Diagnosis of histological gastritis based on the Kyoto classification of gastritis in Japanese subjects

- Including evaluation of aging and sex difference of histological gastritis

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ABSTRACT

Objectives: The Kyoto classification of gastritis was established for diagnosing *Helicobacter pylori* infection via endoscopic findings. We investigated the role of the Kyoto classification of gastritis in the diagnosis of *H. pylori* infection and histological gastritis in Japanese individuals. Moreover, the histological findings of gastritis in *H. pylori* infection were examined based on age and sex differences.

Methods: We selected 561 patients aged 20–79 years who underwent gastroduodenal endoscopy at our hospital between 2010 and 2018. Endoscopic biopsy specimens from the antrum and corpus were used to investigate *H. pylori* infection and histology. Endoscopic findings were based on the Kyoto classification of gastritis, and histological findings were based on the updated Sydney System.

Results: Endoscopic findings based on the Kyoto classification of gastritis (*H. pylori* positive, 303 patients; *H. pylori* negative, 258 patients, based on endoscopic findings) had 98.8% sensitivity and 97.4% specificity for histological gastritis. In addition, endoscopic findings in the three age groups (20–39, 40–59, and 60–79 years) had high sensitivity and specificity. Atrophy and intestinal metaplasia were found only in the *H. pylori*-positive group and progressed with age. Histological inflammation of pyloric

mucosa in the younger age group of *H. pylori*-positive patients was significantly higher than that in the elderly group. Significant inflammation was observed in young women. **Conclusions:** The Kyoto classification of gastritis can not only diagnose *H. pylori* infection but also detect histological gastritis. Histological gastritis has varying characteristics of inflammation, atrophy, and intestinal metaplasia, depending on age and sex.

Keywords: *Helicobacter pylori*, Gastritis, Kyoto classification of gastritis, Updated Sydney System, Histology

INTRODUCTION

Warren and Marshall discovered *Helicobacter pylori* in 1983 and provided evidence stating that *H. pylori* infection causes chronic gastritis, peptic ulcer, and gastric cancer [1-3].

A standardised classification of gastritis was proposed by a working group at the World Congress of Gastroenterology in Sydney in 1990 (Sydney System), and this classification has been adopted as the updated Sydney System [4, 5]. Thus, endoscopic and histological gastritis has been classified in recent years according to the updated Sydney System.

Since February 2013, all *H. pylori*-positive patients have been treated under the National Health Insurance in Japan. To perform eradication therapy, it is necessary to confirm *H. pylori* infection by endoscopic findings, and additionally, a urease, serum antibody, stool antigen, and urease breath test is performed. Moreover, it is necessary to exclude organic diseases using endoscopy, such as gastric cancer. Therefore, it is important to evaluate *H. pylori* infection using endoscopy. We recently established the Kyoto classification of gastritis to diagnose *H. pylori* infection using endoscopy in the Japanese population [6].

Ever since the Kyoto Classification of Gastritis has been established, there have been

78 many reports of *H. pylori* infection and background gastric mucosa [7-10]. However,
79 the association between endoscopic gastritis diagnosed by the Kyoto Classification of
80 gastritis and histological findings has not been investigated. This study aimed to
81 examine whether histological gastritis can be diagnosed using the Kyoto classification
82 of gastritis. In addition, we examined age and sex differences in the histological
83 findings of gastritis.
84
85 **MATERIALS AND METHODS**
86 ***Patients***
87 We enrolled patients aged 20–79 years who underwent upper gastrointestinal
88 endoscopy at Kawasaki Medical School Hospital between January 2010 and September
89 2018. During the study period, 1,395 patients underwent biopsies of the gastric antrum
90 and corpus of the greater curvature. We excluded patients who met the following
91 criteria: the use of nonsteroidal anti-inflammatory drugs, antacids, H_2-receptor
92 antagonists, proton pump inhibitors, rebamipide (2-(4-chlorobenzoylamino)-3-[2-(1H)-
93 quinolinon-4-yl] propionic acid), immunosuppressors, immunomodulators, or
94 antibiotics during the month preceding endoscopy; a history of gastric surgery; pregnant
95 during the study period; a history of systemic conditions, such as collagen disease,

96 inflammatory bowel disease, autoimmune gastritis, eosinophilic gastroenteritis, acute
97 gastric mucosal lesion, portal hypertensive gastropathy, or Ménétrier disease; presence
98 of gastroduodenal lesion, such as gastric cancer, gastric adenoma, or peptic ulcer at the
99 time of endoscopy; or a history of treatment for *H. pylori* infection. Patients who were
100 not Japanese were excluded because of the perceived variations in the type of gastritis
101 compared with Japanese patients. Finally, we enrolled 561 patients (243 men and 318
102 women; average age, 50.1 years) who underwent upper gastrointestinal endoscopy
103 (Figure 1).
104 The gastric mucosa was observed by endoscopy, and the presence or absence of *H.*
105 *pylori* infection was diagnosed based on the Kyoto classification of gastritis [6]. Scopes
106 were restricted to the GIF240 and GIF260 series of Olympus Co. (Tokyo, Japan) and
107 EG-530, EG-580, and EG-590 series of Fujifilm Co. (Tokyo, Japan). At least two
108 biopsy specimens (one from the great curvatures of the antrum and one from the great
109 curvatures of the corpus) were used to assess the status of *H. pylori* infection and
110 histological gastritis. We examined whether the findings of *H. pylori*-positive or *H.*
111 *pylori*-negative patients diagnosed by the Kyoto classification of gastritis reflected the
112 histological findings of gastritis.
113 The study was approved by the Ethics Committee of our university (approval

number: 3319-3), and the study was conducted according to the principles of the Declaration of Helsinki with the study participants' understanding and consent.

Assessment of endoscopic findings

All patients were evaluated using endoscopy by three Japanese endoscopists (NS, KH, and TK) who were unaware of the symptoms, laboratory data, histological reports of biopsy specimens, and *H. pylori* infection status according to the Kyoto classification of gastritis criteria [6]. The endoscopic findings were evaluated using white light images without the magnifying tool, and disagreements were resolved through discussion among the three endoscopists. The degree of corpus atrophy was classified as C1 (none) to O3 (very severe) according to the Kimura–Takemoto classification [11]. C2-graded atrophic findings, diffuse redness, nodular gastritis (NG), swelling of the folds, and intestinal metaplasia were defined as *H. pylori* infection.

Assessment of histological gastritis

Gastric biopsy specimens were obtained during endoscopy and histologically assessed for all patients. Specimens were fixed in 10% buffered formalin, embedded in paraffin, sliced into 4-μm sections, and stained with haematoxylin and eosin (H&E) for

histological examination and Giemsa stain or Gimenez staining for *H. pylori* identification. All Giemsa-, Gimenez-stained, and H&E-stained biopsy specimens were reviewed by trained pathologists (NS and KH) who were blinded to the patients' data. Histological interpretation was based on the updated Sydney System. Inflammation of the gastric mucosa was defined as the presence of inflammatory infiltrates comprising neutrophils, lymphocytes, and plasma cells. Mucosal atrophy was defined as a loss of glandular tissue. Inflammation, mucosal atrophy, and intestinal metaplasia were classified according to their degree of severity into four categories: none, mild, moderate, and severe. Histological gastritis was defined as the presence of at least one mild (or higher) inflammation, atrophy, or intestinal metaplasia.

Assessment of H. pylori infection status

H. pylori infection status was determined by Giemsa or Gimenez staining along with histological findings. Patients were determined to be uninfected if both investigations (positive *H. pylori* by Giemsa or Gimenez staining and presence of histological inflammation, atrophy, and intestinal metaplasia) were negative.

Statistical analysis

All statistical analyses were non-parametric. To determine whether the findings of *H. pylori*-positive or *H. pylori*-negative patients diagnosed by the Kyoto classification of gastritis reflected the histological findings of gastritis, analysis was performed by the chi-square test and evaluated by sensitivity and specificity. The comparisons of the histological scores between the two groups, such as sex differences, were analysed using the Mann–Whitney U test, and three groups, such as age differences, were analysed using the Kruskal–Wallis test. Data were statistically analysed using EZR [12], a modified version of R commander designed to add statistical functions that are frequently used in biostatistics. Statistical significance was set at $p<0.05$.

RESULTS

Comparison of the findings of gastritis diagnosed by the Kyoto classification and histological gastritis

In total, 303 patients (172 women; mean age, 55.5 years) were diagnosed as *H. pylori* positive, and 258 patients (146 women; mean age, 43.7 years) were diagnosed as *H. pylori* negative according to the Kyoto classification of gastritis. There was no sex difference in the *H. pylori* infection rate (women, 54.1%; men, 53.9%).

A total of 299 patients were diagnosed as *H. pylori* positive by endoscopic findings according to the Kyoto classification of gastritis with confirmed histological gastritis for most cases; however, this was not the case for four patients for whom histological gastritis was not confirmed. In contrast, among the 254 patients with *H. pylori*-negative endoscopic findings, histological gastritis was subsequently confirmed in four patients. Therefore, endoscopic findings using the Kyoto classification of gastritis had 98.7% sensitivity and 98.4% specificity for histological gastritis (Table 1). In addition, patients were allocated to three age groups, 20–39, 40–59, and 60–79 years, and the three age groups showed high sensitivity and specificity (sensitivity of 95.9%, 98.3%, and 100.0% and specificity of 100.0%, 97.6%, and 96.7%, respectively) (Table 2).

Age and sex differences in pathological status by the Sydney System scores in H. pylori-positive and H. pylori-negative cases

Figure 2 shows the average scores for inflammation, atrophy, and intestinal metaplasia in the pyloric and fundic mucosae according to *H. pylori* infection status based on endoscopic findings, as evaluated by the Sydney System score (Figure 2). Inflammation was highly prevalent in the pyloric glands of the younger age group than in other age groups of *H. pylori*-positive patients, and it significantly declined with age

(p<0.05). On the other hand, atrophy and intestinal metaplasia progressed with age (p<0.05). The pyloric and fundic gland inflammation in the younger age group was more severe in women than in men (p<0.05) (Table 3). In addition, fundic gland intestinal metaplasia in the elderly group was more severe in men than in women (p<0.05). No significant sex differences were observed in regard to atrophy in the pyloric and fundic gland mucosae. Conversely, in cases diagnosed as *H. pylori* negative based on endoscopic findings, inflammation, atrophy, and intestinal metaplasia of the antrum and corpus were rarely observed (antrum and corpus: 0.02, 0.01, and 0.01, respectively), and no change was observed with ageing.

DISCUSSION

Our study demonstrated that the Kyoto classification of gastritis is a useful method to diagnose not only *H. pylori* infection but also histological gastritis, regardless of age. In *H. pylori*-positive patients, atrophy and intestinal metaplasia progressed with age, and inflammation reduced with age. Regarding sex differences, inflammation in the younger group was more severe in women than in men, and fundic gland intestinal metaplasia in the elderly group was more severe in men than in women.

The Kyoto classification of gastritis has been established to determine the presence or absence of *H. pylori* infection based on endoscopic findings, and the gastritis category is divided into current infection, eradication, and non-infection [6]. In the Kyoto classification of gastritis, various endoscopic features have been found to be associated with *H. pylori* infection in several countries [7-10]. Our previous study found that the 'Kyoto classification of gastritis' was a useful method for diagnosing histological gastritis based on endoscopic findings and the presence or absence of *H. pylori* infection in young Japanese people (sensitivity, 98.5%; specificity, 100%) [13]. To the best of our knowledge, there are no reports comparing endoscopic findings according to the Kyoto classification of gastritis and histological findings by age and sex differences, and our study is the first of its kind.

Gastric mucosal atrophy and intestinal metaplasia are strongly associated with the development of gastric cancer [2, 3, 14, 15]. The risk of developing gastric cancer increases with age [16, 17]. Song et al. reported that the incidence rate of gastric cancer is elevated in older age groups, regardless of sex [16]. This result is the same as that observed in Japan [17]. In our study, atrophy and intestinal metaplasia progressed with age. This result is correlated with the relationship between increasing age-related alterations in the background gastric mucosa and the development of gastric cancer.

Gastric cancer is more common in men than in women, and the age-standardised and cumulative incidence rates of gastric cancer are twice as high in men compared with those in women [16-19]. In our study, intestinal metaplasia of the corpus was significantly more severe in older men, suggesting that the incidence of gastric cancer is higher in men.

Inflammation among young women was higher than that among men in both the antrum and corpus of the stomach. The reason for this remains unclear; however, it may be due to the high frequency of NG in younger women [20-24]. Luzza et al. [20] reported that gastritis scores such as inflammation were higher (p<0.0001) in those with antral nodularity (n=34) than in those without (n=50) [20]. Miyamoto et al. [21] investigated the proportion of NG due to *H. pylori* infection in adult patients. They reported that the prevalence of NG was highest at 2.2% in the age group of 16–19 years old and gradually decreased with age and the sex ratio of NG in adults showed a female predominance (odds ratio [OR], 3.5; 95% CI, 2.5–4.9) [21]. NG causes strong inflammation and, therefore, poses a high risk of diffuse gastric cancer, and the OR for the risk of gastric cancer in patients with NG was 2.1 (95% CI, 0.3–15.3) in the age group of 40 years old [21, 22]. Overall, the prevalence of gastric cancer by age group published by the National Cancer Center in Japan in 2015 [25] showed that gastric cancer predominantly occurs in men. However, only younger women, such as those aged 20–39 years, are more likely to have

238 gastric cancer than men (sex ratio of gastric cancer incidence in the age group of 20–
239 39 years old: M/F=0.37–0.90). Our study showed that the endoscopic findings of NG
240 were more frequently observed in younger women than in men (12.8% vs. 63%). The
241 effects of different sex hormones have been reported as the reason for sex-related
242 differences in inflammation; however, it is not clear why inflammation is more severe in
243 women [26, 27]. These data may indicate that younger women are more susceptible to
244 gastric cancer than men because of the strong association between inflammation and
245 carcinogenesis [28].

246 Our study has several limitations. First, this was a retrospective study. Second, biopsy
247 specimens were obtained only from the greater or lesser curvature of the antrum and
248 corpus. Thus, our histological findings of gastritis may not be representative of the entire
249 stomach. However, inflammation and atrophy appear as diffuse changes and can be
250 diagnosed using spot biopsies. Finally, we could not exclude patients with previous
251 infections that had been accidentally completely eradicated, and *H. pylori* infection was
252 diagnosed using histological Giemsa or Gimenez staining. Therefore, the result of no
253 histological gastritis, which was diagnosed as endoscopic gastritis, may have occurred
254 after accidental eradication. However, we evaluated *H. pylori* eradication using the results

of past questionnaires and medical records. The sensitivity and specificity of these staining methods were 88% and 98%, respectively [29, 30].

If these data can be reproduced in a prospective validation study, the assessment of the gastric mucosa diagnosed according to the Kyoto classification of gastritis can provide a real-time diagnosis based on the histological findings of the gastric mucosa, which may be cost saving. Furthermore, our study did not use magnification or chromoendoscopy; therefore, it may be more likely to improve the endoscopic diagnosis of gastric mucosal changes using magnification or chromoendoscopy.

In conclusion, our present study demonstrates that the Kyoto classification of gastritis is useful for diagnosing both *H. pylori* infection and histological gastritis based on endoscopic findings, regardless of age. Because Japanese individuals have severe inflammation of the gastric mucosa due to *H. pylori* infection at a young age, early detection of *H. pylori* and prompt curative eradication therapy are important to prevent the onset of gastric cancer.

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DISCLOSURE OF INTEREST

The authors report no conflict of interest.

STATEMENT OF ETHICS

All patients provided informed consent, and the research protocol was approved by the Ethics Committee of Kawasaki Medical School (approval number: 3319-3).

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No funding was received for this study.

AUTHOR CONTRIBUTIONS

NS, KH, TK, and NM conceived and designed the study. NS, KH, MS, NM, YY, SF, and TT analysed and interpreted the data. KH and TA provided pathological reviews. NS, KH, and TT wrote the manuscript. NS, KH, TK, NM, and AS contributed to the study materials and patients. KH and TT contributed to study supervision. All authors approved the final version of the manuscript for submission.

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TABLES

Table 1: The concordance rate between *Helicobacter pylori*-infectious gastritis diagnosed by the Kyoto classification of gastritis and histological gastritis (sensitivity and specificity)

		Histological gastritis via biopsy specimens		
		Positive	Negative	Total
H. pylori infection via the Kyoto classification	Positive	299	4	303
	Negative	4	254	258
Total		303	258	561

Sensitivity: 299/303=98.7%

Specificity: 254/258=98.4%

Positive predictive value: 299/303=98.7%

Negative predictive value: 254/258=98.4%

Accuracy: 553/561=98.6%

Table 2: The concordance rate between *Helicobacter pylori*-infectious gastritis diagnosed by the Kyoto classification of gastritis and histological gastritis by age difference (sensitivity and specificity)

Young age group (20–39 years old)

		Histological gastritis via biopsy specimens		
		Positive	Negative	Total
H. pylori infection via the Kyoto classification	Positive	47	0	47
	Negative	2	115	117
Total		49	115	164

Sensitivity, 47/49=95.9%; specificity, 115/115=100.0%; $p<0.05$

Middle age group (40–59 years old)

		Histological gastritis via biopsy specimens		
		Positive	Negative	Total
H. pylori infection via	Positive	118	2	120

the Kyoto classification	Negative	2	81	83
Total		120	83	203

Sensitivity, 118/120=98.3%; specificity, 81/83=97.6%; $p<0.05$

Elderly age group (60–79 years old)

		Histological gastritis via biopsy specimens		
		Positive	Negative	Total
H. pylori infection via the Kyoto classification	Positive	134	2	136
	Negative	0	58	58
Total		134	60	194

Sensitivity, 134/134=100.0%; specificity, 58/60=96.7%; $p<0.05$

Table 3: The comparison of background gastric mucosal histological findings in *Helicobacter pylori*-positive cases by sex

Inflammation

	Biopsy	Male	Female	*P* value
20–39 (M, n=20; F, n=27)	Antrum	2.15±0.08	2.44±0.11	0.039 (<0.05)
	Corpus	1.15±0.23	1.89±0.16	0.014 (<0.05)
40–59 (M, n=51; F, n=69)	Antrum	2.12±0.09	2.14±0.09	0.736 (NS)
	Corpus	1.08±0.12	1.35±0.11	0.11 (NS)
60–79 (M, n=60; F, n=76)	Antrum	1.90±0.10	1.72±0.09	0.17 (NS)
	Corpus	1.48±0.13	1.43±0.11	0.84 (NS)

Atrophy

	Biopsy	Male	Female	*P* value
20–39	Antrum	1.00±0.22	0.85±0.16	0.726 (NS)

(M, n=20; F, n=27)	Corpus	0.30±0.14	0.48±0.15	0.358 (NS)
40–59	Antrum	1.47±0.13	1.54±0.11	0.756 (NS)
(M, n=51; F, n=69)	Corpus	0.76±0.13	0.91±0.10	0.195 (NS)
60–79	Antrum	1.68±0.13	1.53±0.11	0.385 (NS)
(M, n=60; F, n=76)	Corpus	1.05±0.13	0.91±0.09	0.534 (NS)

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402 Intestinal metaplasia

	Biopsy	Male	Female	*P* value
20–39	Antrum	0.40±0.22	0.22±0.13	0.656 (NS)
(M, n=20; F, n=27)	Corpus	0.05±0.04	0.04±0.05	0.854 (NS)
40–59	Antrum	0.29±0.11	0.20±0.07	0.649 (NS)
(M, n=51; F, n=69)	Corpus	0.10±0.13	0.04±0.10	0.192 (NS)
60–79	Antrum	0.70±0.13	0.64±0.12	0.525 (NS)

(M, n=60; F, n=76)	Corpus	0.32±0.11	0.05±0.03	0.040 (<0.05)

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404 *P* value, male versus female; NS, not significant

405 The mean±SE of inflammation, atrophy, and intestinal metaplasia scores

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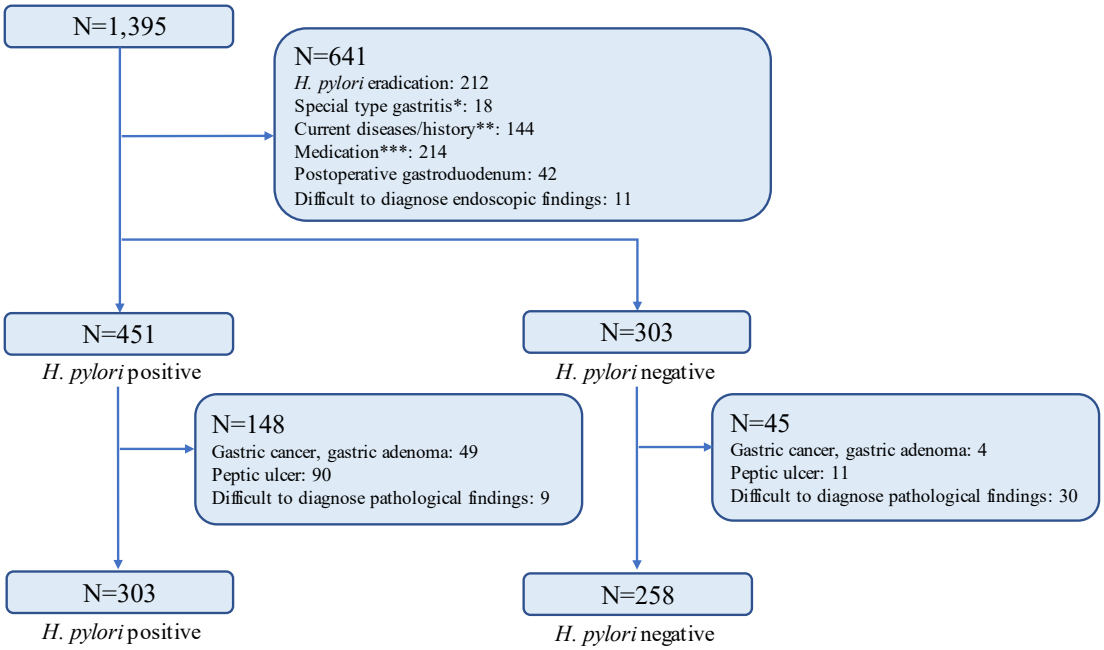
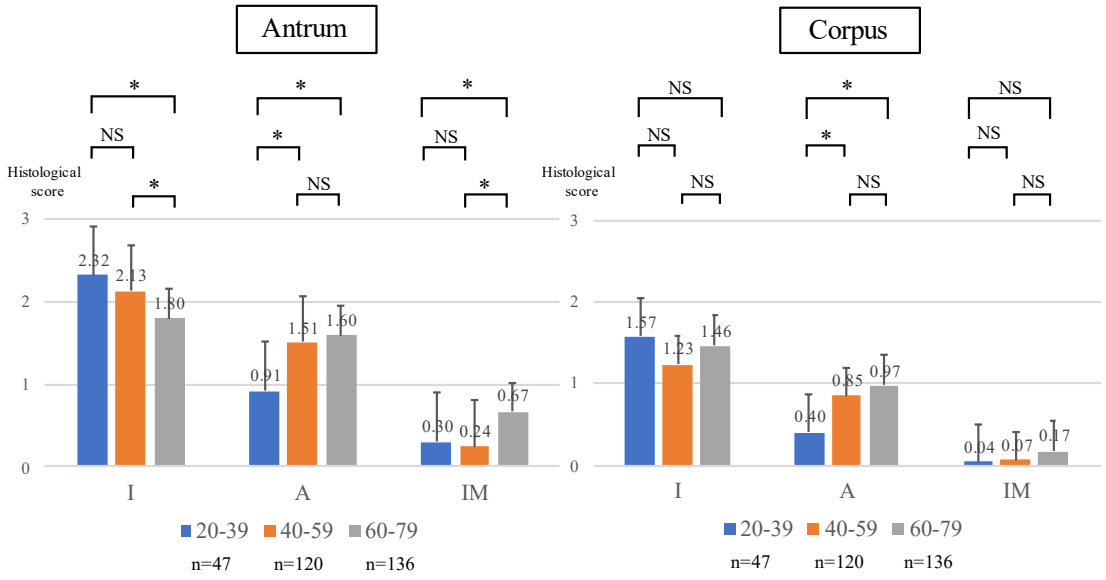
FIGURES

Figure 1



*Autoimmune gastritis, eosinophilic gastroenteritis, acute gastric mucosal lesion, portal hypertensive gastropathy, and Ménétrier disease
**Inflammatory bowel disease, hematological tumor, renal dysfunction, and collagen disease
***Nonsteroidal anti-inflammatory drugs, H_2-receptor antagonists, proton pump inhibitors, rebamipide, immunesuppressors, and immunomodulators

Figure 2



Histological score 0：none, 1：mild, 2：moderate, 3：severe

*p<0.05　　NS：Not Significant

FIGURE CAPTIONS:

Figure 1. Diagram of the enrolment of study participants.

Figure 2. Comparison of background gastric mucosal histological findings in *Helicobacter pylori*-positive patients by age.

The mean ± SE of inflammation, atrophy, and intestinal metaplasia scores of pyloric and fundic mucosal biopsies in *H. pylori*-positive patients according to three age groups.

The vertical axis shows the updated Sydney System score. The horizontal axis shows inflammation, atrophy, and intestinal metaplasia divided into the pyloric and fundic glands. The bar graph is colour-coded by three age groups.

I, inflammation; A, atrophy; IM, intestinal metaplasia.