Original Article

Utility of Kyoto Classification of Gastritis in subjects with a high-negative titer of anti-*Helicobacter pylori* antibody during a medical check-up

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Subjects with a high-negative titer (3–9.9 U/ml) of serum anti-*Helicobacter pylori* (*H. pylori*) antibody represent a heterogeneous group of currently *H. pylori*-infected, *H. pylori*-uninfected, and previously *H. pylori*-infected cases. We investigated the characteristics of subjects with a high-negative titer during a medical check-up and the utility of *H. pylori* infection score, the sum of scores of endoscopic findings based on the Kyoto Classification of Gastritis, for diagnosing *H. pylori* infection. Subjects with ^{13}C-urea breath test-positive or *H. pylori* stool antigen test-positive were diagnosed as currently *H. pylori*-infected. Although around half of subjects with a high-negative titer were after eradication therapy (48.6%), currently *H. pylori*-infected were considerably confirmed (11.7%). *H. pylori* infection score showed a high value of area under the receiver operating characteristic curve [0.92; 95% confidence interval (CI), 0.84–1.00] with the most suitable cut-off value of 1.0 (sensitivity: 0.92; specificity: 0.90). Multivariate logistic regression analysis revealed that *H. pylori* infection score was an independent factor associated with increased prevalence of *H. pylori* infection (odds ratio, 9.53; 95% CI, 2.64–34.40; $p<0.001$). Currently *H. pylori*-infected subjects were considerably included among the subjects with a high-negative titer, and the Kyoto Classification of Gastritis was useful to predict current *H. pylori* infection.

***Key Words*: *Helicobacter pylori*, anti-*H. pylori* antibody, high-negative titer, Kyoto Classification of Gastritis, medical check-up**

Helicobacter pylori (*H. pylori*) is a leading cause of chronic gastritis and peptic ulcers. It is considered that *H. pylori*-induced gastritis is the most important risk factor for gastric cancer.[1] As *H. pylori* causes approximately 90% of non-cardiac gastric cancers and there is evidence that *H. pylori* eradication therapy reduces by 30–40% the incidence of gastric cancer, the international agency for Research on Cancer working group recommends population-based screening and eradication therapy.[2] In Japan, Kyoto global consensus report states that all of *H. pylori*-positive individuals should receive eradication therapy.[3] An accurate, objective, and cost-effective screening method for diagnosing *H. pylori* infection is required in medical check-up.

Detection of serum anti-*H. pylori* antibody, produced during the immune response to *H. pylori* in the gastric mucosa, is a non-invasive test for diagnosing *H. pylori* infection. The antibody titer increases as the immune response becomes stronger and decreases after the successful eradication therapy or the natural disappearance of *H. pylori*. As the test is easy and is not affected by proton pump inhibitors that influence gut microbiota,[4] it is widely used with serum pepsinogen concentration during a medical check-up in Japan. Previously, the cut-off value of the antibody (E plate 'Eiken' *H. pylori* antibody) used in clinical practice for diagnosing *H. pylori* infection was 10 U/ml. However, *H. pylori*-infected subjects were sometimes mixed among the subjects with anti-*H. pylori* antibody <10 U/ml. To increase the sensitivity and to identify subjects with a high-risk for gastric cancer in a medical check-up, the cut-off value has been changed to 3 U/ml since April 2017. Anti-*H. pylori* antibody titer between 3–9.9 U/ml is defined as "high-negative titer," and subjects with a high-negative titer represent a heterogeneous group of currently *H. pylori*-infected, *H. pylori*-uninfected, and previously *H. pylori*-infected cases. They need to undergo esophagogastroduodenoscopy (EGD) and additional examination such as ^{13}C-urea breath test (UBT) or *H. pylori* stool antigen test (HpSA) for diagnosing *H. pylori* infection in Japan. As UBT has high diagnostic accuracy,[5] it is the best recommended non-invasive test in the Maastricht V/Florence consensus report.[6] HpSA is also a non-invasive method that detects directly with high accuracy the *H. pylori*-derived antigen excreted through gastrointestinal tract,[7] and has the advantage of reliably detecting *H. pylori* in the remnants of the stomach after distal gastrectomy.[8]

In evidence-based guidelines for gastric cancer screening 2014 in Japan, EGD is recommended for gastric cancer screening during a medical check-up because there is accumulating evidence that endoscopic screening effectively reduces mortality from gastric cancer.[9–12] EGD is a useful tool to diagnose gastric cancer, and it can also evaluate the progress of atrophic gastritis and the status of *H. pylori* infection at the same time. Kimura-Takemoto Classification was introduced in 1969 to evaluate the progress of atrophic gastritis according to the location of the endoscopic atrophic border.[13] The Kyoto Classification of Gastritis was proposed in 2014 to standardize the endoscopic diagnosis of *H. pylori*-infected gastritis. According to the Kyoto Classification of Gastritis, endoscopic findings of currently *H. pylori*-infected gastric mucosa are diffuse redness, mucosal swelling, enlarged tortuous fold, sticky mucus, and nodularity. These endoscopic findings will be useful to decide whether the gastric mucosa is infected with *H. pylori* or not.

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In this study, we investigated the actual status and the utility of the Kyoto Classification of Gastritis for diagnosing *H. pylori* infection in subjects with a high-negative titer of anti-*H. pylori* antibody during a medical check-up.

Methods

Study design. This is a single-center, retrospective, observational study.

Study population. Between April 2017 to December 2019, a total of 38,789 subjects underwent a medical check-up in the clinic MedCity21. Anti-*H. pylori* IgG antibody was measured in 13,203 subjects and a high-negative titer of anti-*H. pylori* antibody was confirmed in 1,690 subjects (12.8%). This study was focused on 111 subjects with a high-negative titer of anti-*H. pylori* antibody who consulted our clinic and were subsequently examined by UBT or HpSA for diagnosing *H. pylori* infection.

The clinical characteristics [age, sex, body mass index (BMI), alcohol intake, and smoking habit] of these individuals were obtained from their medical records. Exclusion criteria were as follows: lacking data, unknown history of *H. pylori* eradication, and users of proton-pump inhibitor, potassium-competitive acid blocker, low-dose aspirin, nonsteroidal anti-inflammatory drugs, or steroid.

Examinations of *H. pylori* infection. We used the anti-*H. pylori* antibody for the serological diagnosis of *H. pylori* infection (E plate 'Eiken' *H. pylori* antibody; Eiken Chemical Co., Ltd., Tochigi, Japan). The anti-*H. pylori* antibody titer of 3–9.9 U/ml was defined as high-negative titer. Subjects with a high-negative titer underwent UBT using a 100 mg ^{13}C-urea tablet (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) or HpSA (Becton, Dickinson and Company, Bergen, NJ) for diagnosing *H. pylori* infection. A value of UBT ≥2.5‰ was defined as UBT-positive.

Endoscopic examination. Screening with EGD was performed for all subjects with a high-negative titer by several expert endoscopists. We used a 5.4 mm-diameter endoscope for EGD (GIF-XP290N; Olympus Medical Systems Co., Ltd., Tokyo, Japan).

We referred to Kimura-Takemoto Classification to evaluate the progress of atrophic gastritis.[13] The classification scores of gastric atrophy were categorized into seven grades: Closed (C)-0, C-1, C-2, C-3, Open (O)-1, O-2, and O-3. The C-type indicates atrophic pattern with a margin between the non-atrophic fundic mucosa and atrophic mucosa located in the lesser curvature of the stomach. O-type indicates atrophic pattern whose margin does not cross the lesser curvature. We classified them into no atrophy (C-0 or C-1), minor atrophy (C-2 or C-3), and severe atrophy (O-1 to O-3).

Furthermore, we utilized the Kyoto Classification of Gastritis to determine the presence or absence of *H. pylori* infection. The existence of diffuse redness, spotty redness, mucosal swelling, enlarged tortuous fold, sticky mucus, or nodularity suggests currently *H. pylori*-infected gastric mucosa. Diffuse redness is uniform redness with continuous expansion observed in non-atrophic mucosa, and spotty redness is irregular dots-like redness that appears on the background of diffuse redness. We considered spotty redness as one of the findings of diffuse redness in this study. Mucosal swelling is recognized as soft thick mucosa, which may appear uneven in swollen gastric areas.[14,15] Enlarged tortuous fold is a fold that is not flattened or is only partially flattened by insufflation with a thickness ≥5 mm and visually tortuous.[16] Sticky mucus is cloudy mucus adhered to the mucosal surface prior to washing with water. Nodularity is characterized by uniform small granular elevations of the gastric mucosa like goosebumps.[17] Nodularity usually flattens but white dots sometimes remain after eradication therapy of *H. pylori*. We considered the flattening of small granular elevations with or without white dots as negative in this study. Typical images of these endoscopic findings are shown in Fig. 1. The presence of these endoscopic findings, according to the Kyoto Classification of Gastritis, were independently evaluated by three raters with more than five years

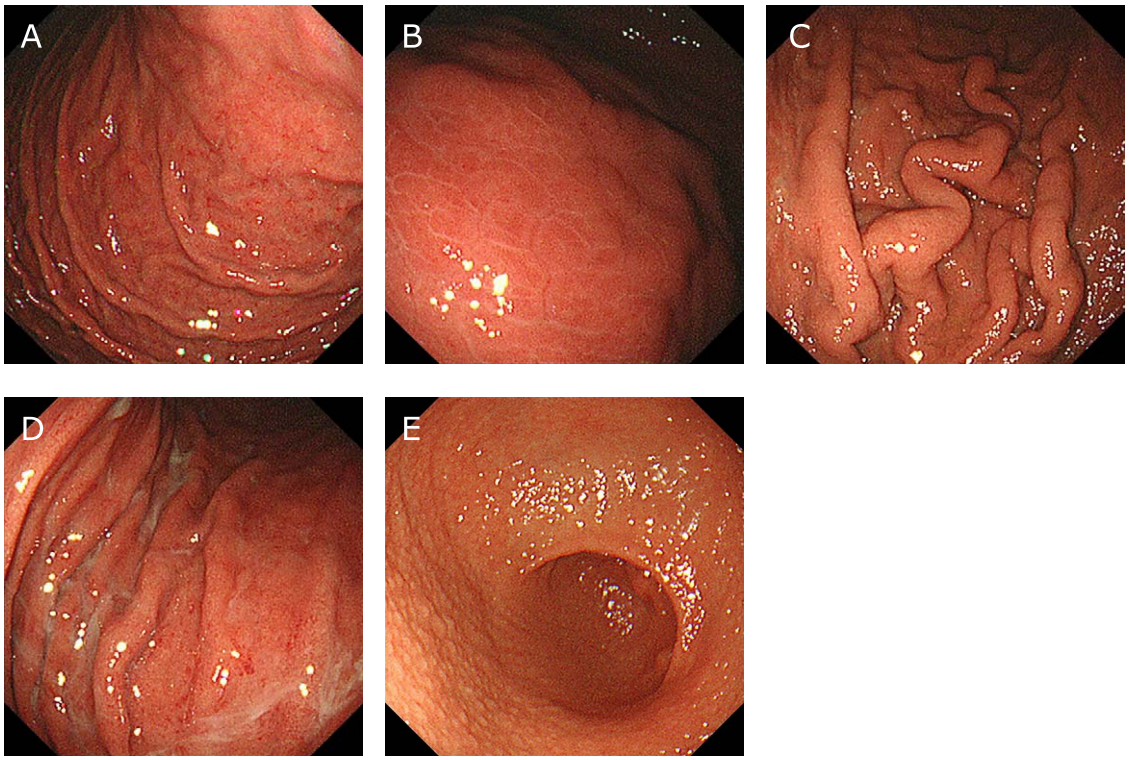

Fig. 1. Typical endoscopic images of currently *H. pylori*-infected gastric mucosa. (A) diffuse redness, (B) mucosal swelling, (C) enlarged tortuous fold, (D) sticky mucus, (E) nodularity.

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of experience of endoscopy who were blinded to eradication history and the results of anti-*H. pylori* antibody, UBT, and HpSA. It was judged to be present if more than two raters agreed on the presence of endoscopic findings.

Assessment of *H. pylori* infection. UBT-positive or HpSA-positive individuals were diagnosed as having current *H. pylori* infection. Individuals with a successful eradication history for *H. pylori* were diagnosed as previously *H. pylori*-infected after eradication therapy. UBT or HpSA was performed for individuals who have not received UBT or HpSA after eradication therapy, and UBT-positive or HpSA-positive individuals were judged as having current *H. pylori* infection.

We developed "*H. pylori* infection score," that is the sum of scores of the following endoscopic findings based on the Kyoto Classification of Gastritis: diffuse redness (none 0, presence 1); mucosal swelling (none 0, presence 1); enlarged tortuous fold (none 0, presence 1); sticky mucus (none 0, presence 1); and nodularity (none 0, presence 1).

Outcome measurement. The primary aim of this study was to examine the actual status and the utility of *H. pylori* infection score based on the Kyoto Classification of Gastritis for diagnosing *H. pylori* infection in subjects with a high-negative titer of anti-*H. pylori* antibody during a medical check-up.

Ethical approval. The study protocol was approved by the ethics committee of Osaka City University Graduate School of Medicine (No. 3763) on May 26, 2017. We have disclosed the information about this study on the webpage of the institution and the subjects had the opportunity to opt out. The study was conducted in accordance with the Declaration of Helsinki ethical principles for medical research involving human subjects.

Statistical analysis. Data are expressed as median and interquartile range (IQR) for continuous variables and as numbers for categorical variables. Receiver operating characteristic (ROC) curves were constructed, and the threshold at which the sum of sensitivity and specificity became maximum was determined as optimal cut-off value for predicting *H. pylori* infection. The Kendall's coefficient of concordance (Kendall's W) was used to assess agreement among raters of endoscopic images. Clinical factors associated with current *H. pylori* infection were investigated using univariate and multivariate logistic regression analysis, and the odds ratio (OR) and 95% confidence intervals (CI) were estimated for each variable. The statistical calculations and analyses were performed using IBM SPSS Statistics ver. 26 (IBM Corporation, Armonk, NY). The ROC curve was constructed using R software, ver. 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria). P values <0.05 were considered statistically significant.

Results

***H. pylori* infection status of subjects with a high-negative titer of anti-*H. pylori* antibody.** Among the 111 subjects with a high-negative titer of anti-*H. pylori* antibody who consulted our clinic for diagnosing *H. pylori* infection, 11.7% were currently *H. pylori*-infected, 48.6% were previously *H. pylori*-infected after eradication therapy, and the others were 39.6% (Table 1).

Table 1. *H. pylori* infection status of subjects with a high-negative titer of anti-*H. pylori* antibody

H. pylori infection status	*n* (%)
Currently *H. pylori*-infected	13 (11.7%)
Previously *H. pylori*-infected after eradication therapy	54 (48.6%)
The others	44 (39.6%)

Table 2. Baseline characteristics of subjects

Variables	Value or *n* (%)
Number of cases	111
Age [years, median (IQR)]	60.0 (51.0, 68.5)
Sex	
Male	53 (47.7%)
Female	58 (52.3%)
BMI [kg/m^2, median (IQR)]	22.7 (20.0, 24.5)
Alcohol intake (5 days/week)	
Yes	28 (25.2%)
No	83 (74.8%)
Smoking habit (current smoker)	
Yes	16 (14.4%)
No	95 (85.6%)
Anti-*H. pylori* antibody [U/ml, median (IQR)]	4.0 (3.0, 6.0)
UBT	
≥2.5‰	10
<2.5‰	88
HpSA	
Positive	3
Negative	10
Atrophy (no atrophy/minor atrophy/severe atrophy)	
All subjects	26/52/33 (23.4%/46.8%/29.7%)
Currently *H. pylori*-infected	0/6/7 (0%/46.2%/53.8%)
Previously *H. pylori*-infected after eradication therapy	1/36/17 (1.9%/66.7%/31.5%)
The others	25/10/9 (56.8%/22.7%/20.5%)
Diffuse redness 1/0	17/94 (15.3%/84.7%)
Mucosal swelling 1/0	5/106 (4.5%/95.5%)
Enlarged tortuous fold 1/0	1/110 (0.9%/99.1%)
Sticky mucus 1/0	8/103 (7.2%/92.8%)
Nodularity 1/0	2/109 (1.8%/98.2%)

IQR, interquartile range; BMI, body mass index; UBT, ^{13}C-urea breath test; HpSA, *H. pylori* stool antigen test.

Table 3. Utility of endoscopic findings based on the Kyoto Classification of Gastritis in predicting *H. pylori* infection

Endoscopic findings	Kendall's W	Sensitivity	Specificity	Accuracy
Diffuse redness	0.81	0.77	0.93	0.91
Mucosal swelling	0.75	0.31	0.99	0.91
Enlarged tortuous fold	0.73	0.08	1.00	0.89
Sticky mucus	0.94	0.39	0.97	0.90
Nodularity	0.90	0.08	0.99	0.88

Baseline characteristics and endoscopic findings of subjects with a high-negative titer of anti-*H. pylori* antibody. The clinical characteristics of the enrolled subjects are shown in Table 2. The median age of subjects with a high-negative titer of anti-*H. pylori* antibody during a medical check-up was 60.0 (IQR, 51.0 to 68.5). The subjects who had been drinking alcohol more than 5 days a week were 28 (25.2%), and those who currently smoked were 16 (14.4%). The median value of the anti-*H. pylori* antibody was 4.0 (IQR, 3.0 to 6.0). UBT positive (≥2.5‰) was confirmed in ten subjects and HpSA was confirmed in three subjects.

In endoscopic findings of Kimura-Takemoto Classification, no atrophy, minor atrophy, and severe atrophy were found in 26, 52, and 33 subjects, respectively. No atrophy was uncommon in currently *H. pylori*-infected and previously *H. pylori*-infected after eradication therapy. In the others, 25 subjects had no atrophy and 19 subjects had minor or severe atrophy. In endoscopic findings of the Kyoto Classification of Gastritis, diffuse redness was found in 17 subjects (15.3%), mucosal swelling was found in five subjects (4.5%), enlarged tortuous fold was found in one subject (0.9%), sticky mucus was found in eight subjects (7.2%), and nodularity was found in two subjects (1.8%).

Utility of endoscopic findings in predicting *H. pylori* infection. We examined the utility of endoscopic findings in predicting *H. pylori* infection in subjects with a high-negative titer of anti-*H. pylori* antibody. The Kendall's W and sensitivity, specificity, and accuracy of diffuse redness, mucosal swelling, enlarged tortuous fold, sticky mucus, and nodularity are shown in Table 3. The Kendall's W was highest in sticky mucus (0.94) and lowest in enlarged tortuous fold (0.73). The sensitivity was highest in diffuse redness (0.77) and the specificity was highest in enlarged tortuous fold (1.00). The accuracy was highest in diffuse redness and mucosal swelling (0.91).

Next, we investigated the utility of the *H. pylori* infection score, which is the summed score of diffuse redness, mucosal swelling, enlarged tortuous fold, sticky mucus, and nodularity, to predict *H. pylori* infection. The ROC curve is shown in Fig. 2. Area under the ROC curve (AUC) of *H. pylori* infection score was 0.92 (95% CI, 0.84–1.00). The optimal cut-off value, the threshold that the sum of sensitivity and specificity became maximum, of *H. pylori* infection score was 1.0 (sensitivity: 0.92; specificity: 0.90).

Clinical factors associated with *H. pylori* infection. We examined the clinical factors associated with *H. pylori* infection, including age, sex, BMI, alcohol intake, smoking habit, anti-*H. pylori* antibody, and *H. pylori* infection score. Univariate logistic regression analysis showed that alcohol intake (≥5 days/week) (OR, 4.28; 95% CI, 1.30–14.10; $p = 0.017$), anti-*H. pylori* antibody titer (OR, 1.73; 95% CI, 1.27–2.34; $p<0.001$), and *H. pylori* infection score (OR, 13.70; 95% CI, 3.85–48.60; $p<0.001$) were significantly associated with *H. pylori* infection. Multivariate logistic regression analysis including alcohol intake, anti-*H. pylori* antibody, and *H. pylori* infection score revealed that the *H. pylori*-infection score was an independent factor associated with the increased prevalence of *H. pylori* infection (OR, 9.53; 95% CI, 2.64–34.40; $p<0.001$) (Table 4).

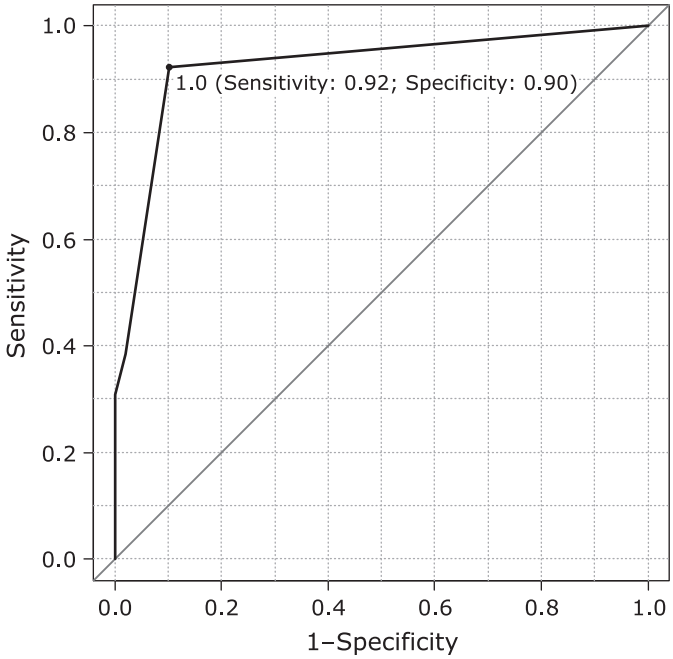

Fig. 2. The ROC curve of *H. pylori* infection score in predicting *H. pylori* infection.

Discussion

In this study, we examined the actual status of subjects with a high-negative titer of anti-*H. pylori* antibody during a medical check-up. We found that currently *H. pylori*-infected subjects were considerably included (11.7%) among the subjects with a high-negative titer. As currently *H. pylori*-infected subjects have a potential risk of developing gastric cancer, they need to be treated with eradication therapy at the earlier stage of mucosal atrophy to prevent gastric cancer.[1] It was previously reported that *H. pylori*-infected was found in 11.7–16.9% in patients with a high-negative titer in clinical practice.[18,19] Although the proportion of currently *H. pylori*-infected was similar to that of our study, this is the first survey on actual status of high-negative titer during a medical check-up. Around half of subjects with a high-negative titer of anti-*H. pylori* antibody (48.6%) were previously *H. pylori*-infected after eradication therapy. Previously *H. pylori*-infected subjects after eradication therapy should be carefully followed up by scheduled endoscopic surveillance. It was reported that the risk of developing gastric cancer was 0.3% per year after the eradication therapy and it increased according to the background mucosal atrophy.[20,21] It is considered that the others include *H. pylori*-uninfected (naïve) and previously *H. pylori*-infected after natural disappearance, unexpected eradication of *H. pylori* due to antibiotics or spontaneous clearance of *H. pylori* after advanced atrophy. It is supposed that 19 subjects (17.1%) with minor or

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Table 4. Univariate and multivariate analyses of factors associated with *H. pylori* infection

Variables	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.01 (0.97–1.07)	0.569		
Sex				
Male	0.93 (0.29–2.97)	0.903		
Female	1.00			
BMI (kg/m^2)	0.98 (0.80–1.19)	0.805		
Alcohol intake (≥5 days/week)				
Yes	4.28 (1.30–14.10)	0.017	1.91 (0.32–11.30)	0.477
No	1.00		1.00	
Smoking habit (current smoker)				
Yes	1.96 (0.48–8.08)	0.351		
No	1.00			
Anti-*H. pylori* antibody (per 1 U/ml increase)	1.73 (1.27–2.34)	<0.001	1.39 (0.92–2.09)	0.119
H. pylori infection score (per 1 score increase)	13.70 (3.85–48.60)	<0.001	9.53 (2.64–34.40)	<0.001

BMI, body mass index; OR, odds ratio; CI, confidence intervals.

severe atrophy among the others are previously *H. pylori*-infected after natural disappearance and should be carefully followed up. Subjects with spontaneous clearance of *H. pylori* after advanced atrophy have the highest risk of developing gastric cancer and they should receive scheduled endoscopic surveillance. Altogether, it is considered that approximately 77.4% of subjects with a high-negative titer (currently *H. pylori*-infected: 11.7%; previously *H. pylori*-infected after eradication therapy: 48.6%; previously *H. pylori*-infected after natural disappearance: 17.1%) have risk of developing gastric cancer. Therefore, high-risk subjects will be overlooked if the previous cut-off value of anti-*H. pylori* antibody (10 U/ml) is applied to diagnose *H. pylori* infection during a medical check-up.

In the current strategy, subsequent additional test (UBT or HpSA) for diagnosing *H. pylori* infection is recommended in subjects with a high-negative titer after the screening EGD. However, we consider that macroscopic endoscopic images enable diagnosis of the *H. pylori* infection status. Toyoshima *et al.*[19] have previously reported that the scores for the endoscopic findings related to the risk of gastric cancer according to the Kyoto Classification of Gastritis can predict *H. pylori* infection in *H. pylori*-infected and *H. pylori*-uninfected subjects with a high-negative titer. The above-mentioned endoscopic findings include atrophy, intestinal metaplasia, fold enlargement, nodularity, and diffuse redness. Although these endoscopic findings may be useful to predict *H. pylori* infection, they cannot distinguish current *H. pylori* infection from a previous *H. pylori* infection because atrophy and intestinal metaplasia remain even after the eradication of *H. pylori*. In this regard, we chose the following five endoscopic findings associated with *H. pylori* infection that disappear relatively quickly after the eradication therapy: diffuse redness, mucosal swelling, enlarged tortuous fold, sticky mucus, and nodularity. We examined the utility of these endoscopic findings to predict *H. pylori* infection in subjects with a high-negative titer. Diffuse redness was mostly found in 15.3% with high sensitivity, specificity, and accuracy. We developed *H. pylori* infection score, the sum of scores of these endoscopic findings, in this study, and the score can be applied even for previously *H. pylori*-infected subjects because the endoscopic findings disappear after the disappearance of *H. pylori*. The *H. pylori* infection score had high AUC (0.92) and high sensitivity and specificity with the cut-off value of 1.0. This means that if the *H. pylori* infection score is ≥1, that is, at least one endoscopic finding is confirmed among the endoscopic findings related to current *H. pylori* infection, the subject is likely to have current *H. pylori* infection. We proved that *H. pylori* infection score could be an independent indicator to predict *H. pylori* infection. Although Suki *et al.*[22] have reported that there is a positive association between *H. pylori* infection and increased BMI, this association was not observed in this study. *H. pylori* infection may be diagnosed during the procedure of screening EGD using the *H. pylori* infection score, and it may substitute additional examinations.

Nishizawa *et al.*[18] revealed that false diagnosis using anti-*H. pylori* antibody was observed in 11.7% of a high-negative titer and combination of anti-*H. pylori* antibody and endoscopic finding based on the Kyoto Classification of Gastritis could provide a more accurate diagnosis of *H. pylori*. This means that we should not easily judge the subjects with a high-negative titer to be *H. pylori*-negative and endoscopic examination is useful to predict the *H. pylori* infection. Furthermore, it is ideal to know not only *H. pylori* infection status but risk of gastric cancer and mortality during a medical check-up. Graham *et al.*[23] have suggested that evaluation of the severity and extent of atrophy leads to the development of a cost-effective surveillance method for gastric cancer. In addition, Inoue *et al.*[24] have recently reported that subjects with a high-negative titer and moderate or severe atrophic gastritis increase the long-term risk of gastric cancer. From these findings, endoscopic diagnosis will be primarily important and we need to establish the best cost-effective surveillance method to diagnose *H. pylori* infection status and pick-up the high-risk subjects for gastric cancer during a medical check-up.

This study has several limitations. First, this is a small sample sized, retrospective study in a single institution; therefore, selection bias is unavoidable. Second, we used UBT or HpSA as the gold standard for diagnosing *H. pylori* infection. However, the combination of more than two types of examinations improves accuracy. Third, we did not assess autoimmune gastritis (type A gastritis). Although autoimmune gastritis is rare, it sometimes results in sticky mucus and urease-positive bacteria other than *H. pylori* gives a UBT-false positive result. We should be careful regarding this point to avoid an endless eradication therapy.[25] Fourth, Kendall's W of mucosal swelling and enlarged tortuous fold was relatively low, and it is considered that these findings are difficult to be judged. To improve the accuracy of *H. pylori* infection score, it is considered that the education for the raters on the Kyoto Classification of Gastritis is necessary.

In conclusion, currently *H. pylori*-infected subjects were considerably included among the subjects with a high-negative titer of anti-*H. pylori* antibody during a medical check-up, and the Kyoto Classification of Gastritis was useful to predict current *H. pylori* infection.

Author Contributions

KO designed, analyzed data, and drafted the paper; TW supervised this study, and revised the paper; SK, YM, and AN evaluated the endoscopic findings based on the Kyoto Classification of Gastritis; YNadatani, SF, SH, FT, NK, KT, YNagami, TT, TK, SF, NK, and YF reviewed the manuscript and provided valid inputs on the study.

Abbreviations

AUC	area under the receiver operating characteristic curve
BMI	body mass index
C	closed
CI	confidence intervals
EGD	esophagogastroduodenoscopy
HpSA	*H. pylori* stool antigen test
IQR	interquartile range
O	open
OR	odds ratio
ROC	receiver operating characteristic
UBT	^{13}C-urea breath test

Conflict of Interest

No potential conflicts of interest were disclosed.

References

1 Uemura N, Okamoto S, Yamamoto S, *et al*. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784–789.
2 Herrero R, Park JY, Forman D. The fight against gastric cancer - the IARC Working Group report. *Best Pract Res Clin Gastroenterol* 2014; **28**: 1107–1114.
3 Sugano K, Tack J, Kuipers EJ, *et al*. Kyoto global consensus report on *Helicobacter pylori* gastritis. *Gut* 2015; **64**: 1353–1367.
4 Takagi T, Naito Y, Inoue R, *et al*. The influence of long-term use of proton pump inhibitors on the gut microbiota: an age-sex-matched case-control study. *J Clin Biochem Nutr* 2018; **62**: 100–105.
5 Gisbert JP, Pajares JM. Review article: ^{13}C-urea breath test in the diagnosis of *Helicobacter pylori* infection — a critical review. *Aliment Pharmacol Ther* 2004; **20**: 1001–1017.
6 Malfertheiner P, Megraud F, O'Morain CA, *et al*. Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. *Gut* 2017; **66**: 6–30.
7 Gisbert JP, Pajares JM. Stool antigen test for the diagnosis of *Helicobacter pylori* infection: a systematic review. *Helicobacter* 2004; **9**: 347–368.
8 Yan J, Yamaguchi T, Odaka T, *et al*. Stool antigen test is a reliable method to detect *Helicobacter pylori* in the gastric remnant after distal gastrectomy for gastric cancer. *J Clin Gastroenterol* 2010; **44**: 73–74.
9 Hamashima C, Ogoshi K, Narisawa R, *et al*. Impact of endoscopic screening on mortality reduction from gastric cancer. *World J Gastroenterol* 2015; **21**: 2460–2466.
10 Matsumoto S, Yoshida Y. Efficacy of endoscopic screening in an isolated island: a case-control study. *Indian J Gastroenterol* 2014; **33**: 46–49.
11 Hosokawa O, Miyanaga T, Kaizaki Y, *et al*. Decreased death from gastric cancer by endoscopic screening: association with a population-based cancer registry. *Scand J Gastroenterol* 2008; **43**: 1112–1115.
12 Matsumoto S, Yamasaki K, Tsuji K, Shirahama S. Results of mass endoscopic examination for gastric cancer in Kamigoto Hospital, Nagasaki Prefecture. *World J Gastroenterol* 2007; **13**: 4316–4320.
13 Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy* 1969; **1**: 87–97.
14 Nomura S, Terao S, Adachi K, *et al*. Endoscopic diagnosis of gastric mucosal activity and inflammation. *Dig Endosc* 2013; **25**: 136–146.
15 Kato T, Yagi N, Kamada T, *et al*. Diagnosis of *Helicobacter pylori* infection in gastric mucosa by endoscopic features: a multicenter prospective study. *Dig Endosc* 2013; **25**: 508–518.
16 Tytgat GN. The Sydney System: endoscopic division. Endoscopic appearances in gastritis/duodenitis. *J Gastroenterol Hepatol* 1991; **6**: 223–234.
17 Miyamoto M, Haruma K, Yoshihara M, *et al*. Nodular gastritis in adults is caused by *Helicobacter pylori* infection. *Dig Dis Sci* 2003; **48**: 968–975.
18 Nishizawa T, Sakitani K, Suzuki H, *et al*. A combination of serum anti-*Helicobacter pylori* antibody titer and Kyoto classification score could provide a more accurate diagnosis of *H pylori*. *United European Gastroenterol J* 2019; **7**: 343–348.
19 Toyoshima O, Nishizawa T, Arita M, *et al*. *Helicobacter pylori* infection in subjects negative for high titer serum antibody. *World J Gastroenterol* 2018; **24**: 1419–1428.
20 Take S, Mizuno M, Ishiki K, *et al*. The long-term risk of gastric cancer after the successful eradication of *Helicobacter pylori*. *J Gastroenterol* 2011; **46**: 318–324.
21 Nishizawa T, Suzuki H, Arano T, *et al*. Characteristics of gastric cancer detected within 1 year after successful eradication of *Helicobacter pylori*. *J Clin Biochem Nutr* 2016; **59**: 226–230.
22 Suki M, Leibovici Weissman Y, Boltin D, *et al*. *Helicobacter pylori* infection is positively associated with an increased BMI, irrespective of socioeconomic status and other confounders: a cohort study. *Eur J Gastroenterol Hepatol* 2018; **30**: 143–148.
23 Graham DY, Asaka M. Eradication of gastric cancer and more efficient gastric cancer surveillance in Japan: two peas in a pod. *J Gastroenterol* 2010; **45**: 1–8.
24 Inoue M, Sawada N, Goto A, *et al*. High-negative anti-*Helicobacter pylori* IgG antibody titers and long-term risk of gastric cancer: results from a large-scale population-based cohort study in Japan. *Cancer Epidemiol Biomarkers Prev* 2020; **29**: 420–426.
25 Furuta T, Baba S, Yamade M, *et al*. High incidence of autoimmune gastritis in patients misdiagnosed with two or more failures of *H. pylori* eradication. *Aliment Pharmacol Ther* 2018; **48**: 370–377.

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