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Original Article

A Nationwide Cohort Study Shows a Sex-Dependent Change in the Trend of Peptic Ulcer Bleeding Incidence in Korea between 2006 and 2015

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Background/Aims: The incidence of peptic ulcer disease has decreased in past decades; however, the trends in peptic ulcer bleeding (PUB) are inconsistent among regions. This study aimed to investigate the trends in PUB incidence and the effect of risk factors on PUB in Korea.

Methods: The records of patients hospitalized with PUB from 2006 to 2015 were retrieved from the Korean National Health Insurance Service Database. Standardized incidences of PUB were calculated, and the clinical characteristics such as age, sex, *Helicobacter pylori* infection, drug exposure, comorbidities, and mortality were obtained.

Results: In total, 151,507 hospitalizations with PUB were identified. The overall annual hospitalization rate was 34.98 per 100,000 person-years. The incidence of PUB showed no significant change from 2006 to 2008 and decreased from 2008 to 2015, with an annual change of –2.7% ($p<0.05$); however, this change was only significant in men. The incidence of PUB was higher in men than in women between 40 and 70 years old and higher in women than in men older than 80 years. From 2006 to 2015, the *H. pylori* infection rate increased significantly in patients with PUB; however, there was no significant change in exposure to nonsteroidal anti-inflammatory drugs or other drugs that increase the risk of PUB.

Conclusions: Over the past decade, the incidence of PUB has decreased in a sex-specific manner. There has been a decreasing trend in the *H. pylori* infection rate and no change in exposure to drugs that increase the risk of PUB in Korea. **(Gut Liver 2021;15:537-545)**

Key Words: Anti-inflammatory agents, non-steroidal; *Helicobacter pylori*; Peptic ulcer hemorrhage; Sex; Incidence

INTRODUCTION

Peptic ulcer disease (PUD) is a common gastrointestinal disorder that can be life-threatening if complications such as bleeding or perforation occur. *Helicobacter pylori* and use of risk drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin, are the main causes of PUD.[1] The incidence of PUD after the eradication of *H. pylori* and the introduction of potent acid-suppressing agents has reportedly decreased in recent population-based studies.[2-5] In contrast, the trends of peptic ulcer bleeding (PUB) are inconsistent among regions; up until 2000, in Europe and the United States, the trends of PUB appear unchanged, or even slightly increased, depending on the study population.[2-4,6,7] After 2000, the hospitalization rates for PUB remained unchanged in the United Kingdom, Wales, and Scotland; however, it decreased in Sweden and Taiwan.[5,8-11] A more recent study in Hong Kong demonstrated that the incidence of PUB was reduced by approximately 66% from 2005 to 2014.[12]

Besides *H. pylori* infection and NSAIDs use, age, sex and comorbidities, such as, smoking, and other ulcerogenic drugs are risk factors in the development of PUD.[13,14] Sex has gained attention as a potential risk factor for PUD; however, it has been rarely analyzed in previous studies. The present study aimed to investigate the trends of PUB incidence between 2006 and 2015. The effect of sex and other risk factors on the incidence of the PUB was also investigated.

MATERIALS AND METHODS

1. Data source and study population

This study was a retrospective cohort study for the entire Korean population using the Korean National Health Insurance Service (NHIS)-Database (DB), which is mandatory for all residents of Korea (affiliated population 52,444,000 as of February 2018). Ethical approval of this study protocol was obtained through the Wonkwang University Sanbon Hospital IRB (No. 7302-201649). We retrieved all patients over 20 years of age who were admitted for PUB between 2006 and 2015 from the Korean NHIS-DB. Demographic data, including age and sex, and clinical data, including diagnostic code, procedure code, blood transfusion during hospitalization, information of prescribed drugs, and death, were obtained.

For the calculation of the standardized incidence, the number of patients with PUB was divided by that of the beneficiaries of the NHIS every year; this was then age-standardized using the world (WHO 2000–2025) standard population (https://seer.cancer.gov/stdpopulations/world.who.html).[15]

2. Hospitalization with PUB from the NHIS-DB

We first retrieved all hospitalization cases who had a diagnostic code of PUD with bleeding (K25.0 K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, and K27.6) from the NHIS-DB based on the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). To accurately extract the patients who were admitted as a result of PUB, we applied an operational definition based on the previous preliminary study using single-hospital data[16] as follows: (1) exclusion of patients with a procedure code of endoscopic mucosal resection or endoscopic submucosal dissection, or any diagnostic code of peritonitis or cancer; (2) limited to patients treated with intravenous administration of proton pump inhibitors (PPIs) during hospitalization; (3) exclusion of patients without a procedural code of esophagogastroduodenoscopy or endoscopic hemostasis during hospitalization. We considered the day of admission to the hospital as the index date.

3. Baseline comorbidities and short-term mortality

Diabetes mellitus (E10x-E14x), dyslipidemia (E78.x), angina pectoris (I20.x), myocardial infarction (I21.x-I23.x), cerebrovascular disorder (I63.x-I64.x), end-stage renal disease (N185), chronic obstructive pulmonary disease (J44.x), and cirrhosis of the liver (K74.x) were evaluated as baseline comorbidities using the ICD-10 codes. We defined short-term mortality as death within 30 days of the index date.

4. Ulcer-related drug exposure

To investigate the association between drug exposure and the incidence of PUB, prescription data from 4 weeks to 1 day before the index date were retrieved for final selected patients with PUB. The drugs analyzed for this study included the risk drug such as NSAIDs, aspirin, steroids, antithrombotic agents, and antiplatelet agents, as well as PPI, the preventive drug.

5. *Helicobacter pylori* infection rate

Since it was not possible to check the results of *H. pylori* tests from the DB, we indirectly estimated the *H. pylori* infection rate by selecting the patients who received eradication therapy within 6 months after the index date out of the patients with PUB who underwent the *H. pylori* tests (CLO Test [urease test], *H. pylori* Culture, Warthin-starry silver stain, urea breath test, *H. pylori* stool Ag test). To do this, we selected patients who were simultaneously prescribed amoxicillin and clarithromycin used as the first-line eradication therapy regimen or metronidazole and tetracycline used as the second-line eradication therapy regimen among patients with PUB.

6. Statistical analysis

Results of continuous variables are expressed as mean with standard deviation, whereas qualitative variables are expressed as frequencies and percentages. The annual change of the hospitalization rate of PUB was calculated by joinpoint regression analysis.[17] To compare the incidence by different risk groups, logistic regression analyses were carried out to compute the odds ratio (OR) of variables and their 95% confidence intervals (95% CI). The final multivariate model included age, sex, ulcer type. For all tests, a two-sided p-value <0.05 was considered statistically significant. A comparison of the difference in incidence rate among Korean people was performed by Poisson regression analysis. Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and the Join-

point Regression Program, Version 4.6.0.0. (Statistical Research and Applications Branch, National Cancer Institute, Bethesda, MD, USA).

RESULTS

1. Demographic data

During 2006 to 2015, 181,177 hospitalizations of all ages were identified by the operational definition. Hospitalizations for the following conditions were additionally excluded: if the patient had no claim code of esophagogastroduodenoscopy or hemostasis (n=24,369), was younger than 20 years (n=2,187), and had any missing eligibility data in patients over 20 years olds (n=3,114). Thus, finally, 151,507 PUB hospitalizations were analyzed (108,178 men and 43,329 women). The patients were classified according to the diagnostic codes as follows: 104,554 gastric ulcer bleeding, 36,434 duodenal ulcer bleeding, 7,077 combined gastric ulcer bleeding and duodenal ulcer bleeding, and 3,442 unspecified PUB (Fig. 1).

2. Annual trend of hospitalization with PUB and the effect of sex and age

The average annual number of hospitalizations with PUB was 15,151 per year, and the average annual incidence rate of hospitalization with PUB was 34.98 per 100,000 person-year (95% CI, 34.81 to 35.16) (Table 1). Between 2006 and 2008, the incidence rate of total hospitalization with PUB increased, but this was not statistically significant. Between 2008 and 2015, the incidence rate of total hospitalization with PUB had significantly decreased by an annual percent change (APC) of –2.7%. When analyzed according to sex, the incidence rate of hospitalization with PUB significantly decreased in men between 2008 and 2015 by an APC of –3.4%. The APC in women was –1.5%, and it was not statistically significant (Table 1, Fig. 2A). Both the absolute and age-standardized number of annual hospitalizations with PUB were higher in men than in women for 10 years (Table 1). When analyzed by age, the absolute number of hospitalization increased up to the seventies and then declined. However, the standardized incidence rate of hospitalization with PUB per 100,000 person-year continuously increased with age (Supplementary Table 1). Furthermore, when analyzed according to sex, it was significantly higher in men aged ≤80 years; however, women had a significantly higher standardized incidence rate of PUB than men aged >80 years (Fig. 2B).

3. Effect of risk factors on the hospitalization with PUB

The overall *H. pylori* infection rate during 2006 to 2015 was 34.37%, and men had a higher infection rate than their women counterparts (37.55% vs 25.32%; multivariate OR of 1.295; 95% CI, 1.246 to 1.347; p<0.0001). The *H. pylori* infection rate significantly decreased with increasing age (multivariate OR of 0.972; 95% CI, 0.971 to 0.973; p<0.0001) (Table 2). During 2006 to 2015, the *H. pylori* infection rate significantly declined; however, there was no significant change in the exposure rate of NSAIDs and other risk drugs associated with ulceration, such as cyclooxygenase-2 inhibitors, steroids, warfarin, other antithrombotic agents, and antiplatelet agents over the 10 years (Fig. 3, Supplementary Table 2). The only exception was

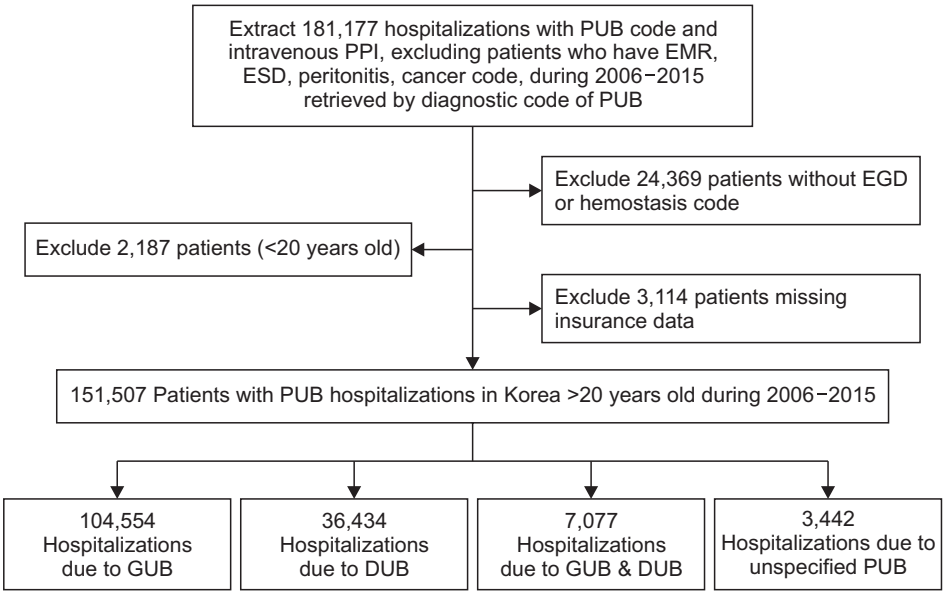

Fig. 1. Flowchart of data retrieval for hospitalizations for peptic ulcer bleeding (PUB) from the National Health Insurance Service Database. In total, 181,177 hospitalizations between 2006 and 2015 with a diagnostic code of PUB and without endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), peritonitis, and cancer were reviewed; 29,670 patients were excluded for the reasons shown, and 151,507 patients were enrolled and divided into four groups according to diagnostic codes.
PPI, proton pump inhibitor; EGD, esophagogastroduodenoscopy; GUB, gastric ulcer bleeding; DUB, duodenal ulcer bleeding.

Table 1. Number of Cases and Incidence Rate of PUB by Year, Sex, and Age between 2006 and 2015

Year	Hospitalizations of PUB (n)			Age-standardized hospitalizations per 100,000 person-year		
	Total	Men	Women	Total	Men	Women
2006	12,720	9,498	3,222	34.28	55.71	15.58
2007	14,636	10,794	3,842	38.03	61.01	17.77
2008	15,159	11,087	4,072	38.11	60.66	18.10
2009	15,014	10,834	4,180	36.50	57.59	17.84
2010	15,120	10,850	4,270	35.63	55.90	17.52
2011	15,505	10,924	4,581	35.40	54.51	18.12
2012	16,208	11,314	4,894	35.74	54.81	18.56
2013	16,061	11,272	4,789	34.30	52.84	17.42
2014	15,741	11,052	4,689	32.55	50.07	16.44
2015	15,343	10,553	4,790	30.70	46.38	16.21
Overall	151,507	108,178	43,329	34.98	54.56	17.35
APC, %*						
2006–2008				4.9	3.6	8.0
2008–2015				−2.7†	−3.4†	−1.5

PUB, peptic ulcer bleeding; APC, annual percent change.
*Joinpoint regression analysis; †p<0.05.

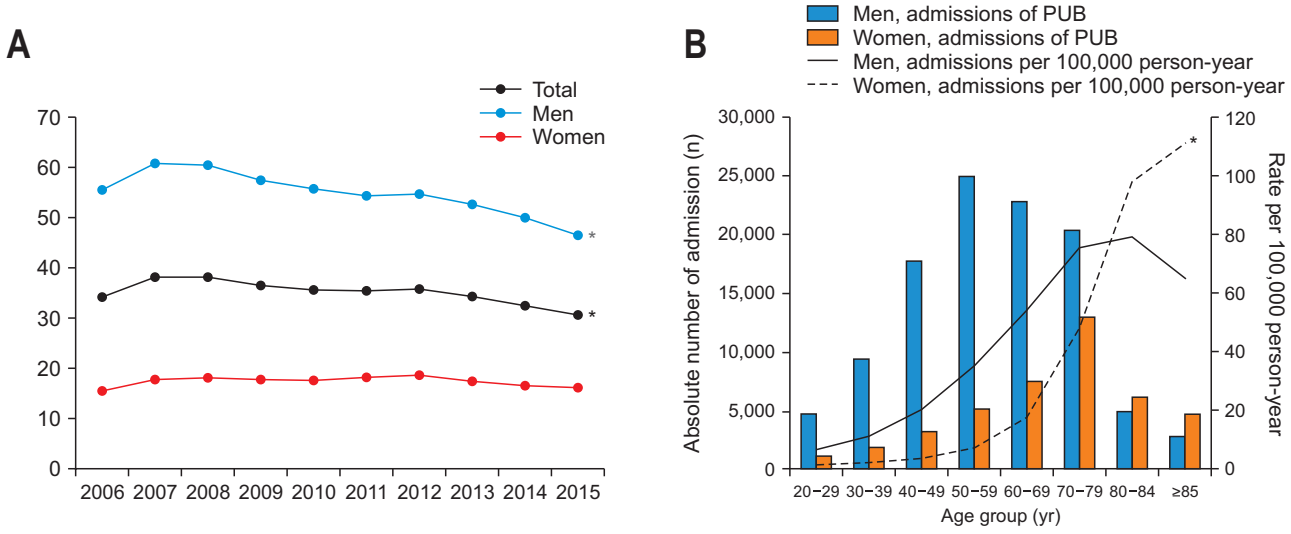

Fig. 2. Trend of peptic ulcer bleeding (PUB) according to year, age, and sex. (A) Sex difference in age-standardized hospitalizations for PUB per 100,000 person-years between 2006 and 2015. (B) Distribution of the absolute number of hospitalizations with PUB and hospitalization rate per 100,000 person-years according to sex and age. *p<0.05, annual percent change during 2008 to 2015.

aspirin, which had significantly but very slightly decreased over time with APC –0.08%; however, it showed no change from 2008 to 2015. The use of PPI, as well as the simultaneous prescription of PPI with NSAIDs or aspirin, also had not changed (Fig. 3B, Supplementary Table 2). The prevalence of hyperlipidemia and end-stage renal disease in patients with PUB was continually increased over the 10 years. Although the incidence of angina and cerebrovascular disorder initially increased, they showed no significant statistical change in the latter period. The prevalence of myocardial infarction and chronic obstructive lung disease were not significantly changed over the 10 years (Supplementary Fig. 1). We analyzed risk factors between men and women according to age range to explain why the incidence rate of PUB between men and women had reversed since the age of 80 years. However, the comorbidities, exposure to risk drugs, and *H. pylori* infection rate are rather significantly higher in men than women aged >80 years (Supplementary Table 3).

4. Severity of PUB

Hemostasis was performed in 47% of patients with PUB, and men were more likely to receive hemostasis than women (49.7% vs 40.3%). The multivariate OR for he-

Table 2. Proportions of PUB Patients with *Helicobacter pylori* Infections, Hemostasis, and Transfusion (%) by Age and Sex

Age	PUB	Perform *H. pylori* test	*H. pylori* infection rate*	Hemostasis	Transfusion
Overall (yr)					
20–29	6,030	3,462 (57.41)	1,744 (50.38)	2,053 (34.05)	2,413 (40.02)
30–39	11,397	6,461 (56.69)	3,342 (51.73)	4,873 (42.76)	5,665 (49.71)
40–49	21,128	11,120 (52.63)	5,043 (45.35)	9,940 (47.05)	13,077 (61.89)
50–59	30,150	14,929 (49.52)	6,004 (40.22)	14,767 (48.98)	20,447 (67.82)
60–69	30,407	14,261 (46.90)	4,436 (31.11)	15,056 (49.51)	21,913 (72.07)
70–79	33,482	15,257 (45.57)	3,435 (22.51)	16,095 (48.07)	25,768 (76.96)
80–89	16,978	7,213 (42.48)	1,156 (16.03)	7,653 (45.08)	13,893 (81.83)
≥90	1,935	712 (36.80)	72 (10.11)	825 (42.64)	1,652 (85.37)
Total	151,107	73,415 (48.46)	25,232 (34.37)	71,262 (47.04)	104,828 (69.19)
p-trend			<0.0001	<0.0001	<0.0001
Men (yr)					
20–29	4,823	2,899 (60.11)	1,500 (51.74)	1,752 (36.33)	2,016 (41.80)
30–39	9,427	5,542 (58.79)	2,944 (53.12)	4,200 (44.55)	4,770 (50.60)
40–49	17,847	9,624 (53.93)	4,425 (45.98)	8,804 (49.33)	11,411 (63.94)
50–59	24,935	12,598 (50.52)	5,159 (40.95)	12,665 (50.79)	17,455 (70.00)
60–69	22,880	10,889 (47.59)	3,528 (32.40)	11,867 (51.87)	16,830 (73.56)
70–79	20,392	9,437 (46.28)	2,263 (23.98)	10,539 (51.68)	15,787 (77.42)
80–89	7,252	3,073 (42.37)	544 (17.70)	3,670 (50.61)	5,981 (82.47)
≥90	622	238 (38.26)	29 (12.18)	311 (50.00)	524 (84.24)
Total	108,178	54,300 (50.20)	20,392 (37.55)	53,808 (49.74)	74,774 (69.12)
p-trend			<0.0001	<0.0001	<0.0001
Women (yr)					
20–29	1,207	563 (46.64)	244 (43.34)	301 (24.94)	397 (32.89)
30–39	1,970	919 (46.65)	398 (43.31)	673 (34.16)	895 (45.43)
40–49	3,281	1,496 (45.60)	618 (41.31)	1,136 (34.62)	1,666 (50.78)
50–59	5,215	2,331 (44.70)	845 (36.25)	2,102 (40.31)	2,992 (57.37)
60–69	7,527	3,372 (44.80)	908 (26.93)	3,189 (42.37)	5,083 (67.53)
70–79	13,090	5,820 (44.46)	1,172 (20.14)	5,556 (42.44)	9,981 (76.25)
80–89	9,726	4,140 (42.57)	612 (14.78)	3,983 (40.95)	7,912 (81.35)
≥90	1,313	474 (36.10)	43 (9.07)	514 (39.15)	1,128 (85.91)
Total	43,329	19,115 (44.12)	4,840 (25.32)	17,454 (40.28)	30,054 (69.36)
p-trend			<0.0001	<0.0001	<0.0001

Data are presented as number or number (%).
PUB, peptic ulcer bleeding.
*Number of eradication cases in patients who received the *H. pylori* test.

mostasis of men compared to women was 1.555 (95% CI, 1.518 to 1.592; p<0.0001). The rate of hemostasis slightly increased as the age increased (OR for age, 1.008; 95% CI, 1.007 to 1.009) (Table 2). Furthermore, blood transfusions were performed in 69% of patients with PUB; transfusions were performed more frequently in older patients than in younger patients (OR for age, 1.035; 95% CI, 1.034 to 1.035) and had a higher frequency in men when age-adjusted (OR for men vs women, 1.359; 95% CI, 1.324 to 1.395) (Table 2).

5. Thirty-day mortality following hospitalization with PUB

The overall mortality following hospitalization with PUB was 3.87%, and the mortality rate declined slightly between 2006 and 2015 (OR, 0.980; 95% CI, 0.970 to 0.989). Patients with PUB due to duodenal ulcer had higher mortality than those with gastric ulcer (GU) or combined ulcers, and patients with unspecified ulcers showed the highest mortality of all (OR for duodenal ulcer vs GU, 1.099; 95% CI, 1.031 to 1.172; OR for combined ulcer vs GU, 0.716; 95% CI, 0.616 to 0.831; OR for unspecified vs GU, 1.337; 95% CI, 1.146 to 1.559) (Table 3). Male sex and old age were significantly associated with higher mortality (adjusted OR for men vs women, 1.121; 95% CI, 1.057 to 1.188; OR for age, 1.047; 95% CI, 1.045 to 1.049) (Supplementary Table 4). In terms of comorbidities, cirrhosis and chronic obstructive pulmonary disease showed higher mortality (10.83% and 8.21%, respectively) than myocardial infarction, end-stage renal disease, cerebrovascular disorder, diabetes mellitus, and angina (6.83%, 6.43%, 5.69%, 5.52%, and 4.59%, respectively) (Supplementary Table 5).

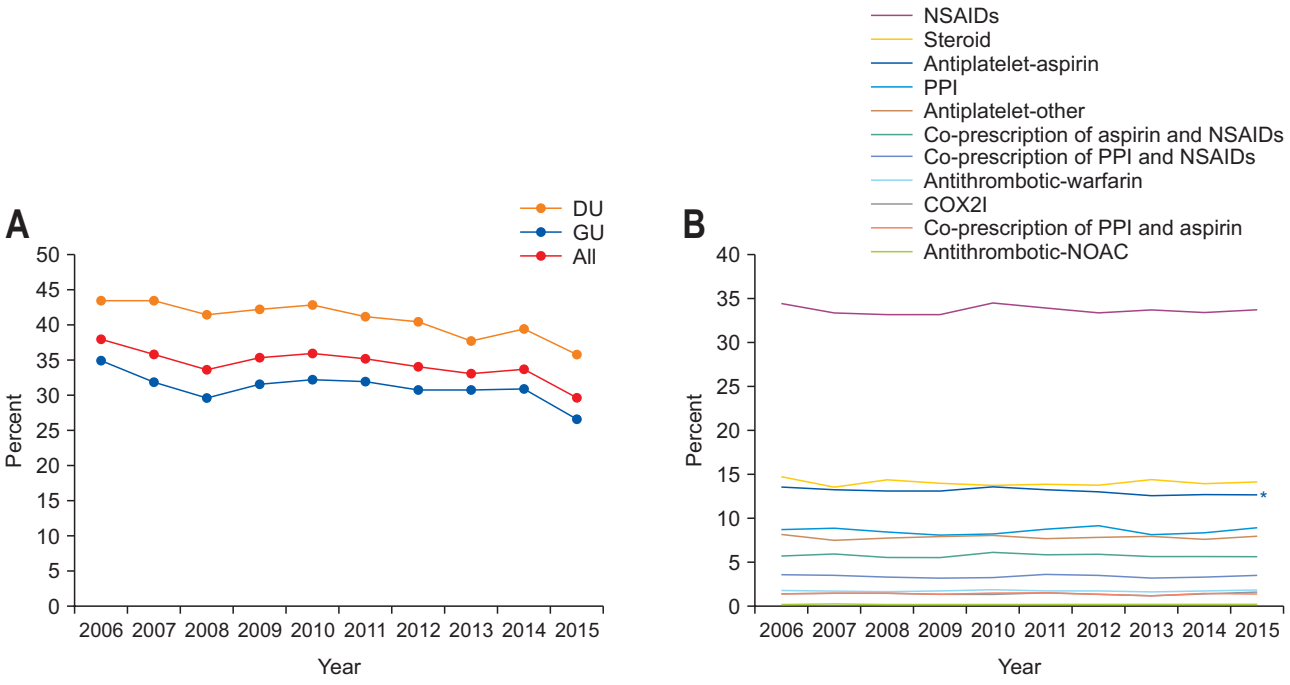

Fig. 3. *Helicobacter pylori* infection rate and drug exposure according to year. (A) Annual trends in the *H. pylori* infection rate in patients with peptic ulcer bleeding (PUB) between 2006 and 2015. (B) Annual trends in the rates of exposure to protective and risk-enhancing drugs in patients with PUB between 2006 and 2015.
DU, duodenal ulcer; GU, gastric ulcer; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; COX2I, cyclooxygenase-2 inhibitor; Antiplatelet-aspirin includes indobufen; Antiplatelet-other includes clopidogrel, ticlopidine, dipyridamole, cilostazol, and sarpogrelate HCl; NOAC (non-vitamin K antagonist oral anticoagulant) includes rivaroxaban, apixaban, edoxaban, and dabigatran etexilate mesylate. *p<0.05.

Table 3. Trends in 30-Day Mortality in Patients with PUB between 2006 and 2015

Variable	Year									
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Overall	457 (3.59)	576 (3.94)	619 (4.08)	584 (3.89)	607 (4.01)	608 (3.92)	612 (3.78)	598 (3.72)	604 (3.84)	606 (3.95)
Sex										
Men	318 (3.35)	387 (3.59)	423 (3.82)	369 (3.41)	381 (3.51)	366 (3.35)	401 (3.54)	378 (3.35)	376 (3.40)	384 (3.64)
Women	139 (4.31)	189 (4.92)	196 (4.81)	215 (5.14)	226 (5.29)	242 (5.28)	211 (4.31)	220 (4.59)	228 (4.86)	222 (4.63)
Type of ulcer										
GU	335 (3.85)	417 (4.13)	438 (4.18)	404 (3.94)	451 (4.31)	429 (4.05)	445 (3.96)	425 (3,81)	433 (3.94)	416 (3.93)
DU	102 (3.17)	114 (3.24)	145 (4.0)	141 (3.79)	117 (3.24)	137 (3.61)	128 (3.38)	139 (3.67)	135 (3.67)	151 (4.1)
Combined	10 (1.64)	29 (3.81)	20 (2.68)	16 (2.22)	22 (3.05)	22 (3.02)	25 (3.22)	16 (2.23)	14 (2.05)	12 (1.97)
Unspecified	10 (5.35)	16 (6.04)	16 (5.05)	23 (7.03)	17 (5.12)	20 (5.28)	14 (3.38)	18 (4.66)	22 (5.8)	27 (5.92)

Data are presented as number (%).
PUB, peptic ulcer bleeding; GU, gastric ulcer; DU, duodenal ulcer.

DISCUSSION

In this study, we investigated the trend of PUB and the effect of various factors contributing to the incidence of PUB between 2006 and 2015 in Korea. We discovered that the incidence of PUB and *H. pylori* infection rate had slightly decreased for the last decade, and the sex showed different effects on the incidence of PUB according to age. However, there was no significant change in the pattern of exposure to risk drugs in patients with PUB for 10 years.

The present study showed that there was a significant decrease only during the later study period, 2008 to 2015, and this decrease was significant only for men as –3.5%; however, this was not substantial when compared to Sweden, Hong Kong, and Taiwan, where showed around 40% to 60% decrement of PUB. These inconsistent results may be due to the differences in the risk factors, such as *H. pylori* infection, the proportion of the elderly population that is linked to the comorbidities and risk drug, and prescription pattern in clinical practice.

It is well-known that the incidence of PUB increases sharply with age, and is significantly higher in men than women in all age groups.[9,18] The current study demonstrates a higher incidence of PUB in men until they reach their 70s; however, the incidence was higher in women over 80 years old. Sex hormones could play a role in the sex difference of PUD. Although very limited, several studies have shown protective effects of female sex hormones for PUD, such as increased mucus, phospholipid levels, and bicarbonate secretion.[18,19] A study of Japanese with low dose aspirin showed a higher prevalence of PUD in men in their 70s, but a similar prevalence between men and women aged 80 and over.[20] The different population structures in terms of age and sex could be a reason for the inconsistent trend of PUB among countries. Korea has rapidly changed into a super-aged society, and Korean women are likely to take the longest life expectancy in the future.[21] Therefore, there may be an increasing number of older women patients with PUB with time, and close attention should be paid to this population. We analyzed risk factors such as co-morbidity, exposure to risk drugs, and *H. pylori* infection rates between men and women; however, it was impossible to find a factor to explain the differences in PUB incidence between men and women according to age. One plausible explanation is that women over 80 years of age have a high PUB rate may be because high-risk men are already dead. Further research is warranted to figure out the reason for sex difference, including social factors. The prevalence of *H. pylori* infection varies greatly among regions.[22] In Korea, previous nationwide studies showed that the seroprevalence of *H. pylori* has gradually declined. Indeed, the seroprevalence of 1998, 2005, 2011, 2015/2016, and 2016/2017 in Korea was 66.9%, 59.6%, 54.4%, 51.0%, and 41.5%, respectively.[23-27] Although we measured the infection rate in patients with PUB indirectly, we found that the estimated *H. pylori* infection rate decreased from 37.88% in 2005 to 29.62% in 2015. Nevertheless, this infection rate was lower compared to the seropositivity in previous studies. Considering the low sensitivity of the *H. pylori* test in the case of upper gastrointestinal bleeding and higher positivity of serologic test compared to real infection, this result seems to sufficiently reflect real trends of *H. pylori* infection rate in Korea.[28]

Besides *H. pylori* infection, the use of NSAIDs is another major independent risk factor for PUD.[29] As the age of the population increases, the use of NSAIDs due to osteoarthritis, as well as the use of aspirin or antiplatelet agents for primary and secondary prevention of cardiovascular or cerebrovascular disorders, is increasing. The successful eradication of *H. pylori* and the development of effective acid-reducing drugs have contributed to the decreased incidence of uncomplicated PUD in both Western and Eastern countries.[4,5] From 1997 to 2006 in Taiwan, the PUB incidence significantly decreased (from 116.9 to 61.1 and 108.0 to 40.1 per 100,000 for GU and duodenal ulcer, respectively) despite increased use of NSAIDs in patients with PUB from 32.6% to 45.8%. This change may be related to a significant increase in PPI prescriptions in Taiwan (1,071% increase) during the same period.[5] Another study showed that sales of acid-reducing drugs are negatively correlated with PUD hospitalization.[4] In contrast, the current study showed that exposure to risk drugs and the use of PPI in patients with PUB did not change over time in Korea. This finding suggested that the decrease of PUB incidence in Korea may be related to a gradual declining of *H. pylori* infection rate, which is also have demonstrated in other cohort studies.

The overall mortality in patients with PUB in Korea was 3.87% in this study. In individuals aged ≥70 years, the mortality rate was 2.6-fold higher than those ≤60 years old; this was consistent with the previous study.[6,9] Sex also influences mortality, and men showed higher mortality than women (Supplementary Table 3). The previous study reported that the frequency of blood transfusion was well correlated with both severity and mortality.[30] The patients with PUB in our study received hemostasis of 47% and transfusion of 66%; this was higher than those of the previous U.K. study in which 43% of patients received transfusion for acute upper gastrointestinal bleeding.[30]

There are several limitations to this study. First, the accuracy of retrieving the PUB is somewhat lower compared to the England study, in which the accuracy of medical records was 90%.[31] The authors' previous preliminary study showed a sensitivity and sensitivity of 82% and 88%, respectively, even if the best operative conditions were combined.[16] The national insurance data used in this study is used to claim insurance premiums rather than accurate medical records; therefore, incorrect diagnostic codes might be registered due to the busy clinical work or for an insurance claim. Second, the *H. pylori* infection rate was indirectly measured only in half of the PUB patients who were tested for *H. pylori* infection. For this reason, the proportion of idiopathic ulcers, which is not related to *H. pylori* infection or NSAIDs, could not be determined. Lastly, we retrieved the drug prescription data from health insurance records within only 4 weeks from the index date, so prescription before 4 weeks could not be determined. Moreover, over-the-counter drugs purchased at drug stores could not be investigated. The retrieving drug prescription for *H. pylori* eradication was also confined within 6 months from index date; therefore, the effect of risk drugs or *H. pylori* infection may have been underestimated.

In conclusion, we demonstrated that the incidence of PUB has decreased, showing a sex difference in terms of the annual trend and age-related incidence of PUB. The *H. pylori* infection rate also has decreased; however, the exposure to ulcerogenic risk drugs such as NSAIDs has not changed in patients with PUB in Korea.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study design and data collection: Y.S.K., J.L., J.M.L., J.H.P., A.S., H.Y.J. Data analysis and interpretation: Y.S.K., J.L., J.M.L., J.H.P., A.S. Drafting of manuscript: Y.S.K., J.L., A.S., H.Y.J. Critical revision: Y.S.K., A.S., H.Y.J.

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