Helicobacter pylori Eradication within 120 Days Is Associated with Decreased Complicated Recurrent Peptic Ulcers in Peptic Ulcer Bleeding Patients

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Background/Aims: The connection between Helicobacter pylori and complicated peptic ulcer disease in peptic ulcer bleeding (PUB) patients taking nonsteroidal anti-inflammatory drugs has not been established. In this study, we sought to determine whether delayed Helicobacter pylori eradication therapy in PUB patients increases complicated recurrent peptic ulcers.

Methods: We identified inpatient PUB patients using the Taiwan National Health Insurance Research Database. We categorized patients into early (time lag ≤120 days after peptic ulcer diagnosis) and late H. pylori eradication therapy groups. The Cox proportional hazards model was used. The primary outcome was rehospitalization for patients with complicated recurrent peptic ulcers.

Results: Our data indicated that the late H. pylori eradication therapy group had a higher rate of complicated recurrent peptic ulcers (hazard ratio [HR], 1.52; p=0.006), with time lags of more than 120 days. However, our results indicated a similar risk of complicated recurrent peptic ulcers (HR, 1.20; p=0.275) in time lags of more than 1 year and (HR, 1.10; p=0.621) more than 2 years.

Conclusions: H. pylori eradication within 120 days was associated with decreased complicated recurrent peptic ulcers in patients with PUB. We recommend that H. pylori eradication should be conducted within 120 days in patients with PUB.

Key Words: Helicobacter pylori; Peptic ulcer hemorrhage; Delayed; Eradication

INTRODUCTION

Peptic ulcer bleeding (PUB) is the most common complication associated with peptic ulcer disease, and is the major cause of morbidity and mortality in patients with peptic ulcers. Understanding the role of Helicobacter pylori in the pathogenesis of PUB is crucial to the prevention of life-threatening upper-gastrointestinal hemorrhage. Approximately 85% to 95% of duodenal ulcer patients and up to 70% of gastric ulcer patients have concurrent H. pylori infections. It is well-recognized that H. pylori eradication therapy can reduce the recurrence of peptic ulcer. Hopkins et al. reported that the recurrence of peptic ulcers can be reduced from 70% to 10% or less following H. pylori eradication. However, acute PUB patients frequently test negative H. pylori infection, and Gisbert and Abraira reported that between 30% and 50% of PUB patients had false-negative results for H. pylori diagnostic testing. Moreover, false-negative test results contribute to delays in the initiation of H. pylori eradication therapy in many PUB patients.

Nonsteroidal anti-inflammatory drugs (NSAIDs) use is a risk factor of complicated peptic ulcer disease and the most common cause of H. pylori negative peptic ulcers. However, the connection between H. pylori and complicated peptic ulcer disease in PUB patients taking NSAIDs remains unclear and divergent. We want to explore whether delayed H. pylori eradication therapy in PUB patients increases the risk of complicated recurrent peptic ulcers with hemorrhages and/or perforations.

We selected patients who were endoscopically diagnosed with PUB and hospitalization in Taiwan between 2000 and 2010 from the National Health Insurance Research Database (NHIRD). Based on the date of their treatment, participants were assigned...
to an early or a late *H. pylori* eradication therapy group. We compared the clinical outcomes between the study groups to determine whether delayed *H. pylori* eradication therapy in PUB patients increased rehospitalization for the risk of complicated recurrent peptic ulcers.

**MATERIALS AND METHODS**

1. **Data source**

Our nationwide cohort study was based on patient data obtained from the NHIRD, which is managed by the National Health Research Institute (NHRI). The NHIRD contains outpatient and inpatient claim records from the National Health Insurance (NHI) system of Taiwan, which provides coverage for approximately 23 million residents (99% of the population) of Taiwan. The NHIRD files contain comprehensive health care and enrollment information for a randomly selected sample of one million NHI beneficiaries, representing approximately 5% of all enrollees in 2000. The diagnoses codes used in the NHI data were based on the International Classifications of Diseases, Revision 9, Clinical Modification (ICD-9-CM). Our study was approved by the NHRI. The Institutional Review Board (IRB) of Taipei City Hospital approved this study (IRB number: TCHIRB1020424-E).

2. **Participant selection**

We conducted a retrospective cohort study of patient records from January 1, 2000 to December 31, 2010. Based on inpatient discharge records, the PUB patients with endoscopic confirmation of the following ICD-9-CM diagnoses for the first time after January 1, 2000, were identified: 531.0; 531.2; 531.4; 531.6 (gastric ulcer with hemorrhages); 532.0; 532.2; 532.4; 532.6 (duodenal ulcer with hemorrhages); 533.0; 533.2; 533.4; and 533.6 (nonspecific peptic ulcer with hemorrhages). Patients under the age of 20 years, and patients with prior gastrectomies or vagotomies were excluded. We excluded patients who were diagnosed with gastric cancer or Zollinger-Ellison syndrome between January 1, 1997, and the index date of our study. Pa-

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**Fig. 1.** Flowchart depicting participant selection. NHI, National Health Insurance; PUB, peptic ulcer bleeding; PPI, proton pump inhibitor; *H. pylori*, *Helicobacter pylori*.
Patients who received _H. pylori_ eradication therapy between 1997 and 1999 were also excluded. Patients with cerebral vascular disease (CVD), liver cirrhosis (LC), and chronic kidney disease (CKD) showed significantly higher rehospitalization rate. In addition, there is a correlation between coexisting diseases and complicated recurrent peptic ulcers. Therefore, patients with CVD, LC, and CKD were excluded. Fig. 1 shows a flow chart containing the total patients included.

3. **Definitions of early and late _H. pylori_ eradication groups**

According to the reimbursement policy of the NHI, patients with an endoscopically confirmed diagnosis of peptic ulcers and concurrent laboratory verification of _H. pylori_ infection are reimbursed for 7 to 14 days of the _H. pylori_ eradication therapy. The diagnosis of _H. pylori_ infection in our study participants had been based on the results of a rapid urease test (RUT) or histological assessment using hematoxylin and eosin (H&E) staining. Measuring from the time of PUB diagnosis to the _H. pylori_ eradication therapy, we classified patients as being either in the early _H. pylori_ eradication therapy group (time lag ≤120 days after peptic ulcer diagnosis), or in the late _H. pylori_ eradication therapy group (time lag >120 days after peptic ulcer diagnosis). However the definition of time lag is arbitrary; therefore, we also analyzed the effects of time lag more than 1 year and more than 2 years. The _H. pylori_ eradication therapy using a triple or quadruple therapy that consists of proton pump inhibitors (PPIs), clarithromycin or tetracycline, amoxicillin or metronidazole, and bismuth or no bismuth.

4. **Definition of gastroduodenal ulcer history**

All endoscopically diagnosed gastroduodenal ulcers in patients from 1997 to the claim date of first PUB, based on ambulatory care and inpatient discharge records, are defined as having gastroduodenal ulcer history.

5. **Patient characteristics**

We recorded the age and sex of the patients. The locations of the endoscopically diagnosed PUB in each patient were recorded as gastric (531.0; 531.2; 531.4; 531.6), duodenal (532.0; 532.2; 532.4; 532.6), or nonspecific (533.0; 533.2; 533.4; 533.6). Patients were defined as users of PPIs, H₂-blockers, aspirin, NSAIDs, cyclooxygenase-2 (COX-2) specific inhibitors, steroids, clopidogrel, ticlopidine, and warfarin based on whether they had used at least one prescription of the respective medication within 28 days of the end date of the early or late _H. pylori_ eradication therapy period.

Conditions that required inpatient care or three or more ambulatory-care visits between January 1, 1997, and the index date of our study were defined as comorbidities. The comorbidities identified in our cohort and the corresponding ICD-9-CM diagnosis codes were as follows: diabetes mellitus (DM) ICD-9-CM: 250; congestive heart failure (CHF) ICD-9-CM: 428; coronary artery disease (CAD) ICD-9-CM: 410-414; CVD ICD-9-CM: 430-438; chronic obstructive pulmonary disease (COPD) ICD-9-CM: 491-492, 494, and 496; LC ICD-9-CM: 571.2, 571.5, and 571.6; and CKD ICD-9-CM: 580-589, 250.4, 274.1, 283.11, 403.1, 404.x2, 404.x3, 440.1, 442.1, 447.3, 572.4, 642.1x, 646.2x, and 794.4.

6. **Endpoint**

Based on inpatient discharge records, rehospitalization for complicated recurrent peptic ulcers with hemorrhages and/or perforations following endoscopic confirmation after _H. pylori_ eradication between 2000 and 2010 were defined using the following ICD-9-CM codes: 531.0; 531.1; 531.2; 531.4; 531.5; 531.6; 532.0; 532.1; 532.2; 532.4; 532.5; 532.6; 533.0; 533.1; 533.2; 533.4; 533.5; and 533.6.

7. **Statistical analysis**

Demographic data were expressed as categorical data and mean±standard deviation. The data for categorical variables are presented as percentages. We compared the differences between the early and late _H. pylori_ eradication therapy groups using a chi-square analysis. We calculated the hazard ratios (HR) based on a 95% confidence interval (CI) using a multivariate Cox regression analysis to compare the risk of rehospitalization for complicated recurrent peptic ulcers between the early and late _H. pylori_ eradication therapy groups. A p-value less than 0.05 was considered to indicate a statistically significant relationship. All statistical analyses were performed using the SAS statistical package version 9.2 (SAS Institute, Cary, NC, USA).

**RESULTS**

The early and late _H. pylori_ eradication therapy groups consisted of 1,256 and 664 PUB patients in time lag 120 days, respectively. The demographic data are presented in Table 1. A significantly lower percentage of patients in the early _H. pylori_ eradication therapy group used PPIs or H₂-blockers (p<0.001), and NSAIDs (p<0.001), than patients in the late _H. pylori_ eradication therapy group. The average follow-up duration is 5.47±3.22 years in early _H. pylori_ eradication therapy and 3.93±3.22 years in late _H. pylori_ eradication therapy (Table 1).

1. **Combined effects of _H. pylori_ eradication therapy and NSAID use for complicated peptic ulcers**

After adjusting for possible confounders, the results from Cox proportional hazards model analysis indicated that the late _H. pylori_ eradication therapy group had a higher rate for complicated recurrent peptic ulcers (HR, 1.52; 95% CI, 1.13 to 2.04; p=0.006, in time lag more than 120 days (Table 2), HR, 1.20; 95% CI, 0.87 to 1.66; p=0.275, in time lag more than 1 year (Table 3), and HR, 1.10; 95% CI, 0.75 to 1.62; p=0.621, in time lag more than 2 years (Table 3), compared with the early _H. pylori_ eradication therapy group. However, the latest effects of time lag were not significant (p=0.096, in time lag more than 120 days, and p=0.075, in time lag more than 1 year) (Table 2 and 3).
Table 1. Different Characteristics of Peptic Ulcer Bleeding Patients with Helicobacter pylori Eradication within 120 Days and after 120 Days of the Initial Diagnosis

| Variable                        | Early ≤120 days | Late >120 days | p-value |
|---------------------------------|-----------------|----------------|---------|
| No. of patients                 | 1,256           | 664            | 0.065   |
| Age, yr                         |                 |                |         |
| 20–49                           | 469 (37.34)     | 227 (14.19)    |         |
| 50–69                           | 518 (41.24)     | 264 (39.76)    |         |
| ≥70                             | 269 (21.42)     | 173 (26.05)    |         |
| Sex                             |                 |                | 0.461   |
| Male                            | 884 (70.38)     | 478 (71.99)    |         |
| Female                          | 372 (29.62)     | 186 (28.01)    |         |
| Rehospitalization*              |                 |                | <0.001  |
| No                              | 1,153 (91.80)   | 573 (86.30)    |         |
| Complicated†                    | 103 (8.20)      | 91 (13.70)     |         |
| Comorbidities                   |                 |                |         |
| DM                              | 154 (12.26)     | 107 (16.11)    | 0.019   |
| CHF                             | 34 (2.71)       | 20 (3.01)      | 0.701   |
| CAD                             | 167 (13.30)     | 112 (16.87)    | 0.035   |
| COPD                            | 146 (11.62)     | 92 (13.86)     | 0.158   |
| Gastroduodenal ulcer history    | 74 (5.89)       | 56 (8.43)      | 0.035   |
| Ulcer position                  |                 |                | <0.001  |
| Gastric ulcer                   | 511 (40.68)     | 351 (52.86)    |         |
| Duodenal ulcer                  | 728 (57.96)     | 298 (44.88)    |         |
| Peptic ulcer†                   | 17 (1.35)       | 15 (2.26)      |         |
| Medication                      |                 |                |         |
| PPIs or H2-blockers             | 110 (8.76)      | 124 (18.67)    | <0.001  |
| Aspirin                         | 67 (5.33)       | 31 (4.67)      | 0.528   |
| NSAIDS                          | 184 (14.65)     | 145 (21.84)    | <0.001  |
| COX-2 specific inhibitors       | 46 (3.66)       | 39 (5.87)      | 0.025   |
| Steroids                        | 52 (4.14)       | 36 (5.42)      | 0.202   |
| Clopidogrel                     | 20 (1.59)       | 12 (1.81)      | 0.727   |
| Ticlopidine                     | 9 (0.72)        | 6 (0.90)       | 0.658   |
| Warfarin                        | 4 (0.32)        | 3 (0.45)       | 0.645   |
| Follow-up year                  | 5,473±3,222     | 3,934±2,83     |         |

Data are presented as number (%) or mean±SD.

DM, diabetes mellitus; CHF, congestive heart failure; CAD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; PPIs, proton pump inhibitors; H2-blockers, histamine receptor-2 blockers; NSAIDS, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2.

*Rehospitalization for recurrent peptic ulcers; †Rehospitalization for complicated recurrent peptic ulcers with hemorrhages and perforations; ‡Including gastric ulcer and duodenal ulcer.

Table 2. Multivariate Cox Regression of Rehospitalization for Complicated Recurrent Peptic Ulcers with a Time Lag of More than 120 Days in the Overall Study Group

| Variable                        | HR      | 95% CI          | p-value |
|---------------------------------|---------|-----------------|---------|
| Time to H. pylori eradication*   |         |                 |         |
| >120 days vs ≤120 days          | 1.52    | 1.13–2.04       | 0.006   |
| Age, yr                         |         |                 |         |
| 20–49 vs ≥70                    | 0.23    | 0.15–0.35       | <0.001  |
| 50–69 vs ≥70                    | 0.44    | 0.32–0.62       | <0.001  |
| Sex                             |         |                 |         |
| Male vs female                  | 1.25    | 0.91–1.73       | 0.167   |
| Gastroduodenal ulcer history    | 1.40    | 0.89–2.22       | 0.149   |
| Ulcer position                  |         |                 |         |
| Gastric ulcer vs duodenal ulcer | 1.40    | 1.03–1.89       | 0.031   |
| Peptic ulcer† vs duodenal ulcer | 0.86    | 0.29–2.51       | 0.782   |
| Comorbidities                   |         |                 |         |
| DM                              | 1.06    | 0.71–1.58       | 0.782   |
| CHF                             | 0.75    | 0.29–1.91       | 0.542   |
| CAD                             | 1.05    | 0.72–1.55       | 0.788   |
| COPD                            | 0.84    | 0.57–1.24       | 0.375   |
| Medications                     |         |                 |         |
| PPIs or H2-blockers             | 2.30    | 1.65–3.19       | <0.001  |
| Aspirin                         | 0.50    | 0.26–0.93       | 0.029   |
| NSAIDS                          | 4.18    | 3.12–5.59       | <0.001  |
| COX-2 specific inhibitors       | 2.63    | 1.72–4.04       | <0.001  |
| Steroids                        | 0.68    | 0.37–1.24       | 0.209   |
| Ticlopidine                     | 0.85    | 0.31–2.36       | 0.753   |
| Ticlopidine                     | 0.37    | 0.05–2.71       | 0.326   |
| Warfarin                        | 3.67    | 0.82–16.51      | 0.090   |

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; CHF, congestive heart failure; CAD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; PPIs, proton pump inhibitors; H2-blockers, histamine receptor-2 blockers; NSAIDS, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2.

*Time of peptic ulcer diagnosis to the Helicobacter pylori eradication therapy; †Peptic ulcer includes gastric ulcer and duodenal ulcer.

more than one year (HR, 1.30; 95% CI, 0.82 to 2.07; p=0.264), and in time lag more than 2 years (HR,1.20; 95% CI, 0.69 to 2.07; p=0.523) (Fig. 2).

2. Relative risk of complicated peptic ulcers

The Cox proportional hazards analysis identified the patients who were 20 to 49 years of age (HR, 0.23; 95% CI, 0.15 to 0.35; p<0.001) or 50 to 69 years of age (HR, 0.44; 95% CI, 0.32 to 0.62; p<0.001) had a significantly lower risk for complicated recurrent peptic ulcers, compared with the patients who were 70 years of age and older. In addition, gastric ulcer (HR, 1.40; 95% CI, 1.03 to 1.89; p=0.031), PPIs or H2-blockers (HR, 2.30; 95% CI, 1.65 to 3.19; p<0.001), NSAIDS (HR, 4.18; 95% CI, 3.12 to 5.59; p<0.001), and COX-2 specific inhibitors (HR, 2.63; 95% CI, 1.72
### Table 3. Multivariate Cox Regression of Rehospitalization for Complicated Recurrent Peptic Ulcers with Time Lags of More than 1 Year and 2 Years in the Overall Study Group

| Variable                                    | HR (95% CI) | p-value | HR (95% CI) | p-value |
|----------------------------------------------|-------------|---------|-------------|---------|
| **Time to *H. pylori* eradication**          |             |         |             |         |
| >1 yr vs ≤1 yr                               | 1.20 (0.87–1.66) | 0.275 | -            | -       |
| >2 yr vs ≤2 yr                               | -           | -       | 1.10 (0.75–1.62) | 0.621 |
| **Age**                                      |             |         |             |         |
| 20–49 vs ≥70                                 | 0.23 (0.15–0.36) | <0.001 | 0.23 (0.15–0.36) | <0.001 |
| 50–69 vs ≥70                                 | 0.44 (0.32–0.61) | <0.001 | 0.45 (0.32–0.62) | <0.001 |
| **Sex**                                      |             |         |             |         |
| Male vs female                               | 1.29 (0.94–1.78) | 0.121 | 1.31 (0.95–1.80) | 0.103 |
| **Gastrointestinal ulcer history**           | 1.47 (0.93–2.32) | 0.100 | 1.47 (0.93–2.33) | 0.097 |
| **Ulcer position**                           |             |         |             |         |
| Gastric ulcer vs duodenal ulcer              | 1.47 (1.09–1.99) | 0.012 | 1.49 (1.10–2.02) | 0.010 |
| Peptic ulcer† vs duodenal ulcer              | 0.85 (0.29–2.49) | 0.766 | 0.86 (0.29–2.53) | 0.776 |
| **Comorbidities**                            |             |         |             |         |
| DM                                           | 1.06 (0.71–1.57) | 0.795 | 1.05 (0.70–1.56) | 0.824 |
| CHF                                          | 0.74 (0.29–1.88) | 0.520 | 0.73 (0.29–1.87) | 0.516 |
| CAD                                          | 1.07 (0.73–1.57) | 0.741 | 1.08 (0.74–1.58) | 0.699 |
| COPD                                         | 0.84 (0.56–1.24) | 0.369 | 0.83 (0.56–1.23) | 0.344 |
| **Medication**                               |             |         |             |         |
| PPIs or H₂-blockers                         | 2.38 (1.71–3.31) | <0.001 | 2.41 (1.73–3.35) | <0.001 |
| Aspirin                                      | 0.49 (0.26–0.92) | 0.027 | 0.49 (0.26–0.92) | 0.027 |
| NSAIDs                                       | 4.22 (3.15–5.66) | <0.001 | 4.27 (3.19–5.71) | <0.001 |
| COX-2 specific inhibitors                    | 2.67 (1.73–4.12) | <0.001 | 2.74 (1.78–4.21) | <0.001 |
| Steroid                                      | 0.72 (0.40–1.32) | 0.290 | 0.71 (0.39–1.30) | 0.267 |
| Clopidogrel                                  | 0.83 (0.30–2.29) | 0.712 | 0.82 (0.29–2.27) | 0.698 |
| Ticlopidine                                  | 0.36 (0.05–2.65) | 0.315 | 0.36 (0.05–2.64) | 0.313 |
| Warfarin                                     | 3.82 (0.84–17.30) | 0.083 | 3.82 (0.83–17.51) | 0.085 |

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; CHF, congestive heart failure; CAD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; PPIs, proton pump inhibitors; H₂-blockers, histamine receptor-2 blockers; NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2.

†Time of peptic ulcer diagnosis to the *Helicobacter pylori* eradication therapy; †Peptic ulcer includes gastric ulcer and duodenal ulcer.
to 4.04; \( p<0.001 \) as independent risk factors for complicated recurrent peptic ulcers. Patients receiving aspirin had a lower risk for complicated recurrent peptic ulcer \( (HR, 0.50; 95\% CI, 0.26 \text{ to } 0.93; \ p=0.029) \) (Table 2).

**DISCUSSION**

The timing of eradication is an important issue. We defined the late \( H. pylori \) eradication therapy group as those patients for whom therapy was delayed by more than 120 days and obtained the late \( H. pylori \) eradication therapy increased the risk of complicated recurrent \( H. pylori \) ulcers in \( PUB \) patients \( (HR, 1.52; 95\% CI, 1.13 \text{ to } 2.04; \ p=0.006) \). However, the definition of time lag is arbitrary; therefore, we also analyzed the effects of time lag more than 1 year \( (HR, 1.20; 95\% CI, 0.87 \text{ to } 1.66; \ p=0.275) \) and time lag more than 2 years \( (HR, 1.10; 95\% CI, 0.75 \text{ to } 1.62; \ p=0.621) \) (Tables 2 and 3). Our data indicated \( H. pylori \) eradication within 120 days was associated with decreased complicated recurrent peptic ulcers in \( PUB \) patients. \( H. pylori \) eradication treatment should be started within 120 days in cases of bleeding ulcer. Acute \( PUB \) patients frequently test negative \( H. pylori \) infection. Delaying treatment to after discharge leads to reduced compliance or loss to follow-up without receiving treatment. We must increase patient compliance to avoid loss to follow-up. Physicians should check the \( H. pylori \) status of patients, and initiate eradication therapy for patients who test positive within 120 days in \( PUB \) patients.

Cameron et al.\( ^{15} \) reported an \( H. pylori \) reinfection rate of approximately 0.4\%. In our study, the results for \( PUB \) patients in the early and late \( H. pylori \)-eradication therapy groups indicated that the \( H. pylori \) had persisted in their stomach mucosa before the eradication therapy was initiated. The results of our nationally representative observational study reflect that the actual conditions of 35.1\% of \( H. pylori \)-positive peptic ulcer patients are not initially treated with eradication therapy. The number and site of gastric biopsies may contribute to heterogeneity in \( H. pylori \) detection.\( ^{15,16} \) \( PUB \) patients had higher false-negative results for \( H. pylori \) diagnostic testing.\( ^{7} \) Moreover, the need for expedient intervention during endoscopic examination of hemodynamically unstable and intolerable patients may not allow the time required to determine their \( H. pylori \) status.\( ^{17} \) These reasons explain the delayed diagnosis of \( H. pylori \) positive peptic ulcers.

Gastroprotective agents such as \( H_{2} \)-blockers and PPIs are lower in cost: most cost less than US $0.25 and $0.8 per tablet, respectively. Therefore, participants in early and late \( H. pylori \) eradication therapy group were receiving prophylactic PPIs or \( H_{2} \)-blockers \( (8.76\% \text{ vs } 18.67\%, \ p<0.001) \) (Table 1). These patients may have higher risk of \( PUB \) by physicians’ decisions. Moreover, our data showed there is higher risk of complicated recurrent peptic ulcer in patients using PPIs or \( H_{2} \)-blockers \( (HR, 2.30; 95\% CI, 1.65 \text{ to } 3.19; \ p<0.001) \) (Table 2).

There are limitations to our findings. First, there were no confirmations of the \( H. pylori \) status of our participants following eradication therapy. The reality is that this may change over time, especially in the context of rising bacterial resistance. However, a latest multicenter study in Taiwan\( ^{18} \) reported a PPI-based \( H. pylori \) eradication rate of approximately 87.1\%. The \( H. pylori \) eradication rates, which is PPI-based \( H. pylori \) eradication therapy, are also similar in cirrhotic patients \( (81.8\%)^{19} \) and end-stage renal disease patients \( (81.2\%)^{20} \). Our study only enrolled \( PUB \) patients using PPI-based \( H. pylori \) eradication therapy; moreover, both cohorts in our study were enrolled from the same population and the same time. In addition, we obtained lower second \( H. pylori \) eradication rate \( 5.97\% \) \( (75/1,256) \) in early group and 7.08\% \( (47/664) \) in late group during the 11-year period (data not shown). Therefore, the eradication failure rates in our early and late \( H. pylori \) eradication therapy groups should have been similar and should not have significantly influenced our results. Second, differences in physician behavior and admission criteria for peptic ulcers were also potential confounders for our study. However, we only analyzed the risk of rehospitalization for endoscopically confirmed complicated recurrent peptic ulcers in \( PUB \) patients to limit the influence of such subjective factors on our results. Lastly, testing for \( H. pylori \) is affected by concomitant medications such as NSAIDs, aspirin, or PPIs. Moreover, there is not uniformity in the diagnostic tests between RUT or a histological assessment using H&E staining. Because we only address our endpoint over the complicated recurrent peptic ulcer episode after early and late \( H. pylori \) eradication therapy, these limitations were unlikely to bias our results.

In summary, our real-world data showed that only 2,463 patients receiving \( H. pylori \) eradication in 12,686 \( PUB \) hospitalized patients. Other than NSAIDs use,\( ^{20} \) idiopathic peptic ulcer, and comorbidities\( ^{21,22} \) related \( H. pylori \) negative peptic ulcers, most \( PUB \) patients delayed \( H. pylori \) diagnostic testing and eradication therapy, which is unlikely aggressive \( H. pylori \) testing and eradication in prospective study or guideline recommendation.\( ^{23,24} \) These patients did not receive re-endoscopy examination or \( 13\text{C}-\text{urea breath test to reconfirm } H. pylori \) status when these were initially \( H. pylori \) negative by diagnostic testing.

In conclusion, our study showed that \( H. pylori \) eradication within 120 days was associated with decreased complicated recurrent peptic ulcers in \( PUB \) patients. Thus, we recommend \( H. pylori \) eradication should be carried out within 120 days in \( PUB \) patients.

**CONFLICTS OF INTEREST**

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

1. Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med 1994;331:717-727.
2. NIH Consensus Conference. Helicobacter pylori in peptic ulcer disease. NIH Consensus Development Panel on Helicobacter pylori in Peptic Ulcer Disease. JAMA 1994;272:65-69.
3. Chen TS, Luo JC, Chang FY. Prevalence of Helicobacter pylori infection in duodenal ulcer and gastro-duodenal ulcer diseases in Taiwan. J Gastroenterol Hepatol 2010;25:919-922.
4. Hopkins RJ, Girardi LS, Turney EA. Relationship between Helicobacter pylori eradication and reduced duodenal and gastric ulcer recurrence: a review. Gastroenterology 1996;110:1244-1252.
5. Sanchez-Delgado J, Gene E, Suarez D, et al. Has H. pylori prevalence in bleeding peptic ulcer been underestimated? A meta-regression. Am J Gastroenterol 2011;106:398-405.
6. Lee JM, Breslin NP, Fallon C, O’Morain CA. Rapid urease tests lack sensitivity in Helicobacter pylori diagnosis when peptic ulcer disease presents with bleeding. Am J Gastroenterol 2000;95:1166-1170.
7. Gisbert JP, Abraira V. Accuracy of Helicobacter pylori diagnostic tests in patients with bleeding peptic ulcer: a systematic review and meta-analysis. Am J Gastroenterol 2006;101:848-863.
8. Hermansson M, Ekedahl A, Ranstam J, Zilling T. Decreasing incidence of peptic ulcer complications after the introduction of the proton pump inhibitors, a study of the Swedish population from 1974-2002. BMC Gastroenterol 2009;9:25.
9. Hippisley-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005;331:1310-1316.
10. McColl KE. How I manage H. pylori-negative, NSAID/aspirin-negative peptic ulcers. Am J Gastroenterol 2009;104:190-193.
11. Cheng SH, Chiang TL. The effect of universal health insurance on health care utilization in Taiwan. Results from a natural experiment. JAMA 1997;278:89-93.
12. Nozaki K, Shimizu N, Ikehara Y, et al. Effect of early eradication on Helicobacter pylori-related gastric carcinogenesis in Mongolian gerbils. Cancer Sci 2003;94:235-239.
13. Wu CY, Kuo KN, Wu MS, Chen YJ, Wang CB, Lin JF. Early Helicobacter pylori eradication decreases risk of gastric cancer in patients with peptic ulcer disease. Gastroenterology 2009;137:1641-1648.
14. Cameron EA, Bell GD, Baldwin L, Powell KU, Williams SG. Long-term study of re-infection following successful eradication of Helicobacter pylori infection. Aliment Pharmacol Ther 2006;23:1355-1358.
15. Working Party of the European Helicobacter pylori Study Group. Technical annex: tests used to assess Helicobacter pylori infection. Gut 1997;41 Suppl 2:S10-S18.
16. Working Party of the European Helicobacter pylori Study Group. Guidelines for clinical trials in Helicobacter pylori infection. Gut 1997;41 Suppl 2:S1-S9.
17. Bianchi Porro G, Lazzaroni M. The conflicting relationship between Helicobacter pylori and non-steroidal anti-inflammatory drugs in peptic ulcer bleeding. Scand J Gastroenterol 1999;34:225-228.
18. Liou JM, Chen CC, Chen MJ, et al. Sequential versus triple therapy for the first-line treatment of Helicobacter pylori: a multicentre, open-label, randomised trial. Lancet 2013;381:205-213.
19. Lo GH, Yu HC, Chan YC, et al. The effects of eradication of Helicobacter pylori on the recurrence of duodenal ulcers in patients with cirrhosis. Gastrointest Endosc 2005;62:350-356.
20. Tseng GY, Lin HJ, Fang CT, et al. Recurrence of peptic ulcer in uraemic and non-uraemic patients after Helicobacter pylori eradication: a 2-year study. Aliment Pharmacol Ther 2007;26:925-933.
21. Chang SS, Hu HY. Helicobacter pylori is not the predominant etiology for liver cirrhosis patients with peptic ulcer disease. Eur J Gastroenterol Hepatol 2013;25:159-165.
22. Kang JY, Ho KY, Yeoh KG, et al. Peptic ulcer and gastritis in uraemia, with particular reference to the effect of Helicobacter pylori infection. J Gastroenterol Hepatol 1999;14:771-778.
23. Chan FK, Sung JJ, Chung SC, et al. Randomised trial of eradication of Helicobacter pylori before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. Lancet 1997;350:975-979.
24. Malfertheiner P, Megraud F, O’Morain CA, et al. Management of Helicobacter pylori infection: the Maastricht IV/ Florence Consensus Report. Gut 2012;61:646-664.