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Association between Antacid Exposure and Risk of Interstitial Lung Diseases

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Abstract

Background: The mechanisms leading to lung fibrosis are still under investigation. This study aimed to demonstrate whether antacids could prevent the development of interstitial lung disease (ILD).

Methods: This population-based longitudinal cohort study was conducted between January 2006 and December 2010 in South Korea. Eligible subjects were ≥40 years of age, exposed to proton pump inhibitors (PPI)±histamine-2 receptor antagonists (H-2 blockers) or H-2 blockers only, and had no history of ILD between 2004 and 2005. Exposure to antacids was defined as the administration of either PPI or H-2 receptor antagonists for >14 days, whereas underexposure was defined as antacid treatment administered for less than 14 days. Newly developed ILDs, including idiopathic pulmonary fibrosis (IPF), were counted during the 5-year observation period. The association between antacid exposure and ILD development was evaluated using adjusted Cox regression models with variables, such as age, sex, smoking history, and comorbidities.

Results: The incidence rates of ILD with/without antacid use were 43.2 and 33.8/100,000 person-years, respectively and those of IPF were 14.9 and 22.9/100,000 person-years, respectively. In multivariable analysis, exposure to antacid before the diagnosis of ILD was independently associated with a reduced development of ILD (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.45 to 0.71; p<0.001), while antacid exposure was not associated with development of IPF (HR, 0.88; 95% CI, 0.72 to 1.09; p=0.06).

Conclusion: Antacid exposure may be independently associated with a decreased risk of ILD development.

Keywords: Interstitial Lung Disease; Idiopathic Pulmonary Fibrosis; Antacid Exposure; Incidence

Introduction

Pulmonary fibrosis is a progressive lung disorder characterized by the excessive deposition of fibrous tissue, leading to the impairment of lung function. Among these, idiopathic pulmonary fibrosis (IPF) is an irreversible progressive form of lung fibrosis with a median survival from 2 to 3 years after diagnosis[1,2]. While the etiology of pulmonary fibrosis is still not fully understood, various risk factors and triggers have been identified, including exposure to environmental agents, medications, and systemic diseases[3]. The mechanisms leading to IPF is still under investigation[4,5].

Gastroesophageal reflux disease (GERD) is an over-represented comorbidity of interstitial lung disease (ILD)/IPF[6-10], suggesting that micro-aspiration of gastric

acids increases the risk of IPF development[7]. Genetic and population-based studies suggest GERD increases the risk of IPF[11,12]. Chronic micro-aspiration may lead to fibrotic remodeling of the pulmonary parenchyma, resulting in lower pulmonary elasticity and increases negative intrathoracic pressure[6]. This latter event could worsen GERD by decreasing the pressure of the upper esophageal sphincter, thus predisposing to multiple episodes of micro-aspiration that aggravate the course of the lung disease[6]. While some patients would respond with a cough or wheezing, in others, the refluxate is transported to the distal airspaces, which may induce alveolar epithelial injury or apoptosis[13].

Injury to type II alveolar epithelial cells is thought to be the key event for the initiation of the IPF[4]. Studies have highlighted that lung injury is independent of acidity and factors other than acid may be involved in its pathogenesis[14,15]. A study showed that exposure of bronchial epithelial cells to gastric juice from patients on antisecretory therapy is able to induce high interleukin-8 production, the most relevant cytokine for the acute phase response of inflammation[16].

Understanding the potential relationship between antacid therapy and pulmonary fibrosis is crucial for patient care and management. Clinicians need to weigh the benefits of antacid therapy against the potential risks, particularly in patients with pre-existing lung disease or those at higher risk of developing pulmonary fibrosis. Several studies have suggested possible anti-inflammatory and antifibrotic properties of proton pump inhibitors (PPIs)[17-20].

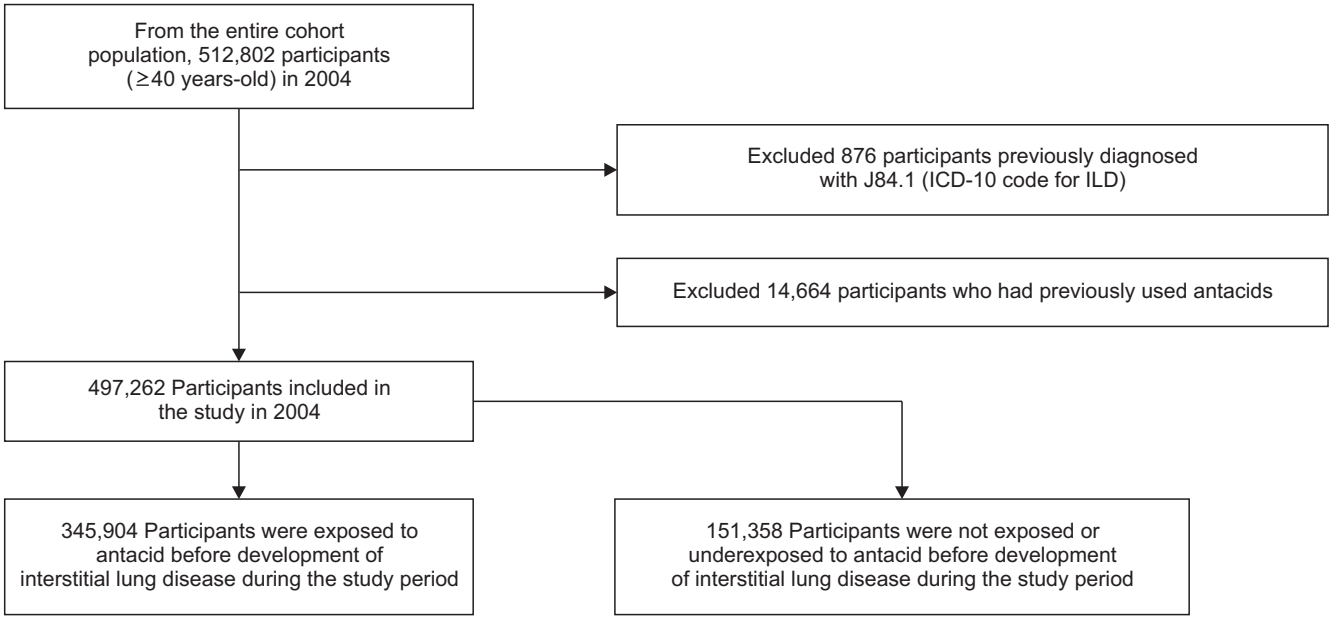
In this population-based study, we aimed to determine whether antacid exposure decreases the risk of ILD development.

Materials and Methods

1. Data sources and study design

We used the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS), which included 514,802 Koreans (Figure 1). This cohort represents the selection of screened participants aged 40 to 80 years in the index years of 2002 or 2003. Data were collected from January 2006 to December 2010 (Figure 1). First data were reviewed for 2 years (January 2004 to December 2005) of smoking history and body mass index from health exams, as routinely are conducted every 2 years in South Korea. Of these, patients with ILD diagnoses during this period were excluded. We defined exposure to antacid as a documented prescription. Data on cumulative antacid prescriptions until ILD development and ILD diagnosis were extracted from January 2006 to December 2010. For patients newly diagnosed with ILD during the follow-up period (from January 2006 until ILD diagnosis), the duration of antacid prescription was calculated. For patients without ILD, the antacid prescription period was calculated for a 5-year follow-up period. This study was approved

Figure 1. Flow chart of participant selection. ICD-10: International Classification of Diseases, 10th revision; ILD: interstitial lung disease.



by the Institutional Review Board (IRB) of Myongji Hospital (2022-10-018) and conducted in accordance with the ethical standards of the Declaration of Helsinki. The IRB waived the requirement for informed consent due to the retrospective nature of this study. All methods were performed in accordance with the relevant guidelines and regulations.

2. Study population

Patients diagnosed with ILD between January 2006 and December 2010 were enrolled (Figure 1). This study enrolled only patients aged more than 40 years. Subjects were excluded when ILD was diagnosed between January 2004 and December 2005. The International Classification of Diseases, 10th revision (ICD-10) codes were used as a key reference for diagnosing disease, as well as for identifying data within the National Health Insurance database. Diagnoses were made by identifying ICD-10 codes from 2004 until the index date, for interstitial lung disease (J84.1), and idiopathic pulmonary fibrosis (J84.1A). Patient comorbidities included diabetes (E11.x), chronic kidney disease (N18.x), hypertension (I10.x), history of myocardial infarction (I21.x, I25.2), chronic obstructive pulmonary diseases (J44.x), cerebrovascular diseases (ICD codes I60-I69), gastroesophageal reflux disease (K21.x), and peptic ulcer (K27.x).

3. Assessment of antacid prescription

Antacids were defined as either histamine-2 (H-2) antagonists or PPIs. The cumulative duration of antacid prescription between January 1, 2006 and December 31, 2010, was calculated for each participant until the diagnosis of ILD or the end of follow-up. We were unable to count actual patient usage. Consequently, the patients were classified into the underexposure group based on two criteria: a duration of antacid administration less than 14 days or no use for 5 years. As biological potency and half-life vary among drugs, we did not take such characteristics into account. We considered only the duration of antacid treatment in this study. There were not enough patients treated with PPIs alone to assess the incidence of ILD based on the antacid type. The antacid drug codes are listed in Supplementary Table S1.

4. Statistical analysis

Baseline characteristics at the initiation of the study (age, sex, residential area, household income, smoking status, body mass index, and comorbidities) for both cases and controls were summarized using descriptive statistics such as proportions. A chi-square test was used to compare frequencies of risk factors between exposed and underexposed groups. Cox proportional hazards models were used to evaluate risk factors for ILD development.

Multivariate Cox regression models were constructed using patient age groups (40–49, 50–59, 60–69, 70–79, and ≥80 years), sex, household income (high, middle, low, very low, and Medicaid), geographic location (capital, large cities, and other), smoking status, comorbidities, body mass index, and antacid exposure. The Kaplan-Meier method was used to calculate the 5-year risk of ILD development between the exposed and underexposed group. Sensitivity analyses on risk of ILD/IPF development stratified by age of 60 years, sex, and antacid exposure duration. We performed additional analyses to assess the association between the development of ILD/IPF and the exposure to antacid, which was defined as the summary of prescription days (categorized as <14, 14–34, 35–77, 78–207, and ≥208 days). Statistical significance was set at $p<0.05$. All statistical analyses were performed using the SAS version 9.2 (SAS Institute, Cary, NC, USA) and SPSS version 21 (IBM Corp., Armonk, NY, USA).

5. Data access statement

Additional data are available after approval from the Korean NHIS.

Results

1. Patient characteristics

A total of 497,262 participants of age more than 40 years were included in the study (Figure 1). Among 345,904 (69.56%) antacid exposed subjects, 510 (0.14%) were diagnosed with ILD during the study. The median duration of antacid use in the antacid exposed group was 77 days (Table 1). Among 151.358 (30.44%) antacid underexposed subjects, 152 (0.10%) were diagnosed with ILD during the study period (Table 1). The median follow-up time was 37.9 months for the antacid underexposed group, and 40.9 months for the antacid exposed group. Subjects from the antacid exposed group were older than those from the antacid underexposed group (Table 1). Additionally, less than half of patients in the antacid exposed group were male (n=157,905, 45.65%), whereas more than half of patients in the antacid underexposed group were male (n=86,789, 57.34%) (Table 1).

2. Antacid exposure in ILD/IPF

The incidence rates for ILD with/without antacid use were 43.2 and 33.8/100,000 person-years, respective-

Table 1. Baseline characteristics of population with or without antacid therapy

Variable	Underexposure to antacid (n=151,358)	Exposure to antacid (n=345,904)	p-value
Male sex	86789 (57.34)	157,905 (45.65)	<0.001
Age group, yr			
40–49	68,217 (45.06)	106,392 (30.75)	<0.001
50–59	42,334 (27,96)	109,978 (31.79)	<0.001
60–69	17,216 (11.37)	67,192 (19.42)	<0.001
70–79	13,397 (8.85)	47,005 (13.58)	<0.001
≥80	10,194 (6.73)	15,337 (4.43)	<0.001
Baseline comorbidity			
Diabetes	28,948 (19.12)	107,840 (31.17)	<0.001
Chronic kidney disease	1,890 (1.24)	6,143 (1.77)	<0.001
Hypertension	48,417 (31.98)	162,840 (47.07)	<0.001
History of myocardial infarction	2,530 (1.67)	8,050 (2.32)	<0.001
Chronic obstructive pulmonary disease	7,518 (4.96)	32,679 (9.44)	<0.001
Cerebrovascular diseases	15,445 (10.20)	59,394 (17.17)	<0.001
Gastroesophageal reflux disease	35,736 (23.61)	238,725 (69.01)	<0.001
Peptic ulcer	32,858 (21.70)	184,596 (53.36)	<0.001
Diagnosis			
ILD development	162 (0.10)	510 (0.14)	<0.001
IPF development	110 (0.07)	176 (0.05)	0.951
Death	20,961 (13.84)	14,715 (4.25)	<0.001
Pneumonia, requiring hospitalization	5,556 (3.67)	10,772 (3.11)	<0.001
Risk factors			
BMI ≥25 kg/m^2	35,099 (23.18)	110,245 (31.87)	<0.001
Smoker			
Never smoker	59,302 (39.17)	197,333 (57.04)	<0.001
Former or current smoker	45,303 (29.93)	104,931 (30.33)	<0.001
Residential area			
Seoul, capital city	30,073 (19.86)	66,647 (19.26)	<0.001
Large city	33,631 (22.21)	89,180 (25.78)	<0.001
Small city and rural area	71,469 (47.21)	189,864 (54.88)	<0.001
Household income			
9–10	39,838 (26.32)	102,303 (29.57)	<0.001
6–8	40,039 (26.45)	102,211 (29.54)	<0.001
3–5	31,526 (20.82)	73,582 (21.27)	<0.001
1–2	19,313 (12.75)	49,818 (14.40)	<0.001
0	20,643 (13.63)	17,990 (5.20)	<0.001
Antacid therapy duration, day			
<14	151,358 (100.00)	0	<0.001
14–34	0	85,956 (24.84)	<0.001
35–77	0	85,905 (24.83)	<0.001
78–207	0	87,393 (25.26)	<0.001
≥208	0	86,650 (25.05)	<0.001

Table 1. Continued

Variable	Underexposure to antacid (n=151,358)	Exposure to antacid (n=345,904)	p-value
Antacid medication			
H-2 blocker	0	123,017 (35.56)	<0.001
H-2 blocker and PPI	0	213,777 (61.80)	<0.001
PPI	0	9,110 (2.63)	<0.001

Values are presented as number (%).
ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; BMI: body mass index; H-2: histamine-2; PPI: proton pomp inhibitor.

ly, whereas those of IPF were 14.9 and 22.9/100,000 person-years, respectively. In multivariable analysis, antacid exposure before the diagnosis of ILD was independently associated with a reduced development of ILD (hazard ratio [HR], 0.57; 95% confidence interval [CI], 0.45 to 0.71; p<0.001) (Table 2). Antacid treatment did not reach statistical significance regarding the reduction of IPF development (HR, 0.88; 95% CI, 0.72 to 1.09; p=0.06) (Figure 2).

3. Sensitivity analysis

We assessed the risk of ILD development based on the duration of antacid exposure. Compared to antacid exposure of less than 14 days, the HR was 0.76 (95% CI, 0.61 to 0.94; p<0.001) for antacid exposure 14 to 34 days, 0.53 (95% CI, 0.42 to 0.66; p<0.001) for antacid exposure of 35 to 77 days, 0.57 (95% CI, 0.46 to 0.71; p<0.001) for antacid exposure of 78 to 207 days, and 0.46 (95% CI, 0.36 to 0.57; p<0.001) for antacid exposure of more than 208 days (Figure 2). Regarding antacid exposure and ILD risk, the HR in female was 0.41 (95% CI, 0.29 to 0.59; p<0.001) and in male, the HR was 0.68 (95% CI, 0.51 to 0.91; p<0.001). In the group exposed only to H-2 blocker, HR 0.64 (95% CI, 0.57 to 0.72; p<0.001), in the group exposed to H-2 blocker and PPI together, HR 0.43 (95% CI, 0.36 to 0.51; p<0.001) (Figure 2).

Discussion

In this large cohort study, we provided evidence supporting a potential beneficial effect of antacid therapy on ILD, as demonstrated by reduced development of ILD (43%) independently to age, sex, smoking status, and comorbidities. We analyzed the cumulative effect of antacid use, and the data suggest that antacid therapy can reduce the development of ILD significantly in a time-dependent manner. The HR for ILD development was the lowest in patients who had antacid exposure >208 days over 5 years.

Antacid therapy with PPIs in patients with IPF has been associated with reduced progression and improved survival[21,22]. However, other studies have not demonstrated any beneficial effects in patients with IPF treated with PPIs[17,23-25]. Unlike previous studies, the majority of antacid prescriptions in this study were H-2 blockers, and only 2.6% used PPI alone. As a result, the prominent contribution in our study can be attributed to the use of H-2 blockers rather than the effect of PPIs. This pharmacological distinction may explain the divergent outcomes observed compared to previous studies. Importantly, in contrast to the risk reduction observed for ILD, antacid use did not significantly lower the risk of IPF in our study. While IPF is an advanced disease characterized by extensive pulmonary fibrosis, ILD exhibits less fibrosis than IPF. Since antacids may not have a significant effect on preventing fibrosis, it is presumed that they are effective for reducing the risk of ILD but not for IPF.

Although antacid was not significant in the univariate analysis in the ILD group, it was significant in the multivariate analysis. Table 1 shows that there are more female and elderly patient in antacid exposure group. Differences in comorbidities may have resulted from these gender and age differences. In univariate analysis, the antacid exposed and underexposed groups did not differ in relation to the risk of ILD due to unbalancing of variables. However, the statistical significance was achieved after correction by the multivariate analysis[26,27].

Studies have shown that the incidence of ILD/IPF is higher in male[5,28,29]. Sensitivity analysis in our study, based on sex, showed that exposure to antacid in female reduced the development of ILD with 27% more than in male. It seems that antacid therapy may be more beneficial in female than male.

ILD usually affects the elderly and its incidence and prevalence increase with age[5,28,29]. Most cases of ILD

Table 2. Univariate and multivariate Cox regression analyses for factors associated with the development of interstitial lung diseases

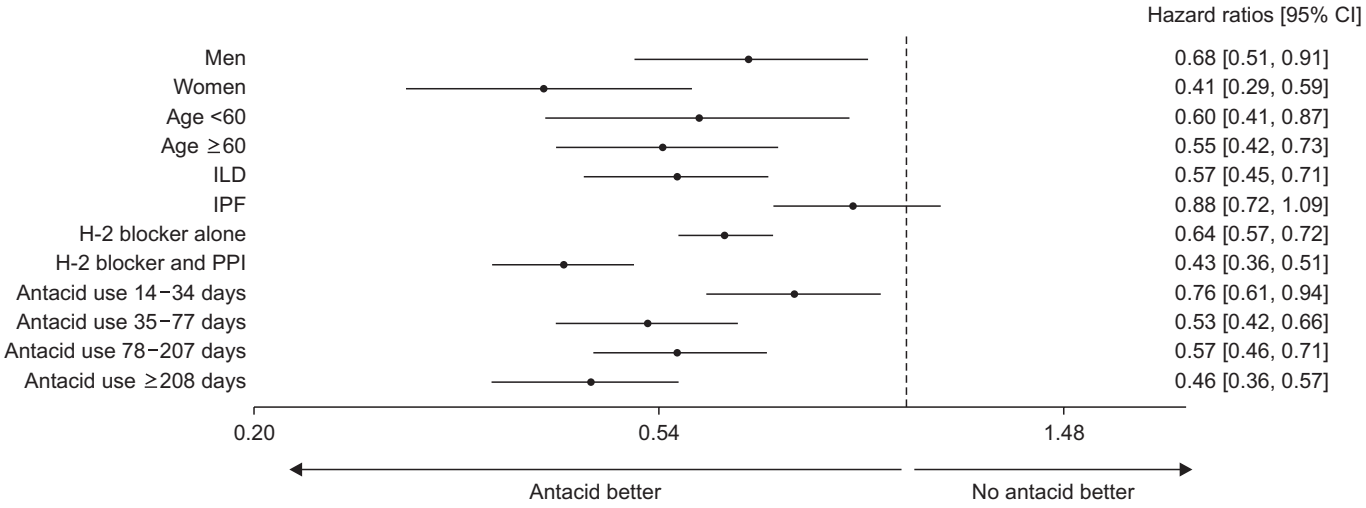
Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male (reference: female)	1.48 (1.27–1.73)	<0.001	1.27 (1.02–1.58)	0.030
Age group, yr (reference: 40–49)				
50–59	2.45 (1.81–3.31)	<0.001	2.39 (1.72–3.32)	<0.001
60–69	6.42 (4.82–8.56)	<0.001	6.02 (4.35–8.32)	<0.001
70–79	11.17 (8.41–14.83)	<0.001	9.26 (6.59–13.02)	<0.001
≥80	14.25 (10.26–19.79)	<0.001	12.14 (8.06–18.29)	<0.001
Baseline comorbidity				
Diabetes (reference: no)	1.93 (1.65–2.25)	<0.001	1.10 (0.92–1.32)	0.276
Chronic kidney disease (reference: no)	2.68 (1.78–4.04)	<0.001	1.33 (0.82–2.15)	0.237
Hypertension (reference: no)	2.11 (1.81–2.47)	<0.001	0.82 (0.68–0.99)	0.044
History of myocardial infarction (reference: no)	2.12 (1.43–3.14)	<0.001	1.11 (0.72–1.72)	0.610
COPD (reference: no)	5.81 (4.94–6.84)	<0.001	3.32 (2.75–4.01)	<0.001
Cerebrovascular diseases (reference: no)	2.19 (1.84–2.60)	<0.001	0.98 (0.79–1.20)	0.860
GERD (reference: no)	1.39 (1.19–1.63)	<0.001	1.23 (1.01–1.49)	0.035
Peptic ulcer (reference: no)	1.63 (1.40–1.90)	<0.001	1.23 (1.03–1.48)	0.019
Risk factors				
BMI, kg/m^2 (reference <25)	0.85 (0.71–1.01)	0.081	0.87 (0.73–1.04)	0.147
Ex-smoker smoker or current smoker (reference: never smoker)	1.52 (1.29–1.79)	<0.001	1.49 (1.20–1.85)	<0.001
Residential area (reference: Seoul, capital city)				
Large city	1.00 (0.80–1.26)	0.974	0.96 (0.75–1.23)	0.779
Small city and rural area	1.03 (0.84–1.26)	0.744	0.88 (0.71–1.10)	0.271
Household income (reference: 9–10)				
6–8	0.71 (0.58–0.87)	0.001	0.76 (0.61–0.95)	0.016
3–5	0.70 (0.56–0.88)	0.002	0.88 (0.69–1.11)	0.301
1–2	0.89 (0.70–1.13)	0.348	0.99 (0.77–1.28)	0.996
0	1.92 (1.46–2.51)	<0.001	1.66 (1.15–2.38)	0.006
Antacid therapy duration, day (reference: <14)				
14–34	1.09 (0.86–1.39)	0.456	0.76 (0.58–1.00)	0.052
35–77	1.08 (0.85–1.38)	0.503	0.62 (0.47–0.81)	0.001
78–207	1.15 (0.91–1.46)	0.222	0.48 (0.36–0.64)	<0.001
≥208	1.58 (1.27–1.97)	<0.001	0.39 (0.29–0.52)	<0.001
Antacid exposure (reference: no exposure)	1.23 (1.03–1.469)	0.021	0.57 (0.45–0.71)	<0.001

HR: hazard ratio; CI: confidence interval; COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal reflux disease; BMI: body mass index.

are diagnosed over the age of 60 years. In our study, exposure to antacid showed to be independently associated with lower incidence of ILD, whether age is less than or older than 60 years.

Systematic reviews and meta-analyses have shown that antacid therapy might not be safe and could be associated with an increased risk of pulmonary infections[24,30]. In this study, pneumonia patients requiring hospitalization were analyzed by infection frequency. Although no correction was made and simple com-

Figure 2. Hazard ratios for the development of interstitial lung disease (ILD) according to antacid exposure by subgroups. All analyses have been adjusted for age, sex, body mass index, smoking status, residential area, household income, and all baseline comorbidities. CI: confidence interval; IPF: idiopathic pulmonary fibrosis; H-2: histamine-2; PPI: proton pomp inhibitor.



parison was performed, the incidence of pneumonia was lower in the antacid exposure group than underexposed group.

Cigarette smoking, GERD, and environmental exposures have been reported as risk factors for developing ILD[5,31,32] and this was also showed in the multivariate analysis of this study. Furthermore, the group with the lowest household income had a higher risk of ILD, and annual income could be a weak proxy for occupational exposure[33].

This study had some limitations. First, this study was confounded by immortal time bias. However, due to the nature of our data, it was not feasible to establish a time-dependent variable for antacid use, as it involved the utilization of two distinct drugs. Therefore, we were unable to control for immortal time bias. Second, diagnosis of ILD/IPF and other comorbidities were defined based on ICD codes, which should have been validated through patient records. However, this database consists of random samples of national insurance claim data without identification numbers. Therefore, it was not possible to validate the data of individual cases through a chart review. Third, we could not evaluate PPI alone contribution to ILD development because most of the patients were exposed to both H-2 blockers and PPI. Only 2.6% of all antacid prescribed subjects were exposed to PPI alone. Fourth, the history of antacid use before 2006 was not taken into consideration, and this may cause selection bias.

In this population-based cohort study, patients exposed to antacid had a reduced development of ILD compared to those who were underexposed to antacid. Our study revealed a dose-response relationship, with a longer duration of antacid exposure associated with a greater reduction in ILD development. These findings have important implications for the progression and prevention of ILD.

Authors' Contributions

Conceptualization: Lee DY, Choi WI. Methodology: Lee DY, Jeong J, Choi WI. Formal analysis: Lee DY, Jeong J, Choi WI. Data curation: Lee DY, Jeong J, Choi WI. Software: Jeong J. Investigation: Lee DY, Jeong J, Choi WI. Funding acquisition: Choi WI. Resources: Jeong J, Choi WI. Visualization: Lee DY, Jeong J, Choi WI. Writing - original draft preparation: Bae S, Loloci G, Jang HJ. Writing - review and editing: Bae S, Loloci G, Jang HJ, Jeong J, Choi WI. Approval of final manuscript: all authors.

Conflicts of Interest

Hye Jin Jang is an editorial board member of the journal, but she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).

Supplementary Table S1. Drug codes for selecting proton pump inhibitors and histamine-2 receptor antagonists.

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