ORIGINAL ARTICLE

High Recurrence Rate of Idiopathic Peptic Ulcers in Long-Term Follow-up

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Background/Aims: Our aim was to compare the long-term clinical outcomes of idiopathic peptic ulcer disease (IPUD) with those of *Helicobacter pylori*-positive and nonsteroidal anti-inflammatory drug (NSAID)-induced peptic ulcer disease (PUD). **Methods:** Patients with endoscopically diagnosed PUD were retrospectively reviewed. According to their *H. pylori*-infection status and history of NSAIDs use, patients were categorized into three groups: *H. pylori*-positive PUD, NSAID-induced PUD, and IPUD. Clinical outcomes were analyzed, and the recurrence rate of PUD was compared among the three groups. **Results:** A total of 238 patients were enrolled. Those with IPUD, NSAID-induced PUD, and *H. pylori*-positive PUD comprised of 56, 60, and 122 patients, respectively. The 5-year cumulative incidences of recurrent ulcers were 24.3% (95% confidence interval [CI], 11.6% to 37.0%) in IPUD, 10.9% (95% CI, 2.6% to 19.2%) in NSAID-induced PUD, and 3.8% (95% CI, 0.1% to 7.5%) in *H. pylori*-positive PUD (IPUD vs NSAID-induced PUD/*H. pylori*-positive PUD, p=0.43/ p<0.001 by log-rank test). In the Cox-proportional hazards model, only IPUD remained as an independent risk factor associated with recurrent ulcers (hazard ratio, 5.97; 95% CI, 1.94 to 18.34; p=0.002). **Conclusions:** IPUD exhibited a higher recurrence rate than *H. pylori*-positive and NSAID-induced PUD in long-term follow-up and was an independent risk factor for ulcer recurrence. **(Gut Liver 2013;7:175-181)**

INTRODUCTION

The discovery that *Helicobacter pylori* is associated with peptic ulcer recurrence was the turning point of peptic ulcer treatment. Eradication of *H. pylori* in the patients with peptic ulcer disease (PUD) has dramatically reduced the recurrence rate of disease.[1] Aside from *H. pylori* infection, nonsteroidal anti-inflammatory drugs (NSAIDs) have been one of the leading causes of PUD. However, the definite cause of peptic ulcer cannot be identified in some patients in spite of comprehensive evaluation.

Idiopathic PUD (IPUD) is defined as a peptic ulcer without definite causes such as *H. pylori* infection, NSAIDs use or hypergastrinemia. The prevalence of IPUD remarkably varies from 1.3% to 27% with the background prevalence of *H. pylori* infection in the region.[2,3] In Korea, recent study suggested that the proportion of IPUD in PUD was 22.2%.[4] Considering that the prevalence of *H. pylori* infection has been decreasing, the proportion of IPUD in Korea is expected to increase furthermore.[5]

However, the natural history and long-term clinical outcome of IPUD have not yet been well clarified. In cohort studies, the patients with IPUD have a high risk of recurrent ulcer bleeding and mortality,[6,7] but the long-term clinical outcome of nonbleeding IPUD were not evaluated in regard to risk of ulcer recurrence. In another study, uncomplicated *H. pylori*-negative duodenal ulcers had high recurrence rate during 2-year follow-up,[8] in which the sample size and the duration of follow-up was not enough to evaluate the long-term outcomes. Moreover, a history of NSAIDs use was not considered as possible etiology of peptic ulcer. A small-scaled study in China showed high recurrence rate of IPUD during several years of follow-up,[9] however, the study subjects were children.

Therefore, the aim of this study was to compare the long-term recurrence rate of IPUD in adults with two major etiologic groups of PUD; *H. pylori*-positive PUD and NSAIDs-induced PUD.

MATERIALS AND METHODS

1. Patients

We identified patients over 18 years of age with a diagnosis code of peptic ulcer, benign gastric ulcer, or duodenal ulcer in

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2005 at Seoul National University Hospital, Seoul, South Korea through electronic medical records. Among identified 870 patients, 425 individuals were confirmed to have gastric or duodenal ulcer in the endoscopic finding. Ulcer was defined as a mucosal break with an apparent depth over 5 mm in diameter. In the next step, patients with history of partial gastrectomy, malignancy within the previous 5 years, ulcer in scar stage, malignant ulcer, endoscopic procedure-related ulcer, Dieulafoy's ulcer, or no result of *H. pylori* infection status were excluded. Of the remaining 291 patients, after excluding 53 individuals who had less than 6 months of follow-up duration, finally 238 patients with PUD were analyzed. The Institutional Review Board of the Seoul National University Hospital approved this study.

2. Characteristics and etiologic categorization of PUD

Data about location, stage, and number of ulcers were retrospectively reviewed with electrical medical records for each patient. In cases where ulcers were found in both stomach and duodenum, organ with more prominent lesion was defined as ulcer location. The number of comorbid diseases was calculated by reviewing diagnosis codes in each patient. Types of drugs used to treat ulcers and treatment duration were also investigated. To collect the history of recent NSAIDs use, we scrutinized outpatient records and prescription list through electronic medical records system. For each patient, the status of *H. pylori* infection at the diagnosis of PUD was reviewed by the result of histology and rapid urease test (CLO test; Kimberly-Clark, Draper, UT, USA). Biopsy for histologic evaluation and rapid urease test was done in the ulcer margin and the antrum, respectively. *H. pylori* infection was defined as positive if at least one of two tests was positive. Because false negative results of rapid urease test can occur in patients taking antibiotics or proton pump inhibitors (PPIs),[10] in cases where these drugs were prescribed in the preceding 4 weeks, patients without histological evaluation were excluded from the study.

Based on the etiology of PUD, patients were categorized into three groups: 1) NSAIDs-induced PUD group with history of regular NSAIDs or aspirin use within 1 month before diagnosis regardless of *H. pylori* infection status,[11] 2) *H. pylori*-positive PUD group, and 3) IPUD group without the evidence of hypergastrinemia.

3. Follow-up

Initial event was defined as the day when a patient was diagnosed as PUD by endoscopy. In cases with gastric ulcer, follow-up endoscopy had been performed after 8 to 12 weeks of treatment to confirm the cure of ulcer, and when the patients had recurrent symptom with PUD. Recurrent ulcer was defined as gastric or duodenal ulcer of active or healing stage confirmed by endoscopy during the follow-up period. Terminal event was defined as the day when the recurrent ulcer was diagnosed or the last follow-up day to August 2010. The history of drug use including *H. pylori* eradication, NSAIDs, PPIs, or histamine 2 receptor antagonists (H_2RAs) to the terminal event was scrutinized by the electronic medical records. Continued NSAIDs use was defined by the exposure to that drug for more than 50% of the follow-up period. In addition, new infection and eradication history of *H. pylori* during the follow-up period were also studied.

4. Statistical analysis

IBM SPSS for Windows version 18.0 (IBM, Armonk, NY, USA) was used for the statistical analysis. Baseline clinical characteristics of patients and analysis of ulcer recurrence were presented as descriptive data. Continuous variables were analyzed using Kruskal-Wallis test. In cases where there was significant difference in the three study groups, pairwise-comparisons were additionally done using Mann-Whitney U test. The chi-square test or Fisher's exact test were used to analyze categorical variables. Cumulative probabilities of ulcer recurrence were estimated by the Kaplan-Meier method. The log-rank test was used to compare time-to-event curves between the three groups. A Cox-proportional hazards model was used to identify possible covariates as significant predictors of ulcer recurrence which included sex, age ($\geq$60 years), number of comorbid diseases ($\geq$2), location of ulcer (gastric vs duodenal), duration of ulcer treatment ($\geq$9 weeks), *H. pylori* infection status, and concomitant use of NSAIDs. All results were considered statistically significant when p-values were less than 0.05.

RESULTS

1. Baseline clinical characteristics

Among a total of 238 patients, *H. pylori*-positive PUD, NSAIDs-induced PUD, and IPUD were 122 (51.3%), 60 (25.2%), and 56 (23.5%), respectively (Table 1). NSAIDs-induced PUD group was significantly older than *H. pylori*-positive PUD group (p<0.001). The rate of patients with comorbid diseases more than one was significantly higher in NSAIDs-induced PUD group than in other groups (NSAIDs-induced PUD vs *H. pylori*-positive PUD and IPUD, p<0.001 and p=0.005). Patients with *H. pylori*-positive PUD had a higher proportion of duodenal ulcer than other groups (*H. pylori*-positive PUD vs NSAIDs-induced PUD and IPUD, p=0.002 and p<0.001). The most commonly used medicine for the treatment of ulcer was PPIs (177/238, 74.4%) and patients with IPUD were treated for a longer period than patients with *H. pylori*-positive PUD (p<0.001).

2. Follow-up and ulcer recurrence

Table 2 shows analysis of follow-up and ulcer recurrence in the three groups. The follow-up duration of NSAIDs-induced PUD group was longer than that of *H. pylori*-positive PUD group (p<0.001). IPUD group had more follow-up endoscopies than *H. pylori*-positive PUD group (p=0.009). During follow-

Table 1. Baseline Clinical Characteristics of 238 Patients with Peptic Ulcer

Characteristic	*H. pylori* PUD	NSAIDs PUD	Idiopathic PUD	p-value
No.	122	60	56	
Age, median, yr	55.5	66.0	60.5	<0.001[*,†]
Male	86 (70.5)	34 (56.7)	36 (64.3)	0.178
No. of comorbid disease				<0.001[*,‡]
≤1	108 (88.5)	35 (58.3)	46 (82.1)	
≥2	14 (11.5)	25 (41.7)	10 (17.9)	
Ulcer location				<0.001[*,§]
Gastric ulcer	69 (56.6)	48 (80.0)	48 (85.7)	
Duodenal ulcer	53 (43.4)	12 (20.0)	8 (14.3)	
Ulcer stage				0.646
Active stage	61 (50.0)	30 (50.0)	32 (57.1)	
Healing stage	61 (50.0)	30 (50.0)	24 (42.9)	
No. of ulcer				0.285
Single	97 (79.5)	42 (70.0)	40 (71.4)	
Multiple	25 (20.5)	18 (30.0)	16 (28.6)	
Medication for ulcer treatment				0.306
PPI	88 (72.7)	48 (80.0)	41 (73.2)	
H$_2$RA	28 (23.1)	7 (11.7)	12 (21.4)	
No treatment	5 (4.1)	5 (8.3)	2 (3.6)	
Duration of ulcer treatment, median, wk	7	8	10	0.002[*,‖]

Data are presented as number (%).
PUD, peptic ulcer disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; H$_2$RA, H$_2$ receptor antagonist.
*Indicates statistical significance; [†]p<0.001 (*Helicobacter pylori* PUD vs NSAID PUD, post-hoc analysis); [‡]p<0.001/p=0.005 (NSAID PUD vs *H. pylori* PUD/idiopathic PUD, post-hoc analysis); [§]p=0.002/p<0.001 (*H. pylori* PUD vs NSAID PUD/idiopathic PUD, post-hoc analysis); [‖]p<0.001 (*H. pylori* PUD vs idiopathic PUD, post-hoc analysis).

Table 2. Analysis of Follow-Up and Ulcer Recurrence in the Three Groups

	H. pylori PUD	NSAIDs PUD	Idiopathic PUD	p-value
Duration of F/U, median, mo	46	57	53	<0.001[*,†]
No. of additional endoscopy during F/U, median	1	1	2.0	0.019[*,‡]
No. of ulcer recurrence	5 (4.1)	7 (11.7)	13 (23.2)	
Location of ulcer recurrence				0.544
Gastric ulcer	3 (60.0)	6 (85.7)	11 (84.6)	
Duodenal ulcer	2 (40.0)	1 (14.3)	2 (15.4)	

Data are presented as number (%).
PUD, peptic ulcer disease; NSAID, nonsteroidal anti-inflammatory drug; F/U, follow-up.
*Indicates statistical significance; [†]p<0.001 (*H. pylori* PUD vs NSAID PUD, post-hoc analysis); [‡]p=0.009 (*H. pylori* PUD vs idiopathic PUD, post-hoc analysis).

up period, recurrent ulcer was confirmed by endoscopy in the 25 patients (10.5%); the ulcer recurrence rates in the *H. pylori*-positive, NSAIDs-induced, and IPUD groups were 4.1%, 11.7%, and 23.2%, respectively.

In the *H. pylori*-positive PUD group, eradication of *H. pylori* was confirmed in 85 patients (69.7%) (Fig. 1). However, four individuals among these patients newly started to take NSAIDs during follow-up period. In the NSAIDs-induced PUD group, 38

patients (63.3%) continued the medication, and seven patients (18.4%) of these 38 patients took preventive PPIs or H$_2$RAs concurrently more than 50% of the period in which the patients took NSAIDs. In the IPUD group, 82.1% of patients neither had a new infection of *H. pylori* nor newly started to take NSAIDs.

The 5-year cumulative incidence of recurrent ulcer was 24.3% (95% confidence interval [CI], 11.6% to 37.0%) in the IPUD group, 10.9% (95% CI, 2.6% to 19.2%) in the NSAIDs-induced
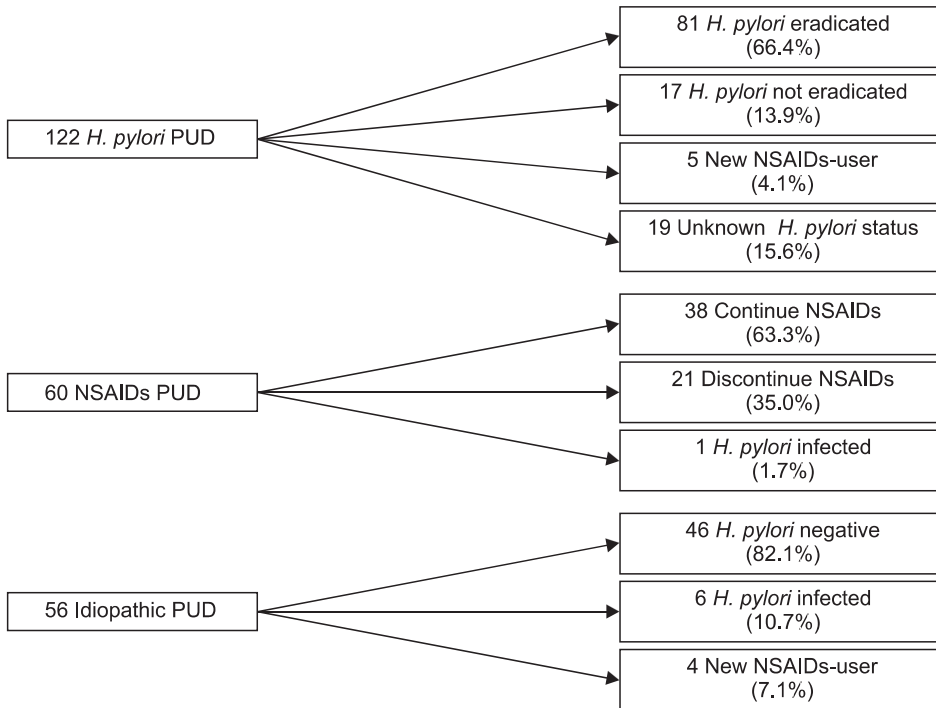
| 81 *H. pylori* eradicated (66.4%) |
| 17 *H. pylori* not eradicated (13.9%) |
| 5 New NSAIDs-user (4.1%) |
| 19 Unknown *H. pylori* status (15.6%) |

122 *H. pylori* PUD

| 38 Continue NSAIDs (63.3%) |
| 21 Discontinue NSAIDs (35.0%) |
| 1 *H. pylori* infected (1.7%) |

60 NSAIDs PUD

| 46 *H. pylori* negative (82.1%) |
| 6 *H. pylori* infected (10.7%) |
| 4 New NSAIDs-user (7.1%) |

56 Idiopathic PUD

Fig. 1. The end status of the three peptic ulcer disease (PUD) groups at the point of censoring.
NSAID, nonsteroidal anti-inflammatory drug.

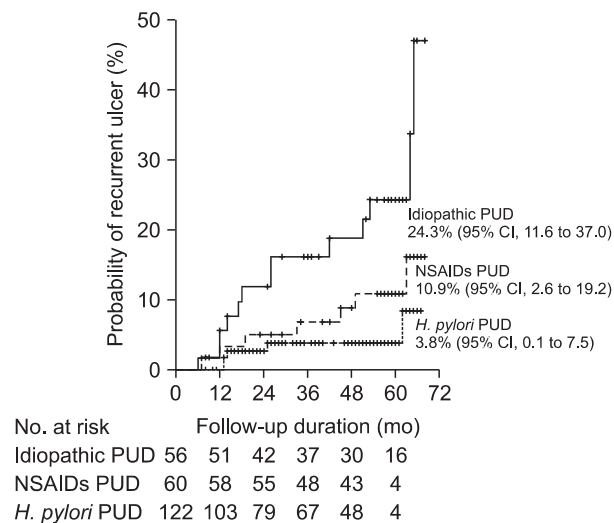| No. at risk | Follow-up duration (mo) |
Idiopathic PUD	56	51	42	37	30	16
NSAIDs PUD	60	58	55	48	43	4
H. pylori PUD	122	103	79	67	48	4

Fig. 2. Kaplan-Meier estimates of 5-year cumulative probabilities of recurrent peptic ulcer in the three peptic ulcers disease (PUD) groups. CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug.

Table 3. Analysis of Risk Factors for Ulcer Recurrence with a Cox-Proportional Hazards Model in the Patients with Peptic Ulcers

Variable	OR	95% CI	p-value
Male	2.28	0.90–5.79	0.084
Age ≥60 yr	1.05	0.47–2.37	0.905
No. of comorbid diseases ≥2	1.92	0.80–4.63	0.147
Ulcer in the stomach	0.76	0.29–2.01	0.582
Duration of ulcer treatment <9 wk	0.76	0.33–1.77	0.525
NSAIDs PUD	1.99	0.58–6.76	0.273
Idiopathic PUD	5.97	1.94–18.34	0.002*

OR, odds ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; PUD, peptic ulcer disease.
*Indicates statistical significance.

Table 4. Causes of Recurrent Ulcers in the Three Groups

	H. pylori PUD	NSAIDs PUD	Idiopathic PUD
H. pylori infection	2	0	4
NSAIDs use	1	5	2
Idiopathic	2	2	7
Total	5	7	13

Data are presented as number.
H. pylori, *Helicobacter pylori*; PUD, peptic ulcer disease; NSAID, nonsteroidal anti-inflammatory drug.

PUD group, and 3.8% (95% CI, 0.1% to 7.5%) in the *H. pylori*-positive PUD group, respectively (Fig. 2). The differences between IPUD group and other PUD groups were significant (IPUD vs *H. pylori*-positive PUD and NSAIDs-induced PUD, p<0.001 and p=0.43 by log-rank test). After adjusting for possible confounding covariates including age, sex, number of comorbid diseases, location of ulcer, and duration of ulcer treatment in the Cox-proportional hazards model, only IPUD remained an independent risk factor associated with recurrent ulcer (hazard ratio, 5.97; 95% CI, 1.94 to 18.34; p=0.002) in relation to *H.*

pylori-positive PUD (Table 3).

Among five patients with recurrent ulcer in the *H. pylori*-positive PUD group, *H. pylori* was not eradicated in two patients,
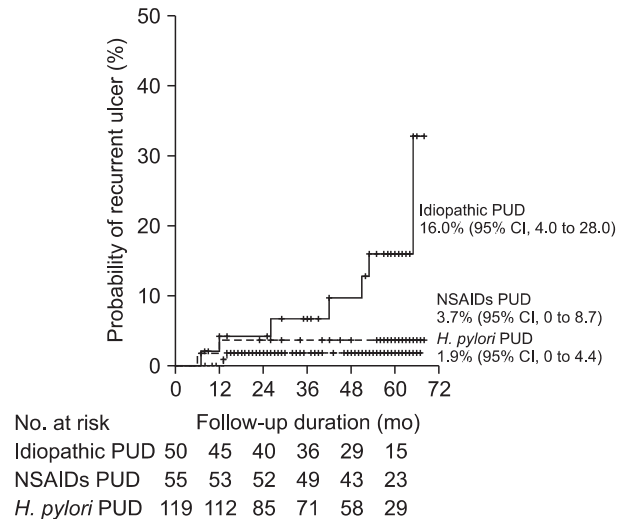
Fig. 3. Kaplan-Meier estimates of 5-year cumulative probabilities of recurrent peptic ulcers after excluding recurrent ulcers associated with nonsteroidal anti-inflammatory drug (NSAID) use or *Helicobacter pylori* infection in the three peptic ulcer disease (PUD) groups. CI, confidence interval.

and one patient used NSAIDs (Table 4). Among seven patients with recurrent ulcer in the NSAIDs-induced PUD group, none of them were newly infected with *H. pylori*, but five patients continued to use NSAIDs. Among 13 patients with recurrent ulcer in the IPUD group, four patients were positive for *H. pylori* and two patients used NSAIDs during follow-up. After excluding 14 recurrent ulcer associated with NSAIDs use or *H. pylori* infection, 5-year cumulative incidence of recurrent ulcer in the three groups was re-estimated by Kaplan-Meier method (Fig. 3). The 5-year cumulative incidence of recurrent ulcer was 16.0% (95% CI, 4.0 to 28.0) in the IPUD group, 3.7% (95% CI, 0 to 8.7) in the NSAIDs-induced PUD group, and 1.9% (95% CI, 0 to 4.4) in the *H. pylori*-positive PUD group, respectively. The differences between IPUD group and other PUD groups were significant (IPUD vs *H. pylori*-positive PUD and NSAIDs-induced PUD, p=0.003 and p=0.036 by log-rank test).

DISCUSSION

Our study indicates that the long-term recurrence rate of IPUD is significantly higher than NSAIDs-induced PUD as well as *H. pylori*-positive PUD, which corresponds with the results of earlier studies in patients with peptic ulcer bleeding.[6,7] In addition, contrary to previous studies,[7,12] the patients with IPUD were not older than the patients with *H. pylori*-positive PUD, and IPUD was the only independent risk factor for recurrent ulcer after adjusting for possible confounding covariates including age.

The clinical importance of management of IPUD has recently been highlighted with the increasing prevalence and high recurrence rate.[6,7,13] However, there is no established guideline of management for IPUD at the present time.[14-16] This stems from the fact that we do not know the exact pathophysiology of IPUD. The development of a peptic ulcer has been classically explained by the balance of defensive and aggressive forces acting on the gastric mucosa.[15,17] Therefore, collapse of this balance in unknown etiology has been postulated as the cause of IPUD. The possible causes of IPUD are hypergastrinemia, gastric acid hypersecretion, or rapid gastric empting.[15,18,19] However, some controversies have existed concerning these hypotheses.[16,20] Furthermore, these hypotheses cannot explain development of gastric ulcer. The main treatment of IPUD, nevertheless, is antisecretory drugs such as PPIs similar to treatment of *H. pylori*-positive PUD and NSAIDs-induced PUD. On the basis of decreased effect of antisecretory drugs without *H. pylori* infection,[21,22] some authors have suggested that a prolonged course or even maintenance therapy of antisecretory drugs for management of IPUD.[15,23,24] However, there are so far no prospective studies evaluating the efficacy of antisecretory drugs in the management of IPUD. In addition, in the present study, although patients with IPUD were treated for a longer period than patients with *H. pylori*-positive PUD, recurrence rate of ulcer was significantly higher in patients with IPUD. Therefore, further studies are needed to determine the optimal dose, duration of treatment, and necessity of maintenance therapy of antisecretory drugs for the prevention of idiopathic peptic ulcer recurrence.

Among the 81 patients in *H. pylori*-positive PUD group in whom eradication of *H. pylori* was confirmed and who did not take NSAIDs during follow-up period, two patients (2.5%) had recurrence of ulcer. This finding is consistent with the result of earlier study which reported that about 3% of *H. pylori*-eradicated patients had a relapse of ulcer during up to 4 years.[25] In addition, among the 21 patients in NSAIDs-induced PUD group who discontinued NSAIDs and did not have a new infection of *H. pylori* during follow-up period, two patients (9.5%) had recurrence of ulcer. Therefore, there is the possibility that *H. pylori* infection or NSAIDs use may not be the primary cause of peptic ulcer in some patients. Interestingly, although two-thirds of NSAIDs-induced PUD patients could not discontinue NSAIDs and only one-fifth of patients who continued to use NSAIDs took preventive antisecretory drugs during follow-up period as recommended by recent guideline,[26] the rate of ulcer recurrence in the NSAIDs-induced PUD group was significantly lower than that in the IPUD group. This result suggests that prognosis of IPUD may be poorer than that of NSAIDs-induced PUD.

To diagnose IPUD, the most important clinical point is to adequately ensure that other causes should be ruled out.[27] Because *H. pylori*-infection status was determined only by rapid urease test without histologic evaluation in 14.3% (8/56) of IPUD group, it may be difficult to completely exclude the possibility that *H. pylori*-positive patients might be included in the IPUD group. However, to minimize a possibility of false negative results of

rapid urease test, we excluded patients who took antibiotics or PPIs in the preceding 4 weeks from the study. In addition, although the status of *H. pylori* infection was re-examined by histology, rapid urease test or urea breath test at least once during follow-up in 33.9% (19/56) of the IPUD group, the results were still all negative. Another concern is the possibility that some of IPUD group might have been surreptitious NSAIDs users. However, because NSAIDs are not over-the-counter drugs in Korea, it is difficult for patients to take arbitrarily these drugs. In an epidemiologic study which was prospectively conducted in Korean patients at around the same time, although the methods for detection of *H. pylori* infection and NSAIDs use are more robust than ours, the proportion of IPUD (22.2%) in PUD was similar to our result (25.7%).[4] This suggests that the rate of IPUD was not overestimated in the present study. Finally, because this study was conducted in a tertiary referral center and median follow-up duration of the IPUD group was 52 months, there is little possibility that other causes of peptic ulcer were missed. For example, it has been known that patients with Zollinger-Ellison syndrome are properly diagnosed on the average after 5 years of follow-up.[28] Furthermore, because Zollinger-Ellison syndrome is a very rare disease of which the incidence is less than 1% of patients with PUD,[29] the probability is very low that patient with this disease was included among patients of the present study.

In conclusion, long-term recurrence rate of IPUD were significantly higher than NSAIDs-induced PUD as well as *H. pylori*-positive PUD, and IPUD was an independent risk factor associated with recurrent ulcer.

CONFLICTS OF INTEREST

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

ACKNOWLEDGEMENTS

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