ORIGINAL ARTICLE

Long-Term Recurrence Rates of Peptic Ulcers without *Helicobacter pylori*

Jae Hyun Seo[1], Su Jin Hong[2], Jie-Hyun Kim[3], Byung-Wook Kim[1], Sam Ryong Jee[4], Woo Chul Chung[1], Ki-Nam Shim[5], Gwang Ho Baik[6], Sung Soo Kim[1], Sang Gyun Kim[7], and Jin Il Kim[1]

[1]Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, [2]Department of Internal Medicine, Digestive Disease Center and Research Institute, Soonchunhyang University College of Medicine, Bucheon, [3]Division of Gastroenterology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, [4]Department of Internal Medicine, Inje University Busan Paik Hospital, Inje University College of Medicine, Busan, [5]Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, [6]Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, and [7]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

Background/Aims: The purpose of this study is to investigate the recurrence rate of peptic ulcer disease (PUD) over a long follow-up period with PUD patients without *Helicobacter pylori*. **Methods:** We retrospectively reviewed patients diagnosed with PUD on endoscopy and divided them into two groups: a *H. pylori*-negative group (HP-negative group), and a group of patients with untreated *H. pylori* (HP noneradicated group). We compared the recurrence rates of PUD in these two groups and analyzed the factors that affected ulcer recurrence. **Results:** Total of nine hospitals in Korea participated, and a total of 1,761 patients were retrospectively reviewed. The HP-negative group included 553 patients, and the HP noneradicated group included 372 patients. The 5-year cumulative probabilities of PUD recurrence were 36.4% in the HP-negative group and 43.8% in the HP noneradicated group (p=0.113). The factors that were found to affect recurrence in the HP-negative group were elder, male, and comorbid chronic kidney disease. **Conclusions:** The 5-year cumulative probability of PUD recurrence without *H. pylori* infection after a long-term follow-up was 36.4% and the factors that affected recurrence were elder, male, and comorbid chronic kidney disease. **(Gut Liver 2016;10:719-725)**

Key Words: Natural course; *Helicobacter* negative; Peptic ulcer disease

INTRODUCTION

The most important cause of peptic ulcer disease (PUD) is *Helicobacter pylori* infection.[1,2] Eradiating *H. pylori* aids PUD treatment and effectively reduces recurrence.[3,4] The important causes of PUD other than *H. pylori* are gastric acid and drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most important drugs, and antiplatelet agents, such as aspirin and steroids, are also considered to be possible causes of PUD.[5,6] Many factors other than *H. pylori* and NSAIDs affect PUD, but the influences of these factors are insignificant relative to *H. pylori* and NSAIDs. The successful eradication of *H. pylori* is the most important factor affecting the recurrence of PUD, although drugs, age, and the presence of chronic disease also affect recurrence.[7-9]

The recurrence rate of PUD with *H. pylori* infection decreases when *H. pylori* is successfully eradicated. Although the results vary between studies, the 5-year cumulative recurrence rate of PUD is below 5% if there is no risk factor due to NSAIDs and *H. pylori* is eradiated.[10-12] There is a randomized controlled study with a 2-year follow-up of peptic ulcers without *H. pylori* infection, but this study does not mention recurrence because it was limited to duodenal ulcers, and the total number of enrolled patients was too small.[13] The factors that affect the recurrence rate of peptic ulcers without *H. pylori* infection have not yet been studied.

Idiopathic peptic ulcer disease (IPUD) is defined by the presence of peptic ulcer without clear causes, such as *H. pylori*, NSAIDs, and hypergastrinemia. The incidence of IPUD varies from 1.3% to 27% due to variations in the *H. pylori* infection rate across different localities.[14,15] Recently, the *H. pylori* infection rates have decreased in Korea, while the IPUD rates have increased. The clinical aspects of IPUD are more severe than PUD due to *H. pylori* and NSAIDs, and the recurrence rate is

higher.[12,16-18] Moreover, the mortality and the risk of recurrent bleeding due to idiopathic bleeding ulcers are higher.[19]

The 5-year cumulative recurrence rate of IPUD was reported to be 24.3% in recent study, and this result is significantly higher than those for NSAIDs-induced PUD and eradicated *H. pylori*-positive PUD.[12] The long-term recurrence rate of PUD without *H. pylori* due to drug effects is assumed to be high; however, the evidence surrounding this issue is currently insufficient. *H. pylori* infection can be easily detected by several methods in PUD patients. However, smoking, alcohol, underlying disease, and drug history are frequently neglected or unknown. Although drug is a definite risk factor of PUD, because the duration and amount of drug are various, it is difficult to quantify its effect. Therefore, it is important to consider *H. pylori* infection status, the most effective and accurate measurable factor, as a predictive factor of PUD recurrence rate. In the present study, we investigate the recurrence rate of PUD in a long-term follow-up of a cohort with PUD without *H. pylori*. To investigate the effects of *H. pylori* on the recurrence of PUD, we also examined the recurrence rate in *H. pylori*-positive PUD without eradication treatment. It is a well-known fact that *H. pylori* infection affects ulcer recurrence. However, our study focused on the recurrence rate of *H. pylori* negative ulcers. Additionally, we studied the patients' drug histories and underlying diseases to identify the factors that affected the recurrence of PUD without *H. pylori* infection.

MATERIALS AND METHODS

1. Patients

We studied PUD recurrence in patients who were diagnosed PUD based on esophagogastroduodenoscopy (EGD) in 2005 and attended more than one follow-up visit. Total of nine hospitals in Korea participated, and a total of 1,761 patients were retrospectively reviewed. PUD was defined by the presence of an ulcer larger than 5 mm including all active-, healing-, and scar-stage tissue. We excluded 242 patients who were initially diagnosed with PUD and followed up with EGD earlier than 6 months after the initial diagnosis because it was unclear whether the disease was untreated or recurrent in these cases. We excluded 449 patients with histories of *H. pylori* eradication and 54 patients with histories of partial gastrectomies, malignant ulcers, or malignancy within 5 years. We also excluded patients whose histories of smoking and alcohol use or underlying disease and drug histories were unclear. Ultimately, total 925 patients were enrolled this study.

Recurrent PUD was defined by the presence of an active-, healing-, or scar-stage ulcer in the stomach or duodenum 6 months after the initial diagnosis. The location, stage, number, *H. pylori* infection status, and drug history were reviewed when recurrent PUD was identified. To discount untreated PUD, we excluded patients with scar-stage ulcers at the same locations as the initial events from the recurrent PUD group.

This study was approved by the Institutional Review Board at The Catholic University of Korea (SC10RCME0191).

2. Characteristics and etiologic categorization of PUD

The locations, stages, and numbers of PUDs were investigated. When a PUD was confirmed on EGD, we also determined the *H. pylori* infection status based on more than one of the following: biopsy, rapid urease test (CLO test), and urea breath test. Once the *H. pylori* infection was confirmed, we checked for eradication. We also identified the smoking and alcohol consumption statuses, chronic diseases (cardiovascular, cerebrovascular, renal, liver, and pulmonary), and the possible association with PUD. The drugs that were considered risk factors (i.e., NSAIDs, aspirin, antiplatelet, and steroid) or protective (i.e., antacids, histamine 2 receptor antagonists, proton pump inhibitors, and mucoprotective agents) were verified.

Table 1. Baseline Clinical Characteristics of the 925 Patients with Peptic Ulcer Disease

Characteristic	HP-negative	HP noneradicated	p-value
Number	553	372	–
Age, yr	58.5±13.7	55.5±12.7	<0.001
Male	299 (54.1)	222 (59.7)	0.092
Ulcer location			0.709
Gastric ulcer	345 (62.4)	222 (59.7)	
Duodenal ulcer	158 (28.6)	114 (30.7)	
Gastric+duodenal	50 (9)	36 (9.7)	
Ulcer stage			0.017
Active stage	202 (36.5)	116 (31.2)	
Healing stage	199 (36.0)	173 (46.5)	
Scar stage	144 (26.0)	78 (21.0)	
Multiple stage	8 (1.4)	5 (1.3)	
No. of ulcer			0.239
Single	486 (87.9)	317 (85.2)	
Multiple	67 (12.1)	55 (14.8)	
Smoking	82 (14.9)	68 (18.3)	0.166
Alcohol	117 (21.2)	69 (18.6)	0.325
Drug			
NSAIDs	28 (5.1)	23 (6.2)	0.465
Aspirin	55 (10.0)	49 (13.2)	0.128
Antiplatelet	19 (3.4)	19 (5.1)	0.209
Steroid	15 (2.7)	4 (1.1)	0.085
No. of comorbid disease			0.655
0	369 (66.7)	247 (66.4)	
1	147 (26.6)	105 (28.2)	
≥2	37 (6.7)	20 (5.4)	

Data are presented as number (%) or mean±SD.
HP, *Helicobacter pylori*; NSAID, nonsteroidal anti-inflammatory drug.

The patients were divided into the following two groups: (1) a *H. pylori*-negative group (HP-negative group) and (2) an untreated *H. pylori*-positive group (HP noneradicated group).

3. Statistical analysis

The statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA). The baseline clinical characteristics of the patients and the analyses of ulcer recurrence are presented as descriptive data. The continuous variables of the two groups are presented as the means±the standard deviations and were tested with analyses of variance. The median values are presented for the variables that failed tests of normality, and the Kruskal-Wallis tests were applied to these variables. For the category-type variables, the ns (%) are presented, and chi-square and Fisher tests were applied. The cumulative probabilities of ulcer recurrence were estimated with the Kaplan-Meier method. The log-rank test was used to compare the time-to-event curves of the two groups. Cox-proportional hazards model analyses were conducted to investigate the relationships of the recurrence of *H. pylori*-negative ulcers with the risk factors. The hazard ratios and 95% confidence intervals were estimated after adjusting for age. The variables with p-values <0.15 in the age-adjusted analyses were selected for the multivariate analyses. The p-values <0.05 were considered statistically significant.

RESULTS

1. Baseline clinical characteristics

Among the 925 patients, 553 were included in the HP-negative group, and 372 were included in the HP noneradicated group (Table 1). The median age at the diagnosis of PUD of the HP-negative group was 58.5±13.7, which was greater than that of the noneradiated group (55.5±12.7, p<0.001). There were no differences between the two groups in terms of the other baseline characteristics.

2. Analysis of follow-up

The mean follow-up duration in the HP-negative group was 962 days, and the mean number of follow-up endoscopic procedures was 1.54 (Table 2). The mean follow-up duration in the HP noneradicated group was 1,028 days and the mean number of follow-up endoscopy procedures was 1.53.

Table 2. Analysis of the Follow-up Data and Ulcer Recurrence of the Two Groups

|	HP-negative	HP noneradicated	p-value
Duration of F/U, day*	962 (400–1,620)	1,028 (503–1,568)	0.274
Age of ulcer recurrence patient	63.2±14.3	56.5±14.0	<0.001
Ulcer recurrence rate	137 (24.8)	115 (30.9)	0.040
No. of additional endoscopy during F/U	1.54±0.76	1.53±0.76	0.813
Sex (male) of ulcer recurrence patient	82 (60.0)	79 (68.7)	0.146
Duration of ulcer recurrence*	518 (310–1,091)	685 (366–1,259)	0.238
No. of ulcer recurrence			0.097
0	416 (75.2)	257 (69.1)	
1	123 (22.2)	102 (27.4)	
2	10 (1.8)	12 (3.2)	
3	4 (0.7)	1 (0.3)	
Ulcer stage at recurrence			0.307
Active stage	41 (29.9)	36 (31.3)	
Healing stage	62 (45.3)	56 (48.7)	
Scar stage	34 (24.8)	21 (18.3)	
Multiple	0	2 (1.7)	
Gastric → gastric	73 (53.3)	61 (53)	0.688
Gastric → duodenal	20 (14.6)	14 (12.2)	
Duodenal → duodenal	20 (14.6)	23 (20)	
Duodenal → gastric	14 (10.2)	12 (10.4)	
Multiple	10 (7.3)	5 (4.4)	

Data are presented as number (%) or mean±SD.
HP, *Helicobacter pylori*; F/U, follow-up.
*Data are presented as median.

3. Ulcer recurrence

The PUD patients were older because the HP-negative group was older in the baseline study. The rate of ulcer recurrence in the HP-negative group was 24.8%, which was significantly lower than that in the HP noneradicated group (p=0.040). The mean PUD recurrence duration in the HP-negative group was 518 days. Males accounted for more than 60% of both groups,
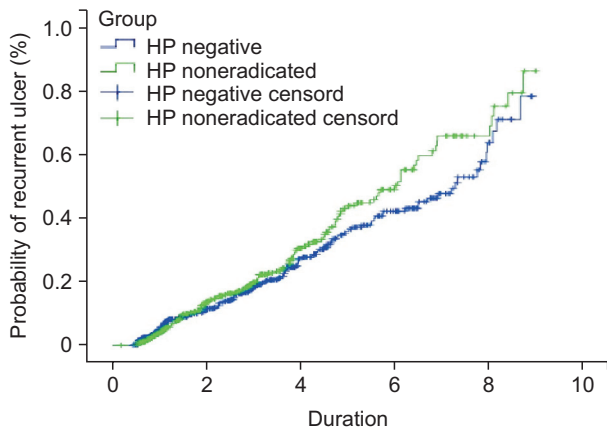
Fig. 1. Kaplan-Meier estimates of the 5-year cumulative probabilities (95% confidence interval) and comparison of the recurrence of peptic ulcers in the two groups using a log-rank test.

and these proportions were higher than those of the baseline study.

In the HP-negative group, 24.8% of the patients experienced only one recurrence event, and 2.5% of the patients experienced more than two recurrence events. The most common stage of the recurrent ulcers was the healing stage (45.5%) followed by the active (29.5%) and scar stages (25%) with similar proportions. The location (i.e., stomach or duodenum) of the recurrent PUD was the same as the original ulcer in 67.9% of the patients, and the majority of recurrence events were single ulcers (81.7%).

The 5-year cumulative probabilities of PUD recurrence in the *H. pylori*-negative group and noneradicated groups were 36.4% and 43.8%, respectively (p=0.113). The difference of recurrence rate between of *H. pylori* negative to positive is no more than 2% until 3 year follow-up. However, the difference of recurrence becomes bigger when we follow the patients more than 3 years (Fig. 1).

4. Ulcerogenic factors

Multivariate logistic regression analyses were performed to identify the factors that affected PUD without *H. pylori* infection (Table 3). Elder, male, and comorbid chronic kidney (CKD) disease were found to be risk factors. Smoking, alcohol, drugs, and other comorbid chronic diseases did not affect recurrence. The number of comorbid chronic disease did not affect recurrence.

Table 3. Multivariate Logistic Regression Analyses of the Risk Factors for Ulcer Recurrence in the Patients with *Helicobacter pylori*-Negative Peptic Ulcers

	Age adjusted HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Age, yr	1.033 (1.018–1.047)	<0.001	1.031 (1.017–1.046)	<0.001
Male sex	1.627 (1.151–2.299)	0.006	1.519 (1.027–2.247)	0.036
Smoking	1.539 (0.988–2.396)	0.057	1.453 (0.885–2.385)	0.140
Alcohol	1.142 (0.755–1.728)	0.530	–	–
NSAIDs	1.302 (0.655–2.590)	0.452	–	–
Aspirin	0.943 (0.519–1.713)	0.846	–	–
Antiplatelet	0.502 (0.159–1.587)	0.241	–	–
Anticoagulation	2.355 (0.578–9.597)	0.232	–	–
Steroid	1.711 (0.796–3.678)	0.169	–	–
No. of comorbid disease	–	0.468	–	–
Cardiovascular	1.154 (0.788–1.688)	0.462	–	–
Cerebrovascular	0.733 (0.268–2.005)	0.545	–	–
Liver	1.154 (0.668–1.992)	0.608	–	–
Renal	2.057 (1.214–3.485)	0.007	2.026 (1.167–3.516)	0.012
Pulmonary	0.617 (0.225–1.69)	0.348	–	–
Antacids	1.703 (1.187–2.444)	0.004	1.547 (0.988–2.422)	0.057
H2 receptor antagonists	1.461 (0.995–2.145)	0.053	1.297 (0.834–2.017)	0.249
Proton pump inhibitors	1.362 (0.95–1.954)	0.093	1.063 (0.694–1.63)	0.778
Mucoprotective agent	1.301 (0.892–1.897)	0.172	–	–

HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs.

DISCUSSION

As *H. pylori* infection is the most important factor in the development of PUD, *H. pylori* eradication can reduce the rate of PUD development. Various factors, including NSAIDs, can cause *H. pylori*-negative PUD. Various factors not only include modifiable factors, such as drug and smoking, but also nonmodifiable host factors, such as age, sex, and chronic comorbid disease. It is important to predict the recurrence rate of *H. pylori*-negative PUD by these various factors, especially in countries where *H. pylori* infection rate is low.

This study retrospectively reviewed patients with PUD during 962 days, in average, up to 10 years to investigate the recurrence rate of PUD without *H. pylori* infection and the associated risk factor. The *H. pylori*-positive infection rate at baseline was 60.3%, which is similar to the previously reported *H. pylori* infection rates in Korea.[9] The recurrence rate of PUD without *H. pylori* infection was higher, and the symptoms were more severe compared with the results of a previous study that investigated *H. pylori*-positive PUD patients who had undergone eradication.[13] However, the interpretation of the recurrence rate reported in that study is limited because the total number of enrolled patients was too small. In the present study, 24.8% of the 553 patients with PUD without *H. pylori* infection experienced recurrence, and the 5-year cumulative probability of recurrence was 36.4%. The 5-year cumulative recurrence rate of idiopathic ulcers has previously been reported to be 24.3%, which is lower than the rate observed in the present study.[12] There are three possible interpretations of this difference in recurrence rates. The first involves the possible effects of drugs, including NSAIDs, on PUDs, in patients without *H. pylori* infection. The second involves the calculations of the recurrence rates; unlike the other study, we included the scar-stage of PUDs that were present 6 months after the initial diagnoses in the calculation of the recurrence rate. The inclusion of scar-stage ulcers in recurrence is controversial. Depending on the investigator, there is a wide variation regarding this issue. Normal findings can be mistaken for scar-stage ulcers, and scars from previous PUD can be mistaken for recurrent ulcers. However, it is difficult to determine whether recurrence has occurred because small PUDs with nonsevere mucosal defects have no symptoms and without bleeding or symptoms can be mistaken for other diseases.[20] The majority of PUD cases are cured within 6 months; thus, it is appropriate to include scar-stage ulcers present 6 months after the initial diagnosis in the recurrence rate calculation. The third involves that we almost all diagnosed *H. pylori* using one single method. Because of these conditions, it may be possible that ulcers that were diagnosed as *H. pylori* negative may actually were *H. pylori* positive. As a consequence, the recurrence rate may has been measured higher than that of other previous report. To complement these data, we studied in a large number of patients, more than 900.

The location (i.e., stomach or duodenum) of the recurrent PUD was the same as the original ulcer in 67.9% of the patients. 83.9% of *H. pylori*-positive PUD had PUD recurrence at the same location after eradication therapy.[8] Although the mechanism between stomach and duodenum ulcer development is different, *H. pylori* plays an important role in both cases. The reason why the percentage of recurrent PUD at different location is more than 30% higher in *H. pylori*-negative PUD is because other risk factors, besides *H. pylori*, react through various pathways at different locations.

As mentioned above, it is difficult to quantify the effect of other PUD risk factors. However, it is certain that risk factors other than *H. pylori* and including NSAIDs, play an important role in *H. pylori*-negative PUD. In this study, we examined the factors that affect the recurrence of *H. pylori*-negative PUD. Age, sex (male), and comorbid CKD were the risk factors, which were all nonmodifiable factors. Modifiable factors, such as smoking and drug were not risk factors of recurrence.

Age is an important factor in the occurrence and recurrence of PUD regardless of *H. pylori* infection.[7,9] With aging, the blood supply to the gastric mucosa decreases, prostaglandin levels decrease, and mucosal defense weakens. These factors are known to be mechanisms of ulcer development. In previous research, patients with PUD without *H. pylori* infection have been found to be older,[18,21-24] and the mean age of the PUD patients without *H. pylori* infection patients was greater than that of the *H. pylori*-positive patients at both baseline and recurrence in the present study. *H. pylori* is the most important cause of ulcer development in PUD with *H. pylori* infection, and the weakening of the gastric mucosal defense cause of recurrence. Therefore, the PUD recurrence rate of older PUD without *H. pylori* infection patients is high, and more active treatment and follow-up is necessary for these patients.

In addition to age, the male sex and the presence of CKD are related to PUD recurrence. In Korea, although male was a risk factor of PUD development, it was not related recurrence.[9] However, in this study, male was also a risk factor of recurrence in *H. pylori*-negative PUD. Although the mechanism that CKD develops PUD is not known, increased gastrin level and gastric acid hypersecretion may be relevant to the pathology. In other studies, the *H. pylori* infection rate among PUD patients with CKD has been found to be lower than that of non-CKD patients.[25] Based on these studies, the ulcerative effect of CKD is presumable more dramatic in *H. pylori*-negative patients than *H. pylori*-positive patients. In this study, we did not divide CKD by stages. It would be helpful to confirm ulcerogenic effect of CKD by investigating the relationship between PUD and CKD stages.

In the present study, the other possible causes of *H. pylori*-negative PUD, such as smoking, alcohol use, and comorbid diseases other than CKD, were not found to be related to recurrence.

The most important causes of PUD without *H. pylori* are

NSAIDs and aspirin. NSAIDs reduce the synthesis of prostaglandins and cause toxic injury by inhibiting cyclooxygenase 1 (COX-1). In the present study, ulcer-aggravating drugs (i.e., NSAIDs, aspirin, steroids, and antiplatelet drugs) were not found to affect PUD recurrence because the drug histories were reviewed at the baseline time point and not at the time point of recurrence or because the patients with NSAID-induced PUD stopped taking NSAIDs or switched to cyclooxygenase 2 (COX-2) inhibitor medications.

Proton pump inhibitors are important drugs in the treatment of PUD, and the recurrence of PUD among NSAID-induced PUD patients who cannot stop taking NSAIDs can be reduced with proton pump inhibitors. In the present study, ulcer-protective drugs were investigated when recurrence occurred, but they were not found to affect the recurrence rate. We investigated whether the patients were taking such medicines, but the durations of medicine use were not accurately investigated. To investigate whether ulcer-protective drugs affect recurrence, the duration of the dosing period and the concomitant history of ulcer-aggravating drugs should be investigated.

The strengths of this study were that the total number of enrolled PUD patients without *H. pylori* infection (553) was greater than those in previous studies and the follow-up duration was a maximum of 10 years, which is longer than the follow-ups that have been employed in previous research.

The limitations of this research are the retrospective nature of the study and that endoscopic follow-ups were not performed. Endoscopic procedures were performed more frequently when symptoms were present, which might have affected the results. However, we overcame this limitation by including the scar-stage ulcers in the recurrence rate calculations. An additional shortcoming of this multicenter study is the fact that the diagnostic PUD criteria varied across the centers. The final limitation is that the durations of medicine use were unclear, which is a limitation in terms of the effects of ulcer-protective and aggravating drugs. Moreover, the recurrence rate of *H. pylori* negative ulcer may has been measured higher than other studies because we included the effect of ulcer aggravating drugs, whereas other studies eliminated these conditions. A prospective study is needed to accurately estimate the effect of drug in the recurrence of *H. pylori*-negative PUD.

In conclusion, the 5-year cumulative probability of PUD recurrence without *H. pylori* infection after a long-term follow-up was 36.4%, which is higher than that reported in a previous study, and the factors that affected recurrence were elder, male, and comorbid CKD.

CONFLICTS OF INTEREST

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

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