

# Clinical significance and influencing factors of linked color imaging technique in real-time diagnosis of active *Helicobacter pylori* infection

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## Abstract

**Background:** Determining the *Helicobacter pylori* (*H. pylori*) infection state during the gastroscopic process is important but still challenging. The linked color imaging (LCI) technique might emphasize the mucosal color change after *H. pylori* infection, which might help the diagnosis. In the present study, we aimed to compare the LCI technique with traditional white light imaging (WLI) endoscopy for diagnosing active *H. pylori* infection.

**Methods:** We collected and analyzed gastroscopic images from 103 patients in our hospital from November 2017 to March 2018, including both LCI and WLI modes. All images were randomly disordered and independently evaluated by four endoscopists who were blinded to the *H. pylori* status of patients. In addition, the *H. pylori* state was determined by both rapid urease test and pathology staining. The sensitivity, specificity, positive prediction value (PPV), and negative prediction value (NPV) were calculated for the detection of *H. pylori* infection. Moreover, the kappa value and interclass correlation coefficient (ICC) were used to evaluate the inter-observer variety by SPSS 24.0 software.

**Results:** Of the 103 enrolled patients, 27 of them were positive for *H. pylori* infection, while the 76 patients were negative. In total, 388 endoscopic images were selected, including 197 WLI and 191 LCI. The accuracy rate for *H. pylori* evaluation in the corpus LCI group was significantly higher than other groups (81.2% vs. 64.3%–76.5%,  $\chi^2 = 34.852$ ,  $P < 0.001$ ). Moreover, the corpus LCI group had the optimal diagnostic power with the sensitivity of 85.41% (95% confidence interval [CI]: 76.40%–91.51%), the specificity of 79.71% (95% CI: 74.38%–84.19%), the PPV of 59.42% (95% CI: 50.72%–67.59%), and the NPV of 94.02% (95% CI: 89.95%–96.56%), respectively. The kappa values between different endoscopists were higher with LCI than with WLI (0.433–0.554 vs. 0.331–0.554). Consistently, the ICC value was also higher with LCI than with WLI (0.501 [95% CI: 0.429–0.574] vs. 0.397 [95% CI: 0.323–0.474]). We further analyzed the factors that might lead to misjudgment, revealing that active inflammation might disturb WLI judgment (accuracy rate: 58.70% vs. 76.16%,  $\chi^2 = 21.373$ ,  $P < 0.001$ ). Atrophy and intestinal metaplasia might affect the accuracy of the LCI results (accuracy rate: 66.96% vs. 73.47%,  $\chi^2 = 2.027$ ; 68.42% vs. 73.53%,  $\chi^2 = 1.594$ , respectively); however, without statistical significance ( $P = 0.154$  and 0.207, respectively).

**Conclusions:** The application of LCI at the corpus to identify *H. pylori* infection is reliable and superior to WLI. The inter-observer variability is lower with LCI than with WLI.

**Trial registration:** Chinese Clinical Trial Registry: ChiCTR1800016730; <http://www.chictr.org.cn/showproj.aspx?proj=28400>

**Keywords:** *Helicobacter pylori*; Image enhancement technique; Linked color imaging; Real-time diagnosis

## Introduction

*Helicobacter pylori* (*H. pylori*) is currently recognized as a pathogenic factor and even a carcinogen.<sup>[1]</sup> Chronic infection with *H. pylori* is correlated with gastric mucosal atrophy, intestinal metaplasia, and gastric cancer, as well as other gastric malignancies such as lymphoma.<sup>[2,3]</sup> Patients with different infection states have a distinct disease spectrum. *H. pylori*-positive individuals are prone

to have gastric atrophy and intestinal metaplasia, which might eventually develop into distal gastric cancer, while those *H. pylori*-negative individuals tend to have malignancies at the corpus and cardia areas.<sup>[4]</sup> Therefore, assessment of the *H. pylori* infection status during endoscopy would help to detect lesions, especially to detect malignant diseases more objectively.

At present, several methods can be used to evaluate the *H. pylori* status during the endoscopy process.<sup>[5,6]</sup>

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However, all these methods still have some shortcomings. To be specific, the rapid urease test (RUT) could be affected by several types of medication, the white-light imaging endoscope has limited accuracy rate for *H. pylori* diagnosis, while the application of the magnifying endoscope restricted by both equipment and technical concerns. Hence, a novel technique that is fast, accurate, and easy to master is urgently warranted.

Linked color imaging (LCI) is a novel imaging mode under blue laser endoscopy.<sup>[7]</sup> In this mode, the color change of the mucosa is emphasized especially for the red area, rendering easier identification of the lesions. Dohi *et al*<sup>[8]</sup> have previously found that *H. pylori*-positive stomach mucosa showed diffuse redness, which was distinctively different from the light orange appearance of *H. pylori*-negative mucosa. Therefore, *H. pylori* infection state can be determined by different mucosal color in the LCI mode, which, however, still lacks randomized research.

To this end, herein, we analyzed our endoscope images of both white light imaging (WLI) mode and LCI mode from the eligible patients to explore the significance and influencing factors of the LCI technique in diagnosing *H. pylori* infection.

## Methods

### Ethical approval

The present study was ethically approved by the Institutional Ethics Examining Committee of Human Research (IRB [BMR]-2018-018). And all patients signed written informed consent before endoscopic procedure.

### Patient selection

Images of patients, who received blue laser imaging endoscopy (Fujifilm laser system; Fujifilm Co., Tokyo, Japan) examination at Peking University International Hospital, were collected from November 2017 to March 2018. For each patient, four images were selected from both the corpus and antrum, including both WLI and LCI pictures. The optimal images should be clear, focused and inflated enough for detailed mucosal observation. The exclusion criteria were shown as follows: patients who had gastric malignancies or had undergone stomach surgery, or were burdened with gastric bleeding, and severe anemia [Figure 1]. Due to the delayed morphologic change for a specific time after *H. pylori* eradication,<sup>[9]</sup> the medical records were carefully reviewed and patients receiving eradication therapy within 3 months were excluded.

### *H. pylori* status evaluation and positive features definition

All the retrieved images were randomly numbered and completely disordered using simple randomization method with Excel (Office 365; Microsoft Corporation, State of Washington, USA). Four endoscopists were selected to independently evaluate these images for the *H. pylori*

status, who were only aware of the number of copies, but were blinded with the patients' information.

The WLI images were considered as *H. pylori*-positive in the case of any of the following signs: (1) granular appearance, (2) disappearance of regular arrangement of collecting venules (RAC), and (3) mucus attachment. In terms of LCI images, *H. pylori* infection was indicated in the presence of any one of the followings: (1) diffuse red color, (2) disappearance of RAC, and (3) mucus attachment.

### Diagnostic criteria of *H. pylori* infection

Both RUT and pathological staining were comprehensively considered to determine the *H. pylori* status. Two samples were taken from both antrum and corpus and put together for the RUT test in all the patients to avoid sampling site interference to the RUT result. For the pathologic analysis, another two samples were obtained from the lesser curvature of both antrum and corpus, followed by evaluation of hematoxylin-eosin (H&E) staining and *H. pylori* state. A positive result of either RUT or pathological assessment was considered to indicate current *H. pylori* infection, and negative consequences for both assays were suggestive of *H. pylori*-negative.

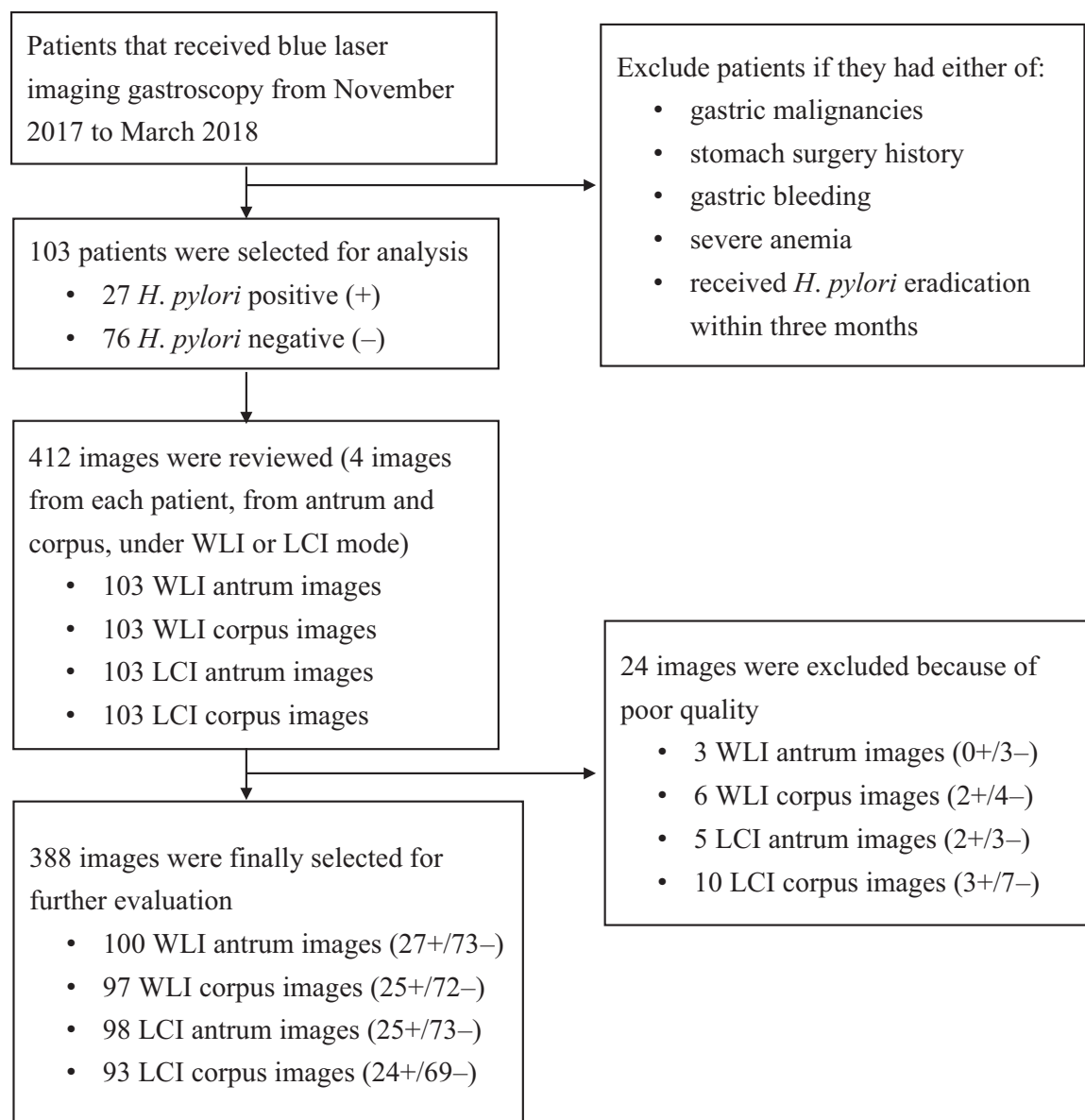
### Statistical analyses

SPSS 24.0 software (IBM, New York, USA) was used for statistical analysis. The differences of the following parameters including the general information of patients, RUT results, pathologic results, *H. pylori* status and the evaluation results of images were compared between WLI and LCI. Numerical variables with normal distribution were analyzed with Student's *t* test, while categorical variables were summarized with percentages and compared using the Pearson Chi-square test. In addition, the sensitivity, specificity, positive prediction value (PPV), and negative prediction value (NPV) were calculated for the detection of *H. pylori* infection compared with negative individuals. The kappa value and interclass correlation coefficient (ICC) and 95% confidence interval (CI) were calculated to evaluate the inter-observer variety with LCI and with WLI. Moreover, correlation analysis was performed to investigate the potential influencing factors for the endoscopic diagnosis of *H. pylori* infection. All tests were two-sided and *P* values <0.05 were considered as statistically significant. According to a previous study,<sup>[8]</sup> kappa values <0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and >0.80 indicated poor, fair, moderate, good, and excellent agreement between endoscopists, respectively.

## Results

### General information of patients

A total of 103 patients were enrolled in the study, including 42 males and 61 females. The median age was 48 years (range: 26–82 years). There were 27 patients with positive *H. pylori* status and 76 patients with negative status. In total, 388 images were obtained from the above patients, including 197 WLI and 191 LCI images. The



**Figure 1:** Flowchart of patients and endoscopic images selection process. The symbols +/- imply positive/negative state of *H. pylori* infection. *H. pylori*: *Helicobacter pylori*; LCI: Linked color imaging; WLI: White light imaging.

other 24 images were discharged due to poor image quality [Figure 1].

### Results of image analysis

The colors were different between *H. pylori*-positive and *H. pylori*-negative mucosa in the LCI mode [Figure 2]. Four endoscopists independently evaluated these 388 images to finally obtained 1552 results, among which 1122 were correct. The total accuracy rate was 72.3% (1122/1552). The accuracy rate was significantly different between the corpus and antrum ( $P < 0.001$ ), and the optimal result was obtained in the corpus LCI group (81.2%) [Table 1]. The overall sensitivity, specificity, PPV, and NPV of *H. pylori* infection was 66.08%, 74.48%, 47.68%, and 86.19%, respectively. Additionally, the diagnostic ability of different parts and different modes were calculated. The sensitivity, specificity, PPV, and NPV

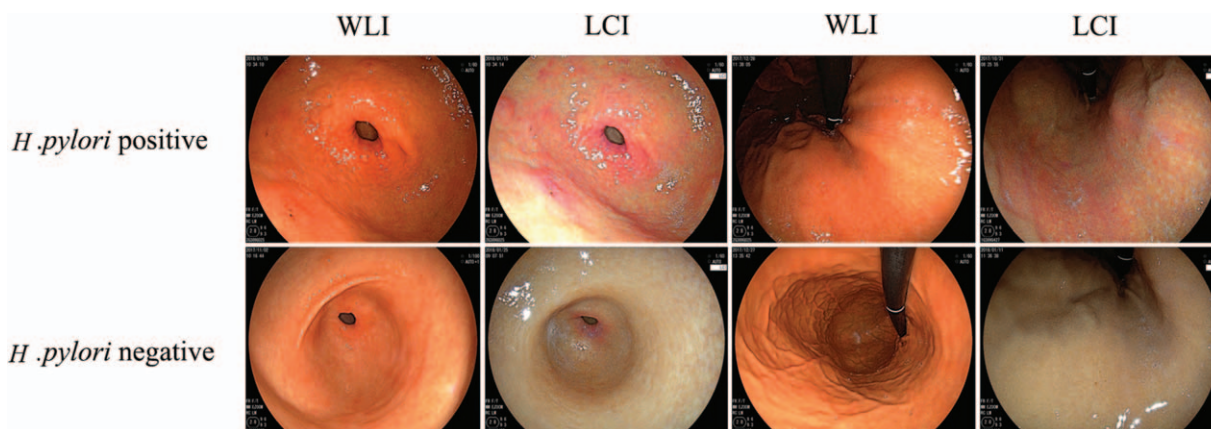
from the corpus LCI group were 85.41%, 79.71%, 59.42%, and 94.02%, respectively, which were superior to other parts and patterns [Table 2].

### Inter-observer variability in different modes

The kappa values among different endoscopists in the LCI group were 0.433 to 0.554, which were higher than WLI group (0.331–0.554) [Table 3]. The ICC was 0.501 (95% CI: 0.429–0.574) in the LCI group, which was also better than WLI group (ICC: 0.397, 95% CI: 0.323–0.474) [Table 4].

### Analysis of factors influencing image-evaluating results

Analysis of factors that might lead to misjudgment of *H. pylori* status revealed that active inflammation in pathologic tests might lead to misinterpretation in WLI mode ( $P < 0.05$ ). In LCI group, although atrophy and



**Figure 2:** Typical endoscopic images of *H. pylori*-positive and -negative stomach mucosa under WLI and LCI modes. It is notable that *H. pylori*-positive mucosa showed slightly red in WLI mode, while the positive mucosa appeared massively red in LCI mode, which was distinctly different from negative mucosa with apricot yellow appearance. *H. pylori*: *Helicobacter pylori*; LCI: Linked color imaging; WLI: White light imaging.

**Table 1: Comparison of *H. pylori* evaluation accuracy rates between different modes (WLI and LCI) and locations of stomach (antrum and corpus).**

Parameters	Accuracy rate	$\chi^2$	P
Location		31.627	<0.001
Antrum	66.0 (523/792)		
Corpus	78.8 (599/760)		
Mode		0.036	0.849
WLI	72.1 (568/788)		
LCI	72.5 (554/764)		
Antrum		1.059	0.303
WLI	67.8 (271/400)		
LCI	64.3 (252/392)		
Corpus		2.445	0.118
WLI	76.5 (297/388)		
LCI	81.2 (302/372)		
Different modes and locations		34.852	<0.001
Antrum WLI	67.8 (271/400)		
Antrum LCI	64.3 (252/392)		
Corpus WLI	76.5 (297/388)		
Corpus LCI	81.2 (302/372)		
Total	72.3 (1122/1552)		

The data were presented as % (n/N). Pearson Chi-squared (two-sided) test was used for comparison between groups. *H. pylori*: *Helicobacter pylori*; LCI: Linked color imaging; WLI: White light imaging.

intestinal metaplasia might disturb the results, none of these factors were significantly correlated with errors [Table 5].

### Discussion

Several studies have focused on the endoscopic diagnosis of *H. pylori* infection. In the WLI endoscope, the granular appearance of the mucosa can be considered to indicate positive *H. pylori* infection<sup>[5]</sup>; however, without satisfactory sensitivity. Yagi *et al*<sup>[10]</sup> analyzed RAC from the lesser curvature of the corpus with magnifying endoscope, and further demonstrated the appearance of RAC as *H. pylori*-negative status. The results revealed that both sensitivity and specificity were higher than 90%. However, some other factors may also cause the disappearance of

RAC, such as inflammation of the stomach from other causes or swelling of the mucosa. Therefore, the NPV of RAC is ideal, while PPV is far from satisfactory. Magnification endoscopy-narrow band imaging could improve the ability of endoscopic diagnosis of *H. pylori* infection. In a meta-analysis, Qi *et al*<sup>[11]</sup> included 18 randomly controlled studies containing 1897 cases. According to the results, the sensitivity and specificity were 0.96 (95% CI: 0.94–0.97) and 0.91(95% CI: 0.87–0.93) based on the pit and vascular pattern under magnifying endoscope. However, magnifying endoscope requires highly technical training, posing great challenge towards the widespread application. Furthermore, at present, the routinely-performed RUT method could contribute to *H. pylori* diagnosis, but may lead to high false-negative rates due to the biopsy location and urease activity.

LCI, a specific mode of the blue-laser imaging endoscopic system, might enhance the contrast of the redness from the background by modulating the intensity and proportion of light components.<sup>[12]</sup> Recently, some studies have revealed that the LCI mode is superior to the traditional WLI mode in the diagnosis of upper gastrointestinal (GI) tract, especially in the early detection of early-stage cancer and determination of the lesion boundaries.<sup>[13]</sup> Several studies have focused on using LCI to screen early-stage cancer of the esophagus and colon.<sup>[14–16]</sup> The feasibility of LCI for *H. pylori* diagnosis has been evaluated by several studies. Dohi *et al*<sup>[8]</sup> evaluated the diagnostic ability of LCI in *H. pylori* infection in the Japanese population, showing that *H. pylori*-positive fundic gland mucosa appeared red as diffuse redness in the LCI mode, which was distinctly different from the apricot yellow appearance of *H. pylori*-negative mucosa. The sensitivity and specificity of the LCI group were 85.8% and 93.3%, respectively, which were superior to the WLI group. However, cases without chronic atrophic gastritis were excluded from the above study, causing bias from the general population. Another study of Chen *et al*<sup>[17]</sup> compared LCI with magnifying endoscopy in the real-time diagnosis of *H. pylori* infection and further reported similar results from the two groups. The magnifying endoscope is a superior method for disease diagnosis; however, only a few centers and endoscopists

**Table 2: Diagnosis power of image-analysis results from the four endoscopists including different modes (WLI and LCI) and locations (antrum and corpus).**

Item	Sensitivity	Specificity	PPV	NPV
Total	66.08 (61.21–70.65)	74.48 (71.83–76.96)	47.68 (43.38–51.91)	86.19 (83.85–88.24)
Antrum WLI	53.70 (43.88–63.26)	72.95 (67.40–77.88)	42.34 (34.04–1.07)	80.99 (75.61–85.44)
Antrum LCI	60.00 (49.70–69.52)	65.75 (59.96–71.12)	37.50 (30.08–45.53)	82.76 (77.14–87.26)
Corpus WLI	67.00 (56.79–75.88)	79.96 (74.66–84.24)	53.60 (44.49–62.49)	87.45 (82.69–91.09)
Corpus LCI	85.41 (76.40–91.51)	79.71 (74.38–84.19)	59.42 (50.72–67.59)	94.02 (89.95–96.56)

The data were shown as % (95% confidence interval). LCI: Linked color imaging; NPV: Negative predictive value; PPV: Positive predictive value; WLI: White light imaging.

**Table 3: Inter-observer variability of image-analysis results between every two observers of WLI and LCI modes pictures.**

Group	Kappa value					
	A to B	A to C	A to D	B to C	B to D	C to D
WLI	0.397	0.554	0.331	0.406	0.372	0.382
LCI	0.525	0.514	0.455	0.546	0.554	0.433

A, B, C, and D indicate the four endoscopists analyzing the pictures in this study, respectively. LCI: Linked color imaging; WLI: white light imaging.

**Table 4: Consistency of the four observers for image-evaluation of WLI and LCI mode pictures.**

Group	ICC	95% CI
WLI	0.397	0.323–0.474
LCI	0.501	0.429–0.574

CI: Confidence interval; ICC: Interclass correlation coefficient; LCI: Linked color imaging; WLI: White light imaging.

could perform magnifying endoscope due to equipment and technique restriction. Therefore, it is rather difficult to routinely apply the magnifying endoscope for *H. pylori* screening in clinical practice. Our study collected a series of patients to reflect on the wider population. One study from China by Sun *et al*<sup>[18]</sup> analyzed the endoscopic images of the LCI mode from the antrum by MATLAB software, and summarized the lightness and tone of the pictures, which were further uses in the diagnosis of several types of stomach diseases, including *H. pylori* infection, atrophy, intestinal metaplasia, and early-stage cancer. As a result, they showed that the consistency of LCI and pathologic findings were preferable. However, it was only a pilot study that only included a limited number of cases, lacking statistical comparison of LCI and other modes. In our study, the sample size was expanded, blind method was applied, and the sensitivity, specificity, PPV, and NPV values were calculated to evaluate the superiority of LCI in the real-time diagnosis of *H. pylori* infection.

Different manifestations were considered in WLI and LCI for the diagnosis of *H. pylori* infection. In the WLI mode, granular appearance, the disappearance of RAC, and attachment of mucous indicate *H. pylori* infection, while in the LCI mode, diffuse redness, disappearance of RAC, and attachment of mucous implicate the infection of *H. pylori*. Notably, disappearance of RAC and attachment of mucous are included in both modes, which, therefore, could be considered as balance factors. Thus, we could infer that

**Table 5: Analysis of specific endoscopic and pathologic conditions that might affect *H. pylori* status evaluation accuracy.**

Specific condition	Accuracy rate	$\chi^2$	P
WLI			
Active inflammation		21.373	<0.001
Yes	58.700 (108/184)		
No	76.160 (460/604)		
Atrophy		0.270	0.604
Yes	70.160 (87/124)		
No	72.440 (481/664)		
Intestinal metaplasia		1.477	0.224
Yes	68.290 (112/164)		
No	73.080 (456/624)		
Erosion		0.011	0.915
Yes	71.880 (230/320)		
No	72.220 (338/468)		
LCI			
Active inflammation		1.298	0.255
Yes	69.050 (116/168)		
No	73.490 (438/596)		
Atrophy		2.027	0.154
Yes	66.960 (75/112)		
No	73.470 (479/652)		
Intestinal metaplasia		1.594	0.207
Yes	68.420 (104/152)		
No	73.530 (450/612)		
Erosion		0.057	0.812
Yes	72.040 (219/304)		
No	72.830 (335/460)		

The data were presented as % (n/N). Pearson Chi-squared (two-sided) test was used for comparison between groups. *H. pylori*: *Helicobacter pylori*; LCI: Linked color imaging; WLI: White light imaging.

the differences between the two groups derived from the granular appearance in WLI and diffuse redness in LCI.

According to these criteria, the accuracy rate was compared between the WLI and LCI groups, which

revealed no significant difference ( $P = 0.849$ ). We further analyzed the image evaluation results between two groups by different modes and locations, showing significant differences among the four groups ( $P < 0.001$ ). To estimate the diagnostic power in each group, the sensitivity, specificity, PPV, and NPV were calculated in these groups, and the optimal results were obtained from the corpus in the LCI group, which were 85.41%, 79.71%, 59.42%, and 94.02%, respectively. To clarify the personal differences among endoscopists, the kappa values of inter-observer variability among the four endoscopists, and ICC were compared, which similarly yielded to better results in the LCI group, indicating a better consistency between endoscopists. Therefore, we could conclude that it was reliable to evaluate *H. pylori* infection by diffuse redness, the disappearance of RAC, and attachment of mucus in the LCI mode, which was easy to master for endoscopists, including both experts and non-experts. However, the diagnostic power of each sign remained unclear, therefore, further prospective studies are warranted to analyze them separately to determine the optimistic criteria.

For all the previous criteria, diffuse redness was the specific sign in the LCI mode. As mentioned above, diagnosis of *H. pylori* infection based on diffuse redness in the LCI mode could be considered as a reliable method due to the evident and intuitive color change during the endoscopic process, which could also be easily mastered by clinicians. Nevertheless, due to the limited available data, studies involving clinicians with diverse experience are still needed to clarify the advantages of LCI for learning, and the results before and after systemic training should also be analyzed.

Afterward, we compared different locations, and found that the sensitivity, specificity, PPV, and NPV from the corpus were all significantly superior to those of the antrum. The diffuse redness of mucosa was considered to indicate *H. pylori*-positive infection in the LCI mode. Nevertheless, several factors could lead to the redness change of stomach mucosa, such as erosion, inflammation, and mechanical injury by food, which might all be confused with *H. pylori* infection. *H. pylori* is likely to induce atrophy changes in the antrum that might disturb the diagnosis. Therefore, a predictive study is still needed to explore these hypotheses during the endoscopic process.

To explore the possible influencing factors on endoscopic diagnosis, we further analyzed the following aspects. As a result, atrophy and intestinal metaplasia might lead to misjudgment in the LCI mode, while active inflammation might disturb the result under the WLI mode, but only active inflammation might significantly disturb WLI outcomes. The color of intestinal metaplasia mucosa was purple-red in LCI mode due to the existence of brush border,<sup>[13]</sup> which was different from that around the normal mucosa. However, it was similar to the diffuse redness change in *H. pylori* infection, especially when the intestinal metaplasia was diffuse. For atrophic mucosa, the condition may be confused, since atrophy could be accompanied with intestinal metaplasia. However, in the case of severe atrophy, the color change after *H. pylori* infection is not

obvious, leading to the absence of the diffuse redness change under LCI mode. Additionally, the morphologic characteristics vary during different stages of atrophic development.<sup>[19]</sup> In the WLI mode, the influencing factors were different. First, the villous appearance of intestinal metaplasia might mimic the swelling and coarse folds in *H. pylori*-positive mucosa, and swelling change in acute inflammation caused by other factors was also similar to *H. pylori* infection. The underlying causes still require further investigation. In this study, only the results of WLI group might be significantly influenced. Therefore, it could be cautiously speculated that the LCI mode was less affected by other factors in terms of *H. pylori* diagnosis.

This study still had several limitations. To begin with, the samples were restricted in one single medical center. Moreover, we only analyzed the endoscopic pictures, while failed to make the diagnosis during the examination, indicating the necessity of multi-center prospective studies in the future. Besides, the diagnostic criteria were still subjective, thus, further research using software for color measuring would help to utilize objective evidence.

In conclusions, the color change together with RAC could determine the *H. pylori* infection status during the endoscopic procedure in the LCI mode, which has ideal sensitivity and specificity, and the consistency between different endoscopists.

### Funding

None.

### Conflicts of interest

None.

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