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Increased Risk of Osteoporosis in Patients With Peptic Ulcer Disease

A Nationwide Population-Based Study

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Abstract: To investigate osteoporosis risk in patients with peptic ulcer disease (PUD) using a nationwide population-based dataset.

This Taiwan National Health Insurance Research Database (NHIRD) analysis included 27,132 patients aged 18 years and older who had been diagnosed with PUD (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 531–534) during 1996 to 2010. The control group consisted of 27,132 randomly selected (age- and gender)-matched patients without PUD. The association between PUD and the risk of developing osteoporosis was estimated using a Cox proportional hazard regression model.

During the follow-up period, osteoporosis was diagnosed in 2538 (9.35 %) patients in the PUD group and in 2259 (8.33 %) participants in the non-PUD group. After adjusting for covariates, osteoporosis risk was 1.85 times greater in the PUD group compared to the non-PUD group (13.99 vs 5.80 per 1000 person-years, respectively). Osteoporosis developed 1 year after PUD diagnosis. The 1-year follow-up period exhibited the highest significance between the 2 groups (hazard ratio [HR] = 63.44, 95% confidence interval [CI] = 28.19–142.74, $P < 0.001$). Osteoporosis risk was significantly higher in PUD patients with proton-pump-inhibitors (PPIs) use (HR = 1.17, 95% CI = 1.03–1.34) compared to PUD patients without PPIs use.

This study revealed a significant association between PUD and subsequent risk of osteoporosis. Therefore, PUD patients, especially those treated with PPIs, should be evaluated for subsequent risk of osteoporosis to minimize the occurrence of adverse events.

(*Medicine* 95(16):e3309)

Editor: Yoram Chaiter.
Received: September 28, 2015; revised: February 16, 2016; accepted: March 14, 2016.
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The authors have no conflicts of interest to disclose.
Supplemental Digital Content is available for this article.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003309

Abbreviations: BMD = bone mineral density, BNHI = Bureau of National Health Insurance, CCI = Charlson comorbidity index, CI = confidence interval, *H. pylori* = *Helicobacter pylori*, HR = hazard ratio, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification, IL = interleukin, IQR = interquartile range, LHID2010 = Longitudinal Health Insurance Database 2010, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institute, OR = odds ratio, PPIs = proton-pump-inhibitors, PUD = peptic ulcer disease, TNF = tumor necrosis factor, VEGF = vascular endothelial growth factor.

INTRODUCTION

Osteoporosis, which is also known as the ''silent disease,'' is characterized by impaired bone strength caused by attenuated bone mineral density (BMD) and compromised bone quality, which result in high susceptibility to fragility fractures. The morbidity, disability, and mortality associated with osteoporosis can impose a substantial burden on affected individuals, their families, and the health caresystem.[1] Therefore, risk factors and populations at risk for osteoporosis must be identified to reduce the potential burden of this disease.

Peptic ulcer disease (PUD) develops when the protective mechanisms of the gastrointestinal mucosa, such as secreted mucus and bicarbonate, are overwhelmed by the damaging effects of pepsin and gastric acid.[2] Peptic ulcers, which occur mainly in the stomach or proximal duodenum, continue to be a relatively common disease that can impose a substantial socioeconomic burden and can negatively affect quality of life. *Helicobacter pylori* (*H. pylori*) infection was originally identified as the main cause of PUD. Whereas the prevalence of *H. pylori* infection has declined in western countries, gastric ulcer is now associated with the use of nonsteroidal antiinflammatory drugs (NSAIDs) and aspirin.[3] Tobacco smoking and alcohol drinking are known risk factors for PUD.[4]

Gastrointestinal tract diseases such as celiac disease and inflammatory bowel disease have well-known roles in bone tissue metabolism. In contrast, the role of PUD in bone tissue metabolism is not as well established.[5] Although a study of 263 women with PUD by Sawicki et al[6] reported that PUD is an independent risk factor for osteoporosis, direct evidence of an association between osteoporosis and PUD is limited. Therefore, this nationwide cohort study investigated the association between PUD and subsequent risk of osteoporosis.

METHODS

Data Sources

The National Health Insurance (NHI) program in Taiwan, a mandatory health insurance program, is a single payer system

implemented on March 1, 1995. According to the Bureau of National Health Insurance (BNHI), the program covers approximately 99% of the 23.74 million residents in Taiwan. The BNHI has authorized the National Health Research Institute (NHRI) to create an encrypted secondary database, the National Health Insurance Research Database (NHIRD), for medical research; this database contains administrative and health claims data collected through the NHI program, including complete information on diagnosis, outpatient/hospitalization claims and prescriptions of contracted pharmacies. Undistinguished identification numbers associated with patient data such as gender, date of birth, medical services registry, and prescribed medications were provided by the NHIRD. This study used the Longitudinal Health Insurance Database 2010 (LHID2010), which is a subset of the NHIRD comprising patient data for 1996 to 2010. The LHID2010 comprises data for 1,000,000 beneficiaries randomly sampled from the original NHIRD. Because of its large sample size, the database provides an opportunity to study osteoporosis risk in PUD patients. Osteoporosis and PUD were defined according to the criteria in the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM).

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki guidelines and was evaluated and approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-EXEMPT (I)-20150040).

Study Population

The study cohort included 27,132 patients aged 18 years and older who had been diagnosed with PUD (ICD-9-CM codes 531–534) during 1996 to 2010. To maximize accuracy, cases were only included if the patient had received $\geq$2 PUD diagnoses during ambulatory visits or $\geq$1 PUD diagnosis during inpatient care. The index date was designated as the date of the first clinical visit for PUD. In efforts to better assure for the validity of the diagnoses of osteoporosis used in this study, only patients with $\geq$2 ambulatory visits or with $\geq$1 inpatient care for osteoporosis and receiving at least 1 BMD examination were included in the osteoporotic group.[7–9] The exclusion criteria were diagnosis with osteoporosis (ICD-9-CM code 733) before the index date, incomplete data, or age younger than 18 years. The ratio of PUD patients to non-PUD patients was maintained at 1:1 to enhance the power of statistical tests and to ensure that the number of osteoporosis cases was sufficient for stratified analyses. The patients in the non-PUD cohort were selected using a simple random sampling method in which one insured NHI beneficiary without PUD was randomly selected and frequency matched with every person diagnosed with PUD in the same period according to age, gender, and index year, which was the year of PUD diagnosis. As a result, 27,132 non-PUD patients were identified.

Outcome and Comorbidities

Patients in both the PUD and non-PUD cohorts were followed up until the end of 2010 or until one of the following events occurred: diagnosis with osteoporosis; censor due to loss to follow-up, withdrawal from insurance, or death. Baseline comorbidities before the index date were identified by ICD-9-CM codes in the claims records data and included the following: hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), chronic kidney disease (ICD-9-CM codes 582, 583, 585, 586, and 588), chronic liver disease (ICD-9-CM codes 571.2, 571.4–571.6, 456.0–456.21, 572.2–572.8), chronic pulmonary disease (ICD-9-CM codes 490–496), hyperthyroidism (ICD-9-CM code 242), hyperparathyroidism (ICD-9-CM code 252), stroke (ICD-9-CM codes 430–438), *H. pylori* infection (ICD-9-CM code 041.86), obesity (ICD-9-CM code 278), tobacco use disorder (ICD-9-CM code 350.1), alcohol attributed diseases (ICD-9-CM codes 291.0–9, 303, 305.0, 357.5, 425.5, 535.3, 571.0–3, 980.0, and V11.3), hip fracture (ICD-9-CM code 820), wrist fracture (ICD-9-CM codes 813, 814, 818, and 819), vertebral fracture (ICD-9-CM codes 805–806), and rib fracture (ICD-9-CM code 807). Charlson comorbidity index (CCI) scores were used to assess the severity of comorbidities, which included myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, PUD, liver disease (mild, moderate, or severe), diabetes (with and without chronic complication), hemiplegia or paraplegia, renal disease, any malignancy (including lymphoma and leukemia and excluding malignancy of skin), metastatic solid tumor, human immunodeficiency virus infection, and acquired immune deficiency syndrome. The CCI scores were then categorized as 0, 1 to 2, 3 to 4, or $\geq$5. The analysis also included use of oral corticosteroids, PPIs, or aspirin.

Statistical Analysis

The distributions of categorical demographics and clinical characteristics were compared between the PUD cohorts and non-PUD cohorts by Chi-square test. The Student *t* test and Wilcoxon rank-sum test were used to compare mean age and follow-up time (y) between the 2 cohorts, as appropriately. The Kaplan–Meier method was used to estimate cumulative incidence, and the differences between the curves were tested using 2-tailed log-rank test. Survival was calculated until the occurrence of hospitalization, an ambulatory visit for osteoporosis, or the end of the study period (December 31, 2010), whichever occurred first. Incidence rates of osteoporosis were estimated in 1000 person-years and compared in both cohorts. Univariable and multivariable Cox proportional hazard regression models were used to investigate the hazard ratios (HRs) and 95% confidence intervals (95% CIs) for osteoporosis. The multivariable Cox models were adjusted for age, CCI, and relevant comorbidities. A 2-tailed *P*-value of <0.05 was considered statistically significant. All data processing and statistical analyses were performed using Statistical Analysis Software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics of Patients With and Without PUD

Figure 1 shows that, of the 54,264 patients enrolled between January 1996 and December 2010, the non-PUD (control) group included 27,132 patients, and the PUD group included 27,132 patients.

Table 1 compares baseline demographic characteristics and comorbidity status between the 2 cohorts. Table 1 shows that mean age was matched between the 2 cohorts (54.3 ± 17.1 years in the non-PUD cohort and 54.4 ± 16.7 years in the PUD cohort). The largest age group was 50 to 59 years (19.94 %) followed by 40 to 49 years (18.96 %). The following comorbidities were significantly more likely in the PUD group

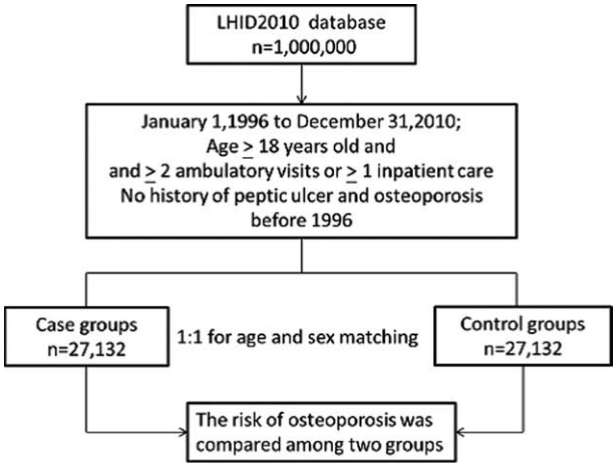

FIGURE 1. Flow diagram of the present study from the National Health Insurance Research Database in Taiwan. LHID = Longitudinal Health Insurance Database.

compared to the non-PUD group: hypertension (61.51 vs 38.94; $P < 0.001$), diabetes mellitus (35.34 vs 20.05; $P < 0.001$), hyperlipidemia (47.66 vs 33.44; $P < 0.001$), chronic kidney disease (23.33 vs 9.72; $P < 0.001$), chronic liver disease (44.76 vs 26.30; $P < 0.001$), chronic pulmonary disease (54.84 vs 36.19, $P < 0.001$), hyperthyroidism (5.03 vs 3.85, $P < 0.001$), hyperparathyroidism (0.62 vs 0.16, $P < 0.001$), stroke (12.48 vs 5.31, $P < 0.001$), *H. pylori* infection (5.45 vs 0.96, $P < 0.001$), obesity (2.18 vs 1.81, $P = 0.002$), tobacco use disorder (1.29 vs 0.67, $P < 0.001$), alcohol attributed diseases (4.16 vs 2.53, $P < 0.001$). Additionally, the PUD group had a significantly higher CCI (41.52 vs 15.40, $P < 0.001$) and significantly higher use of PPIs (8.28 vs 1.80, $P < 0.001$), aspirin (17.09 vs 9.56, $P < 0.001$), and corticosteroids (13.63 vs 5.73, $P < 0.001$). The PUD group also had a significantly higher incidence of hip fracture (4.07 vs 1.50, $P < 0.001$), vertebral fracture (7.76 vs 3.65, $P < 0.001$), wrist fracture (3.95 vs 2.77, $P < 0.001$), and rib fracture (4.82 vs 2.49, $P < 0.001$) during a median observation time of 3.6 years (interquartile range [IQR] = 1.4–6.4). Finally, the incidence of osteoporosis was significantly ($P < 0.001$) higher in the PUD group compared to the non-PUD group. During a median observation time of 6.4 years, 2538 (9.35 %) of the 27,132 patients in the PUD group had osteoporosis, but only 2259 (8.33 %) of the 27,132 age- and gender-matched controls in the non-PUD group had osteoporosis (IQR = 4.0–10.1). The development of osteoporosis was also significantly faster in the PUD group (3.6 years) compared to the non-PUD group (6.4 years) during the following periods.

Osteoporosis Incidence and Risk

Table 2 compares the incidence densities and HRs of osteoporosis by gender, age, and follow-up duration. During the follow-up period, osteoporosis developed in 2538 (9.35%) PUD patients and in 2259 (8.33%) of non-PUD patients. Osteoporosis risk was 1.85 times greater in the PUD group compared to the non-PUD group (13.99 vs 5.80 per 1000 person-years, respectively) after adjusting for age, CCI, related comorbidities (hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, chronic liver disease, chronic pulmonary disease, hyperthyroidism, hyperparathyroidism, stroke, *H. pylori* infection), use of medications (PPIs, aspirin, and corticosteroids) and obesity, tobacco use disorder, and alcohol attributed diseases. In both cohorts, gender-specific analyses revealed a higher incidence of osteoporosis in females (27.71 vs 7.23 per 1000 person-years in PUD cohorts; 12.12 vs 2.64 per 1000 person-years in non-PUD cohorts). In PUD patients, however, the osteoporosis risk was significantly higher in men than in women (HR = 2.28 vs 1.69, P for interaction < 0.001). Additionally, the incidence of osteoporosis was consistently higher in the PUD group at all ages, and the incidence rate increased with age. However, the osteoporosis risk has decreased with age and the age-specific risk analysis showed that the risk of osteoporosis was higher in PUD patients under 50 years old (HR = 6.15, 95% CI = 4.68–8.09, $P < 0.001$) than in those over 50 years old (HR = 1.71, 95% CI = 1.60–1.83, $P < 0.001$). The follow-up duration analysis revealed a significant relationship between the PUD and non-PUD groups. Osteoporosis developed 1 year after PUD diagnosis. The 1-year follow-up period exhibited the highest significance between the 2 groups (HR = 63.44, 95% CI = 28.19–142.74, $P < 0.001$).

Figure 2 compares Kaplan–Meier curves for cumulative incidence of fracture between the PUD and non-PUD groups after 15 years of follow-up. The 1-, 5-, 10-, and 15-year actuarial rates of osteoporosis were 1.76%, 7.48%, 12.90%, 17.51% in the PUD group and 0.02%, 3.12%, 6.20%, 8.32% in the non-PUD group, respectively.

Table 3 shows the Cox regression analysis results, which highlighted several risk factors for osteoporosis in the PUD group: age, CCI, gender, hypertension, chronic pulmonary disease, chronic liver disease, hyperthyroidism, stroke, corticosteroids use, PPIs use, tobacco use disorder, and alcohol attributed diseases.

Hypertension, chronic pulmonary disease, chronic liver disease, hyperthyroidism, and stroke were independent risk factors in PUD patients for osteoporosis as shown in Table 3. Therefore, we further analyzed the risk of osteoporosis between the PUD and non-PUD cohorts stratified by various subtypes of comorbidity and presented the risk of osteoporosis in patients with PUD and relevant comorbidities in Supplementary Tables, http://links.lww.com/MD/A901. Hypertension subtypes were classified into with/without complications (ICD-9-CM codes 402–405/401); chronic liver disease subtypes were classified into mild liver disease (ICD-9-CM codes 571.2, 571.4–6) and moderate or severe liver disease (ICD-9-CM codes 456.0–21, 571.2–8); stroke subtypes were classified into hemorrhagic stroke (ICD-9-CM codes 430–432) and ischemic stroke (ICD-9-CM codes 433–437).

Supplementary Table S1, http://links.lww.com/MD/A901, shows the results of a comorbidity-stratified analysis of osteoporosis risk. Regardless of comorbidities, the patients with PUD exhibited a higher risk of osteoporosis than that of the non-PUD patients. The osteoporosis risk contributed by PUD had decreased by the presence of comorbidity including hypertension, chronic pulmonary disease, chronic liver disease, and stroke except hyperthyroidism. The risk of osteoporosis in hypertension patients contributed by PUD had also decreased by the presence of complication. The risk of osteoporosis in stroke patients contributed by PUD was higher in hemorrhagic stroke group compared with ischemic stroke group.

Supplementary Table S2, http://links.lww.com/MD/A901, shows the effects of PUD and comorbidities on the risk of osteoporosis development. The table suggests that PUD and

TABLE 1. Baseline Characteristics of Patients With and Without Peptic Ulcer Disease in Taiwan, 1996–2010, n = 54,264

	Peptic Ulcer		
	Yes (N = 27,132)	No (N = 27,132)	*P*
Osteoporosis patients, n (%)	2538 (9.35)	2259 (8.33)	<0.001
Period of developing osteoporosis median (IQR), y	3.6 (1.4–6.4)	6.4 (4.0–10.1)	<0.001
Age mean (SD), y	54.4 (16.7)	54.3 (17.1)	0.477
Age group, n (%)			
18–29	2351 (8.67)	2351 (8.67)	
30–39	3517 (12.96)	3517 (12.96)	
40–49	5144 (18.96)	5144 (18.96)	
50–59	5411 (19.94)	5411 (19.94)	
60–69	5110 (18.83)	5110 (18.83)	
≥70	5599 (20.64)	5599 (20.64)	1.000
Sex, n (%)			
Males	17,602 (64.88)	17,602 (64.88)	
Females	9530 (35.12)	9530 (35.12)	1.000
Charlson comorbidity index, n (%)			
0	697 (2.57)	7650 (28.20)	
1–2	7677 (28.30)	10,222 (37.68)	
3–4	7493 (27.62)	5081 (18.73)	
≥5	11,265 (41.52)	4179 (15.40)	<0.001
Comorbidity, n (%)			
Hypertension	16,688 (61.51)	10,565 (38.94)	<0.001
Diabetes mellitus	9589 (35.34)	5440 (20.05)	<0.001
Hyperlipidemia	12,931 (47.66)	9072 (33.44)	<0.001
Chronic kidney disease	6330 (23.33)	2638 (9.72)	<0.001
Chronic liver disease	12,144 (44.76)	7136 (26.30)	<0.001
Chronic pulmonary disease	14,878 (54.84)	9819 (36.19)	<0.001
Hyperthyroidism	1365 (5.03)	1044 (3.85)	<0.001
Hyperparathyroidism	169 (0.62)	43 (0.16)	<0.001
Stroke	3385 (12.48)	1441 (5.31)	<0.001
Helicobacter pylori infection	1478 (5.45)	261 (0.96)	<0.001
Obesity	592 (2.18)	491 (1.81)	0.002
Tobacco use disorder	351 (1.29)	183 (0.67)	<0.001
Alcohol attributed disease	1129 (4.16)	687 (2.53)	<0.001
Medication, n (%)			
Proton-pump-inhibitors	2247 (8.28)	489 (1.80)	<0.001
Corticosteroids	3698 (13.63)	1555 (5.73)	<0.001
Aspirin	4637 (17.09)	2593 (9.56)	<0.001
Relevant fracture, n (%)			
Hip fracture	1103 (4.07)	406 (1.50)	<0.001
Vertebral fracture	2106 (7.76)	991 (3.65)	<0.001
Wrist fracture	1073 (3.95)	751 (2.77)	<0.001
Rib fracture	1307 (4.82)	679 (2.49)	<0.001

IQR = interquartile range, SD = standard deviation.

comorbidities jointly affected the subsequent development of osteoporosis.

Table 4 shows the interacting effects of PUD and PPIs use on osteoporosis risk. Relative to the non-PUD patients without PPIs use, osteoporosis risk was higher in non-PUD patients with PPIs use (HR = 1.48, 95% CI = 1.19–1.82), in PUD patients without PPIs use (HR = 1.88, 95% CI = 1.75–2.01), and in PUD patients with PPIs use (HR = 2.20, 95% CI = 1.91–2.52). Osteoporosis risk was significantly higher in PUD patients with PPIs use (HR = 1.17, 95% CI = 1.03–1.34) compared to PUD patients without PPIs use.

DISCUSSION

To the best of our knowledge, this study is the first to investigate the relationship between PUD and subsequent risk of osteoporosis in a nationwide population in Asia. As reported in Sawicki et al,[6] this study revealed that PUD is a risk factor for osteoporosis. Specifically, osteoporosis risk was 1.85-fold higher in the PUD group compared to the non-PUD group (13.99 vs 5.80 per 1000 person-years, respectively). Relative to PUD patients without comorbidities, osteoporosis risk was higher in PUD patients with relevant comorbidities (hypertension, chronic pulmonary disease, chronic liver

TABLE 2. Incidence and Hazard Ratios of Osteoporosis by Demographic Characteristics and Different Follow-Up Duration Among Patients With or Without Peptic Ulcer Disease

	Patients With Peptic Ulcer			Patients Without Peptic Ulcer					
Variables	Osteoporosis	PY	Rate*	Osteoporosis	PY	Rate*	IRR (95% CI)†	Adjusted HR‡ (95% CI)	P§
All	2538	181438.53	13.99	2259	389478.48	5.80	2.41 (2.28–2.55)¶	1.85 (1.73–1.98)¶	
Gender									
Men	879	121559.37	7.23	685	259629.28	2.64	2.74 (2.48–3.03)¶	2.28 (2.03–2.57)¶	
Women	1659	59879.17	27.71	1574	129849.20	12.12	2.29 (2.13–2.45)¶	1.69 (1.56–1.83)¶	$P < 0.001$
Stratify age									
18–49	330	86477.03	3.82	63	164755.30	0.38	9.98 (7.62–13.07)¶	6.15 (4.68–8.09)¶	
≥50	2208	94961.51	23.25	2196	224723.18	9.77	2.38 (2.24–2.53)¶	1.71 (1.60–1.83)¶	
Follow-up time,‖ y									
1	458	25767.59	17.77	7	27126.94	0.26	80.36 (35.91–179.81)¶	63.44 (28.19–142.74)¶	
3	1104	69844.63	15.81	177	81257.00	2.18	7.30 (6.22–8.56)¶	5.50 (4.65–6.52)¶	
5	1655	105595.74	15.67	849	134446.71	6.31	2.48 (2.29–2.70)¶	2.02 (1.85–2.22)¶	

95% CI = 95% confidence interval, PY = person-years.
*Rate = incidence rate in per 1000 person-years.
†IRR = incidence rate ratio in per 1000 person-years.
‡HR = relative hazard ratio.
§*P*-value for interaction.
‖Follow-up time: the follow-up time after the index date of peptic ulcer diagnosis.
¶$P < 0.001$.

disease, hyperthyroidism, and stroke). Relative to PUD patients with mild liver disease (HR = 2.19, 95% CI = 2.00–2.40), osteoporosis risk was higher in PUD patients with moderate or severe liver disease (HR = 2.40, 95% CI = 1.93–2.98). Relative to PUD patients with hemorrhagic stroke (HR = 1.97, 95% CI = 1.22–3.18), osteoporosis risk was higher in PUD patients with ischemic stroke (HR = 2.59, 95% CI = 2.34–2.87). The significantly higher risk of osteoporosis in PUD patients with PPIs use (HR = 1.17, 95% CI = 1.03–1.34) compared to PUD patients without PPIs use is also consistent with previous reports.[10,11]

Notably, only males showed a significant association between PUD and osteoporosis. Sex hormones may play an important role in the association. For example, a study of male patients with osteoporosis in Figura et al[12] revealed a higher than normal prevalence of *H. pylori* infection and bone turnover but lower than normal levels of estrogen. Another study by Laszlo et al[13] suggested that testosterone increases the aggressiveness of cysteamine-induced gastroduodenal ulceration. In a rat study by Machowska et al,[14,15] gender comparisons showed that testosterone and progesterone have opposite effects on the healing of preexisting ulcers in the oral cavity and stomach. Specifically, testosterone markedly delayed ulcer healing by inducing excessive gastric acid production and by inducing the release of the proinflammatory cytokines interleukin (IL)-1β and tumor necrosis factor (TNF)-alpha. Since IL-1β and TNF-alpha contribute to the pathogenesis of osteoporosis, inflammatory changes disturb the absorption of calcium and other macroelements needed for mineral homeostasis and for bone tissue metabolism. These results suggest that testosterone, the major sex hormone in males, delays gastric ulcer healing, which is consistent with epidemiological data indicating that male gender is an independent risk factor for PUD and with epidemiological data indicating that PUD in men is associated with much higher numbers of adverse symptoms and side effects compared to PUD in women. In males, osteoporosis is more likely to result from a systemic disease, which in this case was PUD. Whereas women are routinely referred for BMD scans, men diagnosed with osteoporosis are likely to have a chronic illness.

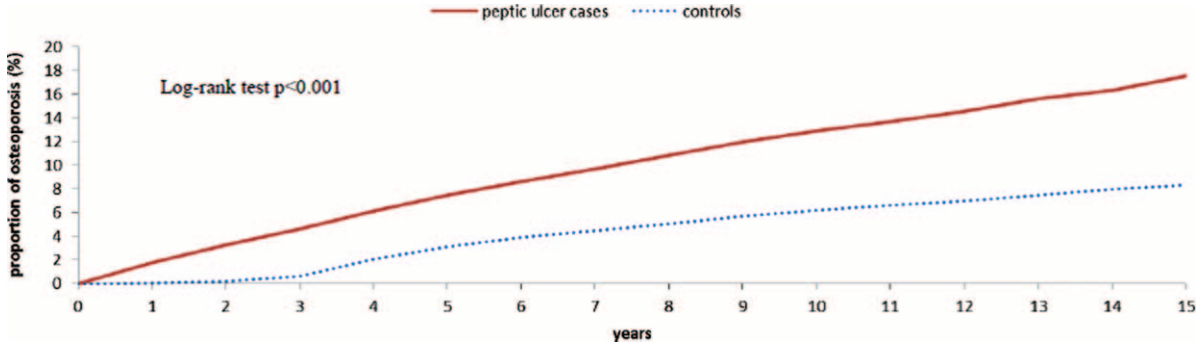

FIGURE 2. Cumulative incidence of osteoporosis for adult patients with peptic ulcer and the general population control cohort.

TABLE 3. Cox regression Model: Significant Predictors of Osteoporosis After Peptic Ulcer disease (n = 27,132)

	Adjusted		
Variables	**HR**	**(95% CI)**	***P***
Age (in 10-year interval)	1.59	(1.53–1.64)	<0.001
Charlson comorbidity index	1.20	(1.12–1.28)	<0.001
Gender	3.68	(3.38–3.99)	<0.001
Hypertension	1.15	(1.02–1.30)	0.025
Chronic pulmonary disease	1.37	(1.24–1.51)	<0.001
Chronic liver disease	1.19	(1.09–1.29)	<0.001
Hyperthyroidism	1.27	(1.10–1.47)	0.001
Stroke	1.46	(1.33–1.61)	<0.001
Corticosteroids use	1.43	(1.31–1.57)	<0.001
Proton-pump-inhibitors use	1.17	(1.02–1.33)	0.022
Alcohol attributed disease	1.23	(1.05–1.44)	0.012
Tobacco use disorder	1.28	(1.01–1.63)	0.040

HR = relative hazard ratio, 95% CI = 95% confidence interval.

The exact etiology and pathogenesis of PUD and osteoporosis remain unclear. In PUD patients, inflammation at gastric and duodenal epithelium may cause the malabsorption of calcium and macroelements, which play a crucial role in mineral homeostasis and bone metabolism.[16] Because *H. pylori* is clearly the most important etiological factor in PUD, the effect of *H. pylori* on the association between PUD and osteoporosis risk is implied. A bacterial infection can cause chronic inflammation of the stomach and duodenum mucosa and can decrease absorption of calcium and production of inflammatory mediators in the bones.[17] PUD caused by *H. pylori* infection is characterized by infiltration of neutrophils and mononuclear cells into the gastric mucosa. Proinflammatory cytokines produced by these activated neutrophils and mononuclear cells include IL-1β, IL-6, IL-8, and TNF-alpha. Since IL-1β, IL-6, IL-8, and TNF-alpha contribute to the pathogenesis of osteoporosis, a contributing effect of *H. pylori* infection on osteoporosis risk is plausible. They stimulate osteoclasts, we speculate this could be the mechanism of their action on bone tissue in patients with PUD.[18,19] In a Japan study of 200 study subjects with *H. pylori* by Asaoka et al., 41 had osteoporosis. Bivariate analysis showed that risk factors for osteoporosis were advanced age, female gender, alcohol use, tobacco use, *H. pylori* and PUD. Since multivariate analysis showed that *H. pylori* (OR 5.33; 95%CI1.73–16.42) and PUD (OR 4.98; 95%CI 1.51–16.45) were related to osteoporosis, the authors concluded that *H. pylori* infection may be a risk factor for osteoporosis.[20]

Studies have established that the major causes of PUD are *H. pylori* and NSAID use. Nevertheless, other factors are important since *H. pylori* infection and long-term NSAIDs are not always implicated in PUD. A Hong Kong study reported that up to 19% of PUD cases did not have *H. pylori* infection and did not use NSAIDs.[21] Patients with PUD also have high risk of alcohol abuse and smoking, which could contribute to PUD disease. Smoking affects mucosal integrity and defense by producing free radicals and vasoconstrictors, which can cause mucosal damage.[22] Finally, cigarette constituents increase PUD risk because they induce production of gastric acid by decreasing mucus production in the stomach and the duodenum and because they impair gastric healing.[23,24] In a study of the relationship between smoking and osteoporosis, Hopper et al[25] reported that smoking more than 20 cigarettes per day affects bone density. The relationship between PUD and osteoporosis may in part be caused by smoking. The effect of alcohol use on PUD and osteoporosis is also mentioned as well. Experimental studies showed that alcohol consumption damages the gastric mucosal barrier through the release of vasoactive and inflammatory molecules.[26] Studies of the relationship between alcohol and osteoporosis include Kanis et al,[27] who reported that an alcohol intake of >20 g per day negatively affects bone density, and Berg et al,[28] who reported that excessive alcohol consumption is an osteoporosis risk factor. Both osteoporosis and PUD has similar risk factors; hence, we postulate that osteoporosis and PUD are related.

Depressive persons have a higher than normal incidence of several physical disorders. For example, depression is reportedly associated with PUD,[29] diabetes,[30,31] and osteoporosis.[32] In a study of an elderly population, Taylor et al[33] reported a 10-fold higher incidence of ulcers in participants with depression compared to controls without depression. In a recent comparison of 1546 participants with recurrent depression and 884 controls, Farmer et al[34] reported a higher rate of gastric ulcer in the recurrent depression group. The relationship between depression and BMD has also been demonstrated in elderly Caucasian women and in Asian men.[35,36] A more recent Taiwan study by Lee et al revealed that, compared to patients without depression, patients with depression had a 1.30-fold greater

TABLE 4. Cox Proportional Hazard Regression Analysis for Interaction of Proton-Pump-Inhibitors Use and Peptic Ulcer Disease on the Risk of Osteoporosis

Variables						
Peptic Ulcer	**Proton-Pump-Inhibitors Use**	**N**	**Osteoporosis**	**Adjusted HR (95% CI)**	**Adjusted HR (95% CI)**	***P*†**
No	No	26,643	2169	1.00 (Reference)		$P < 0.001$
No	Yes	489	90	1.48 (1.19–1.82)‡		
Yes	No	24,885	2290	1.88 (1.75–2.01)‡	1.00 (Reference)	
Yes	Yes	2247	248	2.20 (1.91–2.52)‡	1.17 (1.03–1.34)‡	

HR = relative hazard ratio, 95% CI = 95% confidence interval.
†*P*-value for interaction.
‡$P < 0.001$.

chance of developing osteoporosis. Furthermore, people suffering from PUD are more likely to have anxiety disorder.[37,38] Previous cross-sectional studies of community dwelling individuals showed that, compared to controls without PUD, subjects with PUD are more likely to have mental illnesses such as personality disorders,[39] anxiety disorders,[40] and panic disorders.[41] Other studies have reported an association between anxiety and osteoporosis; compared to adults without anxiety, those with anxiety had lower hip bone mass density, which is a risk factor for osteoporosis.[42] Osteoporosis risk also has a bidirectional association with depression and/or anxiety.[43] Therefore, the authors concluded that PUD should be considered a major risk factor for osteoporosis.

During bone growth, remodeling and repair, osteogenesis and angiogenesis are 2 closely correlated processes.[44] Vascular endothelial growth factor (VEGF) is an essential mediator during the process of angiogenesis. In addition to its role in angiogenesis, VEGF affects both endochondral ossification and intramembranous ossification.[45,46] Its roles in bone differentiation include chondrocyte differentiation, osteoblast differentiation, and osteoclast recruitment.[47] Finally, VEGF is the most important angiogenic factor in many other repair processes such as healing of gastric ulcers.[48] Therefore, inhibited VEGF is a suspected contributor to ulcer formation and osteoporosis. Since ulcer formation and osteoporosis share many similar risk factors, the observed association between PUD and subsequent risk of osteoporosis in this study was not unexpected.

The strength of this study is the use of population-based data that are highly representative of the general population. Although this cohort study revealed an association between PUD and the subsequent risk of osteoporosis, some limitations of this study must be considered. First, the health insurance data analyzed in this study did not include laboratory data, lifestyle data, exercise capacity, body weight, nutrition supplement, or family history of systemic diseases. The measurement of osteoporosis risk in this study did not control for all these factors. Some of these factors include tobacco use, alcohol consumption, and body mass index. Because of the lack of information on healthy behaviors and body weight in NHIRD, we considered tobacco use disorder, obesity, and alcohol attributed diseases instead of cigarette smoke, body mass index, and alcohol consumption in the Cox proportional hazard regression.[9] Second, the main focus of diagnostic codes in the NHI claims data is administrative billing, and verifying data for scientific purposes could not be easily achieved. For example, the patients could not be contacted directly for additional information because identification numbers are used to ensure anonymity. However, medical experts from the BNHI perform regular audits to ascertain the accuracy of insurance claim codes. Third, this retrospective cohort study is subject to bias from unknown confounding variables. However, the data analysis included medications and the number of comorbidities, and osteoporosis risk did not significantly differ between patients who had 3 comorbidities and those who had more than 3 comorbidities. Therefore, the data for PUD and osteoporosis diagnoses can be considered highly reliable. Nevertheless, further unbiased studies in a larger population are needed to explore the underlying mechanisms of these relationships.

In conclusion, since this study identified an increased osteoporosis risk in PUD patients, PUD may be an early predictor of osteoporosis. Use of PPIs was also associated with an increased subsequent risk of osteoporosis. Physicians should be alerted to these associations so that patients at risk for osteoporosis can be identified at an early stage. Since examination for osteoporosis can be performed easily and noninvasively, BMD should be measured in PUD patients, especially those with PPIs use.

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