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Increased risk of herpes zoster in patients with peptic ulcers
A longitudinal follow-up study using a national sample cohort

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Abstract

The purpose of this study was to investigate the association of herpes zoster infection with peptic ulcer disease in a Korean population.

The Korean National Health Insurance Service selects samples directly from the entire Korean population database, and 1,125,691 participants with 114,369,638 medical claim codes were selected from the entire Korean population (50 million). A total of 127,802 peptic ulcer disease participants were matched with 127,802 control participants at a ratio of 1:1, considering age group, sex, income group, region of residence, hypertension, diabetes, and dyslipidemia. We analyzed stratified Cox proportional hazard models to calculate the hazard ratios of peptic ulcer with respect to herpes zoster. For subgroup analyses, we divided the participants by age, sex, and time periods after the index date.

The rate of herpes zoster was higher in the peptic ulcer group (9.1% [11,669/127,802]) than in the control group (7.4% [9,397/127,802], $P < .001$). The adjusted hazard ratio of herpes zoster was 1.24 (95% CI = 1.21–1.28, $P < .001$). In subgroup analyses performed according to age and sex, all crude and adjusted hazard ratios of herpes zoster were higher in the peptic ulcer disease group than in the control group (each $P < .05$). In another subgroup analysis according to follow-up periods, the crude and adjusted hazard ratios of herpes zoster were higher in the peptic ulcer disease group than in the control group except for < 1 year periods after the index dates (each $P < .001$).

The hazard ratios of herpes zoster were significantly increased in the peptic ulcer group compared with those in the control group in all age and sex groups.

Abbreviations: CIs = confidence intervals, HIRA = health insurance review & assessment, HRs = hazard ratios, HZ = herpes zoster, NHIS-NSC = Korean National Health Insurance Service-National Sample Cohort, NSAIDs = Nonsteroidal anti-inflammatory drugs, PUD = peptic ulcer disease, VZV = varicella-zoster virus.

Keywords: herpes zoster, longitudinal follow-up study, peptic ulcers, varicella-zoster virus

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1. Introduction

Peptic ulcer disease (PUD) is an acid-peptic injury in the gastric tract, especially the stomach or proximal duodenum. The main symptoms of gastric ulcers are abdominal pain, nausea and vomiting after eating and weight loss. Patients with duodenal ulcers feel hungry and show nocturnal abdominal pain. The annual incidence was reported to be approximately 0.1% to 0.3% in Western countries.[1,2] *Helicobacter pylori* (*H pylori*) infection is the most common cause of PUD (48%), followed by the use of nonsteroidal anti-inflammatory drugs (NSAIDs, 24%) in the USA.[3] In Korea, *H pylori* infection was the most common cause (48%), followed by ulcerogenic drugs, including aspirin, NSAIDs and warfarin (21%).[4] The main complications of PUD in Korea were reported as ulcer bleeding (13.2%), perforation (0.1%) and gastric outlet obstruction (1%),[5] and the mortality rate ranged from 1.7% to 10.7% after bleeding and from 10.7% to 27.0% after perforation.[6] In addition, PUD can cause chronic malnutrition due to bleeding, dysphagia and sleep disorders, which can weaken an individual's immune system.

Herpes zoster (HZ), known as shingles, is caused by reactivation of varicella-zoster virus (VZV) in the cranial nerve or dorsal root ganglia after primary infection. This reactivation of VZV is associated with decreased cell-mediated immunity as a result of aging or cell-mediated immunosuppression.[7–9] The risk of reactivation has been reported to be increased in women,

blacks, genetically susceptible individuals, psychologically stressed individuals, individuals who smoke cigarettes, individuals who drink alcohol, micronutrient deficient individuals, hypertensive individuals, individuals with diabetes mellitus (DM), individuals with hyperlipidemia, older people and individuals with malignancies.[9–11] HZ is characterized by a painful rash or vesicle on the ipsilateral side following the sensory nerve of the dermatome.[10] In the USA, the incidence rate of HZ was 3.6/1,000 (CI3.4–3.7) from 1996 to 2001, and the incidence rate was increased to 10.7/1000 in patients greater than 80 years old.[12] In Korea, the incidence rate of HZ was 10.4/1000 in 2011, which was increased to 16.5/1000 in individuals greater than 80 years old.[13] The incidence of PUD has increased in older and immunocompromised patients, which is the main causal factor of HZ. However, there was only one previous study on the incidence of HZ in PUD patients.[14]

This study investigated the association of HZ with PUD in a nationwide population-based cohort study using data from the Korean National Health Insurance Service (NHIS). In this study, we estimated the hazard ratios (HRs) of HZ in PUD patients compared to participants in a 1:1 matched control group.

2. Materials and methods

2.1. Study population and data collection

The ethics committee of Hallym University (2017-I102) approved the use of these data. Written informed consent was exempted by the Institutional Review Board.

This national cohort study relied on data from the Korean Health Insurance Review and Assessment Service-National Sample Cohort (HIRA-NSC). A detailed description of these data was provided in our previous studies.[15,16]

2.2. Participant selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, peptic ulcer was defined as the patients who were performed an endoscopy, and visited clinics or hospital as the diagnosis of ICD-10 codes from K25 (gastric ulcer) to K27 (peptic ulcer, site unspecified) ≥ 2 times (n=133,349).

HZ was diagnosed based on ICD-10 code B02. Among these cases, we included only participants who visited clinics or hospital ≥ 2 times as B02 or who were prescribed antiviral medication ≥ 1 time as B02 (n=64,152).

The peptic ulcer group was matched 1:1 with participants (control group) who were not diagnosed with peptic ulcers from 2002 through 2013. The control group was selected from the total population (n=992,342). Matching was performed for age group, sex, income group, region of residence, and past medical histories (hypertension, diabetes, and dyslipidemia). To prevent selection bias when selecting the matched participants, the control participants were sorted using a random number order and were then selected from top to bottom. We set the index date as the date of diagnosis of peptic ulcer. It was assumed that the matched control participants were involved at the same time as the peptic ulcer participants (index date). Therefore, control patients who died before the index date were excluded. The participants with a history of HZ before the index date were excluded from both the peptic ulcer and control groups. In the peptic ulcer group, 2,501 participants were excluded. Peptic ulcer

patients for whom we could not identify sufficient matching participants were excluded (n=8). We also excluded participants younger than 20 years of age (n=3,038). The mean follow-up time from index date to the final date (Dec. 31, 2013) or death date was similar in both the peptic ulcer (98.6 months, standard deviation [SD]=38.1) and the control group (98.0 months, SD=38.4). Finally, 1:1 matching resulted in the inclusion of 127,802 peptic ulcer patients and 127,802 control participants (Fig. 1). However, the participants were not matched with respect to ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and chronic obstructive pulmonary disease (COPD) histories because strict matching based on these characteristics increased the drop-out rate for subjects due to a lack of control participants.

2.3. Variables

The age groups were classified using the following 5-year age intervals: 20–24, 25–29, 30–34, and 85+ years old. A total of 14 age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest income]−5 [highest income]). The region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The participants' prior medical histories were evaluated using ICD-10 codes. To ensure an accurate diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were regarded as present if a participant was treated ≥ 2 times. These metabolic diseases were adjusted in that this study had no records of obesity. Ischemic heart disease (I24 and I25) and cerebral stroke (I60-I66) were regarded as present if a participant was treated ≥ 1 time. Depression was defined based on ICD-10 codes from F31 (bipolar affective disorder) to F39 (unspecified mood disorder) recorded by a psychiatrist ≥ 2 times. Atopic dermatitis (L20) was defined as present if a participant was treated ≥2 times, as in a previous study.[17] COPD was determined by J43 (emphysema) through J44 (other chronic obstructive pulmonary disease) for individuals who were treated with SABA, LABA, LAMA, and a corticosteroid ≥ 2 times.[18] This designation was adjusted in that this study had no records of smoking.

2.4. Statistical analyses

Chi-square tests were used to compare the general characteristics between the peptic ulcer and control groups.

Stratified Cox proportional hazard models were used to assess HRs for peptic ulcers with respect to HZ. In this analysis, crude (simple) and adjusted (for ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and COPD) models were used, and 95% confidence intervals (CIs) were calculated. In these analyses, age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia were stratified. Kaplan-Meier survival analysis and the log-rank test were used (Fig. 2).

For the subgroup analyses, we divided the participants by age (20–39, 40–59, and 60+ years) and sex (men and women). In
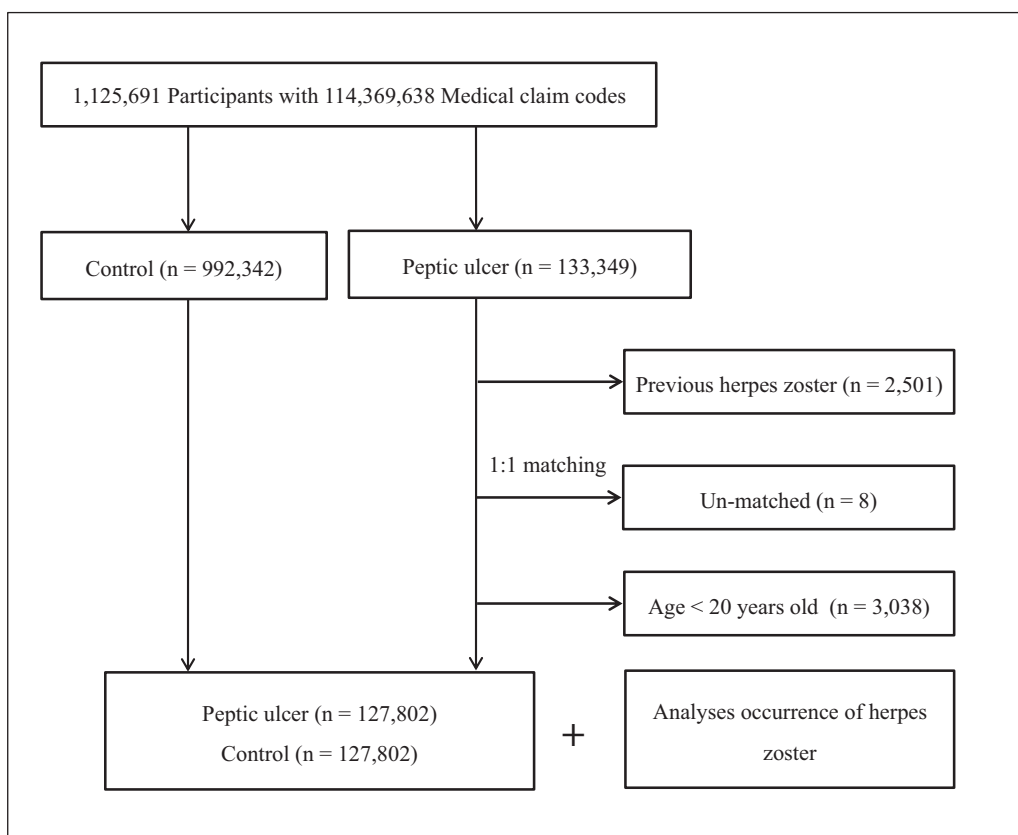
Figure 1. A schematic illustration of the participant selection process used in the present study. Of a total of 1,125,691 participants, 127,802 peptic ulcer patients were matched with 127,802 control participants for age group, sex, income group, region of residence, and past medical histories.

another subgroup analysis, we calculated HRs for follow-up periods of < 1 year, 2 years, 3 years, 4 years and ≥ 5 years after the index date.

Two-tailed analyses were conducted, and *P* values less than .05 were considered to indicate significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY).

3. Results

The time duration from the index date to HZ was 63.3 months (SD = 37.4) in the peptic ulcer group and 63.3 months (SD = 38.3) in the control group. The rate of HZ was higher in the peptic ulcer group (9.1% [11,669/127,802]) than in the control group (7.4% [9,397/127,802], *P* < .001, Table 1). The general characteristics (age, sex, income, region of residence, and hypertension, diabetes, and dyslipidemia histories) of the participants were the same between the two groups due to the matching procedure (*P* = 1.000). The rates of ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and COPD were higher in the peptic ulcer group than in the control group (each *P* < .001).

The crude and adjusted HRs of HZ were 1.26 (95% CI = 1.22–1.29) and 1.23 (95% CI = 1.20–1.27), respectively, in the peptic ulcer group (each *P* < .001, Table 2).

In subgroup analyses performed according to age and sex, all crude and adjusted HRs of HZ were higher in the peptic ulcer group than in the control group (each *P* < .05, Table 3). The adjusted HRs were 1.18 (95% CI = 1.06–1.32) in < 40-year-old men; 1.33 (95% CI = 1.21–1.46) in < 40-year-old women; 1.27 (95% CI = 1.19–1.35) in 40 to 59-year-old men; 1.21 (95%

CI = 1.15–1.27) in 40–59-year-old women; 1.25 (95% CI = 1.16–1.35) in ≥ 60-year-old men; and 1.20 (95% CI = 1.13–1.28) in ≥ 60-year-old women.

In another subgroup analysis according to follow-up periods, the crude and adjusted HRs of HZ were higher in the peptic ulcer group than in the control group, except for the < 1 year period after the index date (each *P* < .001, Table 4). The adjusted HRs were 1.31 (95% CI = 1.20–1.44) in the period of 2 years; 1.26 (95% CI = 1.15–1.38) in the period of 3 years; 1.31 (95% CI = 1.20–1.44) in the period of 4 years; and 1.24 (95% CI = 1.20–1.29) in the period of ≥ 5 years.

4. Discussion

In this study, the peptic ulcer group (9.1%) showed an increased rate of HZ compared to that of the control group (7.4%), and the HR of HZ was significantly higher in the peptic ulcer group than in the control group (HR = 1.26, 95% CI = 1.22–1.29) after matching for age, sex, income, region of residence, and hypertension, diabetes, and dyslipidemia histories. Furthermore, this study showed that PUD was significantly associated with reactivation of HZ (adjusted HR = 1.23, 95% CI = 1.20–1.27) after excluding comorbidities, such as ischemic heart disease, cerebral stroke, depression, atopic dermatitis and COPD histories, which were previously studied as possible causes of HZ.[19–22]

Chen et al., reported an increased HR of HZ in a PUD (adjusted HR = 1.77, 95% CI = 1.64–1.91) group compared to a control group matched for age, gender, year of cohort entry, DM,
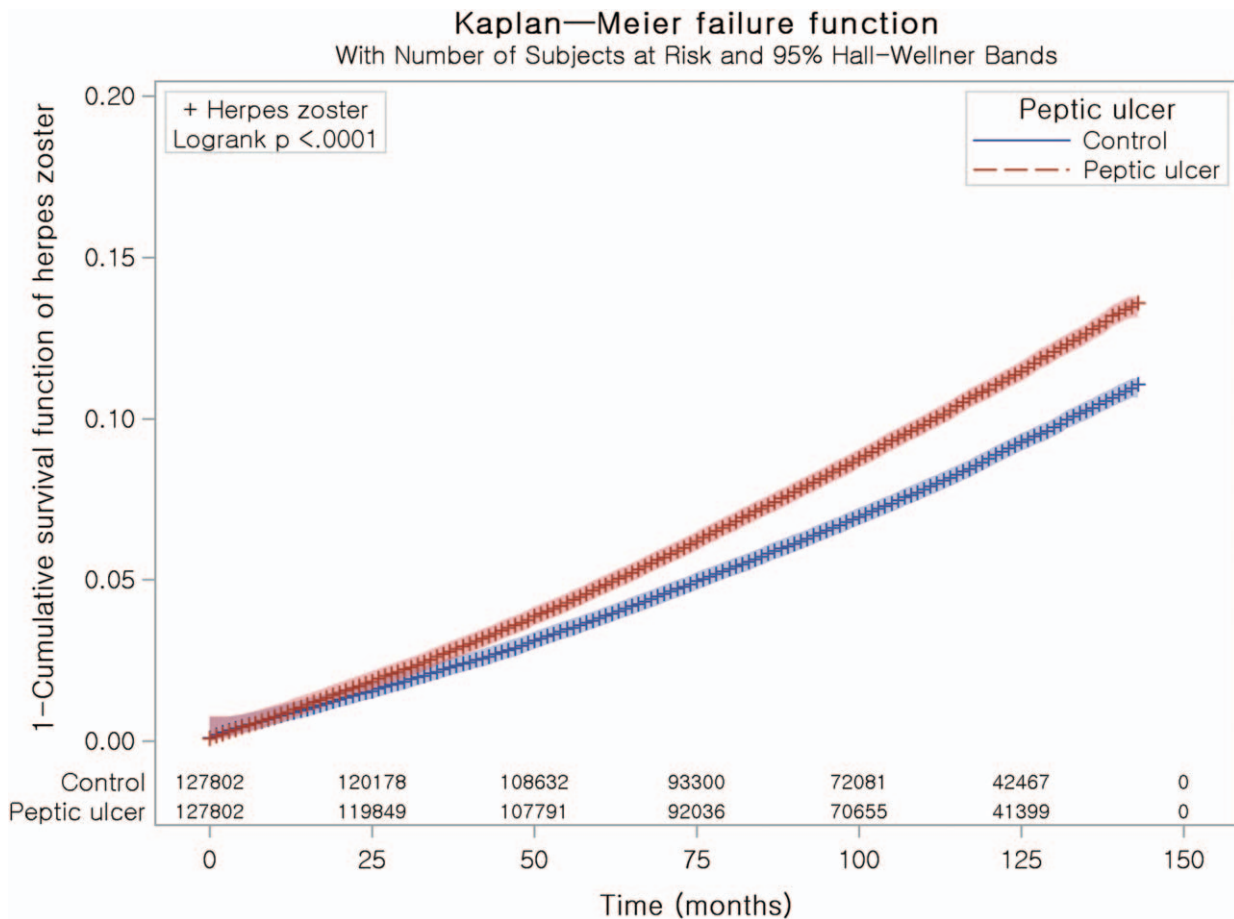
Figure 2. Kaplan–Meier curve of peptic ulcer patients and their controls for herpes zoster.

cancer and hypertension.[14] Our study showed similar results to those of the Taiwan group. Moreover, this report is the largest study to suggest the positive association HZ in the PUD group compared to that in the control group.

The major risk factors of PUD are *H pylori* infection and the use of NSAIDs or aspirin causing mucosal damage. Initially, *H pylori* usually infects in childhood, and related diseases occur in adults. Although *H pylori* has infected approximately 50% of the global population, most infected individuals (>80%) do not develop any disease and remain asymptomatic throughout their life.[23] This outcome of infection is determined by the inflammatory response, host genetic predisposition and environment.[24] *H pylori* strains should be recognized by epithelial innate immune receptors, which stimulate epithelial proinflammatory cytokine release. However, innate immune receptors cannot efficiently recognize *H pylori*, which could contribute to persistent bacterial survival. Chronic stimulation of the innate immune response precipitates the release of antibacterial peptides and immune effector cells, such as phagocytes, complement and natural killer (NK) cells, which play a key role in humoral immunity and cell-mediated immunity.[25] It has been reported that T helper type 1 cells are selectively increased and cause immune-mediated apoptosis of gastric epithelial cells during *H pylori* infection.[24] In this result, PUD patients, with peptic ulcers caused by *H pylori* infection, develop impairment of humoral and cell-mediated immunity. NSAIDs and aspirin are major causes of

non-*H pylori*-associated PUD. Mainly, these drugs induce PUD by gastric mucosal cell apoptosis and necrosis through direct gastric mucosal injury combined with topical toxicity.[26] Similar to *H pylori*-induced PUD, non-*H pylori*-induced PUD shows impaired innate and adaptive immune defense mechanisms. HZ is caused by reactivation of VZV in the cranial nerve or dorsal root ganglia. The incidence is estimated to be 30%, and it increases to 50% in unvaccinated people who live to 85 years. The virus is maintained in its latent form by VZV-specific cell-mediated immunity. Aging and cell-mediated immunosuppressive disorders are definite risk factors, and female sex, black race, malnutrition, metabolic diseases and social habits are possible risk factors for HZ.[9,10] HZ is characterized by severe painful vesicles following a dermatome, and postherpetic pain can persist many months and years after rash resolution in 10 to 50% of patients with HZ. An increased susceptibility for HZ has been reported in patients with autoimmune diseases, malignancies such as lymphoma and leukemia, human immunodeficiency virus infection, sleep disorders, personal and familial history of HZ, inflammatory bowel disease, psoriasis, psychiatric disease and major depression disease.[10,27–33]

In our study, the HR of HZ was significantly higher in PUD patients than in control individuals. There are possible theories that can explain our result. First, as described above, PUD damages the gastric mucosa, which has goblet cells secreting mucous acting as a physical barrier and dendritic cells working as

Table 1

General Characteristics of Participants.

	Total participants		
Characteristics	Peptic ulcer (n, %)	Control (n, %)	P value
Age (years old)			1.000
20–24	5,862 (4.6)	5,862 (4.6)	
25–29	8,464 (6.6)	8,464 (6.6)	
30–34	11,391 (8.9)	11,391 (8.9)	
35–39	13,743 (10.8)	13,743 (10.8)	
40–44	16,240 (12.7)	16,240 (12.7)	
45–49	16,583 (13.0)	16,583 (13.0)	
50–54	14,558 (11.4)	14,558 (11.4)	
55–59	12,189 (9.5)	12,189 (9.5)	
60–64	11,324 (8.9)	11,324 (8.9)	
65–69	8,662 (6.8)	8,662 (6.8)	
70–74	5,187 (4.1)	5,187 (4.1)	
75–79	2,462 (1.9)	2,462 (1.9)	
80–84	873 (0.7)	873 (0.7)	
85+	264 (0.2)	264 (0.2)	
Sex			1.000
Male	61,968 (48.5)	61,968 (48.5)	
Female	65,834 (51.5)	65,834 (51.5)	
Income			1.000
1 (lowest)	18,357 (14.4)	18,357 (14.4)	
2	19,546 (15.3)	19,546 (15.3)	
3	24,054 (18.8)	24,054 (18.8)	
4	30,069 (23.5)	30,069 (23.5)	
5 (highest)	35,776 (28.0)	35,776 (28.0)	
Region of residence			1.000
Urban	57,896 (45.3)	57,896 (45.3)	
Rural	69,906 (54.7)	69,906 (54.7)	
Hypertension	44,813 (35.1)	44,813 (35.1)	1.000
Diabetes	24,342 (19.0)	24,342 (19.0)	1.000
Dyslipidemia	38,770 (30.3)	38,770 (30.3)	1.000
Ischemic heart disease	8,891 (7.0)	6,863 (5.4)	<0.001*
Cerebral stroke	13,192 (10.3)	11,601 (9.1)	<0.001*
Depression	16,153 (12.6)	9,755 (7.6)	<0.001*
Atopic dermatitis	6,107 (4.8)	4,743 (3.7)	<0.001*
Chronic obstructive pulmonary disease	6,978 (5.5)	4,885 (3.8)	<0.001*
Herpes zoster	11,669 (9.1)	9,397 (7.4)	<0.001*

* Chi-square test or Fisher exact test. Significance at $P < .05$.

antigen presenting cells acting as initiators of the adaptive immunity cascade.[34,35] In this scenario, impaired cell-mediated immunity has a key role in VZV reactivation. Second, pain and abdominal discomfort caused by PUD can induce sleep disturbance, dyspepsia and malnutrition, which are known risk factors for VZV reactivation.[28,29,36] Third, anemia is one of the

Table 2

Crude and adjusted hazard ratios (95% confidence interval) of peptic ulcer for herpes zoster.

	Herpes zoster			
Characteristics	Crude†	P-value	Adjusted†,‡	P value
Peptic ulcer	1.26 (1.22–1.29)	<0.001*	1.23 (1.20–1.27)	<.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < .05$.
† Stratified model for age, sex income, region of residence, hypertension, diabetes mellitus, and dyslipidemia histories.
‡ Adjusted model for ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and chronic obstructive pulmonary disease histories.

Table 3

Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of peptic ulcer for herpes zoster according to age and sex.

	Herpes zoster			
Characteristics	Crude†	P value	Adjusted†,‡	P value
Age < 40 years old, men (n=37,804)				
Peptic ulcer	1.20 (1.07–1.34)	.001*	1.18 (1.06–1.32)	.003*
Control	1.00		1.00	
Age < 40 years old, women (n=41,116)				
Peptic ulcer	1.36 (1.24–1.49)	<.001*	1.33 (1.21–1.46)	<.001*
Control	1.00		1.00	
Age 40–59 years old, men (n=59,202)				
Peptic ulcer	1.29 (1.22–1.37)	<.001*	1.27 (1.19–1.35)	<.001*
Control	1.00		1.00	
Age 40–59 years old, women (n=59,938)				
Peptic ulcer	1.23 (1.17–1.29)	<.001*	1.21 (1.15–1.27)	<.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n=26,930)				
Peptic ulcer	1.29 (1.19–1.39)	<.001*	1.25 (1.16–1.35)	<.001*
Control	1.00		1.00	
Age ≥ 60 years old, women (n=30,614)				
Peptic ulcer	1.23 (1.15–1.31)	<.001*	1.20 (1.13–1.28)	<.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < .05$.
† Stratified model for age, sex income, region of residence, hypertension, diabetes mellitus, and dyslipidemia histories.
‡ Adjusted model for ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and chronic obstructive pulmonary disease histories.

plausible explanations for the association between PUD and HZ. Chronic anemia increases infection susceptibility because iron has an important role in immune cell proliferation.[37,38] We could not analyze anemia in this study because we did not have blood test data. However, the main complications of PUD are bleeding and perforation, with a high mortality rate.[1] Anemia caused by acute or chronic bleeding can decrease cell-mediated immunity, NK cell activity and lymphocyte bactericidal activity, which can result in VZV reactivation.[39]

In Table 4, we analyze the incidence of HZ according to the follow-up years. There was no significant difference in the HR of HZ in PUD patients compared to that in control individuals within 1 or less years after PUD diagnosis. However, both the crude and adjusted HRs of HZ in the PUD group were significantly increased after 2 or more years, and this result continued for the more than 5-year follow-up period. There is no report about the reason why the incidence of HZ was increased after more than 1 year of disease history of PUD. There is no study that PUD causes HZ in acute phase directly. Generally, PUD patients can be treated with medication about 2 to 8 weeks according to the cause of PUD. However, successful treatment of H pylori induced PUD is difficult due to increasing prevalence of antibiotics resistance.[1] And NSAIDs or aspirin induced PUD can be recurred easily. Because the patient has to take the causative drug again. The clinical features of PUD like as episodic gnawing or burning epigastric pain two to five hours after meals can be another reason for delayed increasing of HZ incidence. After repeated episodes of PUD, the patient experiences fear of eating and undergoes weight loss, causing nutritional deficiencies.[3] Hence, prolonged treatment duration with recurrence and chronic malnutrition can increase delayed susceptibility for the reactivation of HZ caused by impaired cellular immunity.

Table 4

Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of peptic ulcer for herpes zoster according to follow up periods after index dates.

Characteristics	Herpes zoster			
	Crude[†]	P value	Adjusted[†,‡]	P value
Periods ≤ 1 year				
Peptic ulcer	1.06 (0.98–1.15)	.171	1.04 (0.96–1.13)	.377
Control	1.00		1.00	
Periods 2 year				
Peptic ulcer	1.34 (1.22–1.46)	<.001[*]	1.31 (1.20–1.44)	<.001[*]
Control	1.00		1.00	
Periods 3 year				
Peptic ulcer	1.28 (1.17–1.40)	<.001[*]	1.26 (1.15–1.38)	<.001[*]
Control	1.00		1.00	
Periods 4 year				
Peptic ulcer	1.34 (1.23–1.46)	<.001[*]	1.31 (1.20–1.44)	<.001[*]
Control	1.00		1.00	
Periods ≥ 5 years				
Peptic ulcer	1.27 (1.23–1.31)	<.001[*]	1.24 (1.20–1.29)	<.001[*]
Control	1.00		1.00	

[*] Cox-proportional hazard regression model, Significance at $P < .05$.
[†] Stratified model for age, sex income, region of residence, hypertension, diabetes mellitus, and dyslipidemia histories.
[‡] Adjusted model for ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and chronic obstructive pulmonary disease histories.

This study has several benefits. First, we used participants from a large representative nationwide population who underwent health screening examinations. This report is the largest study to show that PUD is one of the risk factors for HZ. We analyzed the HRs of HZ in a PUD group and compared them to the HRs in a well-matched control group. The control group was randomly selected and matched by age group, sex, income group, region of residence, and medical history (e.g., hypertension, diabetes, and dyslipidemia) to prevent selection bias. Second, this study is the first report on the relationship between PUD and HZ after excluding direct possible reasons for HZ, including ischemic heart disease, cerebral stroke, depression, atopic dermatitis, and COPD, using an adjusted Cox proportional hazard regression model to minimize confounders.

This study has several limitations. First, we used patient claim codes from the HIRA database to diagnose HZ and PUD. Second, we could not evaluate smoking and alcohol habits, diet and obesity, which have an important effect on general health status. However, we considered the metabolic disease history instead of obesity and COPD instead of smoking history. Third, we could not identify whether PUD was treated. Fourth, medication history for NSAIDs or aspirin could not be evaluated because many kinds of these drugs are over-the-counter drugs in Korea.

5. Conclusion

The HR of HZ was significantly increased in the PUD group. After classifying cases into sex and age groups, HZ showed a significantly positive association with PUD.

Acknowledgments

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