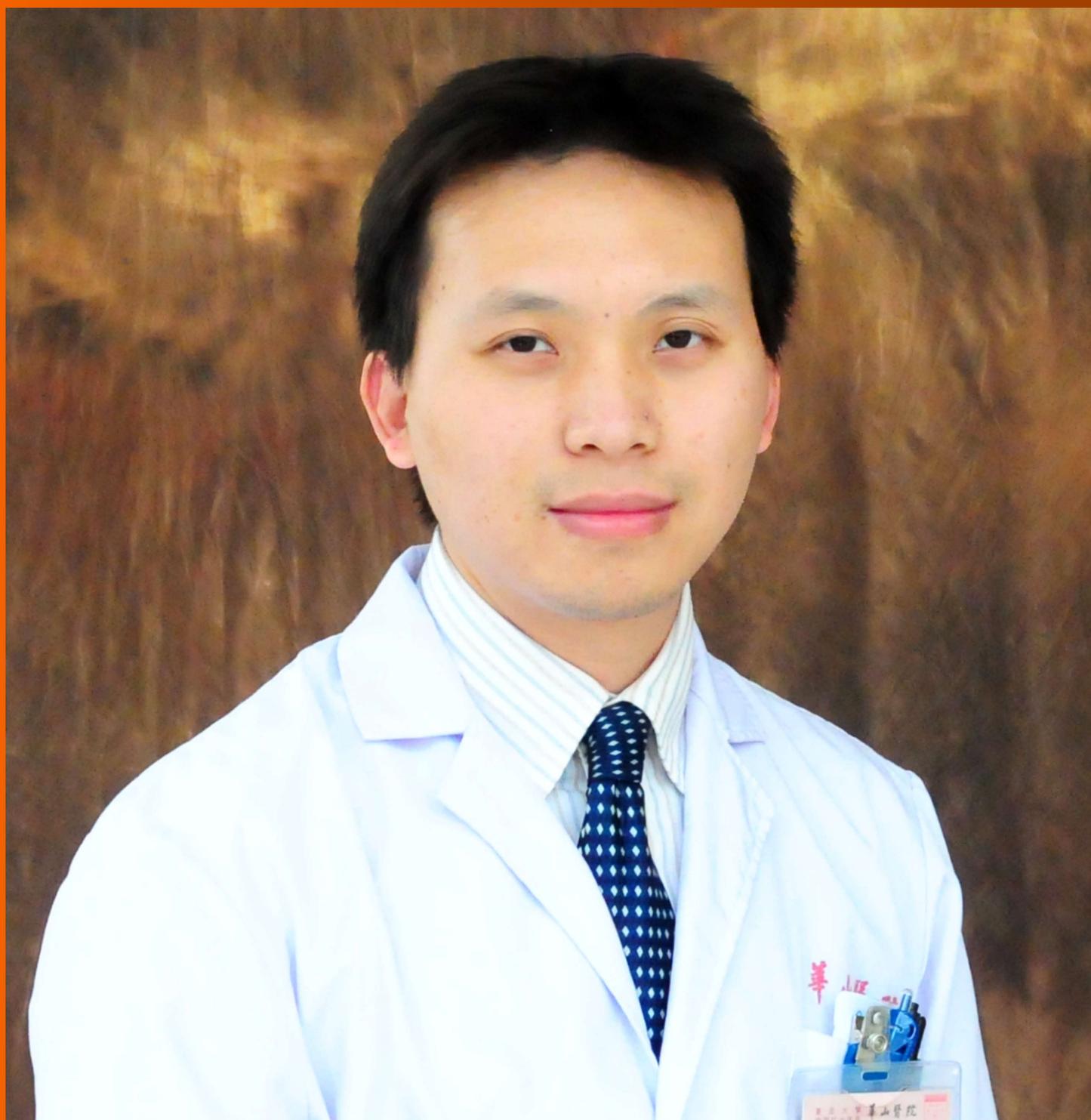


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## Retrospective Cohort Study

***Helicobacter pylori* infection in subjects negative for high titer serum antibody**

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**Author contributions:** All authors were involved in designing the study; Toyoshima O, Nishizawa T and Suzuki H prepared the manuscript; Watanabe H was involved with histological diagnoses; Toyoshima O contributed to statistical analyses.

**Institutional review board statement:** This retrospective study was approved by the Ethical Review Committee of Hattori Clinic on September 7, 2017.

**Informed consent statement:** Written informed consents were obtained from the participants.

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**Abstract****AIM**

To investigate the clinicopathological features of the patients testing negative for high titer serum anti-*Helicobacter pylori* (*H. pylori*) antibody.

**METHODS**

The antibody titers were measured using antigens

derived from Japanese individuals. <sup>13</sup>C-urea breath test-positive individuals were defined as having *H. pylori* infection. We investigated the demographic characteristics, laboratory data, endoscopic findings including Kyoto classification of gastritis, and histology in negative-high titer patients without *H. pylori* eradication therapy. Kyoto classification consisted of scores for gastric atrophy, intestinal metaplasia, enlarged folds, nodularity, and redness.

### RESULTS

Of the 136 subjects enrolled, 23 (17%) had *H. pylori* infection. Kyoto classification had an excellent area under the receiver operating characteristics curve (0.886, 95% confidence interval: 0.803-0.968,  $P = 3.7 \times 10^{-20}$ ) for predicting *H. pylori* infection with a cut-off value of 2. Further, Kyoto classification, *H. pylori* density, and neutrophil activity had high accuracies (89.7%, 96.3%, and 94.1%, respectively). Kyoto classification was independent of the demographic and laboratory parameters in multivariate analysis.

### CONCLUSION

Endoscopic Kyoto classification of gastritis is a useful predictor of *H. pylori* infection in negative-high titer antibody patients.

**Key words:** Kyoto classification; Gastritis; *Helicobacter pylori*; Antibody; Endoscopy

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**Core tip:** Compared with negative-low titer (< 3 U/mL on E-plate Eiken kit), negative-high titer (3-9.9 U/mL) have been reported to be at higher risk for intestinal gastric cancer. *Helicobacter pylori* (*H. pylori*)-infected patients accounted for 94% of gastric cancer patients with an antibody titer of < 10 U/mL. Seventeen percent of subjects with negative-high titer serum anti-*H. pylori* antibody tested positive for *H. pylori* infection. Endoscopic Kyoto classification of gastritis was an excellent predictor of *H. pylori* infection with large area under the receiver operating characteristics curve (0.886), cut-off value of 2, and high accuracy (89.7%), indicating its high confidence.

Toyoshima O, Nishizawa T, Arita M, Kataoka Y, Sakitani K, Yoshida S, Yamashita H, Hata K, Watanabe H, Suzuki H. *Helicobacter pylori* infection in subjects negative for high titer serum antibody. *World J Gastroenterol* 2018; 24(13): 1419-1428 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i13/1419.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i13.1419>

## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is a group 1 carcinogen

for gastric cancer. Therefore, the International Agency for Research on Cancer has recommended screening for and eradication of *H. pylori* for preventing gastric cancer<sup>[1]</sup>. The main non-invasive methods for diagnosing *H. pylori* infection are the serum immunoglobulin G antibody test, <sup>13</sup>C-urea breath test (UBT), and stool antigen test. Endoscopy, histology, culture, and rapid urease test have been used as the main invasive methods. The Maastricht V/Florence consensus report states that the urea breath test using <sup>13</sup>C-urea is the best test to diagnose *H. pylori* infection<sup>[2,3]</sup>. However, some of the available serum antibody kits including E-plate Eiken are excellent kits, with sensitivity and specificity above 90%<sup>[4,5]</sup>. Serology is hardly affected by the changes in the stomach that result in a low bacterial load, including gastrointestinal bleeding, atrophic gastritis, gastric mucosa-associated lymphoid tissue lymphoma, and gastric carcinoma<sup>[2,6]</sup>. Additionally, proton pump inhibitors and antibiotics have little influence on serological tests as well<sup>[7]</sup>. A serological test, with levels of serum anti-*H. pylori* antibody and pepsinogen I and II, is useful for identifying patients at increased risk of gastric cancer<sup>[2,8,9]</sup>. These are some of the merits of serological testing. However, subjects with an E-plate antibody titer of < 10 U/mL include patients with spontaneous disappearance of *H. pylori* from the gastric mucosa, who are known to have extremely severe gastritis and high risk for gastric cancer<sup>[10]</sup>.

In clinical practice, in addition to evaluating the results of *H. pylori* serology as a categorical variable (*i.e.*, positive or negative), it is also important to consider the titer of *H. pylori* antibodies because there is a relationship between the antibody titer and the risk of gastric cancer. We mainly use the E-plate Eiken kit as an anti-*H. pylori* antibody test in Japan. The cut-off titer of this kit for diagnosing *H. pylori* infection is  $\geq 10$  U/mL, while the lower sensitivity limit of this kit is 3 U/mL. Previous reports have defined the titer between 3 and 9.9 U/mL as negative-high titer, and the titer < 3 U/mL as a negative-low titer. Compared with the negative-low titer, the negative-high titer has been reported to carry a higher risk, especially for intestinal gastric cancer in subjects with gastric atrophy<sup>[10-12]</sup>.

There are some false negative results when screening for current *H. pylori* infection in patients with an E-plate antibody titer of < 10 U/mL. *H. pylori*-infected patients accounted for 94% of patients with gastric cancer with an E-plate antibody titer of < 10 U/mL. Additionally, in patients with gastric cancer with an E-plate antibody titer of < 10 U/mL, *H. pylori* infection was associated with higher titers of antibodies<sup>[13]</sup>.

Thus, seronegative-high titer antibody is associated with gastric cancer. However, the clinicopathological characteristics of negative-high titer patients, including the prevalence of *H. pylori* infection, have not been studied extensively. This study focused on serum negative-high titer antibody subjects without history

of *H. pylori* eradication therapy and investigated the features of *H. pylori*-infected patients in the category.

## MATERIALS AND METHODS

### Subjects

We conducted this retrospective case-control study in patients with negative-high titer serum anti-*H. pylori* antibodies, who underwent esophagogastroduodenoscopy (EGD) and histological evaluation based on the updated Sydney system at Toyoshima Endoscopy Clinic between September 2016 to May 2017. EGDs were performed for screening, surveillance for gastrointestinal diseases, and investigation of some symptoms or abnormal results of the other assessments. We did not include subjects with history of gastric cancer, gastrectomy, *H. pylori* eradication therapy, and severe concomitant illnesses, and those who did not consent to this study. The following demographic characteristics were collected from the medical records: age, sex, body mass index (BMI), first-degree family history of gastric cancer, smoking history, and habitual drinking<sup>[14]</sup>. A score of at least 400 on the Brinkman index was defined as positive smoking history. Consumption of at least one drink of alcohol per day was defined as habitual.

This retrospective study was approved by the Ethical Review Committee of Hattori Clinic on September 7, 2017. Written informed consents were obtained from the participants. All clinical investigations were conducted according to the ethical guidelines of the Declaration of Helsinki.

### Diagnosis of *H. pylori* and related findings

The *H. pylori* antibody titer was measured in the blood samples obtained at the time of the first visit or EGD. The antibody titer was measured using an enzyme immunoassay kit using antigens derived from Japanese individuals (E-plate Eiken *H. pylori* antibody II; Eiken Chemical, Tokyo, Japan). A negative-high titer was defined as 3-9.9 U/mL of anti-*H. pylori* antibodies.

UBT-positive individuals were defined as subjects with *H. pylori* infection<sup>[2,15,16]</sup>. We performed UBT using a 100 mg <sup>13</sup>C-urea tablet (Pylonic; Sumitomo Dainippon Pharma, Osaka, Japan) after at least 2 wk of cessation of proton pump inhibitors or antibiotics. The result was declared negative if it was lower than 3 per mil.

Kyoto classification of gastritis is based on the sum of scores of the following five endoscopic findings, which are scored from 0 to 8: atrophy, intestinal metaplasia (IM), enlarged folds, nodularity, and redness. A high score represents increased risk for gastric cancer<sup>[13,17]</sup>. Gastric atrophy was classified according to the extent of mucosal atrophy as described by Kimura and Takemoto<sup>[14,18,19]</sup>. C-II and C-III of Kimura-

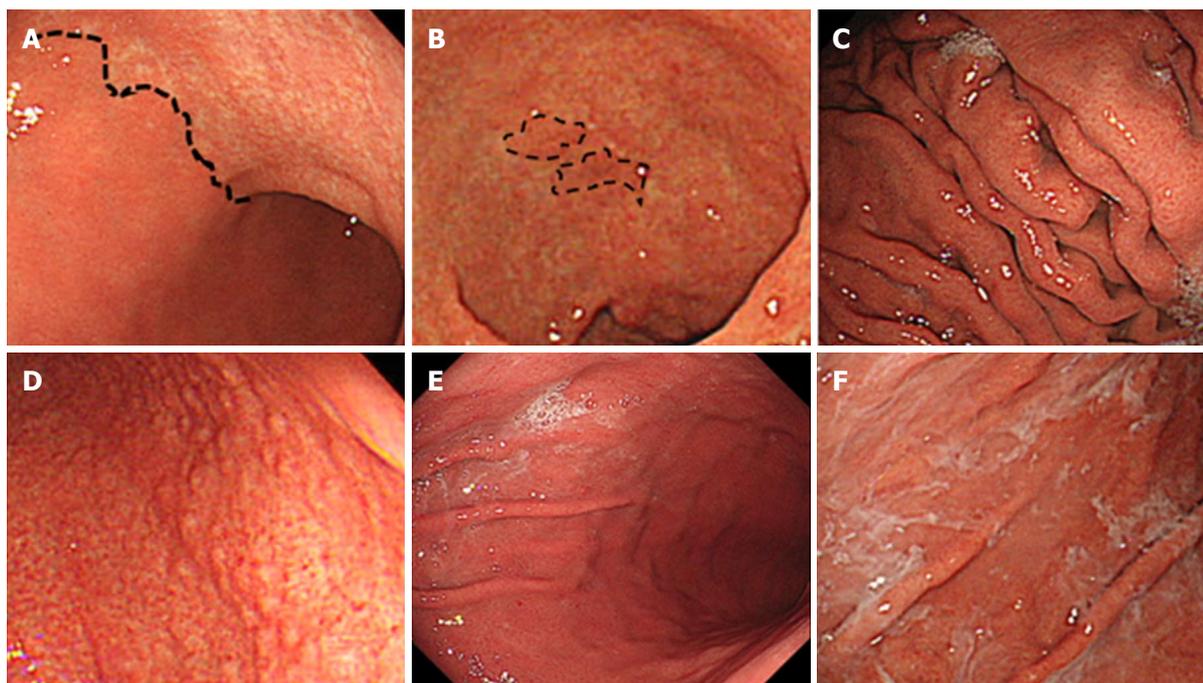
Takemoto classification were scored as 1, and O-I to O-III as 2. IM is observed as grayish-whitish and slightly opalescent patches. IM within the antrum was scored as 1, and IM extending into the corpus as 2. The presence of folds enlarged over 5 mm or more was scored as 1. Nodularity is characterized by the appearance of multiple whitish elevated lesions mainly in the pyloric gland mucosa. The presence of nodularity was scored as 1. Diffuse redness refers to uniform redness involving the entire fundic gland mucosa. The presence of redness with regular arrangements of collecting venules was scored as 1, and that without regular arrangement of collecting venules as 2. We also considered the presence of gastric sticky mucus and gastroduodenal ulcer as positive findings of *H. pylori* infection. On the contrary, gastroesophageal reflux disease, hiatal hernia, and fundic gland polyp were considered as findings of absence of *H. pylori* infection. Sticky mucus refers to grayish or yellowish mucus that adheres to the mucosal surface prior to washing with water. Gastroduodenal ulcer scars were included in the positive group. Grade A or more severe of Los Angeles classification in gastroesophageal reflux disease was defined as positive. We defined hiatal hernia of 2 cm or more as positive. Figure 1A-F shows the representative endoscopic findings related to *H. pylori* infection in negative-high titer patients of this study.

EGDs were performed by 14 expert physicians using Olympus Evis Lucera Elite system with endoscope: GIF-HQ290 or GIF-H290Z (Olympus Corporation, Tokyo, Japan). We carried out EGDs under conscious sedation with midazolam and/or pethidine hydrochloride. The EGD images were retrospectively reviewed by the chief investigator (OT). Any disagreements were resolved by consulting a third reviewer (TN). Discrepancies in diagnoses between the two sets of physicians were resolved through discussions.

Pathological findings were evaluated using the updated Sydney system score, including *H. pylori* density, neutrophil activity, chronic inflammation, IM, and glandular atrophy, with hematoxylin and eosin stains<sup>[20-22]</sup>. The biopsy samples were collected from the greater curvature of the corpus and antrum. We defined one or more score in either of the two points as present. The histological diagnosis was performed by an expert gastrointestinal pathologist, who was not an endoscopist, and was from another organization.

### Statistical analysis

First, we evaluated the effects of age, sex, BMI, family history of gastric cancer, smoking, habitual drinking, serum anti-*H. pylori* antibody titer, endoscopic findings, and histological findings on *H. pylori* infection in univariate analysis using Fisher's exact test or Cochran-Armitage test for categorical variables and Mann-Whitney *U* test for quantitative variables. Next,



**Figure 1** Endoscopic findings related to *Helicobacter pylori* infection. A: Atrophy is diagnosed based on the vascular pattern and rugal atrophy. The dotted line indicates an atrophic border in the anterior wall of the body (43-year-old woman; antibody titer: 4.3 U/mL; UBT: 55.3 per mil; Kyoto classification score: 2); B: Intestinal metaplasia is visible as grayish-whitish, slightly opalescent patches. The dotted line indicates the extent of the lesions in the lesser curvature of the antrum (81-year-old woman; antibody titer: 4.7 U/mL; UBT: 7.3 per mil; Kyoto classification score: 5); C: An enlarged fold is defined as that which is 5 mm or more in diameter. Enlarged folds are present in the greater curvature of the body (56-year-old man; antibody titer: 3.8 U/mL; UBT: 7.0 per mil; Kyoto classification score: 3); D: Nodularity is characterized by the appearance of multiple whitish elevated lesions mainly in the pyloric gland mucosa. Nodularity is present in the antrum (28-year-old man; antibody titer: 9.4 U/mL; UBT: 3.6 per mil; Kyoto classification score: 2); E: Redness refers to uniform redness involving the entire fundic gland mucosa. Redness is visible in the greater curvature of the body (44-year-old man; antibody titer: 8.7 U/mL; UBT: 26.5 per mil; Kyoto classification score: 3); F: Sticky mucus refers to grayish or yellowish mucus adhering to the mucosal surface. There is sticky mucus in the greater curvature of the body (70-year-old woman; antibody titer: 6.5 U/mL; UBT: 26.4 per mil; Kyoto classification score: 4). UBT: Urea breath test.

the values of the area under the receiver operating characteristic curve (AUC) for predicting *H. pylori* infection were compared with the value of 0.5 using the chi-squared test. The cut-off values for predicting *H. pylori* infection were estimated using the Youden index, which is the farthest point on the receiver operating characteristic curve from the positive diagonal<sup>[23]</sup>. We compared AUC values with the use of a chi-square test. Then, the performances of the endoscopic and histological findings for *H. pylori* infection, including accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were investigated. The predictors associated with *H. pylori* infection were subsequently assessed using multiple logistic regression analysis to distinguish the independent factors from other demographic and laboratory variables. A two-sided *P* value less than 0.05 was considered as significant. The data were analyzed using Ekuseru-Toukei 2015 software (Social Survey Research Information, Tokyo, Japan).

## RESULTS

The characteristics of the participants of the present study are shown in Table 1. A total of 136 subjects

were enrolled. The median age of the subjects was 45 (range: 17-82, interquartile range: 37-56) years, and 39% were males. The median titer of *H. pylori* antibody was 4.7 (interquartile range, 3.7-6.6) U/mL. Seventeen percent (*n* = 23) were diagnosed as *H. pylori*-infected based on UBT.

On comparing *H. pylori*-infected and -uninfected patients regarding the demographic characteristics and laboratory data, *H. pylori*-infected patients were older (53 years vs 42 years, *P* = 0.0057), and had higher BMI (22.7 kg/m<sup>2</sup> vs 21.2 kg/m<sup>2</sup>, *P* = 0.028) and serum antibody titer (5.4 U/mL vs 4.7 U/mL, *P* = 0.048). No significant differences due to sex, family history of gastric cancer, habitual smoking, or habitual drinking were demonstrated. Regarding endoscopic findings, we found significant differences between them in Kyoto classification of gastritis score (*P* = 3.8 × 10<sup>-13</sup>), gastric sticky mucus (*P* = 0.013), and fundic gland polyp (*P* = 0.0022). Histologically, *H. pylori* density (*P* = 2.8 × 10<sup>-18</sup>), chronic inflammation (*P* = 4.5 × 10<sup>-10</sup>), and neutrophil activity (*P* = 1.4 × 10<sup>-14</sup>) were significantly different between the two groups (Table 1).

Then, we analyzed AUC for predicting *H. pylori* infection based on the variables that had significant differences between *H. pylori*-infected and -uninfected

Table 1 Characteristics of enrolled subjects

	Total	<i>H. pylori</i> infected <sup>1</sup>	<i>H. pylori</i> uninfected	<i>P</i> value <sup>3</sup>
<i>n</i> (%)	136	23 (17)	113 (83)	
Demographic characteristics				
Age median (IQR), yr	45 (37-56)	53 (44-68)	42 (35-53)	0.0057
Male sex (%)	53 (39)	7 (30)	46 (41)	0.48
Body mass index median (IQR), kg/m <sup>2</sup>	21.2 (19.6-23.7)	22.7 (20.4-25.6)	21.2 (19.5-23.3)	0.028
Family history of gastric cancer, present/absent	12/124	3/20	9/104	0.43
Smoking, present/absent	4/132	0/23	4/109	1.0
Drinking, present/absent	25/111	4/19	21/92	1.0
Laboratory data				
Anti- <i>H. pylori</i> antibody median (IQR), U/mL	4.7 (3.7-6.6)	5.4 (4.2-7.9)	4.7 (3.7-6.4)	0.048
<sup>13</sup> C-urea breath test result median (IQR), per mil	0.3 (0.1-0.8)	19.3 (9.3-26.3)	0.3 (0.1-0.4)	3.6 × 10 <sup>-14</sup>
Endoscopic findings				
Kyoto classification of gastritis <sup>4</sup> , 5/4/3/2/1/0	1/3/14/9/13/96	1/3/8/6/2/3	0/0/6/3/11/93	3.8 × 10 <sup>-13</sup>
Atrophy, 2/1/0	15/20/101	10/4/2009	6/10/97	5.8 × 10 <sup>-12</sup>
Intestinal metaplasia, 1/0	14/122	9/14	5/108	2.9 × 10 <sup>-5</sup>
Enlarged folds, 1/0	5/131	4/19	1/112	0.0029
Nodularity, 1/0	2/134	2/21	0/113	0.028
Redness, 1/0	19/117	12/11	7/106	7.3 × 10 <sup>-7</sup>
Gastric sticky mucus, present/absent	22/114	8/15	14/99	0.013
Gastric ulcer, present/absent	1/135	1/22	0/113	0.17
Duodenal ulcer, present/absent	3/133	1/22	2/111	0.43
Gastroesophageal reflux disease, present/absent	20/116	2/21	18/95	0.53
Hiatal hernia, present/absent	18/118	2/21	16/97	0.74
Fundic gland polyp, present/absent	41/95	1/22	40/73	0.0022
Histological findings <sup>5</sup>				
<i>H. pylori</i> density, present/absent	18/118	18/5	0/113	2.8 × 10 <sup>-18</sup>
Chronic inflammation, present/absent	46/90	21/2	25/88	4.5 × 10 <sup>-10</sup>
Neutrophil activity, present/absent	15/121	15/8	0/113	1.4 × 10 <sup>-14</sup>
Intestinal metaplasia, present/absent	4/132	1/22	3/110	0.53
Glandular atrophy, present/absent	4/132	1/22	3/110	0.53

<sup>1</sup><sup>13</sup>C-urea breath test-positive subjects were defined as *H. pylori*-infected patients; <sup>3</sup>Fisher's exact test, Cochran-Armitage test, or Mann-Whitney *U* test was used as appropriate; <sup>4</sup>Kyoto classification of gastritis was estimated by gastric atrophy, intestinal metaplasia, enlarged folds, nodularity, and redness<sup>[13]</sup>; <sup>5</sup>We defined one or more score classified by the updated Sydney system in either the great curvature of the corpus or the antrum as present. *H. pylori*: *Helicobacter pylori*; IQR: Interquartile range.

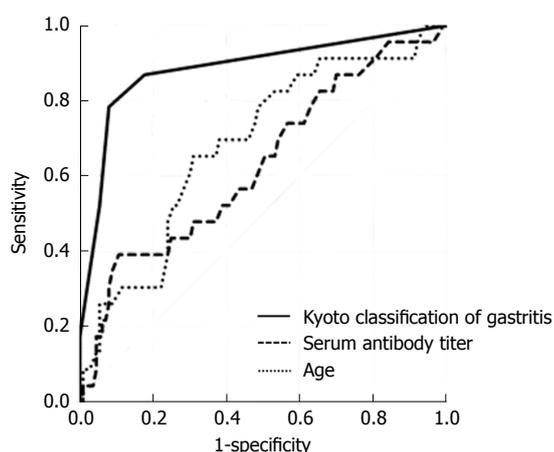


Figure 2 Receiver operating characteristics curves for predicting *Helicobacter pylori* infection. Receiver operating characteristics curves were based on endoscopic Kyoto classification of gastritis score, serum antibody titer, and age in 136 patients with negative-high titer antibody. Positive UBT was defined as *H. pylori* infection. UBT: Urea breath test.

patients (Table 2). AUC of *H. pylori* density (0.891, 95%CI: 0.805-0.977,  $P = 5.6 \times 10^{-19}$ ) was the largest followed by those of Kyoto classification (0.886,

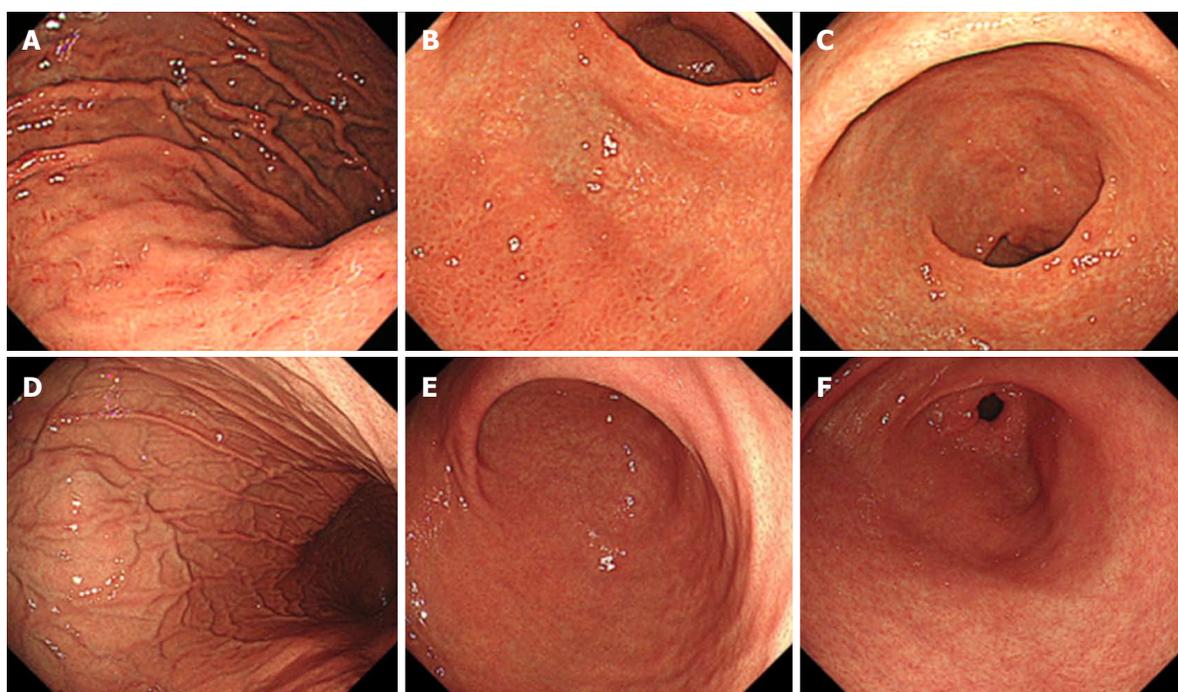
95%CI: 0.803-0.968,  $P = 3.7 \times 10^{-20}$ ) and endoscopic atrophy (0.848, 95%CI: 0.760-0.936,  $P = 7.7 \times 10^{-15}$ ). There was no significant difference between the three AUC values. The cut-off value of Kyoto classification of gastritis score for correlation with *H. pylori* infection was 2 and that of endoscopic atrophy was 1. The receiver operating characteristic curves based on Kyoto endoscopic classification, serum antibody titer, and age in 136 patients with negative-high titer antibody are shown in Figure 2.

The performances of endoscopic and histological findings for *H. pylori* infection are shown in Table 3. The highest accuracy was found in histological *H. pylori* density (96.3%), and its specificity and PPV were 100%. *H. pylori* density also had the second highest NPV (95.8%). The second highest accuracy was in neutrophil activity (94.1%), and its specificity and PPV were 100%. With regards to endoscopic findings, Kyoto classification of gastritis showed the highest accuracy (89.7%). The accuracies of redness, IM, atrophy (1 or more score as positive), enlarged folds, and nodularity followed that of Kyoto classification in order. The highest sensitivity (91.3%) and highest

**Table 2** Area under the receiver operating characteristic curve for predicting *Helicobacter pylori* infection

	AUC	95%CI	P value
Age	0.684	0.564-0.804	0.0027
Body mass index	0.646	0.518-0.774	0.026
Serum antibody titer	0.631	0.500-0.763	0.051
Kyoto classification of gastritis	0.886	0.803-0.968	$3.7 \times 10^{-20}$
Endoscopic atrophy	0.848	0.760-0.936	$7.7 \times 10^{-15}$
Endoscopic intestinal metaplasia	0.674	0.570-0.777	0.0010
Enlarged fold	0.583	0.503-0.662	0.042
Nodularity	0.543	0.485-0.602	0.15
Redness	0.730	0.623-0.837	$2.4 \times 10^{-5}$
Gastric sticky mucus	0.612	0.508-0.716	0.035
Fundic gland polyp	0.655	0.594-0.717	$7.4 \times 10^{-7}$
<i>H. pylori</i> density	0.891	0.805-0.977	$5.6 \times 10^{-19}$
Chronic inflammation	0.846	0.776-0.916	$5.3 \times 10^{-22}$
Neutrophil activity	0.826	0.727-0.926	$1.3 \times 10^{-10}$

Positive urea breath test was defined as *H. pylori* infection. The values of the AUC were compared with the value of 0.5 using the chi-square test. AUC: Area under the receiver operating characteristics curve; CI: Confidence interval; *H. pylori*: *Helicobacter pylori*.



**Figure 3** Representative endoscopic findings of negative-high titer antibody cases. A case with *Helicobacter pylori* infection; 81-year-old woman with antibody titer of 4.7 U/mL, UBT of 7.3 per mil, and Kyoto classification score of 5 (A-C). A: Greater curvature of the body of the stomach. Enlarged folds and redness are present; B: Lower body of the stomach. Endoscopic atrophic border lies in the anterior wall and greater curvature. Redness is present in the greater curvature; C: Antrum. Intestinal metaplasia is present in the lesser curvature. The mucosa is atrophic. A case without *H. pylori* infection; 31-year-old man with antibody titer of 5.7 U/mL, UBT of 1.2 per mil, and Kyoto classification score of 0 (D-F); D: The greater curvature of the body of the stomach. Regular arrangement of collecting venules and fundic gland polyps are present; E: Lower body of the stomach. Atrophy and redness are absent; F: Antrum. Intestinal metaplasia and atrophy are absent. UBT: Urea breath test.

NPV (97.8%) were shown with histological chronic inflammation.

Lastly, Kyoto classification was assessed using multivariate logistic regression analysis to identify any association with the variables such as age, BMI, and serum antibody titer. Kyoto classification was identified as an independent predictor of *H. pylori* infection ( $P = 2.2 \times 10^{-6}$ , Table 4).

Representative endoscopic findings of negative-high titer cases with or without *H. pylori* infection are demonstrated in Figure 3A-F.

## DISCUSSION

We found that 17% of subjects with negative-high titer serum anti-*H. pylori* antibody were positive for *H.*

**Table 3 Performance of endoscopic and histological findings for *Helicobacter pylori* infection**

	Accuracy	Sensitivity	Specificity	PPV	NPV
Endoscopic findings					
Kyoto classification of gastritis <sup>1</sup>	89.7	78.3	92.0	66.7	95.4
Atrophy <sup>2</sup>	85.3	82.6	85.8	54.3	96.0
Intestinal metaplasia	86.0	39.1	95.6	64.3	88.5
Enlarged folds	85.3	17.4	99.1	80.0	85.5
Nodularity	84.6	8.7	100	100	84.3
Redness	86.8	52.2	93.8	63.2	90.6
Gastric sticky mucus	78.7	34.8	87.6	36.4	86.8
Gastric ulcer	83.8	4.3	100	50.0	83.7
Duodenal ulcer	82.4	4.3	98.2	33.3	83.5
Gastroesophageal reflux disease	71.3	8.7	84.1	10.0	81.9
Hiatal hernia	72.8	8.7	85.8	11.1	82.2
Fundic gland polyp	54.4	4.3	64.6	2.4	76.8
Histological findings					
<i>H. pylori</i> density	96.3	78.3	100	100	95.8
Chronic inflammation	80.1	91.3	77.9	45.7	97.8
Neutrophil activity	94.1	65.2	100	100	93.4
Intestinal metaplasia	81.6	4.3	97.3	25.0	83.3
Glandular atrophy	81.6	4.3	97.3	25.0	83.3

<sup>1</sup>A score of 2 or more was defined as positive; <sup>2</sup>A score of 1 or more was defined as positive. The data are presented as %. Positive urea breath test was defined as *H. pylori* infection. PPV: Positive predictive value; NPV: Negative predictive value; *H. pylori*: *Helicobacter pylori*.

**Table 4 Multivariate analysis for independent predictors of *Helicobacter pylori* infection**

	Odds ratio	95%CI	P value
Age	0.98	0.93-1.03	0.49
Body mass index	1.06	0.90-1.24	0.50
Serum antibody titer	1.21	0.87-1.68	0.26
Kyoto classification of gastritis	4.23	2.33-7.67	$2.2 \times 10^{-6}$

*pylori* infection. Higher bacterial counts induce intense immune responses, resulting in subsequent higher antibody titers, while genetic differences between human hosts may affect the antibody levels in response to pathogens<sup>[24]</sup>. Precise diagnosis in patients with seronegativity is necessary to reduce the false negative estimation of gastric cancer risk<sup>[13]</sup>. We should identify *H. pylori*-infected cases in negative-high titer patients and carefully examine them.

Endoscopic Kyoto classification of gastritis proved to be an excellent predictor of *H. pylori* infection with large AUC (0.886), cut-off value of 2, high accuracy (89.7%), and was comparable to histological *H. pylori* density, indicating its high confidence. Kyoto classification also demonstrated to be independent of demographic and laboratory data. These results show that Kyoto classification is useful in the diagnosis of *H. pylori* infection among negative high-titer serum antibody patients. Endoscopic atrophy and nodularity have been attributed to *H. pylori* infection consistently, as was also seen with our results<sup>[25-28]</sup>.

Kyoto classification score is believed to provide an estimate of the risk of gastric cancer. Sugimoto *et al.*<sup>[29]</sup> showed that the mean Kyoto classification score in gastric cancer group was  $4.6 \pm 1.2$ , which

was significantly higher than in gastritis-alone group ( $3.8 \pm 1.1$ ;  $P < 0.001$ ). In subgroup analysis within the cancer group, the mean Kyoto classification score in the *H. pylori*-uneradicated subgroup was  $4.8 \pm 1.1$ , which was significantly higher than that in the eradicated subgroup ( $4.2 \pm 1.2$ ;  $P < 0.001$ ). Our study showed that Kyoto classification score might be useful for not only estimating the risk of gastric cancer but also the prediction of *H. pylori* infection in negative-high titer patients.

Cases with negative-high titer antibodies with negative UBT could include not only subjects who have never been infected but also patients in whom infections resolved spontaneously<sup>[10,30]</sup>. Patients with spontaneous resolution are known to be at very high risk for gastric cancer. In this study, nine patients with Kyoto classification score 2 or more had negative results with UBT. These cases might be after spontaneous disappearance of *H. pylori* infection. Such patients would need careful surveillance.

Histological *H. pylori* density was the strongest contributing factor to *H. pylori* infection with the largest AUC and highest accuracy (96.3%). Neutrophil activity had the second highest accuracy (94.1%). Several investigators have inferred significant associations of anti-*H. pylori* antibody titers with *H. pylori* density and neutrophil activity<sup>[25,31-33]</sup>. Our findings are in accordance with their reports. Chronic inflammation had the highest sensitivity and NPV. Chronic inflammation has been reported to progress in parallel with increases in serum anti-*H. pylori* antibodies, and our results are consistent with this observation<sup>[25,28,32]</sup>.

*H. pylori*-infected patients were older than the uninfected patients among negative-high titer antibody

participants. Kiso *et al*<sup>[13]</sup> reported that in serum *H. pylori* antibody-negative subjects, those with *H. pylori* infection and gastric cancer were older than those with gastric cancer but without the infection. Our results were concordant with their results. In this study, the BMI of *H. pylori*-infected patients was higher than that of -uninfected patients. Our results are in agreement with the results of a report that concluded a positive association between being overweight and serum *H. pylori* antibody<sup>[34]</sup>.

There are some limitations to this study. We used UBT as the gold standard for *H. pylori* infection; however, its accuracy is not 100%. Better performance in serological screening depends on the use of the appropriate antigens and adjustment of cut-off values<sup>[35]</sup>. As we used antibodies against the Japanese strain, further investigation of the other antibodies is needed. Non-*H. pylori Helicobacter* species, including *H. suis* and *H. felis*, could provoke serum anti-*H. pylori* antibody positivity<sup>[36]</sup>, and anti-*H. pylori* antibody correlates with the presence of cytotoxin associated gene A-positive strains<sup>[37]</sup>; however, we did not assess them. Furthermore, we did not analyze the long-term outcomes in 17% of the patients with negative-high titer anti-*H. pylori* antibodies without history of eradication therapy who had *H. pylori* infection. Further studies should be performed to analyze the long-term outcomes and the association between the presence of CagA positive *H. pylori* infection and Kyoto classification.

In conclusion, 17% of the patients with negative-high titer serum anti-*H. pylori* antibodies without history of eradication therapy had *H. pylori* infection. Endoscopic Kyoto classification of gastritis with a score of 2 or more could predict *H. pylori* infection in negative high-titer patients. Further examination including UBT should be considered in these patients with Kyoto classification score 2 or more.

## ARTICLE HIGHLIGHTS

### Research background

Patients who test negative but in the negative-high titer range of serum anti-*Helicobacter pylori* (*H. pylori*) antibodies are at a high risk for gastric cancer, especially the intestinal type, and sometimes have *H. pylori* infection. Patients with negative-high titers with *H. pylori* infection have higher risk for gastric cancer than do those without *H. pylori* infection.

### Research motivation

The clinicopathological features including *H. pylori* infection rate in the negative-high titer patients are unclear.

### Research objectives

The objective of this research was to elucidate the clinicopathological features of the negative-high titer patients.

### Research methods

The antibody titers were measured using antigens derived from Japanese individuals, E-plate Eiken. <sup>13</sup>C-urea breath test (UBT)-positive individuals were defined as having *H. pylori* infection. We investigated the demographic

characteristics, laboratory data, endoscopic findings including Kyoto classification of gastritis, and histology in negative-high titer patients without history of *H. pylori* eradication therapy.

### Research results

Of the 136 subjects enrolled, 23 (17%) had *H. pylori* infection. Kyoto classification had an excellent area under the receiver operating characteristics curve (0.886) for predicting *H. pylori* infection, with a cut-off value of 2. Further, Kyoto classification had high accuracy (89.7%). Kyoto classification was independent of the demographic and laboratory parameters in multivariate analysis.

### Research conclusions

In this study, 17% of patients with negative-high titer had *H. pylori* infection. Endoscopic Kyoto classification of gastritis with a score of 2 or more could predict *H. pylori* infection in negative high-titer patients. Further investigations including UBT should be considered in these patients.

### Research perspectives

Long-term prospective studies are expected to investigate the role of serum antibody titer and Kyoto classification of gastritis in predicting not only *H. pylori* infection but also the risk of gastric cancer.

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