Association of Increased Risk of Pneumonia and Using Proton Pump Inhibitors in Patients With Type II Diabetes Mellitus

Wen-Ling Lin[1,2], Chin-Shin Muo[3,4], Wen-Chuan Lin[1], Yow-Wen Hsieh[1,2],
and Chia-Hung Kao[5,6,7]

Abstract

Background: This study explored the possible association between the use of proton pump inhibitors (PPIs) and the increased incidence of pneumonia in patients with type 2 diabetes mellitus (T2DM).

Methods: We selected 4940 patients with T2DM of whom 988 and 3952 were enrolled in PPI and propensity score-matched control cohorts, respectively. All patients were followed from the index date until admission with pneumonia, withdrawal from the National Health Insurance program or the end of 2013. The PPIs associated with risk of incident pneumonia were examined. Furthermore, we assessed the risk of pneumonia according to annual defined daily doses in the PPI cohort.

Results: After a 14-year follow-up, the cumulative incidence of pneumonia in the PPI users was 11.4% higher than that in the controls (30.3% vs 18.9%). Compared to the controls, the PPI users had a 1.70-fold higher risk of pneumonia in the Cox proportional hazards model after adjustment for matched pairs. The risk of pneumonia increased with the annual PPI defined daily dose.

Conclusion: The results of this population-based retrospective cohort study suggest that PPI use increased the risk of pneumonia in patients with T2DM. The effects were more prominent in patients administered higher doses of PPIs.

Keywords

cohort study, defined daily dose, pneumonia, proton pump inhibitor, Taiwan National Health Insurance, type 2 diabetes mellitus

Key Messages

1. The incidence of pneumonia in PPI users was 11.4% higher than that in controls.
2. PPI users had a 1.70-fold higher risk of pneumonia.
3. Higher risk of pneumonia was in omeprazole, esomeprazole, and pantoprazole.
4. The risk of pneumonia increased with the annual PPI defined daily dose.

Introduction

One of the complications of diabetes is infection. When an individual's blood sugar is too high, he or she is susceptible to bacterial infection, which can lead to pneumonia, urethritis, tuberculosis, bacteremia, or frequent purulent skin infections. The risks of pneumonia (adjusted hazard ratio [aHR] = 1.75, 95% confidence interval [CI] = 1.23-2.48), urinary tract

[1] Graduate Institute of Pharmacy, China Medical University, Taichung
[2] Department of Pharmacy, China Medical University Hospital, Taichung
[3] Management Office for Health Data, China Medical University Hospital, Taichung
[4] College of Medicine, China Medical University, Taichung
[5] Graduate Institute of Biomedical Sciences and School of Medicine, College of Medicine, China Medical University, Taichung
[6] Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung
[7] Department of Bioinformatics and Medical Engineering, Asia University, Taichung

Corresponding Author:
Chia-Hung Kao, Graduate Institute of Biomedical Sciences and School of Medicine, China Medical University, No. 2, Yuh-Der Road, Taichung 404.
Emails: d10040@mail.cmuh.org.tw; dr.kaochiahung@gmail.com

infection (aHR: 3.03, 95% CI: 2.04-4.49), and skin infection (aHR: 2.43, 95% CI: 1.49-3.95) were higher in individuals with diabetes than in those without. Each 1-mmol/L increase in plasma glucose at baseline was associated with 6% to 10% increase in the risks of pneumonia, urinary tract infection, and skin infection after adjustment for other possible confounders.[1]

Diabetes with lung infection is characterized by changes in the host's defenses, including whole body, local lung, respiratory epithelium, and cilia activity defenses.[2] Pneumonia is an inflammatory condition of the lungs that primarily affects small air sacs known as alveoli.[3,4] Pneumonia causes cough, fever, and breathing difficulties. The severity of pneumonia ranges from mild symptoms to life-threatening conditions; infants and young children, people older than 65 years, and people with health problems or impaired immune system function are at the greatest risk.[5]

In addition, many patients with diabetes experience gastroesophageal reflux disease, and most physicians believe that patients with diabetes are at greater risk of this disease. A meta-analysis supported this belief, suggesting that patients with type 2 diabetes mellitus (T2DM) are at greater risk of gastroesophageal reflux disease than individuals without T2DM.[6] Proton pump inhibitors (PPIs) are the primary therapeutic drugs for treating gastroesophageal reflux disease; most patients experience symptom relief or are cured after treatment with PPIs.[7]

The main role of PPIs is considerable long-term reduction in gastric acid production.[8] H-K-ATPase constitutes the final step in acid secretion; its discovery led to the development of PPIs—a class of drugs mainly used to inhibit H-K-ATPase.[9] The 3 main problems regarding the long-term safety of PPIs are the long-term effects of hypochlorhydria, long-term effects of hypergastrinemia, and possible association of PPIs with gastric atrophy. These problems, especially hypochlorhydria, are a concern because they can leave patients prone to infection and malabsorption.[10]

We evaluated PPIs associated with the incidence of pneumonia in patients with T2DM because of the chronic disease's drug indications. We conducted this study by using data from Taiwan's National Health Insurance (NHI) system and analyzed the risk of pneumonia and use of PPIs in patients with T2DM.

Materials and Methods

Data Source

Taiwan's NHI program was established on March 1, 1995, and it covers all residents of Taiwan. The Longitudinal Health Insurance Database (LHID) derived from the NHI program consists of all insurers' inpatient and outpatient medical records from January 1996 to December 2011. Diseases were defined according to *the International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM), and treatment was identified based on the Anatomical Therapeutic Chemical (ATC) classification system. The identities of insurers were recoded to protect patient confidentiality before researchers were allowed access to the data. This study was approved by the Institutional Review Board (IRB) of China Medical University Hospital (CMUH104-REC2-115-CR3).

Study Patients

In this retrospective cohort study (Figure 1), we collected data of 24 539 patients who had been diagnosed as having T2DM (ICD-9-CM codes 250.X0 and 250.X2) for the first time between 2000 and 2005 from the LHID. Patients who were younger than 20 years at the time of T2DM diagnosis, had a history of pneumonia, PPI use (PPI, ATC code A02BC), or had esophageal reflux (ICD-9-CM codes 530.11 and 530.81) were excluded. Patients who had used PPIs were defined as the PPI cohort, and the date of PPI treatment was the index date. Patients who were diagnosed as having pneumonia (ICD-9-CM codes 480-488) within 1 year preceding T2DM diagnosis or the PPI index date were also excluded. The control group was patients with T2DM who had not received PPI treatment. The controls were subject to the same exclusion criteria as the PPI cohort. Four controls were selected based on propensity score-matched analysis conducted using multivariable logistic regression to calculate the probability of PPI use, and greedy algorithms were used for selection. Propensity score-matched analysis can reduce selection bias and control the differences between PPI and non-PPI patients. Confounding in multivariable logistic regression for propensity scores was controlled by matching of all variables shown in Table 1.

End Point and Comorbidities

All study patients were followed from the index date until the occurrence of pneumonia upon admission. Patients without pneumonia were followed until withdrawal from the NHI program or the end of 2013. We considered the following comorbidities: renal disease (ICD-9-CM codes 580-589), stroke at admission (ICD-9-CM codes 430-438), ischemic heart disease (IHD; ICD-9-CM codes 410-414), bronchitis (ICD-9-CM codes 490-491), asthma (ICD-9-CM code 493), and chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 492 and 494-496). All comorbidities were diagnosed before the index date.

Statistical Analysis

The distributions of sex, age (grouped as 20-44, 45-64, and ≥65 years), and comorbidities between the 2 cohorts were tested using the χ^2 test and Fisher exact test. The *t* test was conducted to test the difference in mean age between the 2 cohorts. The relationships between pneumonia and associated factors were assessed using Cox proportional hazards regression after adjustment for matched pairs based on propensity score-matched analysis. Associations of various PPI types (omeprazole, rabeprazole, lansoprazole, esomeprazole, and pantoprazole) with pneumonia risk were estimated.
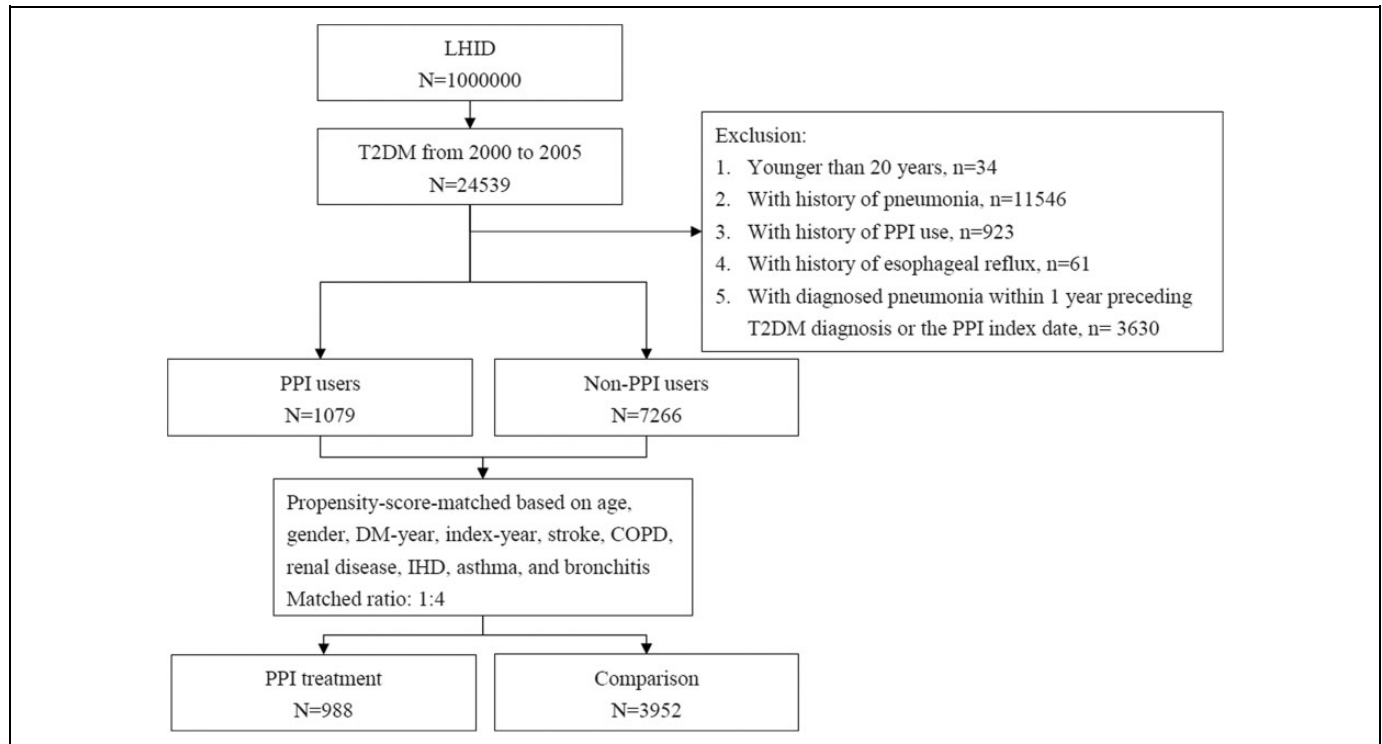
Figure 1. Flow chart of the cohort study.

Table 1. Demographics of Patients Having T2DM With and Without PPI Treatment.[a]

	PPI Treatment, n = 988		Comparison, n = 3952		
	n	%	n	%	P Value
Gender					.75
Women	374	37.9	1474	37.3	
Men	614	62.1	2478	62.7	
Age, years					.64
20-44	148	15.0	546	13.8	
45-64	519	52.5	2101	53.2	
≥65	321	32.5	1305	33.0	
Mean (SD)[b]	58.8	(13.4)	58.8	(13.2)	.98
Comorbidity					
Stroke	86	8.70	291	7.36	.16
COPD	68	6.88	247	6.25	.47
Renal disease	127	12.9	458	11.6	.27
IHD	261	26.4	1041	26.3	.96
Asthma	50	5.06	201	5.09	.97
Bronchitis	124	12.6	481	12.2	.74

Abbreviations: COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; PPI, proton pump inhibitor; SD, standard deviation; T2DM, type 2 diabetes mellitus.
[a]χ^2 test and Fisher exact test.
[b]t test.

Furthermore, we estimated the risk of pneumonia based on various annual defined daily doses of PPIs. The defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults.[11] Annual defined daily doses of PPIs were divided into 4 groups: <30, 30-59, 60-89, and ≥90 defined daily doses. Daily doses in relation to PPI user-associated pneumonia risk were estimated using the Cox proportional hazards model after adjustment for age, sex, and all comorbidities. Kaplan-Meier analysis was used to plot the cumulative incidence of pneumonia, and the log-rank test was conducted to test the difference in cumulative incidence between the 2 cohorts.

Results

We selected 4940 patients with T2DM, of whom 988 and 3952 were included in the PPI and propensity score-matched control cohorts, respectively. No significant differences in age, sex, or comorbidities were observed between the PPI and the non-PPI cohorts (Table 1). The 2 cohorts had seemingly similar baseline conditions. In the PPI cohort, the proportion of men was higher than that of women (62.1% vs 37.9%), and most patients were aged 45 to 64 years (52.5%), with a mean age of 58.8 years (standard deviation = 13.4). The most prevalent comorbidity was IHD, followed by bronchitis, renal disease, stroke, COPD, and asthma.

During the study period, the incidences of pneumonia were 14.22 and 24.22 per 1000 person-years in the control and PPI cohorts, respectively (Table 2). After a 14-year follow-up, the cumulative incidence in the PPI users was 11.4% higher than that in the controls (30.3% vs 18.9%; Figure 2). Compared to the controls, the PPI users exhibited a 1.70-fold higher risk of pneumonia in the Cox proportional hazards model after

Table 2. HRs and 95% CIs for Pneumonia and Pneumonia-Associated Factors.

Variable	N	Event	Person-Years	Rate[a]	HR (95% CI)[b]	P Value
PPI						
No	3952	419	29 466	14.22	1.00	
Yes	988	171	7061	24.22	1.70 (1.43-2.03)	<.0001

Abbreviations: CI, confidence interval; HR, hazard ratio; PPI, proton pump inhibitor.
[a]Per 1000 person-years.
[b]Cox proportional hazards model after adjustment for matched pairs based on propensity score-matched analysis.
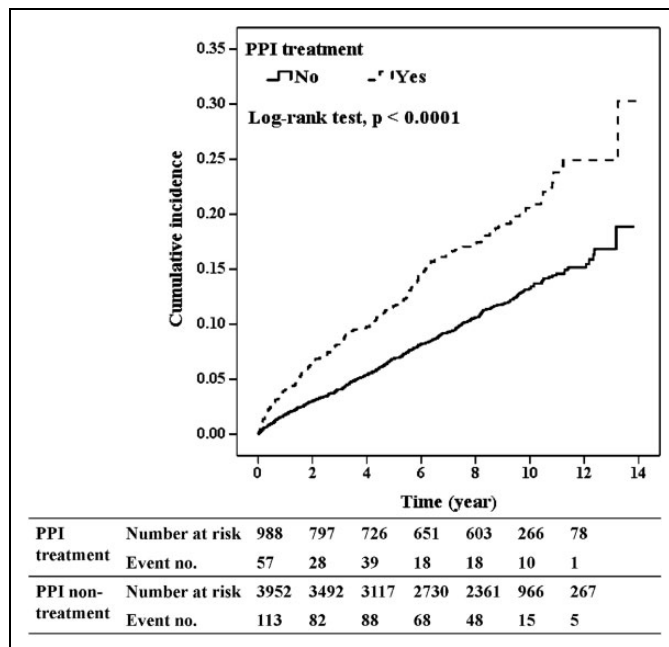
Figure 2. Cumulative incidence of pneumonia between patients having type 2 diabetes mellitus (T2DM) with and without proton pump inhibitor (PPI) treatment.

adjustment for matched pairs based on propensity score-matched analysis (95% CI = 1.43-2.03; Table 2).

The associations between pneumonia and PPI types are presented in Table 3. Compared to the controls, higher risks of pneumonia were observed in users of omeprazole (hazard ratio [HR] = 2.72, 95% CI = 1.99-3.72), esomeprazole (HR = 1.71, 95% CI = 1.27-2.32), and pantoprazole (HR = 1.84, 95% CI = 1.20-2.83) in the Cox proportional hazards model after adjustment for matched pairs based on propensity score-matched analysis. The risk of pneumonia increased with the annual PPI defined daily dose (Table 4). Compared to the controls, the risk of pneumonia was 1.29-fold higher in patients with annual defined daily doses of <30 and 4.32-fold higher in those with annual defined daily doses of ≥90 in the Cox proportional hazards model after adjustment for matched pairs based on propensity score-matched analysis. Among the PPI users, compared to those with annual defined daily doses of <30, the risk

Table 3. HRs and 95% CIs for Pneumonia and PPI Types.

PPI	N	Event	Person-Years	IR[a]	HR (95% CI)[b]	P Value
None	3952	419	29 466	14.22	1.00	
Rabeprazole	62	9	506	17.78	1.56 (0.65-2.42)	.50
Omeprazole	224	48	1235	38.87	2.72 (1.99-3.72)	<.0001
Esomeprazole	254	46	1889	24.35	1.71 (1.27-2.32)	.0005
Pantoprazole	139	23	876	26.27	1.84 (1.20-2.83)	.005
Lansoprazole	309	45	2556	17.61	1.23 (0.91 -1.67)	.17

Abbreviations: CI, confidence interval; HR, hazard ratio; PPI, proton pump inhibitor; IR, incidence rates.
[a]Per 1000 person-years
[b]Cox proportional hazards model after adjustment for matched pairs based on propensity-score-matched analysis.

of pneumonia was 1.41-fold higher in those with annual defined daily doses of 30 to 59 and 2.96-fold higher in those with annual defined daily doses of ≥90, as determined using the Cox proportional hazards model after adjustment for age, sex, and all comorbidities.

Discussion

Proton pump inhibitors effectively inhibit gastric acid secretion by irreversibly binding and inhibiting the H-K-ATPase pump onto the parietal surfaces of parietal cells. Indications for PPI therapy include the following clinical conditions: peptic ulcer disease, gastroesophageal reflux disease, Zollinger-Ellison syndrome, nonsteroidal anti-inflammatory drug-associated ulcers, and eradication of *Helicobacter pylori*.[9,12] We found that higher risks of pneumonia were observed in users of omeprazole (HR = 2.72, 95% CI = 1.99-3.72), esomeprazole (HR = 1.71, 95% CI = 1.27-2.32), and pantoprazole (HR = 1.84, 95% CI = 1.20-2.83).

Treatment with PPIs is associated with an increased risk of community-acquired pneumonia within 30 days; however, long-term treatment with PPIs is not associated with a high risk of community-acquired pneumonia. These findings are primarily based on a nested population-based case–control study of 80 066 adult patients diagnosed as having community-acquired pneumonia and 799 881 control patients in the United Kingdom.[13]

As mentioned, PPI therapy is associated with an increased risk of community-acquired pneumonia; in particular, significant time-related correlations between recently administered PPI therapy and the risk of community-acquired pneumonia have been observed. These findings are based on a large population-based case–control study of 7642 Danish patients with first hospital discharge diagnosis codes for community-acquired pneumonia and 34 176 control patients. The potential mechanism for a higher risk of community-acquired pneumonia is thought to be a reduction in gastric acid secretion, which can lead to oral infection.[14] Patients who use gastric-acid-suppressive drugs may be at greater risk of hospital-acquired pneumonia than nonusers. Gastric acid-suppressive drugs include PPIs and histamine-2 (H2) receptor antagonists.[15]

Table 4. HRs and 95% CIs for Pneumonia Stratified by Annual PPI Defined Daily Dose.

DDD	N	Event	Person-Years	IR[a]	HR (95% CI)[b]	P Value	HR (95% CI)[c]	P Value
None	3952	419	29 466	14.22	1.00			
<30	629	95	5202	18.26	1.29 (1.03-1.60)	.03	1.00	
30-59	137	26	936	27.77	1.96 (1.32-2.90)	.0008	1.41 (0.91-2.18)	.13
60-89	65	15	367	40.82	2.85 (1.73-4.69)	<.0001	2.02 (1.16-3.51)	.01
≥90	157	35	555	63.01	4.32 (2.94-6.33)	<.0001	2.96 (1.99-4.40)	<.0001

Abbreviations: CI, confidence interval; DDD, defined daily dose; HR, hazard ratio; PPI, proton pump inhibitor; IR, incidence rates.
[a]Per 1000 person-years
[b]Cox proportional hazards model after adjustment for matched pairs based on propensity score-matched analysis.
[c]Cox proportional hazards model after adjustment for age, sex, and all comorbidities.

Studies have reported respiratory infections during treatment with esomeprazole.[16,17] Furthermore, some observational studies have noted correlations between PPI use and pneumonia, but some of these observed associations may have been caused by confounding factors, that is, patients who use PPIs may be more likely to have other undetected health problems, rendering them vulnerable to pneumonia.[13,14,18-23] Patients treated with gastric acid inhibitors are at a relatively high risk of community-acquired pneumonia. Several studies have shown that when patients used H2 receptor antagonists, antacids, or PPIs to increase the pH levels in their stomachs, the rate of hospital-acquired pneumonia increased.[15,19,24-27] However, no patients in these studies had been diagnosed as having T2DM.

Use of correlative data regarding PPIs and pneumonia is controversial because such correlations result from residual interference factors; no further research is required to clarify these doubts.[20] We demonstrated the incidences of pneumonia in control and PPI cohorts. After a 14-year follow-up, the cumulative incidence in the PPI users was higher than that in the controls. Compared to the controls, the PPI users exhibited a 1.70-fold higher risk of pneumonia in adjusted models.

The PPI types associated with incident pneumonia are presented in Table 3. Compared to the controls, higher risk of pneumonia was observed in users of omeprazole, esomeprazole, and pantoprazole in the adjusted model. The risk of pneumonia increased with the annual PPI defined daily dose.

The strengths of our study are its population-based design, generalizability of findings, and use of population-based data and NHIRD records using a large sample size and having low loss to follow-up in the longitudinal design, including study and control cohorts. In addition, NHIRD covers a highly representative sample of Taiwan's general population because the reimbursement policy is universal and operated by a single buyer, the government in Taiwan. All insurance claims should be scrutinized by medical reimbursement specialists and peer review according to the standard diagnosed criteria in the study. If these doctors or hospitals make wrong diagnoses or coding, they will be punished with a lot of penalties. Therefore, the diagnoses of pneumonia and T2DM based on ICD-9 codes in this study were highly reliable.[28-31]

Certain limitations should be mentioned. First, critical data such as dietary factors, smoking habits, alcohol consumption habits, body mass index, socioeconomic status, and family history of systemic diseases are not included in the LHID. In addition, relevant medical information such as difficulty swallowing, living in nursing facilities, impaired consciousness, and surgery or trauma is limited. These are major risk factors for pneumonia diagnosis and may be indirectly associated with PPI use. Second, evidence derived from population-based retrospective case–control studies is typically of lower quality than that derived from randomized trials; this is because population-based retrospective case–control studies are subject to biases related to adjustments for confounding variables. Despite our meticulous study design, which featured adequate control of confounding factors, such biases can remain if unmeasured or if unknown confounders are present. We used propensity score-matched analysis to select non-PPI patients based on the age, sex, T2DM diagnosis year, index year, and all comorbidities (ie, stroke, COPD, renal disease, IHD, asthma, and bronchitis) of the PPI patients. Table 1 shows no significant differences between the PPI and the non-PPI cohorts; this suggests that the 2 cohorts had similar baseline conditions. Third, diagnoses recorded in NHI claims primarily serve the administrative purpose of billing and do not undergo verification for scientific purposes. We were unable to contact patients directly to inquire about their use of PPIs because the NHI ensures confidentiality for all beneficiaries. Furthermore, our analysis did not consider PPI prescriptions issued before 1996; this omission could have led to underestimations of cumulative dosage and may have weakened the observed associations. However, the data on PPI prescriptions and T2DM diagnoses were determined to be reliable.

Conclusion

The results of this population-based retrospective cohort study suggest that PPI use increased the likelihood of pneumonia among patients with T2DM. The effects were more prominent in patients administered higher doses of PPIs.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval

The NHI Research Database (NHIRD) encrypts patients' personal information to protect their privacy and provides researchers with

anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study fulfilled the condition for exemption and thus was approved by the IRB of China Medical University (CMUH104-REC2-115-CR3). In addition, the IRB waived the consent requirement.

Funding

ORCID iD

Chia-Hung Kao https://orcid.org/0000-0002-6368-3676

References

1. Benfield T, Jensen JS, Nordestgaard BG. Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. *Diabetologia*. 2007;50(3):549-554.

2. Ljubic S, Balachandran A, Pavlic-Renar I, et al. Pulmonary infections in diabetes mellitus. *Diabetologia Croatica*. 2004;33(4): 115-124.

3. McLuckie A, ed. *Respiratory Disease and Its Management*. New York, NY: Springer; 2009:51.

4. Leach RE. *Acute and Critical Care Medicine at a Glance*. 2nd ed. Hoboken, NJ: Wiley-Blackwell; 2009.

5. National Heart, Lung, and Blood Institute. Pneumonia. http:// www.nhlbi.nih.gov/health/health-topics/topics/pnu. Accessed April 15, 2016.

6. Sun XM, Tan JC, Zhu Y, Lin L. Association between diabetes mellitus and gastroesophageal reflux disease: a meta-analysis. *World J Gastroenterol*. 2015;21(10):3085-3092.

7. Hershcovici T, Jha LK, Gadam R, et al. The Relationship between type 2 diabetes mellitus and failure to proton pump inhibitor treatment in gastroesophageal reflux disease. *J Clin Gastroenterol*. 2012;46(8):662-668.

8. Li MJ, Li Q, Sun M, Liu LQ. Comparative effectiveness and acceptability of the FDA-licensed proton pump inhibitors for erosive esophagitis: a PRISMA-compliant network meta-analysis. *Medicine (Baltimore)*. 2017;96(39):e8120.

9. Shin JM, Sachs G. Pharmacology of proton pump inhibitors. *Curr Gastroenterol Rep*. 2008;10(6):528-534.

10. Friis-Hansen L. Lessons from the gastrin knockout mice. *Regul Pept*. 2007;139(1-3):5-22.

11. WHOCC. Definition and general considerations. http://www.who cc.no/ddd/definition_and_general_considera/ (October 2018, Last updated December 13, 2018).

12. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. *Ther Adv Drug Saf*. 2017;8(9):273-297.

13. Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. *Ann Intern Med*. 2008;149(6):391-398.

14. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA*. 2004;292(16): 1955-1960.

15. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA*. 2009;301(20):2120-2128.

16. Lind T, Rydberg L, Kylebäck A, et al. Esomeprazole provides improved acid control vs. omeprazole in patients with symptoms of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther*. 2000;14(7):861-867.

17. Johnson DA, Benjamin SB, Vakil NB, et al. Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebo-controlled study of efficacy and safety. *Am J Gastroenterol*. 2001;96(1):27-34.

18. Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. *Arch Intern Med*. 2007;167(9):950-955.

19. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ*. 2011;183(3): 310-319.

20. Jena AB, Sun E, Goldman DP. Confounding in the association of proton pump inhibitor use with risk of community-acquired pneumonia. *J Gen Intern Med*. 2013;28(2):223-230.

21. Freedberg DE, Abrams JA. Does confounding explain the association between PPIs and *Clostridium difficile*-related diarrhea? *Am J Gastroenterol*. 2013;108(2):278-279.

22. Myles PR, Hubbard RB, McKeever TM, Pogson Z, Smith CJ, Gibson JE. Risk of community-acquired pneumonia and the use of statins, ace inhibitors and gastric acid suppressants: a population-based case-control study. *Pharmacoepidemiol Drug Saf*. 2009;18(4):269-275.

23. Filion KB, Chateau D, Targownik LE, et al. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis., CNODES investigators. *Gut*. 2014;63(4):552-558.

24. Kollef MH. Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. *Crit Care Med*. 2004;32(6): 1396-1405.

25. Collard HR, Saint S, Matthay MA. Prevention of ventilator-associated pneumonia: an evidence-based systematic review. *Ann Intern Med*. 2003;138(6):494-501.

26. Prod'hom G, Leuenberger P, Koerfer J, et al. Nosocomial pneumonia in mechanically ventilated patients receiving anta-cid, ranitidine, or sucralfate as prophylaxis for stress ulcer.

A randomized controlled trial. *Ann Intern Med*. 1994;120(8): 653-662.

27. Huang J, Cao Y, Liao C, Wu L, Gao F. Effect of histamine-2-receptor antagonists versus sucralfate on stress ulcer prophylaxis in mechanically ventilated patients: a meta-analysis of 10 randomized controlled trials. *Crit Care*. 2010;14(5): R194.

28. Yeh JJ, Lin CL, Hsu CY, Shae Z, Kao CH. Statin for tuberculosis and pneumonia in patients with asthma-chronic pulmonary disease overlap syndrome: a time-dependent population-based cohort study. *J Clin Med*. 2018;7(11):pii: E381.

29. Lin CY, Ma T, Lin CC, Kao CH. The impact of global budgeting on health service utilization, health care expenditures, and quality of care among patients with pneumonia in Taiwan. *Eur J Clin Microbiol Infect Dis*. 2016;35(2):219-225.

30. Kuan YC, Huang KW, Lin CL, Hu CJ, Kao CH. Effects of metformin exposure on neurodegenerative diseases in elderly patients with type 2 diabetes mellitus. *Prog Neuropsychopharmacol Biol Psychiatry*. 2017;79(Pt B):77-83.

31. Hsu CW, Lin CS, Chen SJ, Lin SH, Lin CL, Kao CH. Risk of type 2 diabetes mellitus in patients with acute critical illness: a population-based cohort study. *Intensive Care Med*. 2016;42(1):38-45.