Med.* 2010;104:246–252.
- Crim C, Calverley PM, Anderson JA, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J.* 2009;34:641–647.
- Cuervo AM, Macian F. Autophagy and the immune function in aging. *Curr Opin Immunol.* 2014;29:97–104.
- Wheat LJ. Infection and diabetes mellitus. *Diabetes Care.* 1980;3:187–197.
- Akinosoglou KS, Karkoulis K, Marangos M. Infectious complications in patients with lung cancer. *Eur Rev Med Pharmacol Sci.* 2013;17:8–18.
- Dowd JB, Aiello AE. Socioeconomic differentials in immune response. *Epidemiology.* 2009;20:902–908.
- Baschant U, Tuckermann J. The role of the glucocorticoid receptor in inflammation and immunity. *J Steroid Biochem Mol Biol.* 2010;120:69–75.
- Torres A, Peetermans WE, Viegi G, et al. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax.* 2013;68:1057–1065.