Association of Proton Pump Inhibitors Usage with Risk of Pneumonia in Dementia Patients

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OBJECTIVES: To determine the association between usages of proton pump inhibitors (PPIs) and subsequent risk of pneumonia in dementia patients.

DESIGN: Retrospective cohort study.

SETTING: Taiwanese National Health Insurance Research Database.

PARTICIPANTS: The study cohort consisted of 786 dementia patients with new PPI usage and 786 matched dementia patients without PPI usage.

MEASUREMENTS: The study endpoint was defined as the occurrence of pneumonia. The Cox proportional hazard model was used to estimate the pneumonia risk. Defined daily dose methodology was applied to evaluate the cumulative and dose-response relationships of PPI.

RESULTS: Incidence of pneumonia was higher among patients with PPI usage (adjusted hazard ratio (HR) = 1.89; 95% CI = 1.51–2.37). Cox model analysis also demonstrated that age (adjusted HR = 1.05; 95% CI = 1.03–1.06), male gender (adjusted HR = 1.57; 95% CI = 1.25–1.98), underlying cerebrovascular disease (adjusted HR = 1.30; 95% CI = 1.04–1.62), chronic pulmonary disease (adjusted HR = 1.39; 95% CI = 1.09–1.76), congestive heart failure (adjusted HR = 1.54; 95% CI = 1.11–2.13), diabetes mellitus (adjusted HR = 1.54; 95% CI = 1.22–1.95), and usage of antipsychotics (adjusted HR = 1.29; 95% CI = 1.03–1.61) were independent risk factors for pneumonia. However, usage of cholinesterase inhibitors and histamine receptor-2 antagonists were shown to decrease pneumonia risk.

CONCLUSION: PPI usage in dementia patients is associated with an 89% increased risk of pneumonia. **J Am Geriatr Soc 65:1441–1447, 2017.**

Key words: proton-pump inhibitors; pneumonia; dementia; population-based study

Dementia currently affects 44.35 million patients worldwide at an annual cost of $604 billion dollars.[1,2] Because of the aging global population, the number of people with dementia worldwide is expected to reach 135 million by 2050.[2] One of the complications of dementia, pneumonia, is associated with a high hospitalization rate, a high mortality rate, and a high level of discomfort.[3–5] A previous systematic review and meta-analysis demonstrated that there was a twofold increase in the risk of death of dementia patients with pneumonia compared with dementia patients without pneumonia.[6] Moreover, decision-making during dementia patients' pneumonia management is challenging for healthcare providers. Therefore, the prevention of pneumonia is a critical concern, particularly in advanced dementia patients.

One previous retrospective cohort study determined that the incidence of peptic ulcer disease was significantly higher among dementia patients than among patients without dementia.[7] Proton pump inhibitors (PPIs), which target gastric H(+)/K(+)-ATPase (ATP4), are the most effective available therapeutic drugs for gastric acid-related disorders. Although these drugs were initially considered safe, several studies have shown an association between PPI usage and possible subsequent pneumonia in various disease populations.[8–11] Several mechanisms have been postulated to explain why PPI usage may lead to increased pneumonia risk.[8,12] One experimental study demonstrated impairment in mucociliary clearance after the inhibition of ATP4 in the mature mucociliary epithelium.[13]

One previous study investigated the relationship between PPI usage and subsequent pneumonia in patients

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with dementia and demonstrated a hazard ratio (HR) of 1.29 for pneumonia in military veteran patients already using a PPI.[14] However, the number of dementia patients included in the aforementioned study was small. Further investigation of the association between PPI usage and subsequent pneumonia in patients with dementia is required because inappropriate PPI prescription to elderly patients is common.[15,16] Furthermore, use of PPIs is associated with significant morbidity, including cardiac diseases, metabolic diseases, chronic kidney disease, dementia, and mortality.[16–20] Therefore, the aim of our study was to investigate the association between PPI usage and the risk of pneumonia in dementia patients by using a nationwide dataset.

MATERIALS AND METHODS

Data Source

A retrospective population-based cohort study was conducted using registration and claims data from 2009 through 2013, obtained from the Longitudinal Health Insurance Database 2010 (LHID2010), which is a subset of the National Health Insurance Research Database (NHIRD), managed by the Taiwanese National Health Research Institute. The LHID2010 contains all outpatient, inpatient, and emergency department medical claims for 1 million beneficiaries randomly sampled from the 2010 National Health Insurance (NHI) registry. The disease diagnosis codes used in this study were derived from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The diagnosis coding was highly reliable because all of the insurance claims had been investigated by medical reimbursement specialists and had undergone peer review. In addition, dementia is considered a major illness and the Taiwan NHI Administration mandates that each dementia case be recorded with a special certificate.

Study Population

Adult patients aged ≥40 years with new-onset dementia were included in this study because dementia rarely develops before the age of 40. The diagnosis of dementia in these patients was defined according to the ICD-9-CM, codes 290.0–290.4, 294.1, and 331.0. Patients were defined as having dementia if they had at least three outpatient service records or one hospital admission record with the aforementioned ICD-9-CM dementia coding. To enhance the accuracy of the dementia diagnosis coding, only dementia patients who had received neuropsychological examinations such as a mini-mental status examination (order code: 45046), brain computed tomography (order code: 33067, 33068, 33069, 33070), or brain magnetic resonance imaging (order code: 33084, 33085) were included. Moreover, we only included dementia patients whose diagnosis was coded by a neurologist (code: A0700) or psychiatrist (code: A1300). The index date was defined as the date of the new-onset dementia diagnosis. Patients who had had pneumonia at some point in the 12 months prior to the index date were also excluded.

Exposure to PPIs

In Taiwan, five PPIs are available: omeprazole, pantoprazole, lansoprazole, esomeprazole, and rabeprazole. Patients with newly diagnosed dementia who used any of these PPIs after the index date were included in the case group. A comparison cohort without PPI usage was matched using a 1:1 propensity score, with matching by age, gender, and comorbidities of hypertension (ICD-9-CM 401–405), hyperlipidemia (ICD-9-CM 272.0–272.4), cerebrovascular disease (ICD-9-CM 430–437 and 438), chronic pulmonary disease (ICD-9-CM 490–496, 500–505, and 506.4), congestive heart failure (ICD-9-CM 428–428.9), DM (ICD-9-CM 250), renal disease (ICD-9-CM 582–582.9, 583–583.7, 585, 586, and 588–588.9), malignancy (ICD-9-CM 140–172.9, 174–195.8, and 200–208.9), liver disease (ICD-9-CM 456.0–456.21, 571.2, 571.5, 571.6, 571.4–571.49, and 572.2–572.8), Parkinsonism (ICD-9-CM 332), dysphagia (ICD-9-CM 787.2 and 438.82), gastroesophageal reflux disease (GERD) (ICD-9-CM 530.11 and 530.81), and upper gastrointestinal bleeding (ICD-9-CM 578.9, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, and 534.6). Also matched were the usage of cholinesterase inhibitors (ChEIs), angiotensin II converting enzyme inhibitors (ACEI), histamine-2 receptor antagonists (H2RAs), antiplatelet drugs, anticoagulants, and antipsychotics. We matched these particular medications because they had been reported as potential risk factors for pneumonia in previous studies.[8,21–24] In the present study, the c-statistic was 0.54. The goodness-of-fit Hosmer–Lemeshow test produced a chi-square of 3.12, yielding a *P*-value of .926.

The study endpoint was defined as the occurrence of pneumonia (ICD-9-CM 481, 482.xx, 483.xx, 485, and 486), withdrawal from the NHI program, or December 31, 2013. To measure the effects of PPI dose and exposure duration, we performed drug exposure analysis using the defined daily dose (DDD) methodology recommended by the World Health Organization for the investigation of administrative pharmacy claim data. DDD is the assumed average maintenance dose per day for an adult using the drug for its main indication.[25] A previous study discovered a high concordance between DDD-based methods and the days'-supply method for PPI prescription.[26]

The protocol of the present study was approved by the Institutional Review Board of Chung Shan Medical University Hospital (CSMU No: CS2-15061). Written informed consent from the participants was waived because data in the LHID2010 are de-identified (Figure 1).

Statistical Analysis

Categorical variables were delineated as numbers and percentages and were compared using Fisher's exact test where appropriate. Continuous data were delineated as the mean ± standard derivation and were compared using an independent *t*-test. The cumulative incidence of pneumonia was assessed using Kaplan-Meier analysis, in which significance was based on the log-rank test. Cox

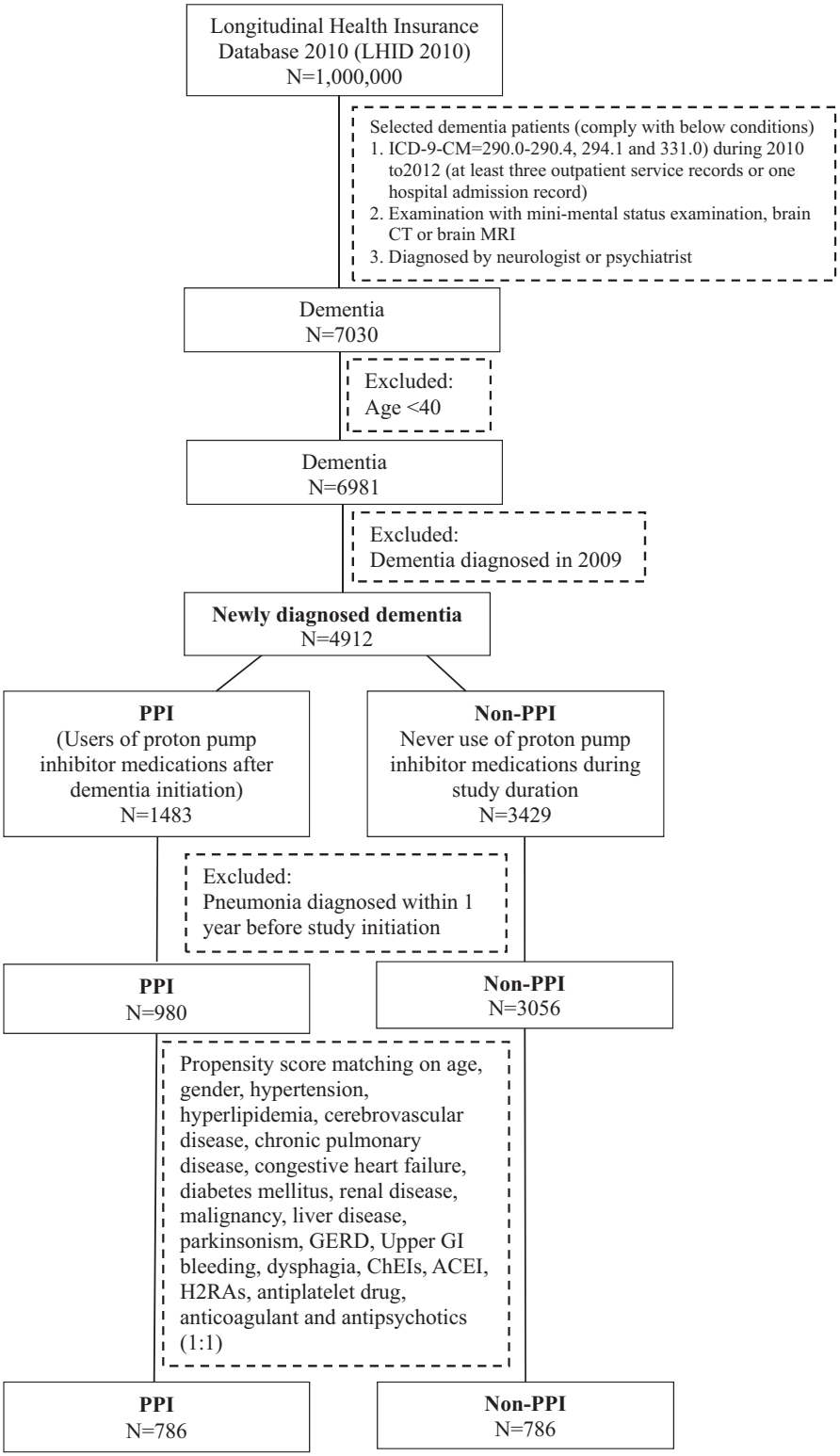

Figure 1. Flow chart for patient selection.

proportional hazard model analysis was performed to estimate the HR of pneumonia and appropriately adjust the potential confounding factors that may have influenced the calculation of pneumonia risk. Statistical analysis was performed using SPSS 18.0 (SPSS Inc.) and SAS 9.4 (SAS Institute). A *P*-value of <.05 indicated statistical significance.

RESULTS

In total, 4,912 patients newly diagnosed with dementia during the years 2010–2012 were identified. After exclusions and propensity-score matching for age, gender, comorbidities, and medications, there were 786 patients in the PPI-usage group and 786 patients in the non-PPI usage

group for the final analysis (Figure 1). The demographic characteristics and comorbidities of the dementia patients in the PPI-usage and non-PPI usage group are presented in Table 1. The mean ages in the PPI-usage and non-PPI usage group were 76.4 ± 9.8 and 76.3 ± 9.8 years, respectively. There was no significant difference in baseline comorbidities between the groups.

Table 2 shows the crude and adjusted HRs for pneumonia development in the PPI-usage and n on-PPI usage groups. The incidences of pneumonia were 176 and 152 in the PPI-usage and non-PPI usage groups, respectively. After adjustment, the dementia patients who used PPIs were discovered to have a 1.89-fold increased risk of subsequent pneumonia compared with the dementia patients in the non-PPI group (95% confidence interval (CI) = 1.51–2.37). Additional risk factors were revealed to be age (adjusted HR = 1.05; 95% CI = 1.03–1.06), male gender (adjusted HR = 1.57; 95% CI = 1.25–1.98), cerebrovascular disease (adjusted HR = 1.30; 95% CI = 1.04–1.62), chronic pulmonary disease (adjusted HR = 1.39; 95% CI = 1.09–1.76), DM (adjusted HR = 1.54; 95% CI = 1.22–1.95), and usage of antipsychotics (adjusted HR = 1.29; 95% CI = 1.03–1.61). However, usage of ChEIs (adjusted HR = 0.40; 95% CI = 0.25–0.65) and H2RAs (adjusted HR = 0.62; 95% CI = 0.50–0.78) were discovered to reduce the patients' risk of developing pneumonia. Table 3 presents the effects of PPI dose and exposure duration on the development of pneumonia in dementia patients. The risk of pneumonia was higher when the PPI DDD was >1 (adjusted HR = 1.95; 95% CI = 1.50–2.53) compared with a PPI DDD of ≤1 (adjusted HR = 1.82; 95% CI = 1.38–2.42), although all doses were associated with a significantly increased risk of pneumonia compared with the non-PPI group. No cumulative effect of PPI on pneumonia risk was discovered (HR, 2.22, 2.32, 1.27).

Figure 2 depicts the Kaplan–Meier curves of pneumonia occurrence in both groups of dementia patients. The cumulative incidence of pneumonia was higher in the PPI-usage group than in the non-PPI usage group throughout the 4-year follow-up period. The difference was significant according to the log-rank test ($P < .001$).

DISCUSSION

In this large population-based study, PPI usage was discovered to be an independent pneumonia risk factor in dementia patients. After adjustment for potential confounders, the risk of PPI-taking dementia patients

Table 1. Characteristics and Demographic Data of Study Population

	Unmatched					Matched				
	PPI N = 980		Non-PPI N = 3056			PPI N = 786		Non-PPI N = 786		
	n	%	n	%	*P*-value	n	%	n	%	*P*-value
Age on index date										
40–64	115	11.7	466	15.2	.001**	102	13.0	106	13.5	.823
≥65	865	88.3	2590	84.8		684	87.0	680	86.5	
Mean ± SD	76.9 ± 9.5		75.7 ± 10.2			76.4 ± 9.8		76.3 ± 9.8		.775
Gender										
Female	531	54.2	1759	57.6	.064	433	55.1	411	52.3	.288
Male	449	45.8	1297	42.4		353	44.9	375	47.7	
Hypertension	686	70.0	1924	63.0	<.001**	546	69.5	527	67.0	.329
Hyperlipidemia	270	27.6	790	25.9	.297	220	28.0	228	29.0	.696
Cerebrovascular disease	437	44.6	1053	34.5	<.001**	329	41.9	316	40.2	.538
Chronic pulmonary disease	227	23.2	520	17.0	<.001**	179	22.8	198	25.2	.288
Congestive heart failure	119	12.1	195	6.4	<.001**	81	10.3	80	10.2	.934
Diabetes mellitus	345	35.2	872	28.5	<.001**	271	34.5	280	35.6	.672
Renal disease	168	17.1	247	8.1	<.001**	115	14.6	121	15.4	.724
Malignancy	150	15.3	193	6.3	<.001**	106	13.5	102	13.0	.823
Liver disease	38	3.9	97	3.2	.307	27	3.4	31	3.9	.596
Parkinsonism	49	5.0	173	5.7	.469	38	4.8	39	5.0	1.000
GERD	186	18.98	111	3.6322	<.001**	99	12.6	96	12.2	.818
Upper GI bleeding	201	20.51	66	2.160	<.001**	72	9.2	66	8.4	.594
Dysphagia	16	1.6	22	0.7	.014*	12	1.5	9	1.1	.661
ChEIs	105	10.7	446	14.6	.002**	92	11.7	102	13.0	.490
ACEI	153	15.6	459	15.0	.645	116	14.8	126	16.0	.529
H2RAs	574	58.6	1219	39.89	<.001**	446	56.7	462	58.8	.414
Antiplatelet drugs	355	36.2	1317	43.1	<.001**	304	38.7	296	37.7	.716
Anticoagulants	4	0.4	14	0.5	1	3	.4	2	0.3	.687
Antipsychotics	381	38.9	1442	47.2	<.001**	310	39.4	305	38.8	.796

PPI: proton pump inhibitor; SD: standard derviation; GERD: gastroesophageal reflux disease; GI: gastrointestinal; ChEIs: cholinesterase inhibitors; ACEI: angiotensin II converting enzyme inhibitors; H2RAs: histamine-2 receptor antagonists.
*$P < .05$, **$P < .01$.

Table 2. Crude and Adjusted HRs of Pneumonia Associated with Proton Pump Inhibitor Usage, Comorbidities, and Medications

					95% CI			95% CI	
	No. of event	PY	ID	Crude HR	Lower	Upper	Adjusted HR	Lower	Upper
Group									
Non-PPI	152	1,542	9.9	1			1		
PPI	176	958.1	18.4	1.73**	1.39	2.15	1.89**	1.51	2.37
Age on index date	328	2,500	13.1	1.05**	1.04	1.07	1.05	1.03**	1.06
Gender									
Female	140	1,385	10.1	1			1		
Male	188	1,115	16.9	1.65**	1.32	2.05	1.57**	1.25	1.98
Hypertension	229	1,698	13.5	1.09	0.86	1.38	0.83	0.64	1.08
Hyperlipidemia	73	739.6	9.9	0.68**	0.52	0.88	0.78	0.60	1.03
Cerebrovascular disease	163	982	16.6	1.52**	1.23	1.89	1.30*	1.04	1.62
Chronic pulmonary disease	101	581.9	17.4	1.46**	1.15	1.84	1.39**	1.09	1.76
Congestive heart failure	48	216.1	22.2	1.75**	1.29	2.38	1.54**	1.11	2.13
Diabetes mellitus	131	834.1	15.7	1.31*	1.05	1.63	1.54**	1.22	1.95
Renal disease	54	327	16.5	1.27	0.95	1.70	1.12	0.83	1.52
Malignancy	43	306	14.1	1.09	0.79	1.50	1.08	0.78	1.49
Liver disease	10	103	9.7	0.74	0.39	1.39	0.86	0.45	1.62
Parkinsonism	19	147	12.9	1.02	0.64	1.63	1.03	0.65	1.65
GERD	31	319	9.7	0.71	0.49	1.02	0.84	0.57	1.23
Upper GI bleeding	36	223	16.2	1.26	0.89	1.78	1.21	0.85	1.72
Dysphagia	6	25	23.5	1.72	0.77	3.86	1.67	0.73	3.80
ChEIs	18	369	4.9	0.34**	0.21	0.55	0.40**	0.25	0.65
ACEI	59	435	13.6	1.07	0.81	1.42	0.96	0.72	1.28
H2RAs	172	1,610	10.7	0.63**	0.51	0.79	0.62**	0.50	0.78
Antiplatelet drugs	134	1,020	13.1	1.02	0.81	1.27	0.92	0.73	1.16
Antipsychotics	162	1,027	15.8	1.42**	1.14	1.76	1.29*	1.03	1.61

*$P < .05$, **$P < .01$.

PY: Person-years; ID: Incidence density (per 100 person-years); HR: hazard ratio; PPI: proton pump inhibitor; GERD: gastroesophageal reflux disease; ChEIs: cholinesterase inhibitors; ACEI: angiotensin II converting enzyme inhibitors; H2RAs: histamine-2 receptor antagonists.

Anticoagulants data not shown, because of none event of pneumonia.

Table 3. Association Between Proton Pump Inhibitor Dose and Pneumonia

	No. of subjects	No. of pneumonia event	Crude HR	95% CI		Adjusted HR†	95% CI	
				Lower	Upper		Lower	Upper
Group								
Non-PPI	786	152	1			1		
≤1 DDD/per-day	369	76	1.67**	1.26	2.20	1.82**	1.38	2.42
>1 DDD/per-day	417	100	1.77**	1.38	2.29	1.95**	1.50	2.53
Cumulative dose								
Non-PPI	786	152	1			1		
Low	261	61	2.46**	1.82	3.32	2.22**	1.64	3.02
Medium	263	70	2.14**	1.61	2.85	2.32**	1.73	3.09
High	262	45	1.03	0.74	1.43	1.27	0.90	1.78

*$P < .05$, **$P < .01$.

†Adjusted for age, gender, hypertension, hyperlipidemia, cerebrovascular disease, chronic pulmonary disease, congestive heart failure, diabetes mellitus, renal disease, malignancy, liver disease, parkinsonism, gastroesophageal reflux disease, upper gastrointestinal bleeding, dysphagia, cholinesterase inhibitors, angiotensin II converting enzyme inhibitors, histamine-2 receptor antagonists, antiplatelet drug and antipsychotics.

CI: confidence interval; HR: hazard ratio; PPI: proton pump inhibitor; DDD: defined daily dose.

Cumulative dose by tertile: Low <29 DDD, Medium 29–116 DDD, High ≥116 DDD.

developing pneumonia was nearly twice that of dementia patients not taking PPIs. Moreover, the PPI dose was revealed to significantly affect the risk of pneumonia.

The mechanism of PPI-related pneumonia has been widely described.[8,12] The PPI reduces gastric acid secretion, altering the pH of the gastric medium and thereby disrupting the stomach's defense mechanism, which results in increased pathogen colonization in the upper gastrointestinal tract. Microaspiration of these pathogens can cause pneumonia. PPIs were previously reported to impair the immunity function of leukocytes.[27] Furthermore, patients' cognitive functions can be affected by PPIs.[28]

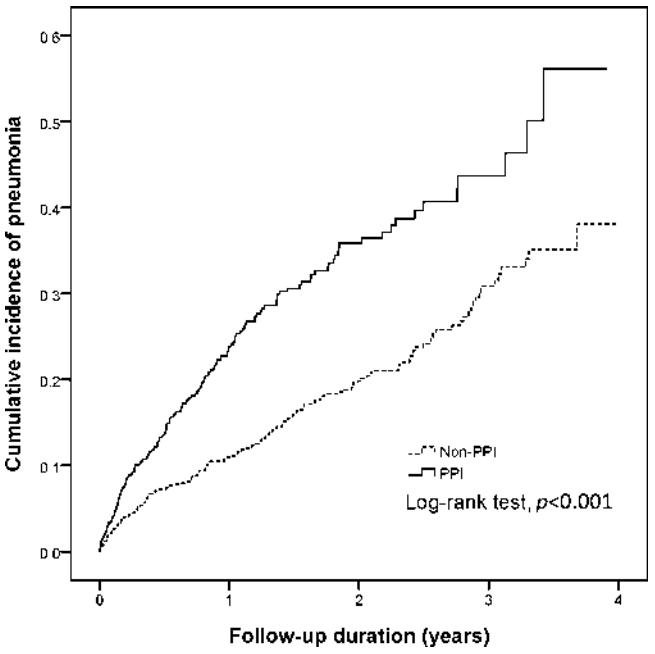

Figure 2. Kaplan-Meier curves of the cumulative incidence of pneumonia in dementia patients who did and did not use proton pump inhibitors.

Dementia patients are likely to be vulnerable to this complication because of a high likelihood of dysphagia, impairment of the gag reflex, and decreased levels of consciousness status and immunity.[29] A large-scale Japanese geriatric study also demonstrated that sputum suctioning, dysphagia, dehydration, and dementia were risk factors for aspiration pneumonia.[30] During the aging process in dementia patients, Ebihara et al.[31] described the natural course of declining brain function as dysphagia, followed by dystussia, and then atussia and aspiration (2016). Interestingly, our study did not demonstrate that dysphagia is an independent risk factor for pneumonia. The proportion of patients who had dysphagia in this study was relatively small. However, the number of dysphagia patients could be underestimated because we used the diagnostic codes ICD-9-CM 787.2 and 438.82 to denote dysphagia. As these diagnostic codes did not represent a disease, not all the physician will key-in the code of dysphagia which may lead to a selection bias.

A recent meta-analysis article indicated that community-acquired pneumonia is related to PPI usage duration and dosage.[32] Dementia patients were targeted in the research, as these patients are more predisposed to peptic ulcer disease (HR = 1.27; 95% CI = 1.18–1.37). In our study, 30.2% (1483/4912) of patients diagnosed with dementia were prescribed a PPI. Prescribing PPI inappropriately to dementia patients is common and between 25% and 80% of older patients in the UK taking these drugs have no appropriate indication.[15,33] However, the prevalence rate of over prescription in Taiwan is relatively low. The Taiwanese government operates the reimbursement policy as reflected by the NHIRD, and medical reimbursement specialists scrutinized all insurance claims detailed in the NHIRD. The policy of the Taiwanese government is that PPIs can be claimed on the NHI only if the patient has a peptic ulcer disease or GERD as confirmed by an endoscopic examination. Physicians who violate this policy can be severely penalized by the National Health Insurance Administration. We believe that this mandatory government policy of monitoring physician's practice can reduce the rate of medication over prescription.

Beside PPI, we discovered that usage of antipsychotics is also an independent risk factor for pneumonia in dementia patients and had an adjusted HR of 1.29 (95% CI = 1.03–1.61). Antipsychotic-associated pneumonia has been proposed in several observational studies. Impairment of swallowing and gag reflex after sedation is a possible mechanism. However, there is no clear evidence for an increased risk of pneumonia in younger patients treated with antipsychotics.[24] Moreover, no possible biological explanation for this phenomenon has been suggested. This issue is clinically relevant because dementia patients are frequently prescribed antipsychotics. Future studies should be conducted to clarify this issue.

Comorbidities such as DM, congestive heart failure, stroke, dementia, Parkinson disease, and chronic kidney disease are well-known risk factors associated with pneumonia in elderly people.[34,35] This was reflected in our study. Underlying diseases such as cerebrovascular disease, chronic pulmonary disease, congestive heart failure, and DM were also risk factors associated with pneumonia in the present study, with HRs of 1.30–1.54.

Several previous studies demonstrated that PPI usage is associated with dementia risk.[18,19] However, the association between PPI usage and pneumonia risk in dementia patients is still unclear. Our study concluded that dementia patients who use a PPI have an increased risk of pneumonia, but this study had some limitations. First, the NHI database did not provide detailed information on the patients' clinical conditions, such as the severity of their dementia or their Glasgow Coma Scale scores. Patients with more severe dementia and lower consciousness may have higher infection rates. Second, the patients' medication compliance could not be determined from the database. Therefore, the effects of PPI usage may have been overestimated. Third, individual information and lifestyle factors, such as smoking, body mass index, and oral dental hygiene, were not included in the database, potentially confounding this study. Fourth, although the principal focus of our study was on the side effects of PPI medications, the utilization of a clinical trial in this research was not feasible because of medical ethics regulations. The NHIRD is an observational database that was constructed for therapy needs and includes comprehensive diagnosis records and medical prescription data. This study design could thus be used to investigate the effect of PPI usage on pneumonia risk in dementia patients. Observational studies are easily confounded by unmeasured variables, but the research used propensity-score matching to minimize possible bias. Fifth, the weakness of the retrospective methodology used in this study should be taken into consideration. Finally, we could only determine a statistical association between PPI usage and risk of pneumonia in dementia patients; the possible biological molecular mechanisms need to be explored in future studies. Despite these limitations, a strength of this cohort study was the use of the LHID2010, which is a nationwide dataset comprising 1 million insurance

beneficiaries randomly selected from the 2010 NHI registry. The Taiwanese NHI system was established in 1995 and covers the medical expenses of approximately 98% of the Taiwanese population; therefore, the data accurately represent conditions in Taiwan. The dataset has a longitudinal design, which minimizes selection biases.

In this study, PPI usage in dementia patients was moderately associated with an increased risk of pneumonia. Therefore, physicians should exercise caution when prescribing PPIs to dementia patients.

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Conflict of Interest: None.

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REFERENCES

1. Libro R, Giacoppo S, Soundara Rajan T et al. Natural phytochemicals in the treatment and prevention of dementia: An overview. Molecules 2016;21:518.
2. Abbott A. Dementia: A problem for our age. Nature 2011;475:S2–S4.
3. Phelan EA, Borson S, Grothaus L et al. Association of incident dementia with hospitalizations. JAMA 2012;307:165–172.
4. Mitchell SL, Teno JM, Kiely DK et al. The clinical course of advanced dementia. N Engl J Med 2009;361:1529–1538.
5. van der Steen JT, Ooms ME, van der Wal G et al. Pneumonia: The demented patient's best friend? Discomfort after starting or withholding antibiotic treatment. J Am Geriatr Soc 2002;50:1681–1688.
6. Foley NC, Affoo RH, Martin RE. A systematic review and meta-analysis examining pneumonia-associated mortality in dementia. Dement Geriatr Cogn Disord 2015;39:52–67.
7. Hsu CC, Hsu YC, Chang KH et al. Association of dementia and peptic ulcer disease: A nationwide population-based study. Am J Alzheimers Dis Other Demen 2016;31:389–394.
8. Laheij RJ, Sturkenboom MC, Hassing RJ et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 2004;292:1955–1960.
9. Eurich DT, Sadowski CA, Simpson SH et al. Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. Am J Med 2010;123:47–53.
10. Herzig SJ, Doughty C, Lahoti S et al. Acid-suppressive medication use in acute stroke and hospital-acquired pneumonia. Ann Neurol 2014;76:712–718.
11. Chen CH, Lin HC, Lin HL et al. Proton pump inhibitor usage and the associated risk of pneumonia in patients with chronic kidney disease. J Microbiol Immunol Infect 2015;48:390–396.
12. Theisen J, Nehra D, Citron D et al. Suppression of gastric acid secretion in patients with gastroesophageal reflux disease results in gastric bacterial overgrowth and deconjugation of bile acids. J Gastrointest Surg 2000;4:50–54.
13. Walentek P, Beyer T, Hagenlocher C et al. ATP4a is required for development and function of the Xenopus mucociliary epidermis–a potential model to study proton pump inhibitor-associated pneumonia. Dev Biol 2015;408:292–304.
14. Hermos JA, Young MM, Fonda JR et al. Risk of community-acquired pneumonia in veteran patients to whom proton pump inhibitors were dispensed. Clin Infect Dis 2012;54:33–42.
15. Hamzat H, Sun H, Ford JC et al. Inappropriate prescribing of proton pump inhibitors in older patients: Effects of an educational strategy. Drugs Aging 2012;29:681–690.
16. Delcher A, Hily S, Boureau AS et al. Multimorbidities and overprescription of proton pump inhibitors in older patients. PLoS ONE 2015;10:e0141779.
17. McDonald EG, Milligan J, Frenette C et al. Continuous proton pump inhibitor therapy and the associated risk of recurrent clostridium difficile infection. JAMA Intern Med 2015;175:784–791.
18. Gomm W, von Holt K, Thome F et al. Association of proton pump inhibitors with risk of dementia: A pharmacoepidemiological claims data analysis. JAMA Neurol 2016;73:410–416.
19. Haenisch B, von Holt K, Wiese B et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. Eur Arch Psychiatry Clin Neurosci 2015;265:419–428.
20. Arora P, Gupta A, Golzy M et al. Proton pump inhibitors are associated with increased risk of development of chronic kidney disease. BMC nephrology 2016;17:112.
21. Helou R, Rhalimi M. Cholinesterase inhibitors and the risk of pulmonary disorders in hospitalized dementia patients. J Popul Ther Clin Pharmacol. 2010;17:e379–e389.
22. Caldeira D, Alarcao J, Vaz-Carneiro A et al. Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: Systematic review and meta-analysis. BMJ 2012;345:e4260.
23. Le VB, Schneider JG, Boergeling Y et al. Platelet activation and aggregation promote lung inflammation and influenza virus pathogenesis. Am J Respir Crit Care Med 2015;191:804–819.
24. Trifiro G. Antipsychotic drug use and community-acquired pneumonia. Curr Infect Dis Rep 2011;13:262–268.
25. Uchida N, Chong MY, Tan CH et al. International study on antidepressant prescription pattern at 20 teaching hospitals and major psychiatric institutions in East Asia: Analysis of 1898 cases from China, Japan, Korea, Singapore and Taiwan. Psychiatry Clin Neurosci 2007;61:522–528.
26. Sinnott SJ, Polinski JM, Byrne S et al. Measuring drug exposure: Concordance between defined daily dose and days' supply depended on drug class. J Clin Epidemiol 2016;69:107–113.
27. Capodicasa E, De Bellis F, Pelli MA. Effect of lansoprazole on human leukocyte function. Immunopharmacol Immunotoxicol 1999;21:357–377.
28. Akter S, Hassan MR, Shahriar M et al. Cognitive impact after short-term exposure to different proton pump inhibitors: Assessment using CANTAB software. Alzheimers Res Ther 2015;7:79.
29. Kalia M. Dysphagia and aspiration pneumonia in patients with Alzheimer's disease. Metabolism 2003;52:36–38.
30. Manabe T, Teramoto S, Tamiya N et al. Risk factors for aspiration pneumonia in older adults. PLoS ONE 2015;10:e0140060.
31. Ebihara S, Sekiya H, Miyagi M et al. Dysphagia, dystussia, and aspiration pneumonia in elderly people. J Thorac Dis 2016;8:632–639.
32. Giuliano C, Wilhelm SM, Kale-Pradhan PB. Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis. Expert Rev Clin Pharmacol 2012;5:337–344.
33. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. BMJ 2008;336:2–3.
34. Wada H, Nakajoh K, Satoh-Nakagawa T et al. Risk factors of aspiration pneumonia in Alzheimer's disease patients. Gerontology 2001;47:271–276.
35. Vinogradova Y, Hippisley-Cox J, Coupland C. Identification of new risk factors for pneumonia: Population-based case-control study. Br J Gen Pract 2009;59:e329–e338.