ORIGINAL ARTICLE

# The impact of acid-suppressing drugs to the patients with chronic obstructive pulmonary disease: A nationwide, population-based, cohort study

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**Background:** A high prevalence of gastroesophageal reflux disease symptoms has observed among chronic obstructive pulmonary disease (COPD) patients, and proton-pump inhibitors (PPIs) are the main medication in clinical practices. The aim of this study is to analyze the impact of PPIs to the risk of pneumonia in the cases with COPD. **Materials and Methods:** This was a nationwide, population-based, cohort study using National Health Insurance Program in Taiwan. The enrolled cases were newly-diagnosed COPD, older than 30 years, between 2001 and 2005. Patients' prescriptions with PPIs and histamine receptor 2 antagonists (HR2As), >2 months, were identified. The appearance of pneumonia and mortality of these enrolled patients was recorded. Multivariate Cox's regression was used to examine the influence of acid-suppressing drugs to pneumonia on individuals with COPD. **Results:** A total of 17,498 patients were included, of whom 109 (0.6%) and 526 (3%) cases had used PPIs and HR2As respectively. The risk of pneumonia existed when patients had used concurrent PPIs (adjusted hazard ratio [HR] = 1.76; 95% confidence interval [CI] = 1.33-2.34) or HR2As (adjusted HR = 1.25; 95% CI = 1.07-1.47). The positive association was lost in the cases over 70 years. The ratio of mortality also increased in those with PPIs or HR2As. **Conclusion:** Acid-suppressing drugs, especially PPIs, are attributed to more pneumonia happening in COPD patients compare with nonusers. The association was lost in elderly cases. Use acid-suppressing drugs should be careful about a higher possibility of pneumonia in younger individuals with COPD.

**Key words:** Chronic obstructive pulmonary disease, histamine receptor 2 antagonists, pneumonia, proton-pump inhibitors

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic, slowly progressive disease with airway obstruction. It is characterized by an accelerating decline in forced expiratory volume in 1 s, and the relationship between COPD and smoking is very strong.[1] A high prevalence of gastroesophageal reflux disease (GERD) symptoms has observed among COPD patients compared with healthy controls.[2,3] Acid reflux is a potential trigger of cough and may increase the frequency of acute COPD exacerbations.[4]

Proton-pump inhibitors (PPIs) are the main medication for GERD in clinical practices. On one hand, PPIs can effectively inhibit gastric acid secretary and might further decrease the numbers of acute COPD exacerbation.[4] But, on the other hand, previous observational studies demonstrate a positive association between PPIs use and the risk of community-acquired pneumonia,[5-8] and pneumonia is a major cause, as high as 11%, of mortality in the patient with COPD.[9] Therefore, the benefit or harmful role of PPIs in the COPD patients is needed more evidences and clinical studies to confirm.

The aim of this study is to investigate the influences of acid-suppressing drugs to the clinical outcomes of the individuals with COPD.

## PATIENTS AND METHODS

This was a nationwide, population-based, cohort study that used claims data. The National Health Insurance (NHI) Program in Taiwan was implemented on 1 March 1995, and covers above 98% population of the island's population. The National Health Research Institute of Taiwan randomly sampled a representative database

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of patients from the year 2000 registry of all NHI enrollees using a systematic sampling method for research purposes. All enrolment and utilization information associated with this random sample are available. This study was conducted with the approval of the Clinical Research Ethics Committee of Taichung Veterans General Hospital (C09038).

The enrolled cases in this study were defined as diagnosed patients with COPD (International Classification of Diseases, 9th revision, clinical modification [ICD-9-CM] code 490-496), older than 30 years, between 2001 and 2005. The data files also contained information on patients' prescriptions with acid-suppressing drugs, continuous >2 months, including PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole) and HR2As (cimetidine, famotidine, ranitidine). The appearance of pneumonia (ICD-9-CM codes 480-486) and mortality happened in the enrolled cases during the follow-up period was recorded. To clarify the etiology of mortality, the numbers of acute COPD exacerbation within 30 days before death, according to databases of admissions or outpatient visits, was also recorded. A potential confounder defined by the following diagnoses recorded as coronary artery disease (ICD-9-CM codes: 410-414), hypertension (ICD-9-CM codes 401-405), diabetes mellitus (ICD-9-CM codes 250), heart failure (ICD-9-CM codes 428.00), chronic kidney disease (ICD-9-CM codes 585, 586, 588.8, 588.9, 250.4, 274.1, 403, 404, 404 and 440.1) was listed in analysis. The concurrent prescriptions of glucocorticoids over 2 weeks that potentially could confound the association between acid-suppressing drug use, and pneumonia were also identified.

The presented results for categorical data were shown as frequency (percentage). Chi-square test was used for statistical analysis to compare baseline characteristics of each categorical variable. Multivariate Cox's regression was used to examine the influence of acid-suppressing drugs to pneumonia on individuals with COPD, as shown by Hazard ratios (HR) with 95% confidence interval (CI). A two-tailed $P < 0.05$ was considered as statistically significant. Kaplan-Meier method was used for comparing the survival curves. All statistical analyses were performed using SPSS V.18.0 for Windows (SPSS, Inc, Chicago, Illinois, USA).

## RESULTS

The following period was 10-year, and a total of 17,498 newly-diagnosed patients with COPD were included as the study cohort, of whom 109 (0.6%) and 526 (3%) cases had used PPIs and HR2As respectively. Table 1 lists the demographic characteristics, medical conditions, and medication use of each group of patients. Table 2 shows a ratio of pneumonia and mortality among the three groups. The distributions of geographical regions and histories of preexisting diseases were different, and the patients with

**Table 1: The number of baseline characteristics in newly identified COPD patients in 2000-2005**

| Variables | None (*n* = 16 863) *n* (%) | PPI (*n* = 109) *n* (%) | HR2A (*n* = 526) *n* (%) | *P*† |
|---|---|---|---|---|
| Age, years | | | | |
| 30-39 | 2155 (12.8) | 1 (0.9) | 18 (3.4) | <0.001 |
| 40-49 | 3079 (18.3) | 4 (3.7) | 45 (8.6) | |
| 50-59 | 3340 (19.8) | 16 (14.7) | 62 (11.8) | |
| 60-69 | 3763 (22.3) | 23 (21.1) | 124 (23.6) | |
| □70 | 4526 (26.8) | 65 (59.6) | 277 (52.7) | |
| Gender | | | | |
| Women | 6978 (41.4) | 27 (24.8) | 140 (26.6) | <0.001 |
| Men | 9885 (58.6) | 82 (75.2) | 386 (73.4) | |
| Comorbidities | | | | |
| Hypertension | 6876 (40.8) | 60 (55.0) | 317 (60.3) | <0.001 |
| DM | 3015 (17.9) | 32 (29.4) | 154 (29.3) | |
| Heart failure | 1179 (7.0) | 19 (17.4) | 72 (13.7) | |
| CAD | 3770 (22.4) | 33 (30.3) | 175 (33.3) | |
| CKD | 445 (2.6) | 13 (11.9) | 41 (7.8) | |
| Glucocorticoids prescription | 2010 (11.9) | 12 (11.0) | 90 (17.1) | 0.002 |

†Chi-square test. CAD = Coronary artery disease; CKD = Chronic kidney disease; COPD = Chronic obstructive pulmonary disease; DM = Diabetes mellitus; PPI = Proton-pump inhibitor; HR2A = Histamine receptor 2 antagonist

**Table 2: The number and ratio of pneumonia and mortality in the COPD patients**

| Variables | None (*n* = 16,863) *n* (%) | PPI (*n* = 109) *n* (%) | HR2A (*n* = 526) *n* (%) | *P*† |
|---|---|---|---|---|
| Pneumonia | 3129 (18.6) | 49 (45.0) | 162 (30.8) | <0.001 |
| Death | 3412 (20.2) | 85 (78.0) | 446 (84.8) | <0.001 |

†Chi-square test. COPD = Chronic obstructive pulmonary disease; HR2A = Histamine receptor 2 antagonist; *n* = Numbers; PPI = Proton-pump inhibitor

concurrent prescriptions with acid-suppressing drugs, either PPIs or HR2As, owned older age, male predominant, more comorbidity, concurrent prescriptions of glucocorticoids, and a higher ratio of pneumonia or mortality.

The strength of the association between medical history of acid-suppressing drugs and pneumonia and mortality is disclosed in Tables 3 and 4. After adjustment for measured potential confounders, including age, sex, glucocorticoids and comorbidities, the risk of pneumonia existed when patients had used concurrent PPIs (adjusted HR = 1.76; 95% CI = 1.33-2.34) or HR2As (adjusted HR = 1.25; 95% CI = 1.07-1.47). The positive association was lost in the cases over 70 years (PPI adjusted HR = 1.25; 95% CI = 0.86-1.80, HR2As adjusted HR = 0.84; 95% CI = 0.68-1.05), and more obvious in the younger ones (PPI adjusted HR = 3.39; 95% CI = 2.17-5.31, HR2As adjusted HR = 2.45; 95% CI = 1.94-3.08). The ratio of mortality increased in those with PPIs (adjusted HR = 2.39; 95% CI = 1.92-2.97) or HR2As (adjusted HR = 3.09; 95% CI = 2.80-3.42), in both younger and elderly individuals.

**Table 3: HR and 95% CI of pneumonia associated with risk factors in multivariate Cox's regression analysis**

| Drug use | HR | 95% CI | HR† | 95% CI |
|---|---|---|---|---|
| Overall | | | | |
| None | 1.00 | Reference | 1.00 | Reference |
| PPI | 3.49 | 2.63-4.63 | 1.76 | 1.33-2.34 |
| HR2A | 2.15 | 1.84-2.52 | 1.25 | 1.07-1.47 |
| Age <70 years | | | | |
| None | 1.00 | Reference | 1.00 | Reference |
| PPI | 5.77 | 3.71-8.98 | 3.39 | 2.17-5.31 |
| HR2A | 3.43 | 2.72-4.31 | 2.45 | 1.94-3.08 |
| Age □70 years | | | | |
| None | 1.00 | Reference | 1.00 | Reference |
| PPI | 1.44 | 1.00-2.08 | 1.25 | 0.86-1.80 |
| HR2A | 0.93 | 0.74-1.15 | 0.84 | 0.68-1.05 |

†Adjusted for age, sex, glucocorticoids, and comorbidities. CI = Confidence interval; HR = Hazard ratio; HR2A = Histamine receptor 2 antagonist; PPI = Proton-pump inhibitor

**Table 4: HR and 95% CI of death associated with risk factors in multivariate Cox's regression analysis**

| Drug use | HR | 95% CI | HR† | 95% CI |
|---|---|---|---|---|
| Overall | | | | |
| None | 1.00 | Reference | 1.00 | Reference |
| PPI | 5.36 | 4.32-6.65 | 2.39 | 1.92-2.97 |
| HR2A | 5.76 | 5.22-6.36 | 3.09 | 2.80-3.42 |
| Age <70 years | | | | |
| None | 1.00 | Reference | 1.00 | Reference |
| PPI | 10.15 | 7.06-14.6 | 5.20 | 3.60-7.51 |
| HR2A | 11.42 | 9.82-13.3 | 7.50 | 6.44-8.75 |
| Age □70 years | | | | |
| None | 1.00 | Reference | 1.00 | Reference |
| PPI | 2.03 | 1.56-2.66 | 1.71 | 1.30-2.23 |
| HR2A | 2.23 | 1.96-2.55 | 2.06 | 1.80-2.35 |

†Adjusted for age, sex, glucocorticoids, and comorbidities. CI = Confidence interval; HR = Hazard ratio; HR2A = Histamine receptor 2 antagonist; PPI = Proton-pump inhibitor

Figure 1 illustrates the results of the Kaplan-Meier method for the incidences of pneumonia in this cohort. Patients who take acid-suppressing drugs, especially PPI, owned a higher possibility of pneumonia than the nonusers. The longer the follow-up, the greater the differences were among the three groups. The ratio of pneumonia in the individuals who taking PPI, HR2As and nonuser was 45%, 30.6% and 18.5% respectively after a 10-year following period. The log-rank test revealed a significant observed difference ($P < 0.001$) over the entire Kaplan-Meier curve. Figures 2 and 3 display the results of the Kaplan-Meier method for the CAP of cases over or below 70 years respectively, and the younger patients taking acid-suppressing drugs had an unfavorable outcome ($P < 0.001$), but the difference disappeared in the elderly ones ($P = 0.111$).

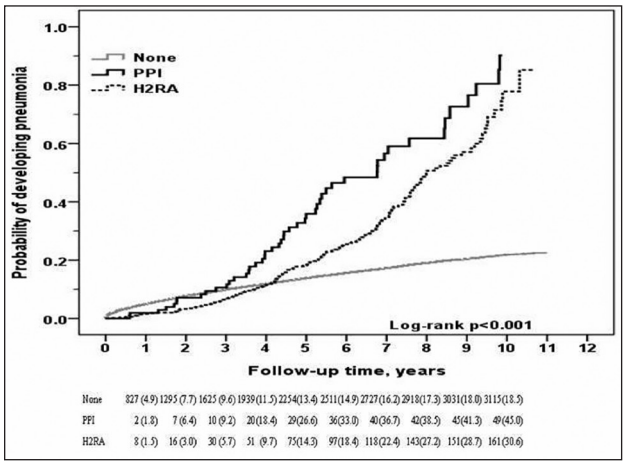


**Figure 1:** Kaplan-Meier method for the incidences of pneumonia in the cohort of newly identified chronic obstructive pulmonary disease patients in 2000-2005

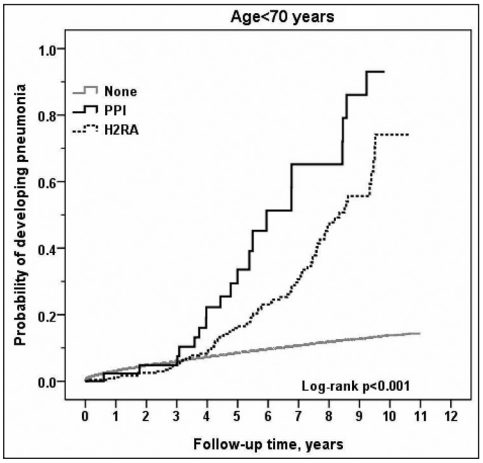


**Figure 2:** Kaplan-Meier method for the incidences of pneumonia in the younger individuals (below 70 years)

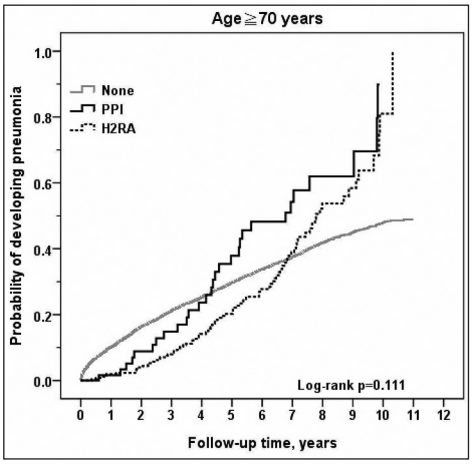


**Figure 3:** Kaplan-Meier method for the incidences of pneumonia in the elderly individuals (over 70 years)

## DISCUSSION

Chronic obstructive pulmonary disease is a chronic disease involving the airways and characterized by airflow limitation. The typical symptoms of COPD are dyspnea, chronic cough, and sputum production, and less common symptoms include wheezing and chest tightness.[1] Patients with COPD are prone to have GERD. According to formal studies, the prevalence of GERD, measured using the Mayo

Clinic GER questionnaire, ranged from 15% to 19% of COPD cases.[3,4] Two studies have measured 24-h esophageal pH monitoring in patients with severe COPD and found a prevalence of GERD in 57-62% of patients.[2,10] PPIs were introduced as the mainstay of therapy for many acid-related gastrointestinal disorders including GERD.[11]

In general population, previous some studies have linked the use of PPI to an increased risk of pneumonia.[5-8] Administration of acid suppressive therapy may predispose individuals to pneumonia due to overgrowth of bacteria in the stomach, and subsequently bacterial overgrowth increases the risk for micro-aspiration of bacteria.[12,13] Besides, the presence of proton-pumps in extra-gastric sites including the larynx and the lungs has also been identified, and PPIs may reduce the acidity of the upper aerodigestive tract, thus resulting in increased bacterial colonization of the larynx, esophagus and lungs, therefore contribute to an increased incidence of pneumonia.[14,15]

A meta-analyzed data across five observational studies and found that PPIs use was associated with an increased risk of pneumonia (odds ratio [OR] = 1.34; 95% CI = 1.14-1.57), especially duration of exposure <7 days.[16] Another meta-analysis enrolled six nested case-control studies found an increased risk of community-acquired pneumonia associated with PPI use (OR = 1.36; 95% CI = 1.12-1.65).[11] The third meta-analysis of nine case-controlled and cohort studies including 120,863 cases disclosed current use of PPIs (OR = 1.39; 95% CI = 1.09-1.76), PPI use within 30 days (OR = 1.65; 95% CI = 1.25-2.19), and high dose (OR = 1.50; 95% CI = 1.33-1.68) were significantly associated with pneumonia.[17]

Our study reported that the risk of pneumonia elevates significantly when COPD patients had used concurrent PPIs or concurrent HR2As. Increasingly, the increase of risk was most pronounced in younger individuals, and loss this association in elderly ones. Some previous studies had a similar finding. A population-based case-control study, enrolled 7642 patients, found positive correlation between current use of PPIs and pneumonia (OR = 1.5; 95% CI = 1.3-1.7), especially cases younger than 40 years (OR = 2.3; 95% CI = 1.3-4.0).[7] Another nested-case control study enrolled community-dwelling adults between the age of 65 and 94 years suggesting PPIs and HR2A were not contributing to the incidence of pneumonia in elderly cases.[18] The reason might be the younger individuals taking acid-suppressing drugs owned an unhealthier characteristic than the younger nonusers did, thus the rate of pneumonia increased dramatically. But to elderly cases, the difference is small and less influent.

Our study had some limitations. Firstly, respiratory illnesses, such as pneumonia, COPD and acute asthma exacerbations may be misdiagnosed as one or the other. Absence of corroborating clinical data such as culture specimens or radiographic imaging may result in false positive and negative classifications of pneumonia. Besides, GERD is known to be associated with aspiration pneumonitis, which could be misclassified as pneumonia. Secondly, over the counter, medication use is not captured by included databases, and data regarding the indication for acid suppression were not available in this study. Thirdly, the characteristic data did not have data on life habitus of enrolled patients, including smoking status or alcohol consumption that might be a risk factor of pneumonia. The least, even after adjustment for potential confounders, confounding by indication and disease severity may still be unmatched, as individuals prescribed PPIs are likely to have unobserved health characteristics that predispose to pneumonia or death when compared to nonusers.

## CONCLUSIONS

In this nationwide population-based cohort study, acid-suppressing drugs, especially PPIs, are attributed to more pneumonia happening in COPD patients compare with nonusers. The association was predominant in younger cases, but loss in elderly ones. Use acid-suppressing drugs should be careful about a high possibility of pneumonia in the young-aged individuals with COPD.

## MAIN MESSAGES

1. A high prevalence of GERD symptoms has observed among COPD patients, and PPIs are introduced as the mainstay of therapy for it.
2. The risk of pneumonia elevates significantly when COPD patients had used concurrent PPIs or HR2As, especially in younger individuals.
3. The relationship of acid-suppressing drugs and pneumonia in COPD patients was apparent in younger individuals.

## CURRENT RESEARCH QUESTIONS

1. Do all kinds of PPIs or HR2As have the same impacts to the COPD patients?
2. Are there a positive correlation between the dosage or duration of acid-suppressing drugs and the risk of pneumonia in the COPD individuals?
3. Why is the increased risk of pneumonia most pronounced in younger COPD cases?

## AUTHOR'S CONTRIBUTION

SWL and HCL contributed in the conception of the work, conducting the study, revising the draft, approval of the

final version of the manuscript, and agreed for all aspects of the work. SWL, ChSCh, and HZY conducting the study, revising the draft. SWL, TYL, and CFT revising the draft.

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