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Differential diagnosis of *Helicobacter pylori*-associated gastritis with the linked-color imaging score☆,☆☆

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ABSTRACT

Background: *Helicobacter pylori* (*H. pylori*) infection in gastric mucosa is the main risk factor for gastric cancer. The purpose of this study was to assess the value of the linked-color imaging (LCI) score for the identification of *H. pylori*-associated gastritis.
Methods: A total of 358 patients were enrolled in the study. *H. pylori* was positive in 127 cases and negative in 231 cases. Redness of fundus glands, granular erosion, purple mucus (+) and mucus lake turbidity were investigated by the LCI mode of endoscopy. Logistic regression was used to screen the observation indexes and their relative partial regression coefficients, which were helpful for the differential diagnosis of *H. pylori* infection. Then, each observation index was scored according to the partial regression coefficient.
Results: Using a total scores of 3.5 as the cut-off value, the sensitivity and specificity were 83.8% and 99.5%, respectively, for the differential diagnosis of *H. pylori* gastritis. The area under the curve was 95.3%.
Conclusions: The LCI score showed high sensitivity and specificity for the differential diagnosis of *H. pylori*-associated gastritis and is an effective method for identifying *H. pylori* infection in gastric mucosa.

1. Introduction

Previous studies have shown that *Helicobacter pylori* (*H. pylori*) can induce the production of certain carcinogens and inhibit the production of certain tumor suppressor substances. Some components of the bacteria can damage the gastric mucosa, causing inflammation, atrophy and dysplasia, ultimately leading to gastric cancer [1–4]. Therefore, *H. pylori* gastritis has a higher risk of cancer than other forms of gastritis and is the main risk factor for gastric cancer. Its treatment strategy is also different from other types of gastritis. The Kyoto consensus considered that the eradication of *H. pylori* infection was an effective way to prevent gastric cancer [5]. Accordingly, it is essential to identify *H. pylori* gastritis and eradicate it as soon as possible. At present, there are many methods for detecting *H. pylori* infection, such as the 13C,14C breath test, serological pepsin and *H. pylori* antibody detection, endoscopy diagnosis, and pathological diagnosis [6]. The breath test and serological test can be used for *H. pylori* screening in the general population but may generate false negative or false positive results due to the influence of equipment and reagents. Some high-risk groups such as those over 40 years old require endoscopic examination to identify the stomach condition due to upper gastrointestinal symptoms. It is very important for these patients that clinicians evaluate *H. pylori* gastritis via endoscopic examination. Presently, for patients undergoing gastroscopy because of digestive symptoms or other factors (including those under review for previous upper gastrointestinal lesions, those with a family history of gastric cancer, or other high-risk groups), endoscopic diagnosis of *H. pylori* infection is mainly achieved by a magnifying endoscopic pass through observation of the details of the mucosa, such as whether the microsurface structure is regular and the collecting vein is visible [7]. However, this procedure takes time and cannot distinguish *H. pylori* gastritis from other types of gastritis. In addition, the requirements for observers and equipment are high.

Linked-color imaging (LCI) is a newly developed endoscopic technique. It is characterized by its sensitivity to color differentiation, which can clearly show slight differences in color caused by pathological changes in the mucosa of the digestive tract. Osamu Dohi thought that LCI could improve the endoscopic diagnosis of *H. pylori*-related gastritis [8]. However, there has been little research on the diagnosis of gastric lesions by LCI, and its clinical value needs to be further confirmed. The purpose of this study is to explore

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the role of LCI in the differential diagnosis of *H. pylori* gastritis and other types of gastritis in order to improve the diagnostic accuracy of endoscopy for *H. pylori* gastritis and reduce the rate of biopsy.

2. Materials and methods

2.1. Patients

Patients who underwent upper gastrointestinal endoscopy between July 2017 and May 2018 were enrolled in the study. The exclusion criteria were as follows: 1. patients younger than 18 years of age; 2. patients who were unable to tolerate biopsies because of taking anticoagulants or other factors; 3. patients after gastrectomy; 4.patients who took PPIs, antibiotics or NSAIDs within one month of the procedure. All patients provided written informed consent to undergo gastroduodenoscopy. The patients with previously eradicated *H. pylori* were classified into a subgroup.

2.2. Endoscopy

All examinations were carried out with a high-definition EGL590WR endoscope corresponding to the LASEREO endoscopic system (FUJIFILM, Tokyo, Japan) [9]. LCI is a new image-enhanced technology that is intended to enhance slight color differences in the red region of the mucosa. This mode is based on the image captured under similar light conditions in BLI-bright; however, further postimage processing is later applied so that a slightly reddish color becomes much redder and a slightly whitish color becomes much whiter than the colors appear under white light imaging (WLI) [8].

2.3. Methods of examinations

Intravenous anesthesia was made before each examination (85–90% of gastroduodenoscopy examinations were performed under intravenous anesthesia). Gastroduodenoscopy was performed by an experienced endoscopic physician. When performing the gastroduodenoscopy examination, the mode was transformed into LCI. The mucus lake was observed first, and then the gastric mucosa was observed. The sequence of observations was to observe the posterior wall and the great curved side of the stomach body from the antegrade view first. Then, the gastroduodenoscope continued to move forward to observe the gastric antrum. The stomach angle was then observed from the retroflex view. The stomach fundus and small curved side of the stomach body were observed by retracting the gastroduodenoscope from the retroflex view. Finally, the four walls of the stomach body were observed from the antegrade view. Photographs and notes were taken during the examinations.

2.4. Biopsy protocol

After a standard examination by the endoscopist, standard biopsy forceps were passed through the channel to the endoscope tip, and different lesions or the most serious lesions were biopsied. This practice was performed separately for the antrum and the corpus. Two additional biopsies were taken for rapid urease testing, one from the antrum and one from the corpus. Biopsy samples were fixed in 10% formalin, processed routinely, and embedded in paraffin. Sections were stained with hematoxylin–eosin, Giemsa, Alcian blue, and Periodic acid–Schiff for histopathologic examination. The assessment of gastritis was performed according to the updated Sydney system [10].

2.5. Diagnosis of H. pylori infection

Patients with *H. pylori* seen on histologic examination and with a positive urease test were considered to be *H. pylori* positive. If one of the test results was negative, a C14-urea breath test was used to confirm the infection [11]. An *H. pylori*-negative normal stomach was defined when biopsy samples were diagnosed histologically as normal in accordance with the updated Sydney system (no *H. pylori* in Giemsa-stained specimens) in addition to a negative rapid urease test result [7].

2.6. Analysis of endoscopic images

Four endoscopists who were blinded to the clinical data evaluated all the endoscopic images. None of them performed the gastroduodenoscopies in this study. The expert endoscopists (observers A and D) had previously performed over 8000 conventional gastroduodenoscopies, while the nonexpert endoscopists (observers B and C) had previously performed fewer than 500 conventional gastroduodenoscopies. All endoscopists were trained by the LCI examiner before the analysis to compare the international standard color card and the endoscopic images in the LCI mode. After they were able to accurately judge the color of the mucosa and the mucus lake and the microstructure of the mucosal surface, these four doctors analyzed the images of the patients.

The color of the endoscopic images of the *H. pylori*-positive group and the control group were compared with the international standard chromogram (Fig. 1). When the color of the fundus gland was close to 710–711C or 1788 2XC, it was defined as fundic gland mucosa redness. When the color was close to 706–707C, it was defined as normal. When the surface of the gastric mucosa was covered with a large amount of mucus and the color of the gastric fundus gland area was close to 674–675C, it was defined as purple mucus (+). The mucus lake was opaque when it contained more mucus and uniform white particles. Therefore, when the color of the mucus lake was close to 663C–665C or 5875C, it was defined as muddy lake turbidity. If the mucus lake contained bile and was close to 604–606C or yellow2XC, it was defined as bile regurgitation. If there was erosion in the mucosa, the surface of the erosion could be observed. If the surface microstructure was granular, covered with mucus and showed granular white opacity, it was called granular erosion (Fig. 1).

2.7. Statistical analysis

Correlation analyses were used to evaluate the correlations between fundic gland mucosa redness, purple mucus (+), mucus lake turbidity, bile regurgitation, granular erosion and *H. pylori* infection. The ROC curve was used to calculate the sensitivity, specificity and accuracy of each observation index in the differential diagnosis of *H. pylori* gastritis and non-*H. pylori* gastritis. The chi-square test was used to compare the diagnostic rates between subgroups and the whole group. Logistic regression analysis of the two classification variables was used to screen the endoscopic observation indexes, which were useful for the differential diagnosis of *H. pylori* gastritis. The partial regression coefficient represents the contribution of each observation index; therefore, the different endoscopy indexes were scored according to the size of the partial regression coefficient. This scoring system was used to score every patient's endoscopic imaging, calculating the total scores of every patient. Finally, correlation analysis was used to evaluate the correlation between the total scores and *H. pylori* gastritis. The ROC curve was used to calculate its value for the differential diagnosis of *H. pylori* gastritis and non-*H. pylori* gastritis, and the corresponding sensitivity, specificity and area under the curve were also calculated. Kappa analysis was used to

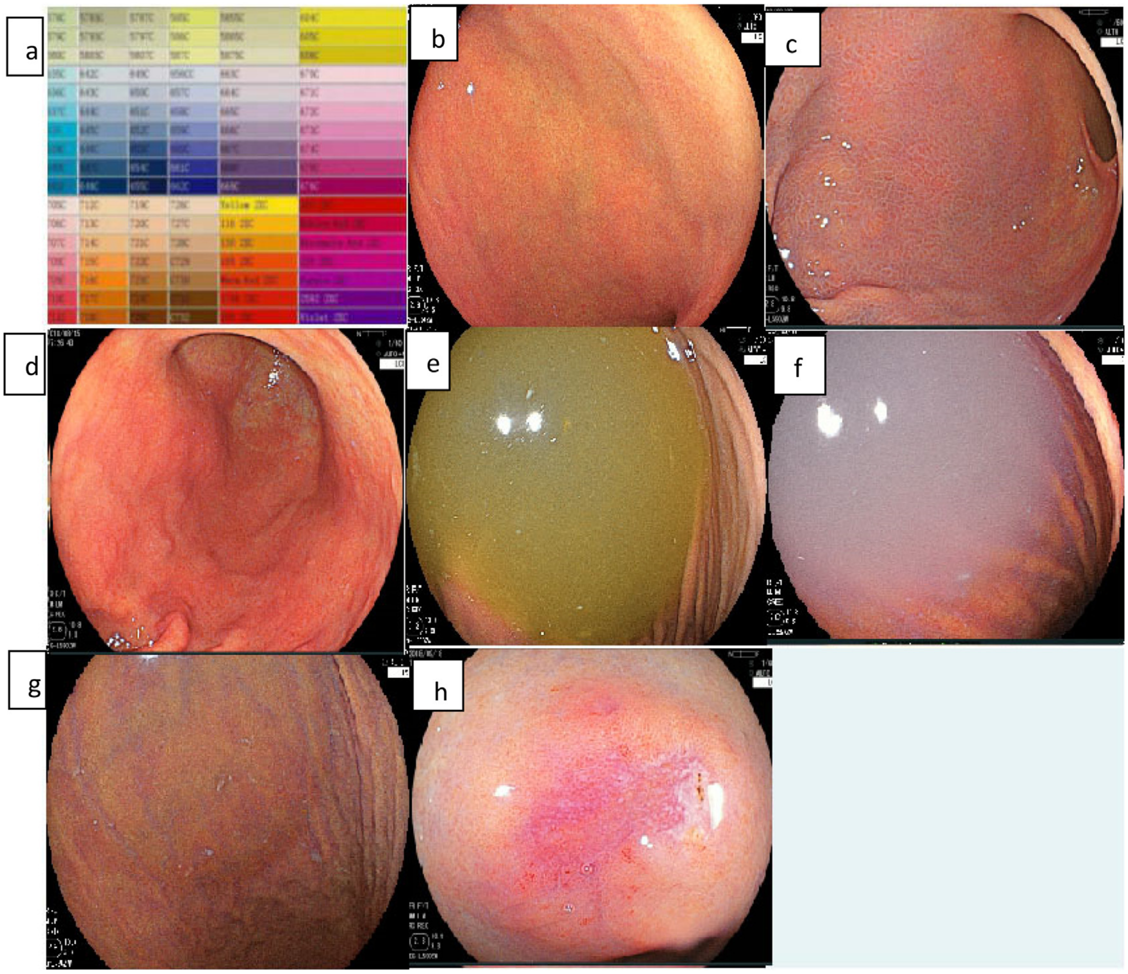

Fig. 1. a: International standard chromogram, b: normal mucosa, c: purple mucus (+), d: fundic gland mucosa redness, e: bile regurgitation, f: muddy lake turbidity, g: mucous lake clear, h: granular erosion.

assess the consistency among the examiners. Interobserver agreement was quantified using the kappa statistic. Kappa values of <0.20,0.21–0.40, 0.41–0.60, 0.61–0.80 and >0.80 were considered to indicate poor, fair, moderate, good and excellent agreement, respectively; $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software.

3. Results

In total, 428 patients were randomly enrolled. Seventy patients were excluded for taking MXA, PPIs and antibiotics within one month before the examination. A total of 358 patients with gastritis were included in this study, including 140 males and 218 females (71 patients have underwent H. pylori eradication, 10 patients re-infected or failed in sterilization), with a maximum age of 78 years and a minimum age of 18 years (average age: 55.6 ± 22.8 years). There were no significant differences in age or gender for performing endoscopy between the two groups ($P > 0.05$) (Table 1). Correlation analysis showed that there was a high correlation between fundic gland mucosa redness and *H. pylori* infection. Purple mucus (+) and mucus lake turbidity were moderately correlated with *H. pylori* infection. Granular erosion and bile reflux were slightly correlated with *H. pylori* infection ($P < 0.05$). The consistency between the experts was good. The consistency between the nonexperts was moderate (Table 2). Observer A and B were selected as representatives of experts and nonexperts, respectively, to calculate their diagnostic efficiency. The sensitivity, specificity and area under the curve for each single observation index in the differential diagnosis of *H. pylori* gastritis were calculated (Tables 3). Chi-square test showed that there was no significant difference in the diagnostic accuracy of LCI for the subgroups and the whole group ($P > 0.05$). For the whole group, a logistic regression model showed that these observation indexes (fundic gland mucosa redness, purple mucus +, mucus lake turbidity, and granular erosion) were meaningful in the fitting curve. They were useful for the diagnosis of *H. pylori* gastritis. Their partial regression coefficients were 2.8, 1.3, 2.0, and 1.8, respectively, for the expert (observer A). The partial regression coefficients of the other observers were similar. The partial regression coefficients of the logistic regression analysis of the two classification variables reflected the contribution of each index. Each observation index was scored according to the partial regression coefficient. Fundic gland mucosa redness was scored as 3 points; granular erosion and mucus lake turbidity were scored at 2 points each. Purple mucus (+) was scored as 1 point. Each patient's endoscopic images were scored according to these criteria and the total scores were calculated. The total scores of each patient were moderately to highly correlated with the inflammation degree of *H. pylori*-associated gastritis, with correlation coefficients ranging from 0.582 to 0.760. The sensitivity, specificity and accuracy of the total scores for the differential diagnosis of *H. pylori* gastritis and non-*H. pylori* gastritis are shown in Table 3. For the expert (observer A), if a total score of 2.5 was used to distinguish *H. pylori* gastritis from non-*H. pylori* gastritis, the sensitivity and specificity were 93.2% and 84.2%, respectively. If a total score of 3.5 was used

Table 1
Characteristics of the total 358 study subjects.

Factor	Total 358 study subjects	*H. pylori* gastritis	Non-*H. pylori* gastritis
Age (years)	55.6 ± 22.8	60.3 ± 27.8	57.7 ± 24.3
Range	18–78	18–78	19–75
Sex			
Male	140	51	89
Female	218	76	142
Observer A			
Redness of the fundus gland mucosa	140	114	26
Mucous lake turbidity	137	83	54
Purple mucus (+)	99	66	33
Granular erosion	33	31	2
Observer B			
Redness of the fundus gland mucosa	168	92	76
Mucous lake turbidity	136	61	75
Purple mucus (+)	122	70	52
Granular erosion	38	35	3

Table 2
Kappa values (coefficient of consistency) between experts and non-experts.

Observer	Kappa values	P
Observer A and D		
Redness of the fundus gland mucosa	0.732	0.000
Mucous lake turbidity	0.611	0.000
Purple mucus (+)	0.613	0.000
Granular erosion	0.667	0.000
Observer B and C		
Redness of the fundus gland mucosa	0.420	0.000
Mucous lake turbidity	0.418	0.000
Purple mucus (+)	0.524	0.000
Granular erosion	0.598	0.000

to distinguish *H. pylori* gastritis from non-*H. pylori* gastritis, the sensitivity, specificity and accuracy were 83.3%, 99.5%, and 95.3%, respectively (95% confidence interval: 92.9%–97.7%) (Table 2).

4. Discussion

Eighty-nine percent of gastric cancers are associated with *H. pylori* infection in the gastric mucosa [12,13]. Studies have shown that *H. pylori* infection causes chronic inflammation of the gastric mucosa, mucosal congestion and increased mucus secretion. Recurrent inflammation induces gland atrophy and intestinal metaplasia. It also causes some changes in DNA, suppressing tumor suppressor genes and activating oncogenes, which eventually leads to dysplasia and gastric cancer. Before irreversible mucosal injury, the eradication of *H. pylori* could effectively inhibit the development of gastric mucosa toward atrophic gastritis, intestinal metaplasia, dysplasia and cancer [14,15]. Therefore, the diagnosis and reasonable treatment of *H. pylori* infection is very important. For high-risk groups or those who need gastroduodenoscopy for upper gastrointestinal symptoms, endoscopic diagnosis of *H. pylori* infection could guide the examination as well as the treatment. Previous studies have shown that the main methods for diagnosing *H. pylori* infection under endoscopy are WLI and magnification narrow band imaging. Dohi et al. observed the redness of fundic gland mucosa with WLI. The accuracy, sensitivity, and specificity for diagnosing *H. pylori* infection were 74.2%, 81.7%, and 66.7%, respectively [8]. Gonen et al. used WLI to observe multiple indicators of gastritis. The results showed that none of the standard endoscopic features showed a sensitivity of more than 70% for *H. pylori* gastritis, except RAC pattern analysis. The absence of a corporal RAC pattern had an 85.7% sensitivity and an 82.8% specificity for predicting *H. pylori* infection [7]. Thus, the diagnostic sensitivity and specificity were not high.

Magnifying endoscopy allows for the observation of the surface microstructure and honeycomb-type subepithelial capillary network (SECN) of the gastric mucosa. It provides a direct observation of the microsurface structure of the gastric mucosa. High resolution endoscopic patterns of the gastric mucosa are highly correlated with histopathological changes, including *H. pylori* infection [16]. Gonen et al. used magnifying endoscopy combined with staining to diagnose *H. pylori* gastritis with less than 90% sensitivity and less than 80% specificity [7].

Thus, the sensitivity and specificity of magnifying endoscopy for the diagnosis of *H. pylori* gastritis is still not high. At the same time, magnifying observations had higher requirements for the examiners and equipment, and these examinations are more time-consuming and are unable to differentiate gastritis caused by *H. pylori* from that caused by other factors; there-

Table 3
The sensitivity and specificity of total scores and each observation index for the diagnosis of *H. pylori* gastritis.

Factor	Sensitivity	Specificity	Area under curve	PPV	NPV
Observer A					
Redness of the fundus gland mucosa	83.1%	89.4%	86.2%	81.4%	94.7%
Mucous lake turbidity	86.4%	74.5%	80.5%	60.6%	80.1%
Purple mucus(+)	72.9%	87.7%	80.3%	66.7%	76.4%
Granular erosion	28.2%	99.2%	67.3%	93.9%	70.5%
Total score ≥2.5	93.2%	84.2%		76.6%	95.6%
Tolal score ≥3.5	83.8%	99.5%	95.3%	99.1%	91.6%
Observer B					
Redness of the fundus gland mucosa	83.6%	70.0%	76.4%	54.8%	81.6%
Mucous lake turbidity	55.5%	70.0%	62.6%	44.9%	64.1%
Purple mucus (+)	63.6%	78.9%	71.3%	57.4%	72.3%
Granular erosion	31.8%	95.3%	63.1%	92.1%	71.3%
Total score	77.4%	84.3%	85.8%	73.1%	87.1%

fore, the clinical application of magnifying endoscopy is also restricted.

LCI is more sensitive to different colors than WLI. It is expected to become a new diagnostic method for *H. pylori*-related gastritis. Dohi et al. previously used LCI to diagnose *H. pylori* gastritis. The accuracy, sensitivity, and specificity were 85.8%, 93.3%, and 78.3%, respectively [8]. The sensitivity was high, but the specificity was low.

The LCI mode is sensitive to color discrimination, and mild inflammation can appear in this mode. In our study, 127 *H. pylori*-positive cases were found, of which there were 111 cases with redness of the gastric fundus mucosa. Its sensitivity and specificity for diagnosing *H. pylori* gastritis was high (83.1% and 89.4%, respectively). However, various bacterial and nonbacterial stimulations can cause inflammation of the gastric mucosa. In addition, *H. pylori* infection can only be shown as local erosions. Therefore, the diagnosis of *H. pylori* gastritis may be problematic. At the same time, because of the high sensitivity of LCI to color changes, the surface microstructures of the gastric mucosa can be observed as differences in color, which is difficult to observe using nonmagnification white light endoscopy. When the mucosa is erosive and swollen, it can be more clearly displayed in the LCI mode. Accordingly, the granular surface of the erosion can be recognized. In this study, the incidence of granular erosion in *H. pylori* gastritis was not high; only 33–35 of 127 *H. pylori*-positive patients had it. However, the specificity of both observers was over 95%. Therefore, we speculate that this expression may be a characteristic manifestation of *H. pylori* infection.

In addition, there is a mucus layer on the surface of the normal gastric mucosa, which separates the gastric lumen and mucous epithelium, resulting in a H+ gradient between them. This layer is transparent under endoscopy and difficult to observe [17]. If the mucus is increased, the mucosa appears purple in the LCI mode. *H. pylori* infection increases mucus secretion and the mucus lake also becomes muddy. These characteristics may contribute to the diagnosis of *H. pylori* infection. Thus, we used correlation analysis to assess their relevance. The results showed that the above indexes were moderately or highly correlated with *H. pylori* infection. However, because these indexes were affected by the rate of occurrence of each indicator in *H. pylori*-associated gastritis and other forms of gastritis, the results may be affected to some extent. Therefore, this study used regression analysis to screen the relevant indicators of *H. pylori* infection and obtain the corresponding weight. The results showed that the redness of the fundic gland mucosa, mucus lake turbidity, purple mucus and granular erosion were included in the regression model, and the fitting curve was significant. These factors were helpful for the differential diagnosis of *H. pylori* gastritis. ROC curves were used to calculate their sensitivity, specificity and accuracy in the diagnosis of *H. pylori* gastritis. For training endoscopists, although their diagnostic efficacy was lower than that of the experts, it was still superior to the previously utilized white light method. For the experts, the sensitivity was high (93.2%), but the specificity was slightly lower (84.2%) when a total score of 2.5 was used to distinguish *H. pylori* gastritis from non-*H. pylori* gastritis, although it was still higher than both normal white light and magnified observation. When a total score of 3.5 was used as the cut-off value for the discrimination, the sensitivity was higher (99.5%), but the specificity was slightly lower (83.8%). Reasonably, it is recommended that a patient should be considered free of *H. pylori* infection when his/her total score is less than 2.5; when the score is higher than 3.5, *H. pylori* gastritis should be assumed. The diagnosis could be regarded as uncertain when the total score is between 2.5–3.5 and should be further determined by rapid urease test or histopathological diagnosis, etc. The above indexes not only make full use of the advantages of the LCI mode but also minimize the interference of other factors. The diagnostic sensitivity and specificity of these indexes were higher than those of previous studies and of each single index alone. The LCI mode did not need to be amplified, and because the indexes were easy to observe in the LCI mode, it was simpler and faster than previous methods.

The results also showed that the consistency between the experts was good. The sensitivity of the experts and nonexperts to color changes in the endoscopic images was different. Therefore, the observed results also differed. The diagnostic efficacy of the nonexperts was lower than that of the experts. However, because of the high sensitivity of LCI to color, the *H. pylori* infected mucosa was obviously red, which was easy to recognize. Therefore, there is good consistency among the observers for gastric fundus mucosal redness. The color differences for the other indicators were not as obvious; therefore, the consistency among the experts and nonexperts was fair to moderate. These results suggest that observer consistency in the LCI mode may be better than that for other modes. Studies by Osamu Doh also showed that there was good consistency in the LCI mode between experts and trainees. However, the consistency of white light was moderate. These results are in line with our results.

There were 9 patients with bile regurgitation in this study. Bile flowed back into the stomach, and the gastric mucosa was stimulated by the basic bile, which could produce obvious congestion and edema and lead to misdiagnosis by LCI. However, the bile was nonbacterial and did not cause mucus to increase generally; thus, purple mucus was not observed in the LCI mode. Therefore, the combination of multiple indicators could reduce the incidence of misdiagnosis. In this study, all 9 patients with bile reflux were negative for *H. pylori* infection, suggesting that bile reflux may be unfavorable for *H. pylori* colonization in gastric mucosa.

LCI with laser source has many advantages in endoscopy diagnosis. At present, the application of LED technology in Endoscope System Imitates Laser and also has LCI mode, its imaging principle and the use of light beam are similar to that of laser, so its LCI images are very similar to that of laser and have a high resolution for the slight differences of mucosa color. Compared with laser, it has great potential because of its low cost.

To summarize, the diagnostic evaluation of *H. pylori* gastritis with LCI score was of high value and was an effective method for the diagnosis of *H. pylori* infection. However, when the total scores were between 2.5 and 3.5, the determination of *H. pylori* infection remained inconclusive. Therefore, additional methods are needed to increase the diagnosis of *H. pylori* infection. The value of bile reflux and granular erosion for *H. pylori* gastritis also needs be further studied. Whether LED technology can replace laser technology needs further research.

Conflict of interest

None declared.

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