

## Predictive findings for *Helicobacter pylori*-uninfected, -infected and -eradicated gastric mucosa: Validation study

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### Abstract

**AIM:** To validate the usefulness of screening endoscopy findings for predicting *Helicobacter pylori* (*H. pylori*) infection status.

**METHODS:** *H. pylori* infection status was determined by histology, serology, and the urea breath test in 77 consecutive patients who underwent upper endoscopy. Based on the findings, patients were categorized as *H. pylori*-uninfected, -infected, or -eradicated cases. Using six photos of certain sites in the stomach per

case, we determined the presence or absence of the following endoscopic findings: regular arrangement of collecting venules (RAC), linear erythema, hemorrhage, fundic gland polyp (FGP), atrophic change, rugal hyperplasia, edema, spotty erythema, exudate, xanthoma, and mottled patchy erythema (MPE). The diagnostic odds ratio (DOR) and inter-observer agreement (*Kappa* value) for these 11 endoscopic findings used in the determination of *H. pylori* infection status were calculated.

**RESULTS:** Of the 77 patients [32 men and 45 women; mean age (SD), 39.7 (13.4) years] assessed, 28 were *H. pylori* uninfected, 28 were infected, and 21 were eradicated. DOR values were significantly high ( $< 0.05$ ) for the following *H. pylori* cases: uninfected cases with RAC (11.5), linear erythema (24.5), hemorrhage (4.1), and FGP (34.5); for infected cases with atrophic change (8.67), rugal hyperplasia (15.8), edema (14.2), spotty erythema (11.5), and exudate (3.52); and for eradicated cases with atrophic change (32.4) and MPE (103.0). *Kappa* values were excellent for FGP (0.93), good for RAC (0.63), hemorrhage (0.79), atrophic change (0.74), and MPE (0.75), moderate for linear erythema (0.51), rugal hyperplasia (0.49), edema (0.58), spotty erythema (0.47), and exudate (0.46), and poor for xanthoma (0.19).

**CONCLUSION:** The endoscopic findings of RAC, hemorrhage, FGP, atrophic change, and MPE will be useful for predicting *H. pylori* infection status.

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**Key words:** Diagnostic odds ratio; Endoscopic finding; Eradication therapy; *Helicobacter pylori*; Inter-observer agreement

**Core tip:** To determine useful findings for predicting *Helicobacter pylori* (*H. pylori*)-uninfected, -infected,

or -eradicated cases, we evaluated following 11 endoscopic findings, regular arrangement of collecting venules (RAC), linear erythema, hemorrhage, fundic gland polyp (FGP), atrophic change, rugal hyperplasia, edema, spotty erythema, exudate, xanthoma, and mottled patchy erythema (MPE). Among these, RAC, hemorrhage, FGP, atrophic change, and MPE were found to be predictive findings for *H. pylori* infection status on screening endoscopy. The knowledge of these findings may contribute to the early detection of gastric cancer.

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## INTRODUCTION

Gastric cancer remains the second leading cause of cancer death, accounting for 600000 deaths annually worldwide<sup>[1]</sup>. The incidence of gastric cancer is particularly high in Asia, especially in China, Japan and Korea where *Helicobacter pylori* (*H. pylori*) infection is highly prevalent. The risk of gastric cancer can differ depending on whether individuals are uninfected or infected with *H. pylori* or whether the infection has been eradicated<sup>[2-4]</sup>. It is therefore extremely important in the early detection of gastric cancer that *H. pylori* infection status is determined for each of these groups of individuals.

Endoscopy is an essential diagnostic tool for gastric cancer, enabling various findings induced by histological inflammation of the gastric mucosa to be detected. The development of histological gastritis is regarded as rare in *H. pylori*-uninfected cases, but it is usually noted in *H. pylori*-infected cases and improved by eradication therapy. This difference is reflected in the appearance of the gastric mucosa, which has been reported in the form of endoscopic findings in several studies<sup>[5-12]</sup>. However, the predictive value of the findings has not yet been validated.

In this study, we assessed, in a systematic manner, 11 endoscopic findings in dyspeptic patients and evaluated which of the findings were associated with *H. pylori*-uninfected, -infected, and -eradicated cases.

## MATERIALS AND METHODS

### Subjects

A total of 148 consecutive patients with dyspepsia who had undergone upper gastrointestinal endoscopy and had been strictly diagnosed with *H. pylori* infection between December 2008 and April 2009 at the National Center for Global Health and Medicine (NCGM) were identified

from an endoscopic electronic database. The exclusion criteria applied were the use of non-steroidal anti-inflammatory drugs or anti-thrombogenic drugs and a history of gastric surgery, hemorrhagic disease, liver cirrhosis, renal failure, heart failure, or early or advanced gastric cancer, because these conditions could affect the mucosal appearance of the stomach<sup>[13-16]</sup>. After exclusion, 77 cases remained for analysis.

Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki and its subsequent revision. The study protocol was approved by the Ethics Committee of NCGM (approval No. 811).

### Diagnosis of *H. pylori* infection status

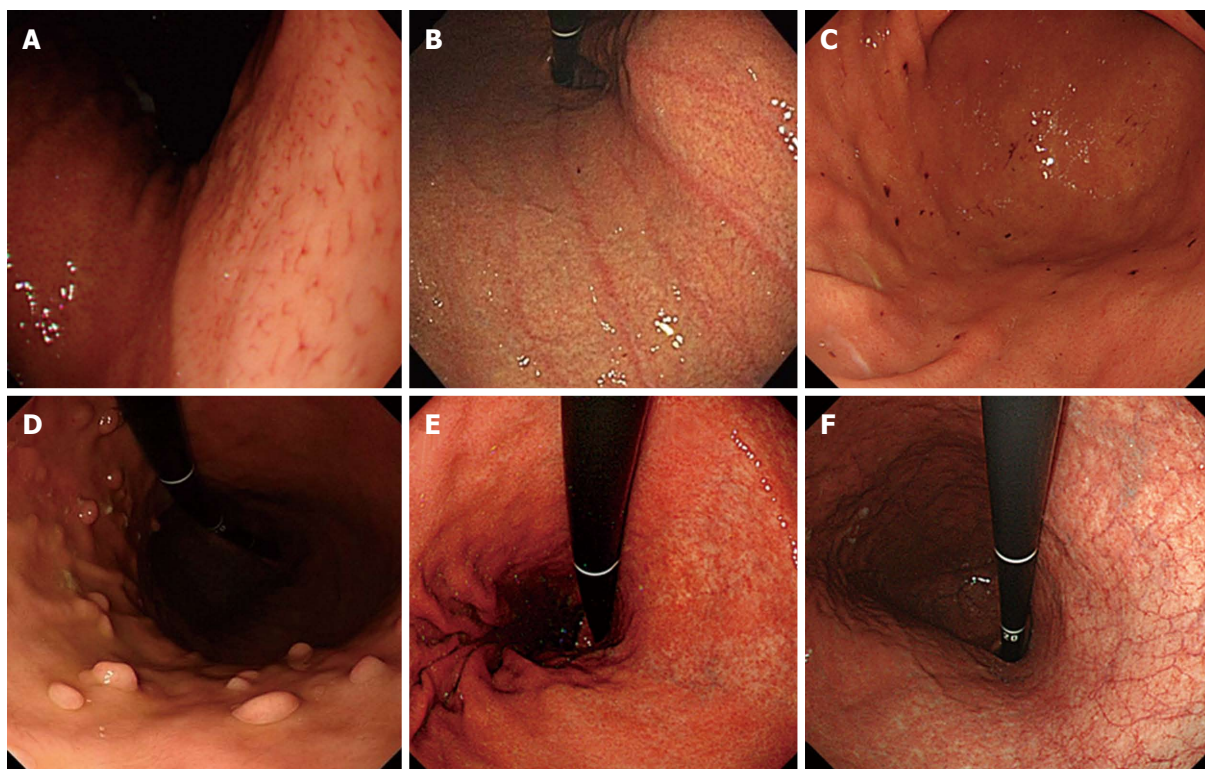
*H. pylori* infection status was evaluated by the presence of serum immunoglobulin G antibody against *H. pylori* (HM-CAP enzyme immunoassay, Enteric Products, Westbury, NY, United States), the [13C]-labeled urea breath test (13C-UBT, with a cut-off value of 2.5‰; Ubit, Otsuka Pharmaceuticals, Tokyo, Japan), and histological examination with toluidine blue staining of 3 endoscopic biopsy specimens taken from the greater curvature of the upper gastric body, angulus, and antrum, respectively. When all three methods yielded negative results, *H. pylori* infection status was considered “uninfected”. When one or more of these methods yielded a positive result and there was no history of previous eradication therapy, *H. pylori* infection status was considered “infected”. When histological examination and 13C-UBT yielded negative results and a history of eradication therapy was recorded, *H. pylori* infection status was considered “eradicated”.

### Endoscopic findings evaluated

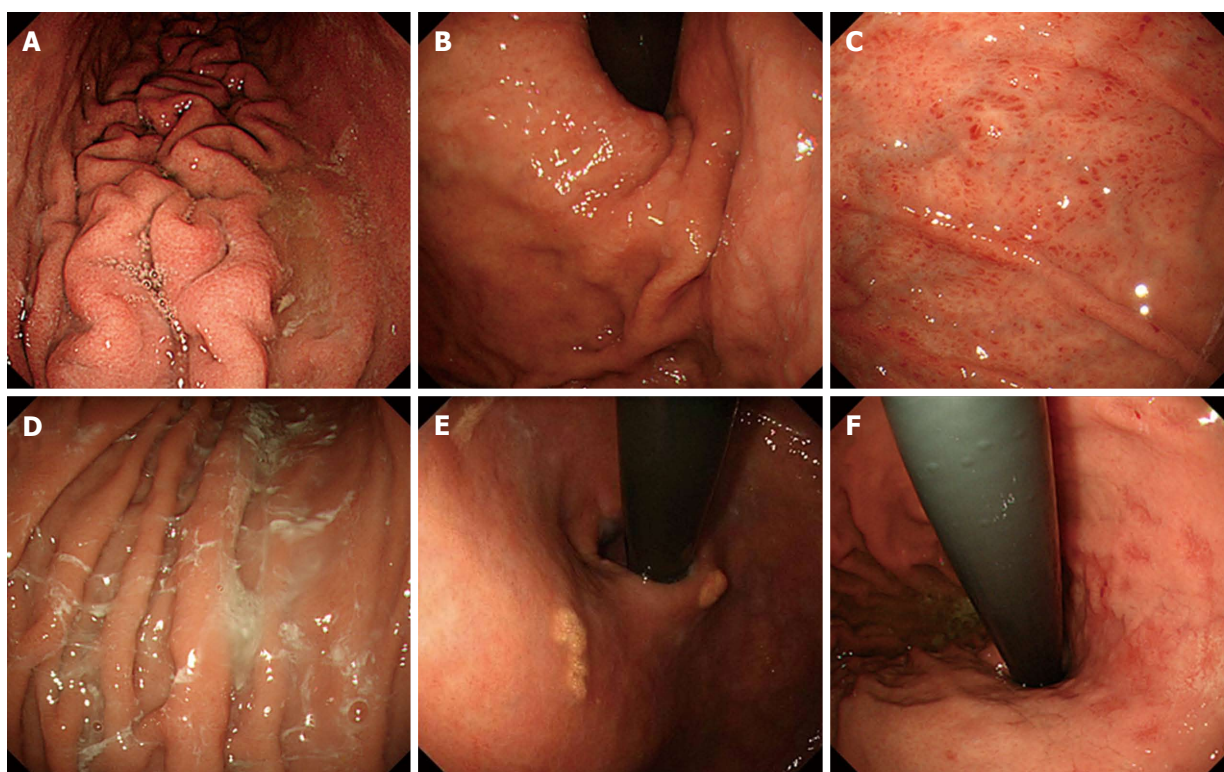
All endoscopies were performed by well-trained endoscopists using a high resolution videoendoscope (GIF-260H, Olympus Co., Tokyo, Japan) with a pre-endoscopic oral solution containing dimethylpolysiloxane (Balgin Antifoaming Oral Solution 2%, Kaigen Co., Ltd., Osaka, Japan). In all cases, around 50-60 endoscopic images had been routinely recorded at fixed sites in the esophagus, stomach, and duodenum and saved to the electronic endoscopic database (Solemio ENDO, Olympus Co.). Six of the recorded images - specifically of the antrum, angulus, lesser and greater curvature of the lower body, greater curvature of the upper body, and cardia of the stomach - were used for analysis in each case.

The presence or absence of the following 11 distinctive endoscopic findings were evaluated (Figures 1 and 2): regular arrangement of collecting venules (RAC)<sup>[5]</sup>, linear erythema<sup>[9]</sup>, hemorrhage<sup>[9]</sup>, fundic gland polyp (FGP)<sup>[10]</sup>, atrophic change<sup>[6,7]</sup>, severity of atrophy (open/closed)<sup>[6,7]</sup>, rugal hyperplasia<sup>[8]</sup>, edema<sup>[9]</sup> (which is visible as a thickened mucosal layer especially at the angulus and cardia), spotty erythema<sup>[9]</sup>, exudate<sup>[9]</sup>, xanthoma<sup>[11]</sup>, and mottled patchy erythema (MPE)<sup>[12]</sup>. A well-experienced endoscopist (Kobayakawa M) assessed the findings, and to determine inter-observer agreement, another experi-





**Figure 1** Five of the 11 endoscopic findings evaluated in this study. A: Regular arrangement of collecting venules in the body; B: Linear erythema in the lesser curvature of lower body; C: Hemorrhage in the lower body; D: Fundic gland polyp in the greater curvature of the body; E: Close type atrophic change in the lesser curvature of the body; F: Open type atrophic change over the lesser curvature of the body.



**Figure 2** Remaining 6 of the 11 endoscopic findings evaluated. A: Rugal hyperplasia in the greater curvature of the middle body; B: Edema visible in the cardia; C: Spotty erythema in the greater curvature of the upper body; D: Exudate in the greater curvature of the upper body; E: Xanthoma in the upper body; F: Mottled patchy erythema in the lesser curvature of the body.

**Table 1** Diagnostic odds ratios of endoscopic findings in the diagnosis of three groups of *Helicobacter pylori* infection status

Endoscopic finding	<i>H. pylori</i>		
	Uninfected	Infected	Eradicated
RAC	11.5 (3.73-35.1)	0.03 (0.00-0.14) <sup>a</sup>	1.65 (0.61-4.47) <sup>a</sup>
Linear erythema	24.5 <sup>1</sup> (4.12-146)	0.05 <sup>1</sup> (0.00-0.83) <sup>a</sup>	0.18 (0.00-1.20) <sup>a</sup>
Hemorrhage	4.11 (1.54-11.0)	0.03 (0.00-0.19) <sup>a</sup>	2.52 (0.92-6.95) <sup>a</sup>
Fundic gland polyp	34.5 <sup>1</sup> (1.89-632)	0.10 <sup>1</sup> (0.01-1.81) <sup>a</sup>	0.15 <sup>1</sup> (0.01-2.81) <sup>a</sup>
Atrophic change	0.01 (0.00-0.06)	8.67 <sup>1</sup> (2.11-35.6) <sup>a</sup>	32.4 <sup>1</sup> (1.87-562) <sup>a</sup>
Rugal hyperplasia	0.02 <sup>1</sup> (0.00-0.34)	15.8 (4.86-51.4) <sup>a</sup>	0.66 (0.22-2.03)
Edema	0.10 (0.03-0.31)	14.2 (4.52-44.1) <sup>a</sup>	0.66 (0.24-1.81)
Spotty erythema	0.09 (0.00-0.60)	11.5 (3.03-42.7) <sup>a</sup>	0.35 (0.00-1.54)
Exudate	0.27 (0.00-1.18)	3.52 (1.16-11.6) <sup>a</sup>	0.77 (0.21-2.93)
Xanthoma	0.86 (0.22-3.46)	2.45 (0.64-9.29)	0.30 (0.00-2.02)
Mottled patchy erythema	0.07 <sup>1</sup> (0.00-1.17)	0.07 <sup>1</sup> (0.00-1.17)	103 <sup>1</sup> (5.64-1888) <sup>a</sup>

Values of odds ratios (95%CI) are shown. <sup>1</sup>Odds ratios were estimated using the substitution formula. 0.5 was added to all cell frequencies before calculation. <sup>a</sup>*P* < 0.05 vs uninfected. RAC: Regular arrangement of collecting venules; *H. pylori*: *Helicobacter pylori*.

enced endoscopist (Sakurai T) also assessed these findings. Both were blinded to clinical information in the cases examined.

### Statistical analysis

To identify the predictive endoscopic findings for *H. pylori* infection status from among the 462 endoscopic images for the 77 patients, diagnostic odds ratios (DOR) for the 11 endoscopic findings in *H. pylori*-uninfected, -infected, and -eradicated cases were calculated. In addition, 95%CI were also estimated. DOR is defined as the positive likelihood ratio divided by the negative likelihood ratio. Positive likelihood ratio was calculated by sensitivity/1-specificity, and negative likelihood ratio was calculated by specificity/1-sensitivity<sup>[17]</sup>.

The inter-observer agreement for each endoscopic finding among the two endoscopists was measured using *kappa* statistics. *Kappa* values (*k*) > 0.80 denoted excellent agreement, > 0.60-0.80 good, > 0.40-0.60 moderate, > 0.20-0.40 fair, and ≤ 0.20 poor<sup>[18]</sup>. Values of *P* < 0.05 were considered significant. All statistical analysis was performed using Stata version 10 software (StataCorp, Lakeway Drive College Station, TX, United States).

## RESULTS

### Patient characteristics

Of the 77 patients [32 men and 45 women; mean age (SD), 39.7 (13.4) years] assessed, 28 were *H. pylori* uninfected, 28 were infected, and 21 were eradicated.

### Diagnostic odds ratio of endoscopic findings

The DOR for each endoscopic finding in the diagnosis of the three groups of *H. pylori* infection status are shown in Table 1. In cases diagnosed as *H. pylori* uninfected, RAC (11.5), linear erythema (24.5), hemorrhage (4.1), and FGP (34.5) had high DORs and were significantly associated (*P* < 0.05). In infected cases, atrophic change (8.67), rugal

**Table 2** Inter-observer agreement for the 11 endoscopic findings evaluated

Endoscopic finding	<i>Kappa</i> value
RAC	0.63
Linear erythema	0.51
Hemorrhage	0.79
Fundic gland polyp	0.93
Atrophic change	0.74
Rugal hyperplasia	0.49
Edema	0.58
Spotty erythema	0.47
Exudate	0.46
Xanthoma	0.19
Mottled patchy erythema	0.75

RAC: Regular arrangement of collecting venules.

hyperplasia (15.8), edema (14.2), spotty erythema (11.5), and exudate (3.52) had high DORs and were significantly associated (*P* < 0.05). Lastly, in eradicated diagnosis, atrophic change (32.4) and MPE (103.0) had high DORs and were significantly associated (*P* < 0.05).

Open type atrophy was significantly (*P* < 0.05) more frequent on endoscopy in *H. pylori* infected patients (20/28, 71.4%) than in *H. pylori* eradicated patients (8/21, 38.1%).

### Inter-observer agreement for the endoscopic findings evaluated

The *kappa* value indicating agreement between the two endoscopists for each endoscopic finding is shown in Table 2.

## DISCUSSION

This study identified several endoscopic findings that are clearly associated with uninfected, infected, and eradicated *H. pylori* infection. Some endoscopic findings have been previously reported to be correlated with *H. pylori* infection. Atrophic change was found to be associated with the infection in an aged group (OR = 9.8)<sup>[19]</sup> as well as in general<sup>[7,20]</sup>. Rugal hyperplasia was reported to be correlated with *H. pylori* infection<sup>[21]</sup>. Edema, with or without exudate, and spotty erythema were considered to be a result of mucosal inflammation, but these positive findings were not definitive<sup>[9]</sup>. Lastly, xanthoma, which refers to yellowish-white small nodules or plaques in the gastric mucosa, is considered to be related with *H. pylori* infection<sup>[11]</sup>. Among these findings, we clarified that all of them - atrophic change, rugal hyperplasia, edema, spotty erythema, and exudate - are valuable endoscopic findings of *H. pylori* infection.

In regard to the predictive findings related with *H. pylori* uninfected mucosa, RAC has been well studied and showed a positive association<sup>[5,22]</sup>. Fundic gland polyp is also considered to be a finding associated only with uninfected cases<sup>[10]</sup>. In the present study these endoscopic findings showed high odds ratios and thus support the results of earlier studies. While hemorrhage and linear er-



ythema were found to be associated with well-preserved gastric acid secretion, they were not clearly associated with *H. pylori* uninfected mucosa<sup>[9]</sup>. In the present study, however, these two findings had high odds ratios, suggesting they are valuable for predicting *H. pylori*-uninfected cases.

This study also investigated *H. pylori*-eradicated cases, because the preventive effect of *H. pylori* eradication therapy for gastric cancer has been reported<sup>[3,4]</sup> and therefore an increasing number of patients will likely receive *H. pylori* eradication therapy into the future<sup>[23,24]</sup>. Gastric cancer can, however, still occur in eradicated cases, but it is generally difficult to diagnose and few predictive endoscopic findings have been reported. Of those that have been suggested are the disappearance of rugal hyperplasia<sup>[8]</sup> and hyperplastic polyp<sup>[25]</sup>, but as these findings need to be compared before and after eradication therapy, on their own it seems difficult to apply them to clinical use. Atrophic change, occurring as a result of *H. pylori* infection, is thought to remain after eradication therapy<sup>[26]</sup>. Moreover, in our previous study, MPE, which is recognized as a flat or slightly depressed reddish lesion that is distinguishable from the congested mucosa, emerged after *H. pylori* eradication therapy<sup>[12]</sup>. In the study too, atrophic change and MPE was highly predictive of *H. pylori* eradicated mucosa, suggesting that a combination of these findings is highly valuable in clinical practice.

In regard to the reproducibility of endoscopic image evaluation for these 11 findings, among the positive endoscopic findings found, RAC, hemorrhage, fundic gland polyp, atrophic change, and MPE all showed good inter-observer agreement, suggesting that these findings can be easily identified and will be generally useful. The other positive findings of edema, rugal hyperplasia, and spotty erythema showed moderate agreement, suggesting that they could also be suitable for general use.

There are several important strengths of this study, including that the diagnosis of *H. pylori* infection status was accurate, made on the basis of a combination of three different diagnostic tests to overcome any shortcomings of a single test. Moreover, DOR was used to estimate the diagnostic value: DOR is not influenced by prevalence rate, so the results are applicable in other populations with a different prevalence of *H. pylori* infection.

Nonetheless, this study has several limitations. First, the sample size of 77 patients is relatively small, and did not permit multivariate analysis to exclude confounders. Second, the population consists of relatively young patients, therefore cases in whom *H. pylori* is naturally eradicated without eradication therapy as a result of long-term course of severe atrophic gastritis, may not be included. Furthermore, photographic not video images were used for analysis and therefore the whole stomach was not observed, so some findings that may be present were not assessed.

In conclusion, the endoscopic findings associated with *H. pylori* infection status that are common and have good inter-observer agreement were clarified to be RAC,

hemorrhage, fundic gland polyp, atrophic change, and MPE. These findings should be generally useful in clinical practice and contribute to the early detection of gastric cancer.

## ACKNOWLEDGMENTS

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## COMMENTS

### Background

The risk of gastric cancer can differ among *Helicobacter pylori* (*H. pylori*) uninfected, infected, and eradicated patients, therefore it is important to determine *H. pylori* infection status. Endoscopic prediction of *H. pylori* infection status can be extremely useful for early detection of gastric cancer, but the diagnostic value of *H. pylori* related endoscopic findings has not yet been validated.

### Research frontiers

Some endoscopic findings were reported to be related with *H. pylori* uninfected, infected case, and little has been reported on eradicated case. The accuracy of these findings varies in each studies, and have not been well examined. In this study, the authors demonstrate the accuracy and reproducibility of endoscopic findings which have been previously reported to be correlated with *H. pylori* infection.

### Innovations and breakthroughs

This is the first study which evaluate the value of predictive endoscopic findings separately for 3 groups of *H. pylori* infection status; uninfected, infected, and eradicated. Moreover, the authors used diagnostic odds ratio (DOR) to estimate the diagnostic value of endoscopic findings. DOR is not influenced by prevalence rate, so the results are applicable in other populations with a different prevalence of *H. pylori* infection.

### Applications

The endoscopic findings associated with *H. pylori* infection status that are common and have good reproducibility were clarified to be regular arrangement of collecting venules, hemorrhage, fundic gland polyp, atrophic change, and mottled patchy erythema. These findings should be generally useful in clinical practice and contribute to the early detection of gastric cancer.

### Terminology

DOR is defined as the positive likelihood ratio divided by the negative likelihood ratio. DOR is single indicator of diagnostic test, and higher value is indicative of better test performance, irrespective of prevalence rate.

### Peer review

The authors showed endoscopic features of gastric mucosa according to *H. pylori* infection status. Although most endoscopists are usually aware of the correlation between endoscopic findings and *H. pylori* status, the simplification and clarification of the correlation by showing typical endoscopic findings and their diagnostic odds ratios may be worth publication.

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