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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 *H. 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. **(Gut Liver 2015;9:346-352)**

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.[1] 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.[2,3] It is well-recognized that *H. pylori* eradication therapy can reduce the recurrence of peptic ulcer. Hopkins *et al*.[4] 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,[5,6] and Gisbert and Abraira[7] 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[8,9] and the most common cause of *H. pylori* negative peptic ulcers.[10] 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

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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.[11] 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: TCHIRB-1020424-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-

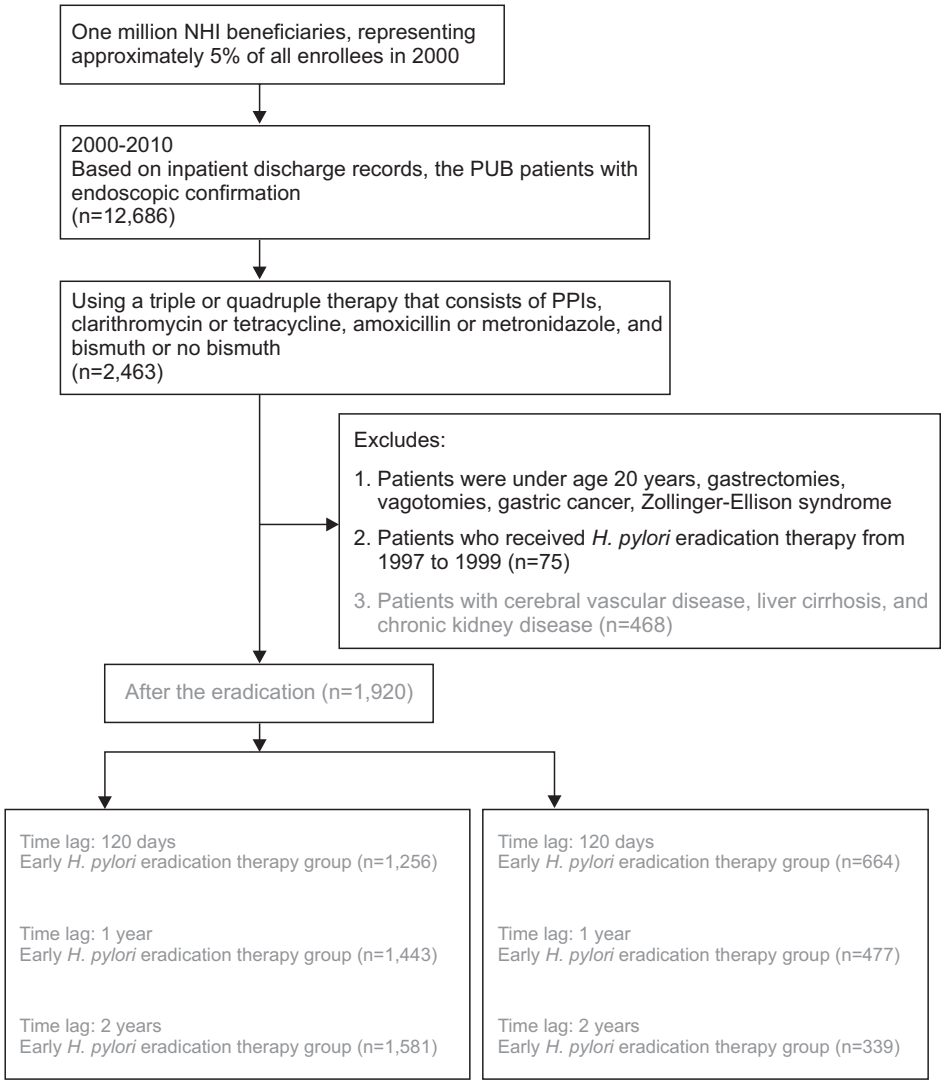

Fig. 1. Flowchart depicting participant selection.
NHI, National Health Insurance; PUB, peptic ulcer bleeding; PPI, proton pump inhibitor; *H. pylori*, *Helicobacter pylori*.

tients 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).[12] However the definition of time lag is arbitrary; therefore, we also analyzed the effects of time lag more than 1 year[13] 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, H_2-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.x1, 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*

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	
Age, yr			0.065
20–49	469 (37.34)	227 (34.19)	
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 H_2-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	5.47±3.22	3.93±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; H_2-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 H_2-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
Clopidogrel	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; H_2-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.

eradication therapy group. On stratified analysis according to NSAID use, patients not receiving NSAIDs in the late *H. pylori* eradication therapy group was not associated with a higher risk for complicated recurrent peptic ulcers in time lag more than 120 days (HR, 1.33; 95% CI, 0.88 to 1.99; p= 0.176), in time lag more than 1 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 H_2-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

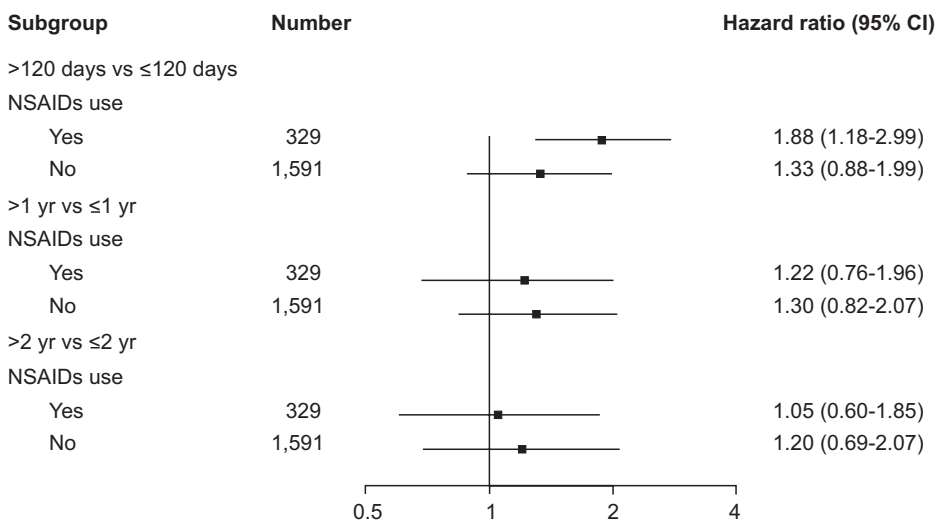

Fig. 2. Multivariate stratified Cox proportional hazards model analysis for predicting rehospitalization in patients with complicated recurrent peptic ulcers according to nonsteroidal anti-inflammatory drug (NSAID) use (adjusted for all other factors). CI, confidence interval.

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
Gastroduodenal 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 H_2-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; H_2-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 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 peptic ulcers in PUB patients (HR, 1.52; 95% CI, 1.13 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[13] and more than 2 years and obtained the similar risk of complicated recurrent peptic ulcers in PUB patients for time lag more than 1 year (HR, 1.20; 95% CI, 0.87 to 1.66; p=0.275) and time lag more than 2 years (HR, 1.10; 95% CI, 0.75 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*.[14] 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% 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 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,[10] 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}C-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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