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ORIGINAL ARTICLE

Retrospective Study

Changing trends and characteristics of peptic ulcer disease: A multicenter study from 2010 to 2019 in Korea

Yoon Jin Choi, Tae Jun Kim, Chang Seok Bang, Yong Kang Lee, Moon Won Lee, Su Youn Nam, Woon Geon Shin, Seung In Seo

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Abstract

BACKGROUND

The clinical trend and characteristics of peptic ulcer disease (PUD) have not fully been investigated in the past decade.

AIM

To evaluate the changing trends and characteristics of PUD according to age and

etiology.

METHODS

We analyzed seven hospital databases converted into the Observational Medical Outcomes Partnership-Common Data Model between 2010 and 2019. We classified patients with PUD who underwent rapid urease tests or *Helicobacter pylori* (*H. pylori*) serology into three groups: *H. pylori*-related, drug [nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin]-related, and idiopathic (*H. pylori*/NSAID/aspirin-negative) PUD and compared the yearly trends and characteristics among the three groups.

RESULTS

We included 26785 patients in 7 databases, and the proportion of old age (≥ 65 years) was 38.8%. The overall number of PUD exhibited no decrease, whereas PUD in old age revealed an increasing trend (P = 0.01 for trend). Of the 19601 patients, 41.8% had *H. pylori*-related, 36.1% had drug-related, and 22.1% had idiopathic PUD. *H. pylori*-related PUD exhibited a decreasing trend after 2014 (P = 0.01), drug-related PUD demonstrated an increasing trend (P = 0.04), and idiopathic PUD showed an increasing trend in the old-age group (P = 0.01) during 10 years. Patients with drug-related PUD had significantly more comorbidities and concomitant ulcerogenic drugs. The idiopathic PUD group had a significantly higher number of patients with chronic liver disease.

CONCLUSION

With the aging population increase, the effects of concomitant ulcerogenic drugs and preventive strategies should be investigated in drug-induced PUD. Further studies are required to clarify the relationship between idiopathic PUD and chronic liver disease.

Key Words: Peptic ulcer disease; Drug; Idiopathic; Trend; Characteristics

Core Tip: In the multicenter study including 26785 peptic ulcer disease (PUD) patients from 7 databases, the overall number of PUD exhibited no decrease, whereas PUD in old age revealed an increasing trend from 2010 to 2019 in Korea. According to etiology, decreasing trend of *Helicobacter pylori*-related PUD after year 2014, and increasing trend of drug-related PUD were observed in the past decade. Drug-related PUD showed significantly more comorbidities and exposure to concomitant ulcerogenic drugs, and the idiopathic PUD group had a significantly higher proportion in the chronic liver disease. Further studies are required to clarify the relationship between idiopathic PUD and chronic liver disease.

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INTRODUCTION

Peptic ulcer disease (PUD) remains a critical cause of hospitalization, particularly when complicated by hemorrhage, perforation, or obstruction[1]. The main etiologies of PUD include *Helicobacter pylori* (*H. pylori*) infection and the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs)[1]. The overall decline of *H. pylori* infection in the general population and advances in the management of *H. pylori* infection have led to a decline in the PUD incidence over the past two decades, however, prescriptions of aspirin and NSAIDs have increased over the same period owing to the rising number of older patients and patients with comorbidities[2]. Furthermore, direct oral anticoagulants (DOAC), newer NSAIDs, and antiplatelet agents continue to be used in chronic disease, and public awareness of *H. pylori* eradication has improved. Consequently, trends of PUD have demonstrated inconsistent results among regions[2-7]. A recent population-based study reported that morbidity and mortality due to PUD decreased significantly from 1990 to 2019, while a gradual upward trend has been observed in the recent 15 years, which might be associated with changes in risk factors [2]. Meanwhile, the incidence of non-*H. pylori*, non-NSAIDs/aspirin PUD, also termed idiopathic PUD, has increased in recent years, particularly in Asian countries[8]. The clinical outcomes of idiopathic PUD revealed recurrent ulcer bleeding and higher mortality in previous studies[9-14]; however, characteristics of idiopathic PUD remain poorly understood and warrant further investigation.

To date, few large-scale studies have comprehensively investigated the recent changing trends and clinical characteristics of PUD, including the multiple risk factors. Therefore, we investigated the trends and characteristics of PUD according to age and etiology in Korea between 2010 and 2019.

MATERIALS AND METHODS

Data source and study design

We analyzed seven hospital databases converted into the Observational Medical Outcomes Partnership-Common Data Model (OMOP-CDM) using the FEEDER-NET platform, which is a coordinating platform that enables data user and supplier connections and multi-institution analyses, with the anonymity of patients' personal information, as applied in previous studies[15-17]. The included institutions were Ajou University Medical Center (AUMC), Daegu Catholic Medical Center (DCMC), Ewha Womans University Medical Center (EUMC), Gyeongsang National University Hospital (GNUH), Kangdong Sacred Heart Hospital (KDH), Kangwon National University Hospital (KNUH), and Wonkwang University Hospital (WKUH). The detailed characteristics of each database are presented in Supplementary Table 1.

The characteristics of PUD were analyzed using the characterization tab on ATLAS, which is a web-based open platform developed by the Observational Health Data Sciences and Informatics community[18]. We analyzed basic demographic information, prescriptions, and comorbidities during the year before entering the cohort. We evaluated for exposure to aspirin and other antiplatelet agents, NSAIDs, anticoagulants, and potential ulcerogenic drugs (steroids, antidepressants, bisphosphonates, and immunosuppressive agents). Further, the mean Charlson Comorbidity Index (CCI) was calculated for each database. The same analytic codes were applied to seven hospital databases, and the results of each database were combined as proportions without extracting the raw data. The combined results were analyzed yearly for trend analysis and compared according to age group and etiology of PUD. This study was approved by the Institutional Review Board (IRB) of Kangdong Sacred Hospital (IRB number: 2021-11-001). The other six hospitals were affiliated with the Research Border Free Zone, which recognizes IRB approval of the research organizing center and waives individual IRB approval.

Definition of PUD

We defined a newly diagnosed PUD as having a 1-year observation period between January 1, 2010, and December 31, 2019, combining diagnostic codes for PUD, esophagogastroduodenoscopy, and exposure to proton pump inhibitors (PPIs). This operational definition was based on previous reports[3,19]. The index date was defined as the initial diagnosis of PUD. Exclusion criteria were as follows: (1) Age < 20 years; (2) Observation period < 1 year before the index date; (3) No exposure to PPIs 30 d before or after the index date; (4) No exposure to esophagogastroduodenoscopy 30 d before or after the index date; (5) Gastric cancer before the index date; and (6) Benign gastric neoplasm before the index date. Each concept name and identifier included in the OMOP-CDM databases matched to diagnostic codes or drugs are listed in Supplementary Table 2.

PUD classification according to etiology

We classified PUD patients who underwent rapid urease tests or *H. pylori* serology tests according to etiology into the following three groups: (1) *H. pylori*-related; (2) Drug-related (*H. pylori*-negative and NSAIDs/aspirin-related); and (3) Idiopathic (*H. pylori*/NSAID/aspirin-negative) PUD. *H. pylori*-related PUD included patients who were concomitantly prescribed *H. pylori* eradication therapy (PPI, amoxicillin, clarithromycin, bismuth, tetracycline, and metronidazole) for 7-14 d. Drug-related PUD included patients who were not exposed to *H. pylori* eradication therapy and were exposed to aspirin or NSAIDs before the index date. Idiopathic PUD included patients without exposure to aspirin, NSAIDs, or *H. pylori* eradication therapy. We further performed a subgroup analysis according to age and sex. We defined the old age group as ≥ 65 years, and the young age group as < 65 years.

Statistical analysis

Categorical variables were compared using the χ^2 or Fisher's exact test based on the results from the ATLAS version 2.7.6. Continuous variables were expressed as means with standard deviations. The yearly trend was analyzed with simple linear regression, and the yearly trend for each group was compared using the Cochran Armitage test for trends. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing).

RESULTS

Characteristics of PUD in total patients

The flowchart of the study is presented in Figure 1. A total of 26785 patients (AUMC, *n* = 4629; DCMC, *n* = 4690; EUMC, *n* = 3118; GNUH, *n* = 2998; KDH, *n* = 6320; KNUH, *n* = 1854; and WKUH, *n* = 3176) were included between 2010 and 2019. Finally, 15544 (58%) were men, and 11241 (42%) were women. The yearly trend of PUD exhibited no declining pattern in the total patients ($P = 0.69$ for trend) (Figure 2A). The yearly PUD trend in each database is presented in Supplementary Figure 1.

The baseline demographics are presented in Table 1. The proportion of gastric ulcers (69.2%) was over twofold that of duodenal ulcers (31.3%). The most prevalent comorbidity was hypertensive disorder, followed by diabetes mellitus. The proportions of exposure to NSAIDs, aspirin, and antiplatelet agents were 19.9%, 15.2%, and 11.4%, respectively. Regarding anticoagulants, warfarin and DOAC were prescribed in 2.2% and 1.1% of total patients, respectively. The proportion of exposure to steroids was 12.7%. Detailed information for each database is presented in Supplementary Table 3.

Table 1 Baseline characteristics of all patients with peptic ulcer disease, *n* (%)

	Total (*n* = 26785)
Age ≥ 65 yr	10392 (38.8)
Men	15544 (58.0)
RUT or serology	19601 (73.2)
Gastric ulcer	18527 (69.2)
Duodenal ulcer	8377 (31.3)
Diagnosis	
Hypertensive disorder	4773 (17.8)
Diabetes mellitus	2239 (8.4)
Hyperlipidemia	2038 (7.6)
Chronic kidney disease	1282 (4.8)
Ischemic heart disease	2221 (8.3)
Cerebrovascular disease	812 (3.0)
Chronic liver disease	1436 (5.4)
Osteoarthritis	425 (1.6)
Chronic obstructive lung disease	515 (1.9)
Medication	
Aspirin	4068 (15.2)
Other antiplatelet agent[1]	3065 (11.4)
Clopidogrel	2386 (8.9)
Cilostazole	691 (2.6)
NSAID	5342 (19.9)
Warfarin	579 (2.2)
DOAC	297 (1.1)
Steroid	3404 (12.7)
Antidepressant	6308 (23.6)
Bisphosphonate	488 (1.8)
Immunosuppressant	578 (2.2)

[1]Antiplatelet agents other than aspirin include clopidogrel, cilostazole, ticlopidine, triflusal, ticagrelor, and prasugrel.
RUT: Rapid urease test; NSAIDs: Nonsteroidal anti-inflammatory drugs; DOAC: Direct oral anticoagulant.

Characteristics of PUD in old age

The proportion of patients with old age (≥ 65 years) was 38.8% (10392/26785). The PUD with the old-age group demonstrated an increasing annual trend (P = 0.01 for trend), whereas the young age group (< 65 years) showed no specific trend overall (P = 0.47 for trend) (Figure 2A). The mean CCI in old age was higher than that in total patients (old-age group *vs* total group; 3.18 ± 2.6 *vs* 2.58 ± 2.4 in AUMC; 2.94 ± 2.2 *vs* 2.30 ± 1.9 in DCMC; 2.37 ± 1.9 *vs* 1.77 ± 1.5 in EUMC; 2.61 ± 2.0 *vs* 2.19 ± 1.8 in GNUH; 2.58 ± 2.0 *vs* 2.05 ± 1.7 in KDH; 2.78 ± 2.1 *vs* 2.36 ± 1.9 in KNUH; and 3.21 ± 2.4 *vs* 2.66 ± 2.2 in WKUH).

Characteristics of PUD according to etiology

Of the total patients, 19601 underwent rapid urease or *H. pylori* serology tests. The number of *H. pylori*-related, drug-related, and idiopathic PUD patients was 8202 (41.8%); 7066 (36.1%); and 4333 (22.1%), respectively. The proportions according to etiology in each hospital are presented in Supplementary Table 3. *H. pylori*-related PUD exhibited a decreasing trend after 2014 (P = 0.01 for trend), and drug-related PUD showed a slightly increasing trend in the past 10 years (P = 0.04 for trend). In contrast, idiopathic PUD revealed no statistically increasing trend in the past 10 years (P = 0.08 for trend) (Figure 2B).

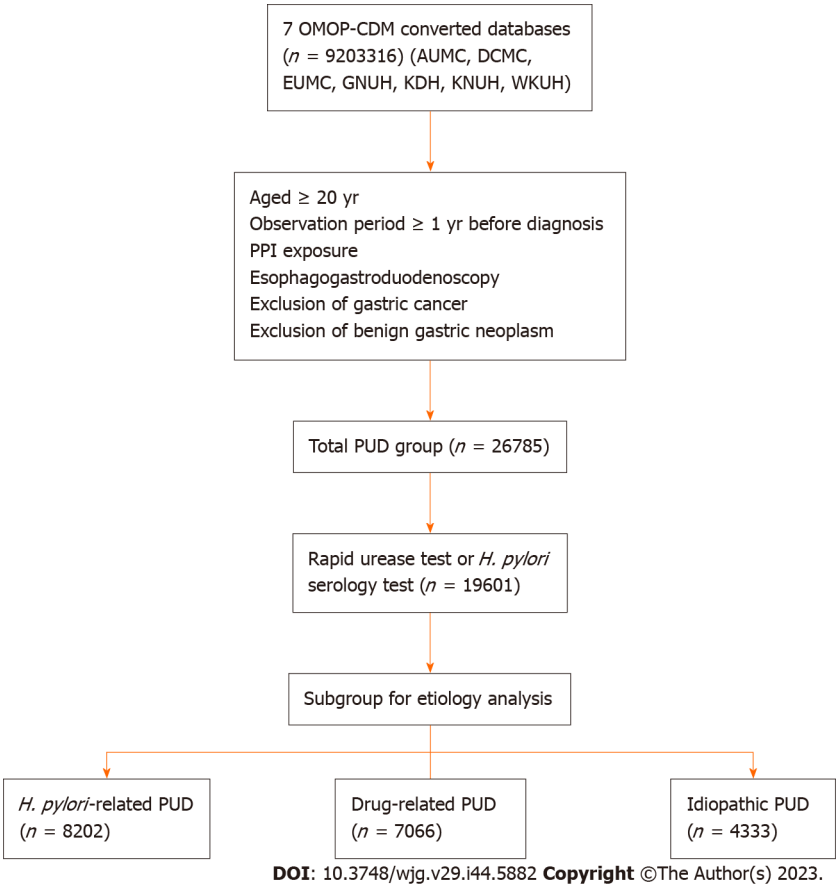

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Figure 1 Flow chart of the study. OMOP-CDM: Observational Medical Outcomes Partnership-Common Data Model; AUMC: Ajou University Medical Center; DCMC: Daegu Catholic Medical Center; EUMC: Ewha Womans University Medical Center; GNUH: Gyeongsang National University Hospital; KDH: Kangdong Sacred Heart Hospital; KNUH: Kangwon National University Hospital; WKUH: Wonkwang University Hospital; PPI: Proton pump inhibitor; PUD: Peptic ulcer disease; *H. pylori* : *Helicobacter pylori*.

The comparison of characteristics among the three groups is presented in Table 2. The *H. pylori*-related PUD group showed the lowest proportion of old age among the three groups. The proportion of duodenal ulcers was significantly higher in the *H. pylori*-related PUD than in the other groups. The drug-related PUD group had significantly more elderly patients, less predominance of men, more gastric ulcers, comorbidities except for chronic liver disease, exposure to concomitant potential ulcerogenic drugs than the other groups (Table 2). Notably, there were more patients with chronic liver disease in the idiopathic PUD group than in the other groups. In addition, there were significantly more patients with alcoholic liver damage and cirrhosis in the idiopathic PUD group (Table 2).

Subgroup analysis according to age and sex

Of 19601 patients, we conducted a subgroup analysis according to age group and sex. In the old-age (≥ 65 years) group (*n* = 7486), *H. pylori*-related PUD was 2043 (27.3%); drug-related was 3842 (51.3%); and idiopathic was 1601 (21.4%). In the young age (< 65 years) group (*n* = 12115), *H. pylori*-related PUD was 6159 (50.8%); drug-related was 3224 (26.6%); and idiopathic was 2732 (22.6%). In the old-age group, *H. pylori*-related PUD exhibited a decreasing trend after 2014 ($P < 0.01$ for trend), whereas drug-related and idiopathic PUD showed an overall increasing trend (drug-related, $P = 0.001$ for trend; idiopathic, $P = 0.01$ for trend) (Figure 2C). In the young age group, there was only a decreasing trend for *H. pylori*-related PUD after 2014 ($P = 0.01$ for trend) (Figure 2D). The yearly trend did not differ according to sex.

In the old-age group, more women had drug-related PUD than total patients (Table 3). The proportion of gastric ulcers was highest in drug-related PUD, regardless of age, whereas the proportion of duodenal ulcers showed different patterns according to age. In the old-age group, the proportion of duodenal ulcer was highest in the idiopathic PUD, and it was highest in *H. pylori*-related PUD in the young age group (Table 3). Other comorbidities or exposure to concomitant drugs did not differ according to age (Table 3). Supplementary Table 4 lists the subgroup analysis according to sex. No significant difference was found according to sex.

DISCUSSION

The findings of this multicenter OMOP-CDM-based study revealed that the total number of PUD patients demonstrated no decreasing trend, whereas newly diagnosed PUD in the old-age group showed an increasing trend in the past 10

Table 2 Comparison of characteristics according to the etiology of peptic ulcer disease

	H. pylori-related PUD (*n* = 8202)	Drug-related PUD (*n* = 7066)	Idiopathic PUD (*n* = 4333)	*P* value	All (*n* = 19601)
Age ≥ 65	2043 (24.9)	3842 (54.4)	1601 (36.9)	< 0.001	7486 (38.2)
Men, *n* (%)	5268 (64.2)	3774 (53.4)	2747 (63.4)	< 0.001	11789 (60.1)
Gastric ulcer	5062 (61.7)	5052 (71.5)	2758 (63.7)	< 0.001	12872 (65.7)
Duodenal ulcer	3272 (39.9)	2171 (30.7)	1574 (36.3)	< 0.001	7017 (35.8)
Diagnosis, *n* (%)					
Hypertensive disorder	928 (11.3)	2036 (28.8)	529 (12.2)	< 0.001	3493 (17.8)
Diabetes mellitus	438 (5.3)	954 (13.5)	256 (5.9)	< 0.001	1648 (8.4)
Hyperlipidemia	587 (7.2)	829 (11.7)	129 (3.0)	< 0.001	1545 (7.9)
Chronic kidney disease	173 (2.1)	604 (8.5)	123 (2.8)	< 0.001	900 (4.6)
Ischemic heart disease	483 (5.9)	1098 (15.5)	49 (1.1)	< 0.001	1630 (8.3)
Cerebrovascular disease	161 (2.0)	372 (5.3)	35 (0.8)	< 0.001	568 (2.9)
Chronic liver disease	224 (2.7)	447 (6.3)	349 (8.1)	< 0.001	1020 (5.2)
Alcoholic liver damage	164 (2.0)	253 (3.6)	234 (5.4)	< 0.001	651 (3.3)
Liver cirrhosis	175 (2.1)	381 (5.4)	325 (7.5)	< 0.001	881 (4.5)
Osteoarthritis	84 (1.0)	191 (2.7)	13 (0.4)	< 0.001	288 (1.5)
Chronic obstructive lung disease	76 (0.9)	209 (3.0)	74 (1.7)	< 0.001	359 (1.8)
Medication, *n* (%)					
Antiplatelet agent[1]	634 (7.7)	1514 (21.4)	77 (1.8)	< 0.001	2225 (11.4)
Warfarin	84 (1.0)	258 (3.7)	34 (0.8)	< 0.001	376 (1.9)
DOAC	33 (0.4)	129 (1.8)	20 (0.5)	< 0.001	182 (0.9)
Steroid	690 (8.4)	1423 (20.1)	227 (5.2)	< 0.001	2340 (11.9)
Antidepressant	1188 (14.5)	2408 (34.1)	868 (20.0)	< 0.001	4464 (22.8)
Bisphosphonate	94 (1.1)	223 (3.2)	18 (0.4)	< 0.001	335 (1.7)
Immunosuppressant	125 (1.5)	275 (3.9)	35 (0.8)	< 0.001	435 (2.2)

[1]Antiplatelet agents other than aspirin include clopidogrel, cilostazole, ticlopidine, triflusal, ticagrelor, and prasugrel.
PUD: Peptic ulcer disease; DOAC: Direct oral anticoagulant; *H. pylori*: *Helicobacter pylori*.

years. We classified PUD patients who underwent *H. pylori* serology or rapid urease tests into *H. pylori*-related, drug-related, and idiopathic PUD to clarify the characteristics and changing trends of PUD according to etiology. *H. pylori*-related PUD showed a decreasing trend after 2014; drug-related PUD, an increasing trend; and idiopathic PUD, an increasing trend only in the old-age group. Drug-related PUD revealed significantly more comorbidities and exposure to concomitant ulcerogenic drugs. Notably, the proportion of patients with chronic liver disease was significantly higher in idiopathic PUD.

Several studies have investigated the trends of PUD, and the overall prevalence has exhibited a decreasing trend in the past few decades; however, the trend differed according to region or sex owing to changes in the distribution of the etiologies of PUD[2,3]. A recent global study has reported that the age-standardized incidence rate exhibited an increasing annual trend with increasing age[2], and our results showed an increasing trend of PUD in the old-age group. A recent Korean nationwide cohort study conducted in 2006-2015 showed a decreasing trend in the *H. pylori* infection rate and no change in drug exposure that increases the risk of peptic ulcer bleeding (PUB)[3]. Furthermore, the *H. pylori* infection rate was 34.4% in that study when it was defined by including patients who received *H. pylori* eradication therapy out of the patients who underwent rapid urease tests, *H. pylori* cultures, urea breath tests, Warthin-Starry silver stains, and *H. pylori* stool antigen tests[3]. The lower *H. pylori* infection rate than that in our study may be attributed to the lack of *H. pylori* serology testing and false-negative results in the PUB setting in that study. *H. pylori*-related PUD was 41.8% in our study, which was consistent with a recent Korean nationwide multicenter study that reported 43.9% *H. pylori* seropositivity from 2016 to 2017[20]. Our proportion of *H. pylori*-related PUD also included patients who had *H. pylori* eradication therapy, which suggests that the knowledge and awareness of the public was improved in the past decade. A

Table 3 Subgroup analysis of characteristics of peptic ulcer disease according to age, *n* (%)

	Age (yr)	*H. pylori*-related PUD (*n* = 8202)	Drug-related PUD (*n* = 7066)	Idiopathic PUD (*n* = 4333)	*P* value
Men	≥ 65	1161/2043 (56.8)	1869/3842 (48.6)	934/1601 (58.3)	< 0.001
	< 65	4107/6159 (66.7)	1905/3224 (59.1)	1813/2732 (66.4)	< 0.001
Gastric ulcer	≥ 65	1481/2043 (72.5)	2855/3842 (74.3)	1093/1601 (68.3)	< 0.001
	< 65	3581/6159 (58.1)	2197/3224 (68.1)	1665/2732 (60.9)	< 0.001
Duodenal ulcer	≥ 65	612/2043 (30.0)	1117/3842 (29.1)	561/1601 (35.0)	< 0.001
	< 65	2660/6159 (43.2)	1054/3224 (32.7)	1013/2732 (37.1)	< 0.001
Diagnosis					
Hypertensive disorder	≥ 65	452/2043 (22.1)	1431/3842 (37.2)	321/1601 (20.0)	< 0.001
	< 65	476/6159 (7.7)	605/3224 (18.8)	208/2732 (7.6)	< 0.001
Diabetes mellitus	≥ 65	194/2043 (9.5)	610/3842 (15.9)	148/1601 (9.2)	< 0.001
	< 65	244/6159 (4.0)	344/3224 (10.7)	108/2732 (4.0)	< 0.001
Hyperlipidemia	≥ 65	201/2043 (9.8)	533/3842 (13.9)	53/1601 (3.3)	< 0.001
	< 65	386/6159 (6.3)	296/3224 (9.2)	76/2732 (2.8)	< 0.001
Chronic kidney disease	≥ 65	76/2043 (3.7)	382/3842 (9.9)	64/1601 (4.0)	< 0.001
	< 65	97/6159 (1.6)	222/3224 (6.9)	59/2732 (2.3)	< 0.001
Ischemic heart disease	≥ 65	247/2043 (12.1)	794/3842 (20.7)	35/1601 (2.6)	< 0.001
	< 65	236/6159 (3.8)	304/3224 (9.4)	14/2732 (0.6)	< 0.001
Cerebrovascular disease	≥ 65	92/2043 (4.5)	288/3842 (7.5)	25/1601 (1.6)	< 0.001
	< 65	69/6159 (1.1)	84/3224 (2.7)	10/2732 (0.5)	< 0.001
Chronic liver disease	≥ 65	42/2043 (2.3)	202/3842 (5.3)	120/1601 (7.5)	< 0.001
	< 65	182/6159 (3.0)	245/3224 (7.6)	229/2732 (8.4)	< 0.001
Alcoholic liver damage	≥ 65	20/2043 (1.1)	85/3842 (2.2)	64/1601 (4.0)	< 0.001
	< 65	144/6159 (2.3)	168/3224 (5.2)	170/2732 (6.2)	< 0.001
Liver cirrhosis	≥ 65	29/2043 (1.6)	161/3842 (4.2)	113/1601 (7.1)	< 0.001
	< 65	146/6159 (2.4)	220/3224 (6.8)	212/2732 (7.8)	< 0.001
Osteoarthritis	≥ 65	56/2043 (2.7)	145/3842 (3.8)	10/1601 (1.1)	< 0.001
	< 65	28/6159 (0.5)	46/3224 (1.6)	3/2732 (0.2)	< 0.001
Chronic obstructive lung disease	≥ 65	53/2043 (2.6)	176/3842 (4.6)	57/1601 (3.6)	0.001
	< 65	23/6159 (0.4)	33/3224 (1.0)	17/2732 (0.6)	0.001
Medication					
Antiplatelet agent	≥ 65	324/2043 (15.9)	1058/3842 (27.5)	51/1601 (3.2)	< 0.001
	< 65	310/6159 (5.0)	456/3224 (14.1)	26/2732 (1.0)	< 0.001
Warfarin	≥ 65	49/2043 (2.4)	190/3842 (4.9)	28/1601 (1.9)	< 0.001
	< 65	35/6159 (0.6)	68/3224 (2.1)	6/2732 (0.3)	< 0.001
DOAC	≥ 65	23/2043 (1.2)	112/3842 (2.9)	19/1601 (1.2)	< 0.001
	< 65	10/6159 (0.2)	17/3224 (0.6)	1/2732 (0.1)	0.015
Steroid	≥ 65	237/2043 (11.6)	807/3842 (21.0)	111/1601 (6.9)	< 0.001
	< 65	453/6159 (7.4)	616/3224 (19.1)	116/2732 (4.2)	< 0.001
Antidepressant	≥ 65	456/2043 (22.3)	1568/3842 (40.8)	435/1601 (27.2)	< 0.001
	< 65	732/6159 (11.9)	840/3224 (26.1)	433/2732 (15.8)	< 0.001

Bisphosphonate	≥ 65	54/2043 (2.6)	174/3842 (4.5)	11/1601 (0.7)	< 0.001
	< 65	40/6159 (0.6)	49/3224 (1.5)	7/2732 (0.4)	< 0.001
Immunosuppressant	≥ 65	49/2043 (2.4)	108/3842 (2.8)	13/1601 (0.9)	< 0.001
	< 65	76/6159 (1.2)	167/3224 (5.2)	22/2732 (1.0)	< 0.001

PUD: Peptic ulcer disease; DOAC: Direct oral anticoagulant; *H. pylori*: *Helicobacter pylori*.

recent meta-analysis also revealed that technology-enhanced communication initiatives effectively improve compliance to the *H. pylori* eradication regimen and increase the eradication rate[21].

The use of NSAIDs or aspirin has increased dramatically in recent decades, and the prevalence of NSAID use in patients aged ≥ 65 years is reported to be as high as 96%[22,23]. The proportion of drug-related PUD revealed an increasing trend, and it was prominent in the old-age group. The drug-related PUD group included more elderly patients and showed comorbidities and exposure to concomitant ulcerogenic drugs compared with the other groups, consistent with previous reports[24]. Drug-related PUD may cause serious complications, including bleeding or perforation[25]. Clinical practice guidelines for the appropriate treatment and prevention of drug-related PUD have been recently developed[26,27]. The guidelines recommend high-risk patients who are on long-term NSAID medications receive low-dose PPIs to prevent PUD and its complications; however, evidence in patients who take multiple ulcerogenic drugs remains lacking[26]. In a previous case series analysis from seven population-based healthcare databases, concomitant use of NSAIDs or aspirin with selective serotonin reuptake inhibitors, aldosterone antagonists, corticosteroids, or anticoagulants significantly increased the risk of upper gastrointestinal bleeding[28]. Our results suggest that drug-induced PUD may have more severe clinical outcomes; therefore, further strategies should be investigated to prevent complications in elderly patients.

The proportion of idiopathic PUD was 22.1% in our study, which is consistent with the proportion in the previous multicenter prospective study in 2008[9] and higher than that in the study by Chung *et al*[8] (8.6%) of patients with PUB in Korea[12]. Idiopathic PUD can be defined after excluding the missed diagnosis of *H. pylori* infection and undocumented use of NSAIDs or aspirin; therefore, the definition and diagnosis of *H. pylori* infection differed among the previous studies. Epidemiological studies have consistently reported an increasing proportion of *H. pylori*-negative PUD, particularly in Asian countries[8]; however, most of these studies were conducted before 2014, and few large-scale studies have investigated the changing trends or characteristics of idiopathic PUD in recent years. Our idiopathic PUD group included patients who had no exposure to aspirin, NSAIDs, or *H. pylori* eradication therapy before the index date. In our study, the exact results of the *H. pylori* tests could not be obtained, and patients with idiopathic PUD may overlap with those with drug-induced PUD. Despite these limitations, our study was the first to demonstrate the increasing trend of idiopathic PUD in old age in the past decade. In addition, we confirmed that the proportion of idiopathic PUD may differ regionally depending on the regional *H. pylori* prevalence.

The proportions of most of the comorbidities and drug exposures were higher in drug-induced PUD in our study, and only chronic liver disease was significantly higher in patients with idiopathic PUD among the three groups. Previous studies have compared the characteristics of idiopathic PUD with those of *H. pylori*-related PUD. The risks for idiopathic PUD included older age, smoking, alcohol, comorbid diseases, and higher psychological stress[8]. In our study, among three PUD groups, only the proportion of chronic liver disease was significantly higher in the idiopathic PUD; therefore, it may be a distinct characteristic compared with drug-induced PUD. The relationship between idiopathic PUD and liver disease has been suggested in several studies. Kim *et al*[29] have reported that despite the decreased *H. pylori* infection in patients with severe liver cirrhosis, PUD was increased in 288 patients with liver cirrhosis. Therefore, factors other than *H. pylori* infection may be involved in the pathogenesis of PUD in patients with cirrhosis[29,30]. A proposed pathophysiological mechanism is that portal hypertension induces splanchnic vascular congestion followed by gastrointestinal mucosal changes involving impaired mucosal secretion and microvascular flow, leading to peptic ulcer formation[31]. Moreover, we demonstrated that alcoholic liver disease was more prevalent in idiopathic PUD, suggesting that alcohol may be another risk factor for idiopathic PUD, although the causal relationship is uncertain.

Our study had several limitations. First, the proportion of idiopathic PUD may have been overestimated since we could not identify the exact *H. pylori* infection or confirmation after *H. pylori* eradication using an administrative database. However, this limitation may be overcome by converting text data to CDM in future studies. Second, our study was not conducted nationwide; therefore, we could not demonstrate the PUD trend as a proportion of the total patients. However, we observed that the pattern or severity of PUD may vary according to the scale of each hospital. Third, patients may overlap across hospital databases. Patients may be diagnosed with PUD in one hospital and treated in another. Fourth, the claims data-based research design may include misclassification bias or inaccurate data. Lastly, we could not include data on smoking or alcohol consumption; therefore, it could not be evaluated as a cause of idiopathic PUD.

Despite these limitations, our study had the following strengths. The main strength is that the analysis was performed using the OMOP-CDM database, which can be applied to other databases worldwide with the same analytic code. Second, our study used the operational definition of PUD based on a previous validation study, which showed high sensitivity and specificity[19]. Lastly, our study confirmed the changing trends and characteristics of PUD according to etiology and age group in the past 10 years using a large-scale multicenter design.

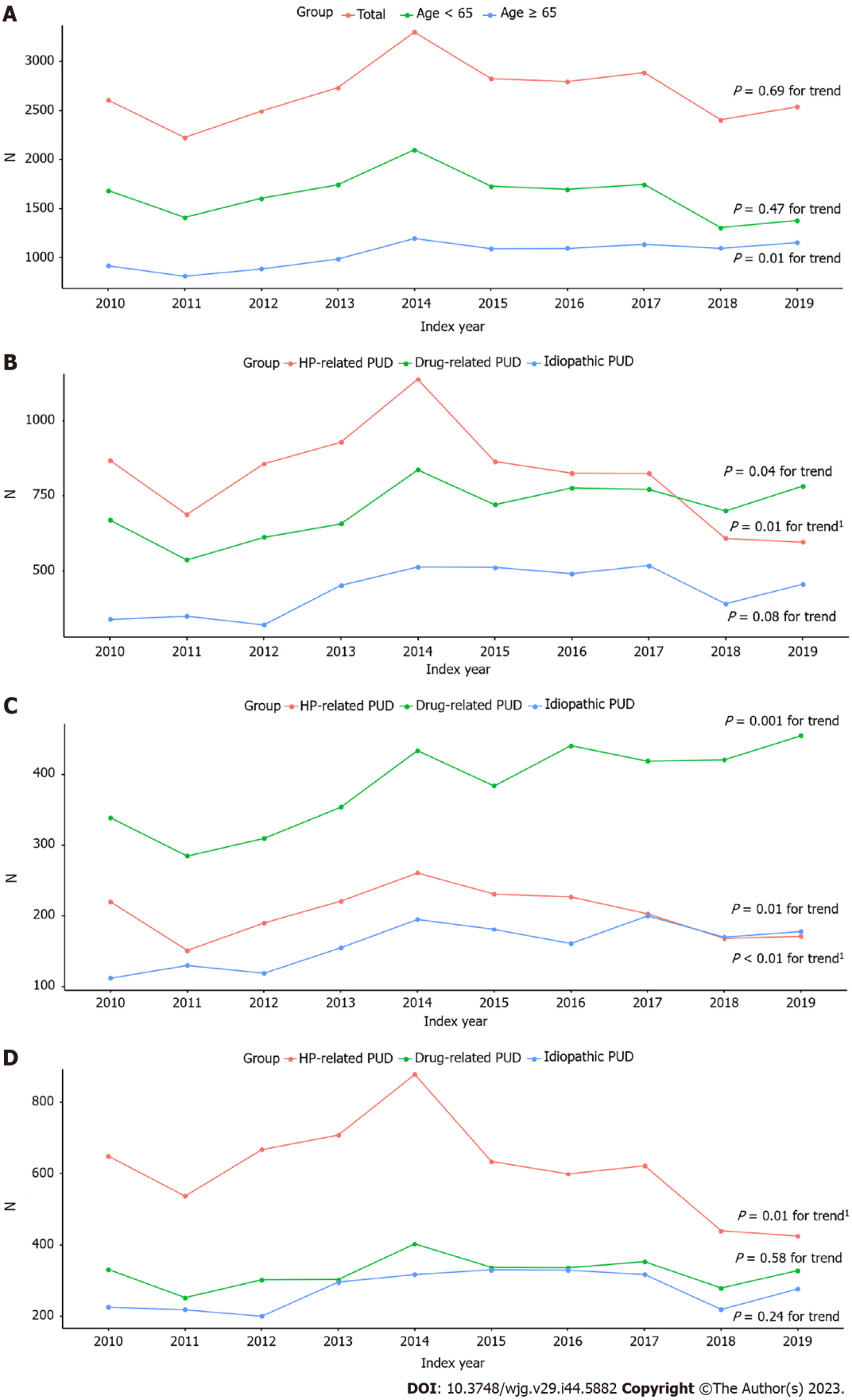

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Figure 2 Yearly trend of peptic ulcer disease according to age group, etiology in total, in the old age (≥ 65) group, and in the young age (< 65) group. A: Age group; B: Etiology in total group; C: Etiology in the old age (≥ 65) group; D: Etiology in the young age (< 65) group. PUD: Peptic ulcer disease; HP: *Helicobacter pylori*. [1]*P* for trend after 2014.

CONCLUSION

In conclusion, PUD exhibited an increasing trend in the old-age group in the past decade. Regarding etiology, *H. pylori*-related PUD decreased, whereas drug-related and idiopathic PUD increased, particularly in the old-age group. With the rising number of older patients, the effects of concomitant ulcerogenic drugs on PUD should be investigated, and preventive strategies for drug-induced PUD should be developed. Further studies are required to clarify the relationship between idiopathic PUD and chronic liver disease.

ARTICLE HIGHLIGHTS

Research background

To date, few large-scale studies have comprehensively investigated the recent changing trends and clinical characteristics of peptic ulcer disease (PUD), including the multiple risk factors.

Research motivation

The incidence of idiopathic PUD, has increased in recent years, particularly in Asian countries. The clinical outcomes of idiopathic PUD revealed recurrent ulcer bleeding and higher mortality in previous studies; however, characteristics of idiopathic PUD remain poorly understood and warrant further investigation.

Research objectives

We aimed to evaluate the changing trends and characteristics of PUD according to age and etiology.

Research methods

We analyzed seven hospital databases that were converted to a common data model between 2010 and 2019. We classified PUD patients who underwent rapid urease testing or *Helicobacter pylori* (*H. pylori*) serology testing into the following three groups according to etiology: (1) *H. pylori*-related; (2) drug-related [*H. pylori*-negative and nonsteroidal anti-inflammatory drugs (NSAIDs)/aspirin-related]; and (3) Idiopathic (*H. pylori*/NSAID/aspirin-negative) PUD.

Research results

The overall number of PUD exhibited no decrease, whereas PUD in old age revealed an increasing trend. *H. pylori*-related PUD exhibited a decreasing trend after 2014, drug-related PUD demonstrated an increasing trend, and idiopathic PUD showed an increasing trend in the old-age group during 10 years. The idiopathic PUD group had a significantly higher number of patients with chronic liver disease.

Research conclusions

There was an increase in the incidence of PUD in the older age group during the last decade. There was a decrease in *H. pylori*-related PUD and an increase in drug-related and idiopathic PUD, especially in the elderly group.

Research perspectives

Further preventive strategies for drug-induced PUD should be developed. Further studies are required to clarify the relationship between idiopathic PUD and chronic liver disease.

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FOOTNOTES

Author contributions: Choi YJ and Seo SI contributed to the acquisition of data, analysis and interpretation of data, drafting of the manuscript; Kim TJ, Bang CS, Lee YK, and Lee MW participated in the technical or material support of this study; Nam SY and Shin WG contributed to the critical revision of the manuscript for important intellectual content; Seo SI involved in the study concept and design, and study supervision.

Institutional review board statement: This study was approved by the Institutional Review Board (IRB) of Kangdong Sacred Hospital (IRB number: 2021-11-001). The other six hospitals were affiliated with the Research Border Free Zone, which recognizes IRB approval of the research organizing center and waives individual IRB approval.

Informed consent statement: As the study used anonymous and pre-existing data, the requirement for the informed consent from patients was waived.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Dataset available from the corresponding author's e-mail doctorssi@kdh.or.kr.

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