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Does *Helicobacter pylori* Exacerbate Gastric Mucosal Injury in Users of Nonsteroidal Anti-Inflammatory Drugs? A Multicenter, Retrospective, Case-Control Study

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Background/Aims: The interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* remains controversial. We retrospectively investigated whether *H. pylori* infection exacerbates severe gastric mucosal injury among chronic NSAID users. **Methods:** From January 2010 to December 2013, a total of 245 long-term NSAID (including low-dose aspirin) users who had undergone an esophagogastroduodenoscopy and had been evaluated for *H. pylori* infection were enrolled at Okayama University Hospital and Tsuyama Chuo Hospital. The degree of gastric mucosal injury was assessed according to the modified Lanza score (MLS). Severe gastric mucosal injury was defined as an MLS ≥4. Univariate and multivariate logistic regression analyses were performed. **Results:** In the univariate analysis, age ≥75 years (odds ratio [OR], 2.4; 95% confidence interval [CI], 1.3 to 4.2), *H. pylori*-positivity (OR, 2.0; 95% CI, 1.2 to 3.5), and the concomitant use of proton pump inhibitors (PPIs) (OR, 0.48; 95% CI, 0.26 to 0.86) were significantly associated with severe gastric mucosal injury. The multivariate analysis was adjusted by age and sex and demonstrated that *H. pylori*-positivity (OR, 1.8; 95% CI, 1.0 to 3.3) and the concomitant use of PPIs (OR, 0.53; 95% CI, 0.28 to 0.99) significantly contributed to severe gastric mucosal injury. **Conclusions:** *H. pylori* infection exacerbates severe gastric mucosal injury among chronic NSAID users. **(Gut Liver 2016;10:69-75)**

Key Words: Anti-inflammatory agents, non-steroidal; *Helicobacter pylori*; Gastric mucosal injury; Proton pump inhibitors

INTRODUCTION

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) including low-dose aspirin (LDA) has increased in recent years, and their use is known to increase the risk of gastric mucosal injury and ulcers.[1,2] It has been reported that the risk factors for future NSAIDs-associated ulcer complications include a history of uncomplicated peptic ulcer, advanced age, comorbidities, high-dose use, and use of concomitant drugs such as antiplatelet drugs and anticoagulants.[3,4]

Gastric acid is another important factor involved in NSAIDs-induced gastric mucosal injury,[5,6] and *Helicobacter pylori* infection is known to exert diverse effects on gastric acid secretion; infection can cause an increase, decrease, or no change in gastric acid secretion depending on the distribution of inflammation or presence of atrophy within the stomach.[7] Thus, the interaction between *H. pylori* and NSAIDs may vary, according to the topography and severity of gastritis. In 2012, Iijima and colleagues[8] reported that the effect of *H. pylori* infection on aspirin-induced gastropathy was biphasic depending on the patient's gastric acid secretion level. The interaction between NSAIDs and *H. pylori* remains incompletely understood and controversial.

There is a paucity of data regarding the interaction between NSAIDs-induced gastric mucosal injury and *H. pylori* infection in Japanese patients because almost all studies to date have been conducted in Western countries. Moreover, the incidence of NSAIDs-induced gastric mucosal injury in *H. pylori*-positive patients has not been adequately studied although the endpoint in most studies was the incidence of peptic ulcer or bleeding in

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NSAIDs users.[1,9,10]

The aim of this study was to assess whether *H. pylori* infection exacerbates severe gastric mucosal injury associated with chronic NSAIDs use.

MATERIALS AND METHODS

1. Study design and subjects

This was a multicenter, retrospective, case-control study. From January 2010 to December 2013, a total of 245 consecutive outpatients and inpatients who had been taking a nonaspirin NSAID (NANSAID) or LDA (75 to 325 mg) continuously for at least 3 months and had undergone esophagogastroduodenoscopy were retrospectively enrolled at Okayama University Hospital and Tsuyama Chuo Hospital. Exclusion criteria for the participants included a history of endoscopic resection or gastric surgery for gastric cancer; gastric/duodenal ulcer, or *H. pylori* eradication treatment; serious systemic diseases; presence of gastric cancer; and age <20 years. Surveyed background factors were age, gender, degree of gastric mucosal injury, degree of gastric atrophy, incidence of *H. pylori* infection, type of NSAIDs used (NANSAID alone, LDA alone, or both NANSAID and LDA), and concomitant medications (antiplatelet agents, anticoagulants, or antisecretory agents). The study was approved by the Okayama University School of Medicine and Tsuyama Chuo Hospital Clinical Ethics Committee on Human Experiments, in accordance with the Helsinki Declaration, and each subject gave their written informed consent.

2. Endoscopic evaluation of gastric mucosal injury and gastric atrophy

The degree of gastric mucosal injury was assessed according to the modified Lanza score (MLS).[11] In this scoring system, gastric mucosal injury is graded according to six categories on a scale from 0 to 5: grade 0, no erosion/hemorrhage; grade 1, 1–2 lesions of erosion and/or hemorrhage localized in one area of the stomach; grade 2, 3–5 lesions of erosion and/or hemorrhage localized in one area of the stomach; grade 3, 6–9 lesions of erosion and/or hemorrhage localized in one area of the stomach, or no more than 10 lesions in two areas of the stomach; grade 4, erosions and/or hemorrhage in three areas of the stomach, or no fewer than 10 lesions in the whole stomach; and grade 5, a gastric ulcer, defined as a mucosal defect larger than 5 mm in diameter.

The degree of atrophy was diagnosed according to the criteria of Kimura and Takemoto[12] as reported previously. The MLS and degree of endoscopic atrophy for all subjects were graded independently in a blinded manner by two endoscopists. When there was disagreement, a consensus was reached through joint review of the endoscopic pictures. In the present analysis, severe gastric mucosal injury was defined as an MLS ≥4.[8,13]

3. Diagnosis of *H. pylori* infection

All subjects were evaluated for *H. pylori* infection. Histology, *H. pylori* IgG antibody, rapid urease test (RUT), or urea breath test were used to detect *H. pylori* infection. *H. pylori* infection was diagnosed when any of the studies was positive. For histology, three biopsy specimens (greater curvature of antrum, lesser curvature of lower gastric body, and greater curvature of upper body) were fixed with buffered formalin and embedded in paraffin. Sections were stained with Giemsa stain solution. An expert pathologist from each of the two centers who was unaware of the endoscopic findings assessed *H. pylori* infection and graded the degree of histological gastritis in each biopsy sample.[14] For *H. pylori* IgG antibody, we studied the titers of serum or urinary IgG antibodies against *H. pylori*, using an enzyme immunoassay (EIA kit) (E Plate "Eiken" *H. pylori*-antibody; Eiken Chemical, Tokyo, Japan),[15] or RAPIRUN *H. pylori* antibody detection kit (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan).[16] The two gastric biopsies taken for RUT were immediately dropped into Helicocheck™ (Otsuka Pharmaceutical Co., Ltd., Osaka, Japan). *H. pylori* was identified on the basis of a color change from yellow to red after 2 hours. ^{13}C-urea breath testing (UbiT; Otsuka Pharmaceuticals, Tokyo, Japan) was also used. The cutoff value for $\Delta^{13}CO_2$ was set at 2.5%.[17]

4. Statistical analysis

Mann-Whitney U test was used for continuous variables, and Fisher exact test or chi-square test were used for categorical variables between *H. pylori*-negative and *H. pylori*-positive subjects.

To identify significant factors contributing to NSAIDs-induced severe gastric mucosal injury, univariate and multivariate logistic regression analyses were performed. Variables found in the univariate analysis to be significantly associated were included in a multivariate logistic regression analysis. Valuables such as age and gender were also included in the multivariate regression analysis to adjust for the effect of confounding factors. The results of analysis were expressed as odds ratio (OR) and confidence interval (CI). All statistical calculations were carried out using JMP software (for Windows, version 10). The p-values<0.05 were considered to be statistically significant in all tests.

RESULTS

1. Clinical parameters in all subjects

Clinical parameters in all subjects are shown in Table 1. About one-third (32%) had severe gastric mucosal injury, and the incidence of *H. pylori* infection and open-type gastric atrophy were 44% and 43%, respectively. Roughly 50% of subjects concomitantly used antisecretory drugs such as proton pump inhibitors (PPIs) or histamine H_2-receptor antagonists (H_2-RAs).

Table 1. Clinical Parameters of the 245 Cases

Parameter	Value
Age, yr	65±14
Gender, female/male	120/125
MLS	1.9±2.2
MLS ≥4	79 (32.2)
Degree of gastric atrophy	
None or closed	140 (57.1)
Open	105 (42.9)
H. pylori infection	
Negative	137 (55.9)
Positive	108 (44.1)
Type of NSAIDs	
NANSAID alone	119 (48.6)
LDA alone	114 (46.5)
Both NANSAID and LDA	12 (4.9)
Concomitant medications	
Antiplatelet agents	49 (20.0)
Anticoagulants	18 (7.3)
Antisecretary agents	127 (51.8)
PPIs	85 (34.7)
H_2-RAs	42 (17.1)

Data are presented as mean±SD or number (%).
MLS, modified Lanza score; *H. pylori*, *Helicobacter pylori*; NSAID, nonsteroidal anti-inflammatory drugs; NANSAID, nonaspirin NSAID; LDA, low-dose aspirin; PPI, proton pump inhibitor; H_2-RA, histamine H_2-receptor antagonist.

Table 2. Comparison of the Clinical Parameters between *H. pylori*-Negative and *H. pylori*-Positive Subjects

Parameter	*H. pylori*-negative (n=137)	*H. pylori*-positive (n=108)	p-value
Age, ≥75 yr	41 (29.9)	33 (30.6)	1.0
Gender, female/male	67/70	53/55	1.0
Type of NSAIDs			
NANSAID alone	70 (51.1)	49 (45.4)	0.25
LDA alone	59 (43.1)	55 (50.9)	0.44
Both NANSAID and LDA	8 (5.8)	4 (3.7)	0.56
Concomitant medications			
Antipletelet agents	27 (19.7)	22 (20.4)	1.0
Anticoagulants	7 (5.1)	11 (10.2)	0.15
Antisecretary agents	83 (60.6)	44 (40.7)	0.003
PPIs	61 (44.5)	24 (22.2)	<0.001
H_2-RAs	22 (16.1)	20 (18.5)	0.61
Open-type gastric atrophy	39 (28.5)	66 (61.1)	<0.001

Data are presented as mean±SD or number (%).
H. pylori, *Helicobacter pylori*; NSAID, nonsteroidal anti-inflammatory drug; NANSAID, nonaspirin NSAID; LDA, low-dose aspirin; PPI, proton pump inhibitor; H_2-RA, histamine H_2-receptor antagonist.

2. Comparison of the degree of NSAIDs-induced gastric mucosal injury between *H. pylori*-negative and *H. pylori*-positive subjects

Clinical parameters in *H. pylori*-negative and *H. pylori*-positive subjects are shown in Table 2. No significant differences were seen in terms of age, gender, type of NSAIDs used, or concomitant medications (antiplatelet agents and anticoagulants). The percentage of open-type gastric atrophy was significantly higher (61% vs 28%, p<0.001), and concomitant use of PPIs was significantly lower (22% vs 45%, p<0.001) in *H. pylori*-positive subjects than in *H. pylori*-negative subjects, respectively.

As shown in Figs 1 and 2, the mean MLS (2.3 vs 1.7, p=0.037) and the percentage of patients with an MLS of ≥4 (41% vs 26%, p=0.013) were both higher in *H. pylori*-positive subjects than in *H. pylori*-negative subjects. Moreover, we investigated the rela-

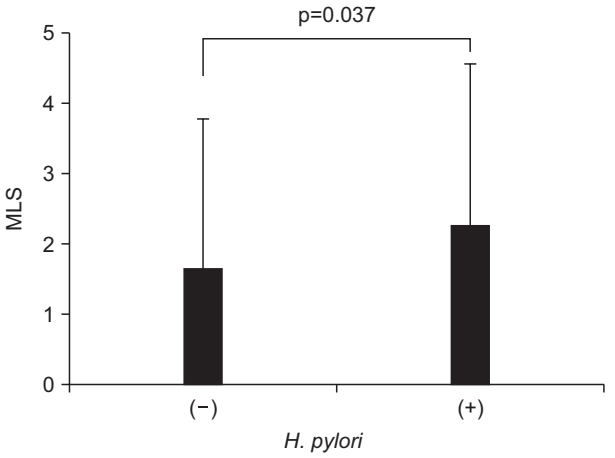

Fig. 1. Comparison of the modified Lanza score (MLS) between *Helicobacter pylori*-negative subjects and *H. pylori*-positive subjects in all cases. The mean MLS was significantly higher in *H. pylori*-positive subjects than in *H. pylori*-negative subjects (each column indicates the mean±SD; 2.3±2.3 vs 1.7±2.1, p=0.037).

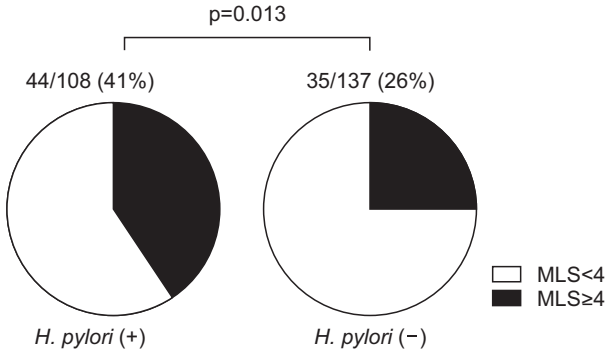

Fig. 2. Comparison of the incidence of severe gastric mucosal injury (modified Lanza score [MLS] ≥4) between *Helicobacter pylori*-negative subjects and *H. pylori*-positive subjects in all cases. The percentage of patients with MLS ≥4 was significantly higher among *H. pylori*-positive patients than in *H. pylori*-negative patients (41% vs 26%, p=0.013).

tionship between degree of gastric atrophy with *H. pylori* infection and MLS (Figs 3 and 4). Among the subjects with none or closed-type gastric atrophy, the mean MLS was higher (2.3 vs 1.6, p=0.093), and the percentage of patients with MLS ≥4 was significantly higher (43% vs 24%, p=0.043) in *H. pylori*-positive subjects than in *H. pylori*-negative subjects. Among the subjects with open-type gastric atrophy, however, the mean MLS and the percentage of patients with MLS ≥4 was not significantly higher in *H. pylori*-positive subjects than *H. pylori*-negative subjects (2.2 vs 1.7, p=0.28, and 39% vs 28%, p=0.29, respectively).

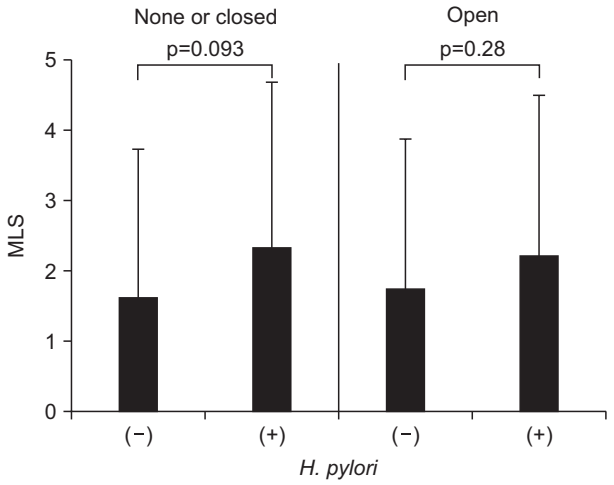

Fig. 3. Comparison of the modified Lanza score (MLS) between *Helicobacter pylori*-negative subjects and *H. pylori*-positive subjects, according to the degree of gastric atrophy. The difference in the mean MLS between *H. pylori*-negative and *H. pylori*-positive subjects was larger among the subjects with no or closed-type gastric atrophy than among those with open-type gastric atrophy (each column indicates the mean±SD; 1.6±2.1 vs 2.3±2.4, p=0.093 in the subjects with no or closed-type gastric atrophy, and 1.7±2.2 vs 2.2±2.3, p=0.28 in the subjects with open-type gastric atrophy, respectively).

3. Factors contributing to NSAIDs-induced severe gastric mucosal injury

Table 3 shows the results of logistic regression analysis for factors contributing to NSAIDs-induced severe gastric mucosal injury (MLS ≥4). In univariate analysis, age ≥75 years (OR, 2.4; 95% CI, 1.3 to 4.2), *H. pylori*-positivity (OR, 2.0; 95% CI, 1.2 to 3.5), and concomitant use of PPIs (OR, 0.48; 95% CI, 0.26 to 0.86) were significantly related to NSAIDs-induced severe gastric mucosal injury. In multivariate analysis adjusted by age and gender, *H. pylori*-positivity (OR, 1.8; 95% CI, 1.0 to 3.3), and concomitant use of PPIs (OR, 0.53; 95% CI, 0.28 to 0.99) were significant factors associated with NSAIDs-induced severe gastric mucosal injury.

DISCUSSION

In summary, we investigated the effect of *H. pylori* infection on severe gastric mucosal injury among chronic NSAIDs users. The incidence of NSAIDs-induced severe gastric mucosal injury was higher in *H. pylori*-positive subjects than in *H. pylori*-negative subjects, especially among the subjects with none or closed type gastric atrophy. In multivariate regression analysis adjusted by age and gender, *H. pylori* was identified as a significantly aggressive factor contributing to NSAIDs-induced severe gastric mucosal injury.

Regarding the interaction between *H. pylori* and NSAIDs on gastric mucosal injury, several contributing factors are possibly working. First, *H. pylori* affects gastric acid secretion depending on the severity and phenotype of the induced gastritis.[10,18] It has been reported that *H. pylori* infection has no significant effect on aspirin-induced mucosal injury after adjusting for gastric acid secretion.[19] Alternatively, we investigated the relationship between degree of gastric atrophy with *H. pylori* infection and MLS, because gastric atrophy, which is closely related to *H.*

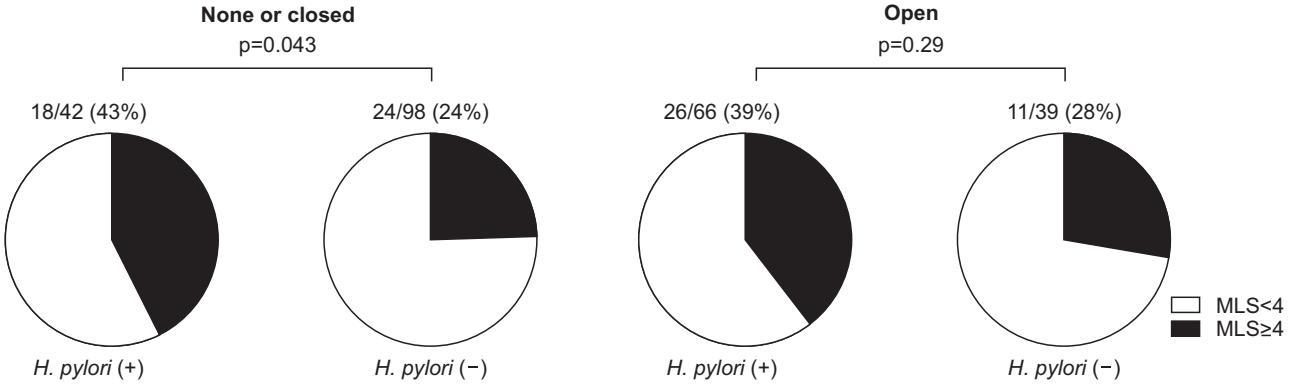

Fig. 4. Comparison of the incidence of severe gastric mucosal injury (modified Lanza score [MLS] ≥4) between *Helicobacter pylori*-negative and *H. pylori*-positive subjects, according to the degree of gastric atrophy. Among the subjects with no or closed-type gastric atrophy, the percentage of patients with MLS ≥4 was significantly higher in *H. pylori*-positive than in *H. pylori*-negative subjects; however, it was not significantly higher among the subjects with open-type gastric atrophy (43% vs 24%, p=0.043 in the subjects with no or closed-type gastric atrophy, and 39% vs 28%, p=0.29 in the subjects with open-type gastric atrophy, respectively).

Table 3. Univariate and Multivariate Logistic Regression Analysis of Factors Contributing to Nonsteroidal Anti-Inflammatory Drugs-Induced Severe Gastric Mucosal Injury (Modified Lanza Score ≥4)

Factor	Subgroup	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age	<75 yr	1.0	1.0
	≥75 yr	2.4 (1.3–4.2)	2.6 (1.4–4.7)†
Gender	Female	1.0	1.0
	Male	1.5 (0.90–2.7)	1.6 (0.92–2.9)
Type of NSAIDs			
NANSAID/LDA	NANSAID	1.0	-
	LDA	1.0 (0.56–1.6)	-
Both NANSAID and LDA	No	1.0	-
	Yes	1.1 (0.27–3.5)	-
Concomitant medications			
Antiplatelet agents	No	1.0	-
	Yes	0.91 (0.45–1.8)	-
Anticoagulants	No	1.0	-
	Yes	0.58 (0.16–1.7)	-
Antisecretary agents			
PPIs	No	1.0	1.0
	Yes	0.48 (0.26–0.86)*	0.53 (0.28–0.99)*
H_2-RAs	No	1.0	-
	Yes	0.61 (0.27–1.3)	-
Degree of gastric atrophy	None or closed	1.0	-
	Open	1.3 (0.74–2.2)	-
H. pylori infection	Negative	1.0	1.0
	Positive	2.0 (1.2–3.5)*	1.8 (1.0–3.3)†

OR, odds ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drugs; NANSAID, nonaspirin NSAID; LDA, low-dose aspirin; PPI, proton pump inhibitor; H_2-RA, histamine H_2-receptor antagonist; *H. pylori*, *Helicobacter pylori*.
*p<0.05; †p<0.01.

pylori infection, is associated with a decline in gastric acid secretion.[20] As shown in Figs 3 and 4, *H. pylori* infection exacerbated NSAIDs-induced gastric mucosal injury among those with open-type gastric atrophy, but it was not statistically significant. In larger study, we may be able to investigate that *H. pylori* infection has a synergic effect on NSAID-induced gastric mucosal injury among those with open-type gastric atrophy, as similarly as among those with none or closed-type gastric atrophy. However, we confirmed in this study that *H. pylori* infection had more synergic effect on NSAIDs-induced gastric mucosal injury among the subjects with none or closed-type gastric atrophy than among those with open-type gastric atrophy. In addition, the different phenotypes of *H. pylori* gastritis may contribute to the contradictory data concerning its effect on gastric mucosal injury in NSAIDs users. In Western countries, several studies have demonstrated that *H. pylori* infection and NSAIDs use represent synergistic risk factors for uncomplicated and bleeding peptic ulcer.[1,21] Furthermore, *H. pylori* exacerbated NSAIDs-induced gastric mucosal injury in our study. These results may be not only due to the degree of gastric acid secretion as mentioned before, but due to a substantial inflammatory reaction in the gastric mucosa with recruitment of leukocytes and overexpression and release of proinflammatory cytokines induced by *H. pylori*.[18,22] The phenomenon of reduced gastric mucosal injury despite repeated doses of NSAIDs (termed adaptation) also should be considered.[23] *H. pylori* is thought to impair adaptation to NSAIDs-induced gastric mucosal injury.[24] The subjects in this study were long-term NSAIDs users, so this impairment of adaptation by *H. pylori* may have also contributed to our results.

Based on our findings, concomitant use of PPIs, but not H_2-RAs, can reduce the risk of NSAIDs-induced severe gastric mucosal injury. Several studies have fully examined the efficacy of PPIs and high-dose H_2-RAs for preventing NSAIDs-induced erosion/ulcer.[25-27] In our study, normal-dose H_2-RAs users were also enrolled, and the number of concomitant H_2-RAs users was small. This may explain why concomitant use of H_2-RAs was not a significant preventive factor for NSAIDs-induced severe gastric mucosal injury in this study.

As shown in Table 2, the percentage of concomitant use of PPI was significantly lower in *H. pylori*-positive patients than in

H. pylori-negative patients. Possible explanations for this findings are as follows: the gastric acid levels in *H. pylori*-positive patients could be lower because the incidence of open-type gastric atrophy was higher in *H. pylori*-positive patients than in *H. pylori*-negative patients. The higher gastric acid levels could contribute to the digestive symptoms such as heartburn, chest pain, or epigastralgia. That was why the *H. pylori*-negative patients used PPI more frequently than *H. pylori*-positive patients. Moreover, we could suggest that PPI was effective for chronic NSAIDs-users in *H. pylori*-positive patients even if they had less gastric acid levels, because the concomitant PPI users in *H. pylori*-positive patients had less injured gastric mucosa status in our study (Supplementary Fig. 1).

Regarding the secondary prevention of peptic ulcer or bleeding, it has been reported that *H. pylori* eradication has no beneficial effect compared with placebo in chronic NSAIDs users,[28,29] and PPIs were more effective than *H. pylori* eradication.[30,31] On the other hand, for primary prevention in chronic NSAIDs users, there is limited evidence indicating the effectiveness of *H. pylori* eradication.[32] The reduced gastric acid secretion would be normalized as a result of eradication of *H. pylori*,[33] so that gastric mucosal injury in chronic NSAIDs users may be exacerbated after *H. pylori* eradication. It is therefore important to investigate changes in gastric mucosal injury among chronic NSAIDs users before and after *H. pylori* eradication for primary prevention.

Our study had several limitations. First, we could not assess the gastric acid levels of individual patients. Secondly, this study was a retrospective study and the number of cases was small. Thirdly, it is possible that *H. pylori*-negative patients included not only those who were truly uninfected with *H. pylori* but also those whose *H. pylori* had been spontaneously eradicated, because 30% of the *H. pylori*-negative patients had open-type gastric atrophy. And there was some possibility of false positive in terms of current infection because all the patients with the positivity of *H. pylori* IgG antibody were diagnosed with *H. pylori* infection positive. Fourthly, we could not fully evaluate the influence of other drugs such as bisphosphonates, corticosteroids, and mucoprotective drugs. In the future, we plan to perform a multicenter, prospective study and screen for *H. pylori* infection in all subjects regardless of whether NSAIDs are used.

In conclusion, *H. pylori* exacerbates severe gastric mucosal injury in chronic NSAIDs users especially among the subjects of none or closed type gastric atrophy. Although the interaction between *H. pylori* and NSAIDs has not been fully elucidated, we hope that our data will be helpful for guiding the management and treatment of *H. pylori*-positive patients who use NSAIDs chronically. It is expected that *H. pylori* eradication would have a beneficial effect for the primary prevention of not only gastric ulcer and cancer, but also of severe gastric mucosal injury in chronic NSAIDs users.

CONFLICTS OF INTEREST

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

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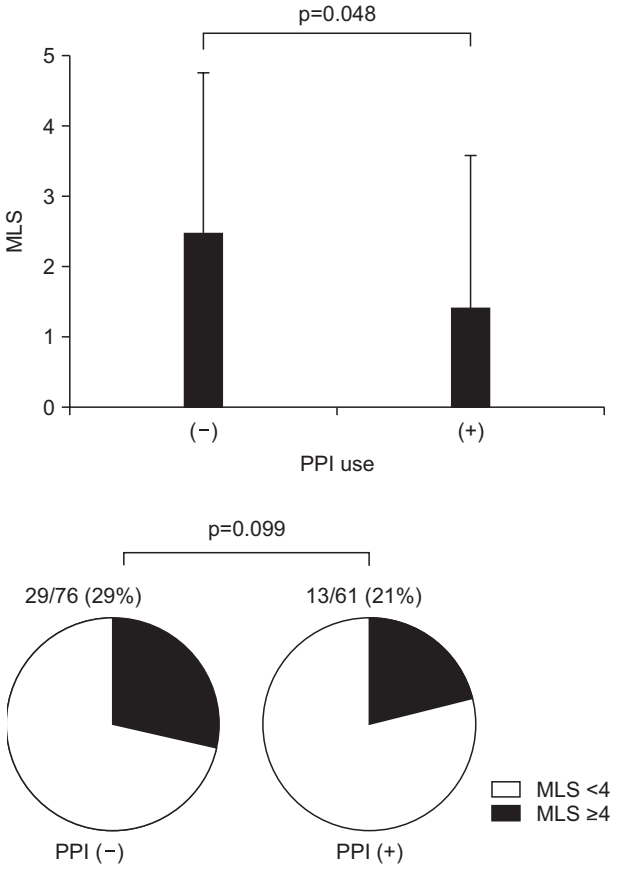

Supplementary Fig. 1. The degree of mucosal injury between proton pump inhibitor (PPI) users and PPI nonusers among *Helicobacter pylori*-positive subjects. The means of modified Lanza score (MLS) and the incidence of MLS ≥4 were lower in the PPI users than in PPI nonusers among *H. pylori*-positive patients (each column indicates the mean±SD; 2.5±2.3 vs 1.5±2.2, p=0.048, Mann-Whitney U test; 29% vs 21%, p=0.099, chi-square test).