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.


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.
with dementia and demonstrated a hazard ratio (HR) of 1.29 for pneumonia in military veteran patients already using a PPI. 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. Furthermore, use of PPIs is associated with significant morbidity, including cardiac diseases, metabolic diseases, chronic kidney disease, dementia, and mortality. 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. 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. A previous study discovered a high concordance between DDD-based methods and the days’-supply method for PPI prescription.

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
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.
Table 1. Characteristics and Demographic Data of Study Population

<table>
<thead>
<tr>
<th>Unmatched</th>
<th></th>
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<th>Matched</th>
<th></th>
<th></th>
<th>P-value</th>
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<td></td>
<td>PPI N = 980</td>
<td>Non-PPI N = 3056</td>
<td></td>
<td>PPI N = 786</td>
<td>Non-PPI N = 786</td>
<td></td>
</tr>
<tr>
<td>Age on index date</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>40-64</td>
<td>115</td>
<td>11.7</td>
<td>466</td>
<td>15.2</td>
<td>.001**</td>
<td>102</td>
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<tr>
<td>≥65</td>
<td>865</td>
<td>88.3</td>
<td>2590</td>
<td>84.8</td>
<td></td>
<td>684</td>
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<tr>
<td>Mean ± SD</td>
<td>76.9 ± 9.5</td>
<td>75.7 ± 10.2</td>
<td>76.4 ± 9.8</td>
<td>76.3 ± 9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>531</td>
<td>54.2</td>
<td>1759</td>
<td>57.6</td>
<td>.064</td>
<td>433</td>
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<tr>
<td>Male</td>
<td>449</td>
<td>45.8</td>
<td>1297</td>
<td>42.4</td>
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<tr>
<td>Hypertension</td>
<td>668</td>
<td>70.0</td>
<td>1924</td>
<td>63.0</td>
<td>&lt;.001**</td>
<td>546</td>
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<tr>
<td>Hyperlipidemia</td>
<td>270</td>
<td>27.6</td>
<td>790</td>
<td>25.9</td>
<td>.297</td>
<td>220</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>437</td>
<td>44.6</td>
<td>1053</td>
<td>34.5</td>
<td>&lt;.001**</td>
<td>329</td>
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<tr>
<td>Chronic pulmonary disease</td>
<td>227</td>
<td>23.2</td>
<td>520</td>
<td>17.0</td>
<td>&lt;.001**</td>
<td>179</td>
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<tr>
<td>Congestive heart failure</td>
<td>119</td>
<td>12.1</td>
<td>195</td>
<td>6.4</td>
<td>&lt;.001**</td>
<td>81</td>
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<tr>
<td>Diabetes mellitus</td>
<td>345</td>
<td>35.2</td>
<td>872</td>
<td>28.5</td>
<td>&lt;.001**</td>
<td>271</td>
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<tr>
<td>Renal disease</td>
<td>168</td>
<td>17.1</td>
<td>247</td>
<td>8.1</td>
<td>&lt;.001**</td>
<td>115</td>
</tr>
<tr>
<td>Malignancy</td>
<td>150</td>
<td>15.3</td>
<td>193</td>
<td>6.3</td>
<td>&lt;.001**</td>
<td>106</td>
</tr>
<tr>
<td>Liver disease</td>
<td>38</td>
<td>3.9</td>
<td>97</td>
<td>3.2</td>
<td>.307</td>
<td>27</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>49</td>
<td>5.0</td>
<td>173</td>
<td>5.7</td>
<td>.469</td>
<td>38</td>
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<tr>
<td>GERD</td>
<td>186</td>
<td>18.98</td>
<td>111</td>
<td>3.6322</td>
<td>&lt;.001**</td>
<td>99</td>
</tr>
<tr>
<td>Upper GI bleeding</td>
<td>201</td>
<td>20.5</td>
<td>66</td>
<td>2.160</td>
<td>&lt;.001**</td>
<td>72</td>
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<tr>
<td>Dysphagia</td>
<td>16</td>
<td>1.6</td>
<td>22</td>
<td>0.7</td>
<td>.014*</td>
<td>12</td>
</tr>
<tr>
<td>ChEIs</td>
<td>105</td>
<td>10.7</td>
<td>446</td>
<td>14.6</td>
<td>.002**</td>
<td>92</td>
</tr>
<tr>
<td>ACEI</td>
<td>153</td>
<td>15.6</td>
<td>459</td>
<td>15.0</td>
<td>.645</td>
<td>116</td>
</tr>
<tr>
<td>H2RAs</td>
<td>574</td>
<td>58.6</td>
<td>1219</td>
<td>39.9</td>
<td>&lt;.001**</td>
<td>446</td>
</tr>
<tr>
<td>Antiplaetlet drugs</td>
<td>332</td>
<td>33.2</td>
<td>1317</td>
<td>43.1</td>
<td>&lt;.001**</td>
<td>304</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>4</td>
<td>0.4</td>
<td>14</td>
<td>0.5</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>381</td>
<td>38.9</td>
<td>1442</td>
<td>47.2</td>
<td>&lt;.001**</td>
<td>310</td>
</tr>
</tbody>
</table>

PPI: proton pump inhibitor; SD: standard deviation; GERD: gastroesophageal reflux disease; GE: gastrointestinal; ChEIs: cholinesterase inhibitors; ACEI: angiotensin II converting enzyme inhibitors; H2RAs: histamine-2 receptor antagonists.

*P < .05, **P < .01.
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. 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. Furthermore, patients’ cognitive functions can be affected by PPIs.

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

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of event</th>
<th>PY ID</th>
<th>Crude HR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>Adjusted HR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>176</td>
<td>958.1</td>
<td>1.73**</td>
<td>1.39</td>
<td>2.15</td>
<td>1.89**</td>
<td>1.51</td>
<td>2.37</td>
</tr>
<tr>
<td>Age on index date</td>
<td>328</td>
<td>2,500</td>
<td>1.05**</td>
<td>1.04</td>
<td>1.07</td>
<td>1.05</td>
<td>1.03**</td>
<td>1.06</td>
</tr>
</tbody>
</table>

Table 3. Association Between Proton Pump Inhibitor Dose and Pneumonia

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>No. of pneumonia event</th>
<th>Crude HR</th>
<th>95% CI</th>
<th>Adjusted HR†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI ≤1 DDD/per-day</td>
<td>369</td>
<td>76</td>
<td>1.67**</td>
<td>1.26</td>
<td>2.20</td>
<td>1.82**</td>
</tr>
<tr>
<td>PPI &gt;1 DDD/per-day</td>
<td>417</td>
<td>100</td>
<td>1.77**</td>
<td>1.38</td>
<td>2.29</td>
<td>1.95**</td>
</tr>
</tbody>
</table>

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

PY: Person-years; ID: Incidence density (per 100 person-years); HR: hazard ratio; PPI: proton pump inhibitor; GED: 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.

*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.
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

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

Sponsor’s Role: The sponsor had no role in this study.

Author Contributions: Study concept, data analysis, interpretation, and writing the manuscript: Ho SW, Teng YH, Yang SF, and Yeh CB. Literature search and analysis: Yeh HW, Wang YH, and Chou MC. All authors contributed to and approved the final manuscript. Sai-Wai Ho and Ying-Hock Teng contributed equally to this work.

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