

Linked color imaging confers benefits in profiling *H. pylori* infection in the stomach



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ABSTRACT

Background and study aims There is a high prevalence of *Helicobacter pylori* infection. White light endoscopy (WLE) can be used for evaluating the mucosal lesions, but it does not have high diagnostic efficiency. Linked color imaging (LCI) is a newly developed endoscopic imaging technique. The aim of this study was to compare LCI with WLE in detecting and staging *H. pylori* infection in the stomach in a randomized controlled clinical trial.

Patients and methods A total of 253 patients who had indications for gastroduodenoscopy were enrolled and randomized into Group A (n = 127), who underwent WLE followed by LCI, and Group B (n = 126), who underwent LCI followed by WLE. Clinical data were collected and the diagnostic accuracy of WLE and LCI was calculated and compared.

Results The overall diagnostic accuracy of WLE and LCI for *H. pylori* infection was 31.5% (n = 40) and 50.4% (n = 64) in Group A (P = 0.001), and 36.5% (n = 46) and 49.2% (n = 62) in Group B (P = 0.029). In both groups, LCI had higher sensitivity, specificity, and Youden index scores than WLE. Four stages were defined in the course of *H. pylori* infection in the stomach. LCI staging results were more highly consistent with pathological staging than were WLE staging results (kappa value 0.772 vs. 0.516). The LCI observations were closely correlated with the pathology.

Conclusion LCI had a higher diagnostic efficacy for *H. pylori* infection in the stomach. Endoscopic color features under LCI can help to stage and profile *H. pylori*-associated gastritis.

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TRIAL REGISTRATION: Multi-center double-blinded randomized controlled trial NCT02724280 at clinicaltrials.gov

Introduction

Prevalent worldwide, *Helicobacter pylori* infection can increase risk of gastric cancer and is associated with the occurrence of a variety of human diseases, including lymphoma and autoim-

mune disorders [1,2]. *H. pylori* infection is most common in the stomach, and patients with it may have heartburn, epigastric pain, dyspepsia, and other nonspecific symptoms, which are easily overlooked in a majority of cases [3]. Diagnosis of *H. pylori* infection can be made based on judgment of the clinical manifestation, detection of a specific antibody in serum,

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and based on results of a C¹³ breath test [4,5]. In addition, endoscopic examination may provide useful evidence for confirming the diagnosis, and tissue from biopsy performed under endoscopy can be sent for a rapid urease test and pathology.

Inflammation, atrophy, and intestinal metaplasia of the gastric mucosa caused by presence of *H. pylori* have different appearances under endoscopy [6,7]. However, changes in mucosa observed under white light endoscopy (WLE) are not distinctive, and the stages of *H. pylori* infection in the stomach rarely have been reported. Linked color imaging (LCI) is a color-enhanced technique, which enables easier identification of mucosal lesions during endoscopy by significantly improving color contrast between lesions and normal tissue [8,9]. Our previous data validated that LCI can greatly improve endoscopic diagnostic accuracy of gastrointestinal mucosal lesions [10,11], while the role of LCI endoscopy in evaluating and staging *H. pylori* infection in the stomach has not been clearly investigated. In the current study, we conducted a randomized controlled clinical trial (RCT) to compare the diagnostic efficiency of WLE and LCI for *H. pylori* infection and further analyzed the endoscopic characteristics of different stages. The findings will help optimize current management of patients with *H. pylori* infection.

Patients and methods

Patients

Consecutive adult patients who had indications and underwent gastroduodenoscopy between September 2016 and February 2017 were enrolled from five endoscopic centers: Affiliate Hospital to Academy of Military Medical Science (307 Hospital; the Fifth Clinical Center of Chinese PLA General Hospital), the People's Hospital of Guangxi Zhuang Autonomous Region, Shanghai Tenth People's Hospital, the Second Affiliated Hospital of Soochow University and the Sixth Affiliated Hospital of Sun Yat-sen University. Patients who had thrombocytopenia (platelet count <50,000/μL) or elevated International Normalized Ratio (INR >1.5), hemodynamic instability, pregnancy and lactation, had ever undergone *H. pylori* eradication therapy, or were unable or unwilling to give an informed consent were excluded. Demographic and clinical data were retrieved from the computerized database.

All patients gave informed consent. The study was approved by the Ethics Committee of Affiliate Hospital to Academy of Military Medical Science. This study was registered at ClinicalTrials.gov (ClinicalTrials.gov ID: NCT02724280). We had access to the study data and had reviewed and approved the final manuscript.

Study design

The flow chart of this RCT is shown in **Supplemental Fig. 1**. McNemar test was used to calculate the sample size by using SPSS software. The sample size was calculated based on a probability of 0.8 and α error of 0.05. The actual expected sensitivity of LCI and WLE for diagnosing *H. pylori* was around 80% and 45% according to our previous study and experience [10,12]. The required sample size was set to 250 patients. 253 patients

were enrolled. All patients were randomized into Group A (n=127) or Group B (n=126) at a 1:1 ratio using the random number method. The random sequence was generated by Excel and concealed. In Group A, patients received WLE followed by LCI endoscopic examination. In Group B, patients received LCI, followed by WLE mode for gastroscopy. This study was double-blind, and patients and endoscopists were not informed of the grouping information, which was achieved by the participation of a third endoscopist who intubated and withdrew the endoscopy.

Procedures

All endoscopic procedures were performed under anesthesia. EG-L590WR endoscopes equipped with the LASEREO endoscopic system (FUJIFILM Co., Tokyo, Japan) were used. WLE and LCI examinations were conducted by two different endoscopists who had comparable skills and experience with endoscopic examinations. No magnification was applied. The biopsies were completed by a third endoscopist for the purposes of conducting a rapid urease test and histological examination. According to the Sydney System [13], two biopsies from lesser and greater curvature (around 8 cm from the cardia), two biopsies from the pre-pyloric antrum (3–5 cm from the pylorus), and one biopsy from the gastric angle were taken in each case. *H. pylori* infection was manifested as diffuse or spotty red with nodularity and enlarged/tortuous folds under WLE, and red mixed with heterogeneous purple under LCI [12,13]. To minimize the inconsistency of diagnostic accuracy among different endoscopists, typical endoscopic images of LCI and WLE were distributed to train the participating endoscopists.

Outcomes

Diagnosis of *H. pylori* infection was made by positivity in a rapid urease test and/or histological examination of any of the biopsies in one patient. If rapid urease test and the histological examination were all negative in all the biopsies of one patient, it was judged as *H. pylori* infection-negative. Overall diagnostic efficacy evaluation was performed and the receiver operating characteristic (ROC) curve was drawn. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and Youden index of WLE and LCI in Groups A and B were calculated in the diagnostic test, respectively. *H. pylori* infection in the stomach was comprehensively determined by histological analysis or rapid urease test, which was administered for all patients. Overall diagnostic efficacies of WLE and LCI in diagnosing *H. pylori* infection in the stomach were compared. *H. pylori* infection in different parts of the stomach was analyzed for profiling the stages. Kappa values were calculated for the correlation analysis of pathological staging with WLE staging and LCI staging.

Statistical analysis

All statistical analyses were conducted using SPSS 17.0 software (SPSS Inc., Chicago, Illinois, United States). Continuous and categorical data were presented as means (range) and percentages (%), respectively. Data were analyzed using independent *t*-test and Chi-square or Fisher's exact probability test, if

► **Table 1** Demographic and clinical characteristics.

	Group A (n = 127)	Group B (n = 126)	t/x ²	P value
Age, years, mean (range)	47.20 (19–76)	49.66 (19–72)	1.540	0.125
Gender, n (%)			0.102	0.750
Male	66 (52.0)	68 (54.0)		
Female	61 (48.0)	58 (46.0)		
Indications, n (%)			7.178	0.127
Heartburn	19 (15.0)	17 (13.5)		
Abdominal distension	21 (16.5)	32 (25.4)		
Dyspepsia	15 (11.8)	14 (11.1)		
Epigastric pain	23 (18.1)	31 (24.6)		
Other	49 (38.6)	32 (25.4)		
<i>H. pylori</i> infection evaluation, n (%)				
Rapid urease test			0.005	0.941
Positivity	54 (42.5)	53 (42.1)		
Negativity	73 (57.5)	73 (57.9)		
Histological examination			0.001	0.970
<i>H. pylori</i> infection	34 (26.8)	34 (27.0)		
No <i>H. pylori</i> infection	93 (73.2)	92 (73.0)		
WLE diagnosis			0.708	0.400
<i>H. pylori</i> infection	40 (31.5)	46 (36.5)		
No <i>H. pylori</i> infection	87 (68.5)	80 (63.5)		
LCI diagnosis			0.674	0.412
<i>H. pylori</i> infection	64 (50.4)	57 (45.2)		
No <i>H. pylori</i> infection	63 (49.6)	69 (54.8)		

WLE, white light endoscopy; LCI, linked color imaging

applicable. Two-tailed *P* values less than 0.05 were considered statistically significant.

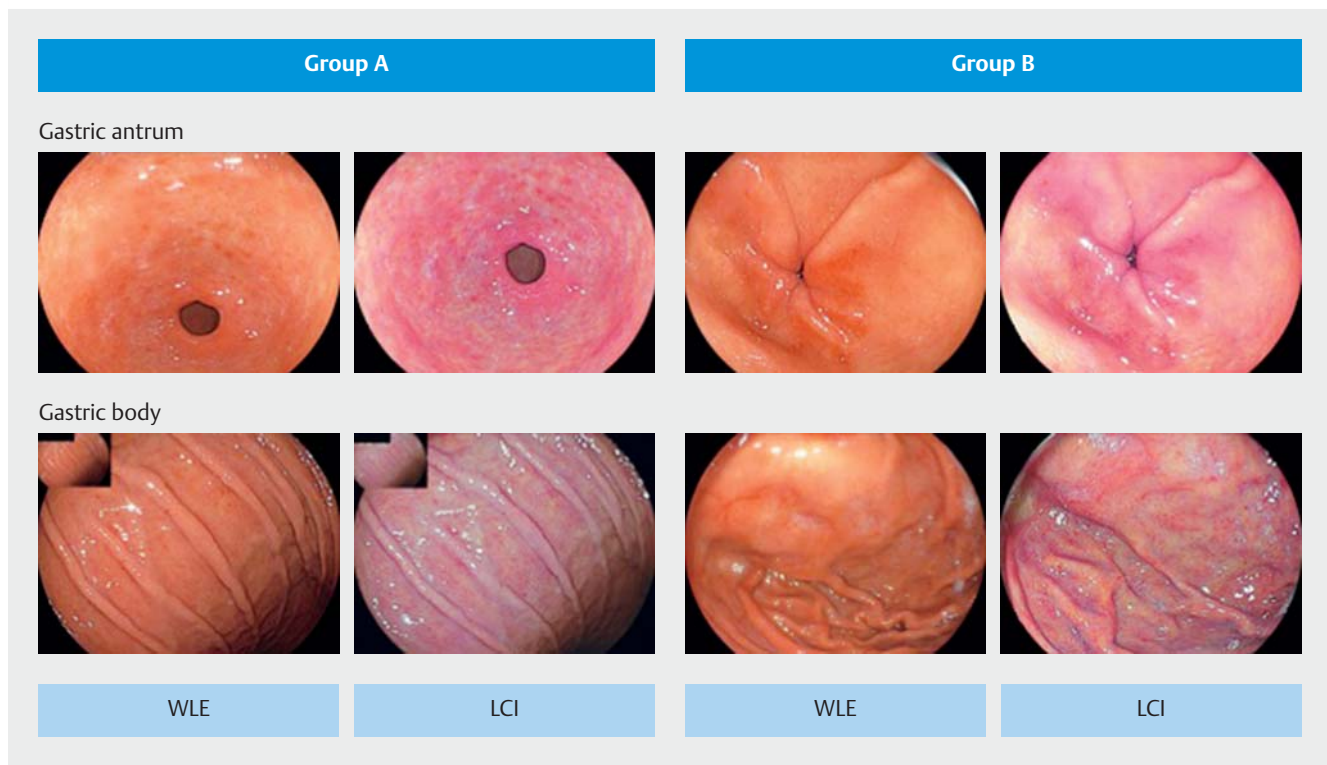
Results

Demographic and clinical characteristics

There were 127 patients in Group A and 126 patients in Group B. There were no significant differences in age, gender, or indications for endoscopy between the two groups (all *P* > 0.05, ► **Table 1**). Rapid urease test, histology, WLE, and LCI were applied for evaluating *H. pylori* infection in the stomach. The detection rate for *H. pylori* infection, which was around 27.0% to 50.4%, was comparable in Group A and Group B (all *P* > 0.05, ► **Table 1**). A total of 107 patients with *H. pylori* infection were finally diagnosed by rapid urease test and/or histology.

Diagnostic efficacy for *H. pylori* infection

H. pylori infection in the stomach was independently evaluated by WLE followed by LCI in Group A, and by LCI followed by WLE in Group B (► **Fig. 1**). The overall diagnostic accuracy of WLE and LCI in Group A (n = 127) were 31.5% (n = 40) and 50.4% (n = 64), respectively (*P* = 0.001), while the overall diagnostic accuracy of WLE and LCI were 36.5% (n = 46) and 49.2% (n = 62) in Group B (n = 126; *P* = 0.029). In addition, the ROC curve of LCI and WLE for *H. pylori* infection was analyzed (**Supplemental Fig. 2**). The results were consistent in indicating that LCI had higher diagnostic efficacy for *H. pylori* infection than did WLE. In both groups, LCI had higher sensitivity, specificity, NPV, PPV, and Youden index than did WLE. The AUC for WLE and LCI was 0.542 and 0.850 in Group A, and 0.559 and 0.891 in Group B (► **Table 2**).



► **Fig. 1** Typical endoscopic images for *H. pylori* infection in the stomach.

► **Table 2** Diagnostic efficacy evaluation of WLE and LCI for *H. pylori* infection.

	Group A (n=127)	Group B (n=126)
WLE		
AUC (<i>P</i> value)	0.542 (0.416)	0.559 (0.256)
Sensitivity, % (95 % CI)	35.8 (27.5–44.1)	43.4 (34.7–52.1)
Specificity, % (95 % CI)	72.6 (64.8–80.4)	68.5 (60.4–76.6)
NPV, % (95 % CI)	48.7 (40.0–57.4)	50.0 (41.3–58.7)
PPV, % (95 % CI)	60.9 (52.4–69.4)	62.5 (54.0–71.0)
Youden index, % (95 % CI)	8.4 (3.6–13.2)	11.9 (6.2–17.6)
LCI		
AUC (<i>P</i> value)	0.850 (<0.001)	0.891 (<0.001)
Sensitivity, % (95 % CI)	90.6 (85.5–95.7)	90.6 (85.5–95.7)
Specificity, % (95 % CI)	79.5 (72.5–86.5)	87.7 (82.0–93.4)
NPV, % (95 % CI)	76.2 (68.8–83.6)	84.2 (77.8–90.6)
PPV, % (95 % CI)	92.1 (87.4–96.8)	92.8 (88.3–97.3)
Youden index, % (95 % CI)	70.1 (62.1–78.1)	78.3 (71.1–85.5)

WLE, white light endoscopy; AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; LCI, linked color imaging

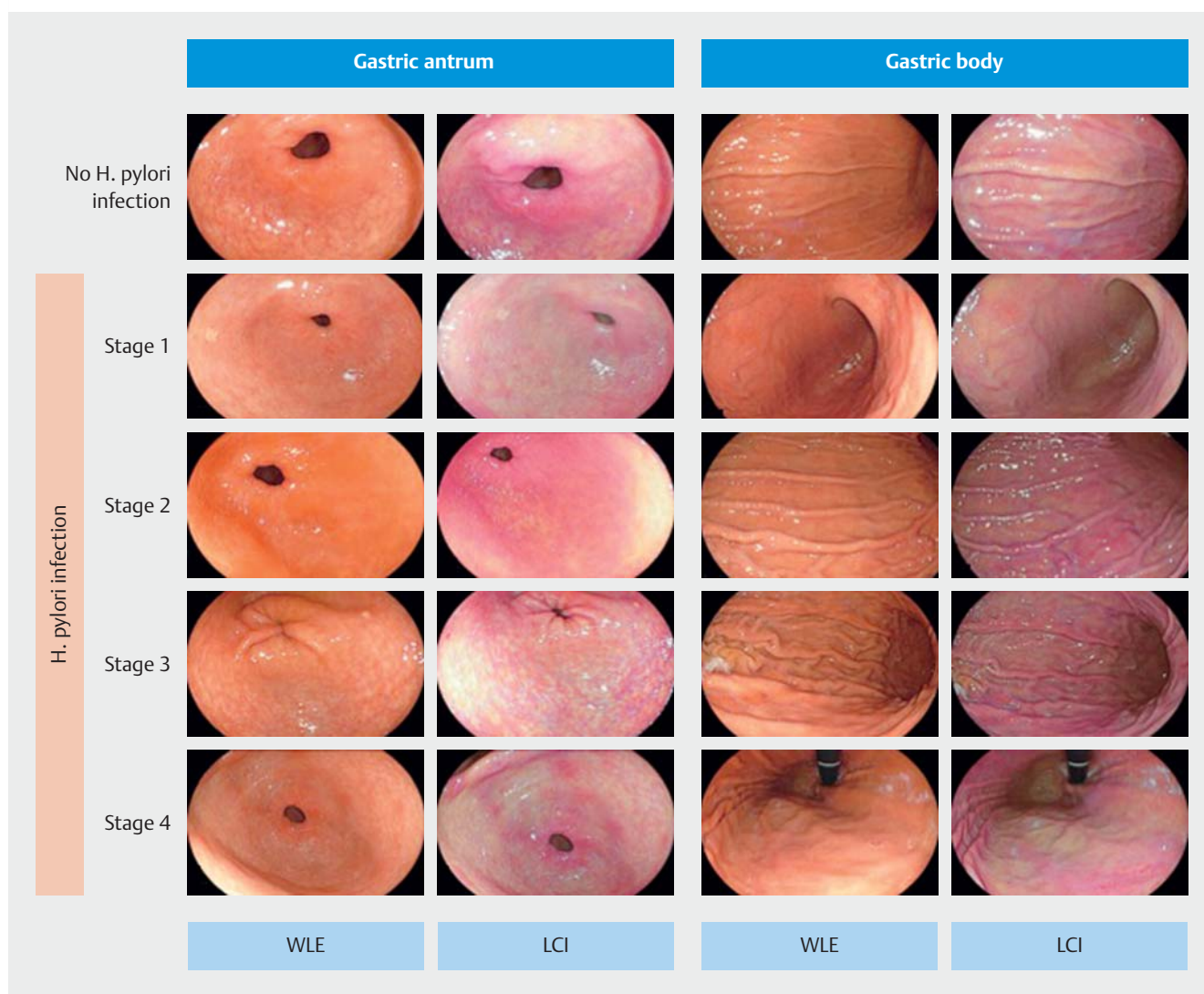
LCI could determine stage of *H. pylori* infection in the stomach

Distribution of *H. pylori* infection and morphological changes in the stomach mucosa may evolve during the course of disease. This kind of evidence may help determine the stage, about which little is known. Thus, we analyzed data from 107 patients with confirmed *H. pylori* infection and investigated that infection in the gastric body and antrum together with pathological changes (► **Table 3**). According to previous reports [14–16], *H. pylori* infection commonly starts in the gastric antrum, migrates into the gastric body, and then spreads throughout the entire stomach (gastric body and antrum). During the course of infection, incidences of atrophy and intestinal metaplasia in gastric antrum were noticeably increased.

We further hypothesized that *H. pylori* infection may have four stages: 1) Stage 1, *H. pylori* infection in the antrum without intestinal metaplasia; 2) Stage 2, *H. pylori* infection in the antrum and body without intestinal metaplasia; 3) Stage 3, intestinal metaplasia in the antrum and *H. pylori* infection in the body; and 4) Stage 4, both intestinal metaplasia and *H. pylori* infection in the antrum and body. However, in some patients, infection could not be staged and they were thus classified as Stage X (indeterminable). Different stages had different endoscopic appearances (► **Fig. 2**). LCI staging yielded greater consistency with pathological staging than did WLE staging (Kappa value 0.772 vs. 0.516, ► **Table 4**). Of 16 patients with LCI Stage X, 12 were pathological Stage X and four were pathological Stage 4. Under LCI mode, the inflammation appeared as diffuse red, mucosal atrophy appeared as white, and intestinal

► **Table 3** *H. pylori* infection in different parts of the stomach.

	No <i>H. pylori</i> infection (n = 146)	<i>H. pylori</i> infection in gastric antrum (n = 64)	<i>H. pylori</i> infection in gastric body (n = 9)	<i>H. pylori</i> infection in gastric body and antrum (n = 34)
Gastric body, n (%)				
Atrophy	16 (11.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intestinal metaplasia	26 (17.8)	3 (4.7)	1 (11.1)	2 (5.9)
Gastric antrum, n (%)				
Atrophy	13 (8.9)	3 (4.7)	2 (22.2)	4 (11.8)
Intestinal metaplasia	31 (21.2)	11 (17.2)	2 (22.2)	11 (32.4)

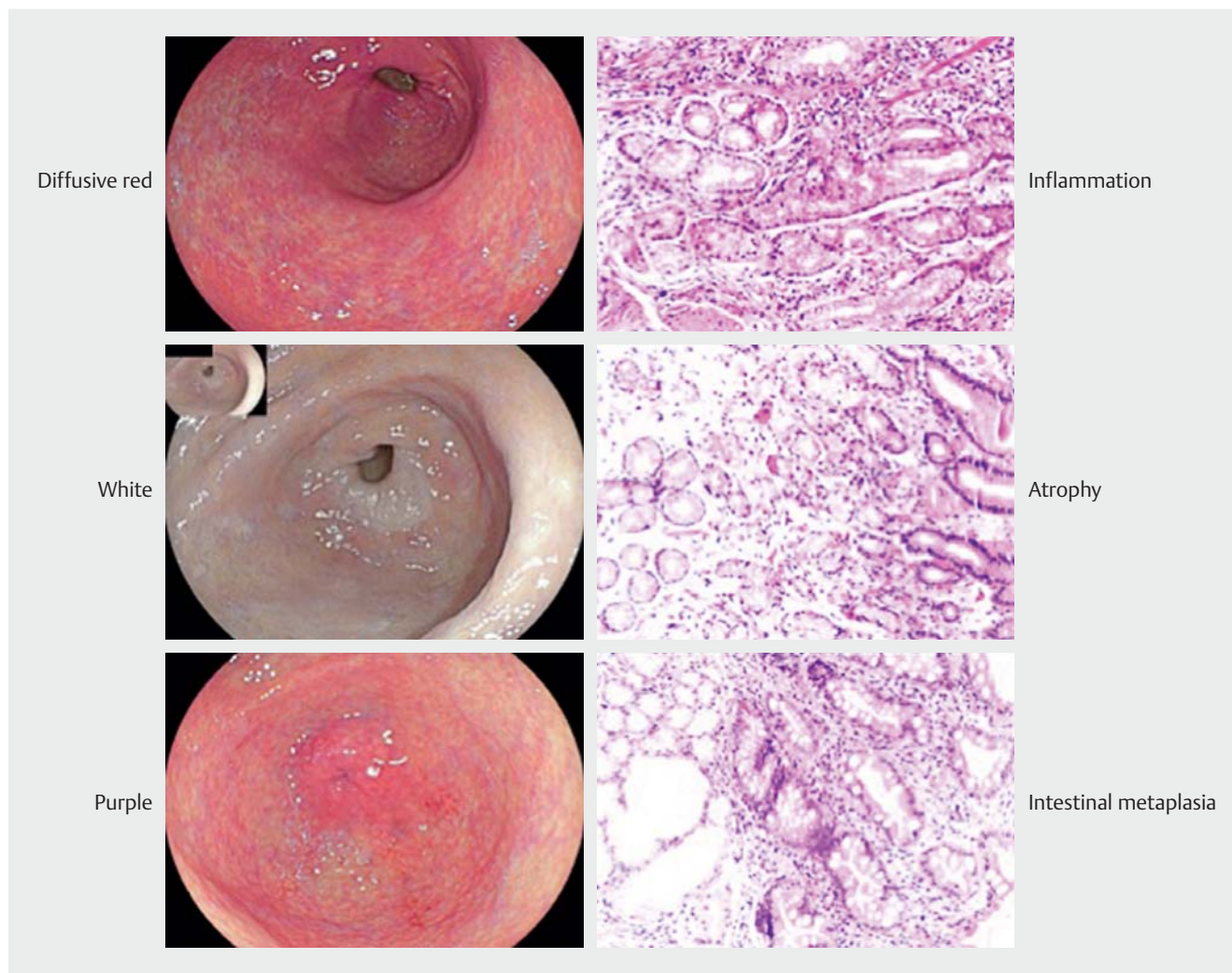


► **Fig. 2** Typical endoscopic images of *H. pylori* infection-associated gastritis at different stages. In Stage 1, *H. pylori* infection was observed mainly in the gastric antrum; it can gradually spread into the gastric body in Stage 2. In Stage 3, along with *H. pylori*-associated inflammation in the mucosa, intestinal metaplasia was found in the antrum. Intestinal metaplasia characterized by presence of goblet cells in the epithelial layer was the main feature of the mucosa of the gastric body in Stage 4; the inflammation can be subtle.

► **Table 4** Stages in the course of *H. pylori* infection in the stomach.

		WLE staging, n					LCI staging, n					Total, n
		Stage 1	Stage 2	Stage 3	Stage 4	Stage X	Stage 1	Stage 2	Stage 3	Stage 4	Stage X	
Pathological staging, n	Stage 1	30	2	0	0	0	28	4	0	0	0	32
	Stage 2	8	15	2	1	0	4	22	0	0	0	26
	Stage 3	0	1	9	2	0	0	0	10	2	0	12
	Stage 4	3	1	1	7	11	0	0	3	16	4	23
	Stage X	0	2	1	5	6	0	0	0	2	12	14
Total, n		41	21	13	15	17	32	26	13	20	16	107
		Kappa = 0.516, <i>P</i> < 0.001					Kappa = 0.772, <i>P</i> < 0.001					

WLE, white light endoscopy; LCI, linked color imaging



► **Fig. 3** LCI findings were closely associated with the pathology.

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metaplasia appeared as purple (**Supplemental Table 1**). The LCI observations were closely correlated with the pathology (► **Fig. 3**). During LCI endoscopy, purple was associated with intestinal metaplasia ($P=0.025$) and diffusive red was associated with inflammation ($P=0.016$). As intestinal metaplasia is a typical mucosal change in *H. pylori* infection, presence of red ringed with purple under LCI can predict *H. pylori* infection in the stomach ($P=0.022$). This provides a rapid and convenient evaluation for screening the stomach. However, no such correlations were found under WLE mode.

Discussion

Gastric mucosa infected with *H. pylori* can undergo a series of pathological changes, including inflammation, atrophy, and intestinal metaplasia [17, 18]. A single-center study reported that *H. pylori*-associated gastritis was connected with endoscopic modifications and histopathology in a prospective cohort of children [19]. It was also shown that the conventional endoscopy features can be used to diagnose *H. pylori* [20–22], but the efficiency of WLE was relatively poor [23, 24]. Endocytoscopy may facilitate in vivo gastric mucosal histopathology [25], but it is time-consuming and some patients cannot tolerate it. However, whether endoscopy can be used to predict these kinds of mucosal lesions, a question that has been rarely explored in a randomized setting, remains unclear [2]. In the current study, we compared the diagnostic efficacy of WLE and LCI in a multicenter RCT, and for the first time propose that observation of red ringed with purple under LCI mode could predict diagnosis of *H. pylori* infection in the stomach.

LCI is a recently developed endoscopic technique that incorporates image post-processing into the laser endoscopic system [26]. LCI makes it easier for endoscopists to identify color changes in the gastrointestinal mucosa by enhancing color contrast. Our previous study demonstrated that LCI can improve the efficiency and accuracy of differentiating gastrointestinal mucosal lesions and improve the performance of target biopsies [10]. Calculation of pixel brightness based on a red-green-blue color model may be introduced as an objective evaluator for analyzing typical endoscopic images. Consistently, we also correlated color features under LCI with pathology. Statistical analysis validated that a purple color observed under LCI could predict existence of intestinal metaplasia, and red predicts observation of inflammation. However, analysis of the correlation between atrophy and a white color under LCI was not conducted, due to the small number of patients with atrophy. Sensitivity of LCI for diagnosis of *H. pylori* infection was similar to previous studies, but that of WLE was quite low compared to the previous studies [8], and the possible reasons may be the different clinical practice in different medical institutions and the selected sample.

H. pylori infection, which is considered a precancerous lesion, is an independent risk factor for gastric cancer [27]. Gastroduodenoscopy is well known as an effective strategy for early detection of gastric mucosal lesions [28–30]. Our staging system was mainly based on comprehensive analysis of endoscopic images in different locations. Our data profiled four

stages of *H. pylori* infection in the stomach. In Stage 1, *H. pylori* infection was observed mainly in the gastric antrum; it can gradually spread into the gastric body in Stage 2. In Stage 3, along with *H. pylori*-associated inflammation in the mucosa, intestinal metaplasia was found in the antrum. Intestinal metaplasia characterized by presence of goblet cells in the epithelial layer was the main feature of the mucosa of the gastric body in Stage 4; the inflammation can be subtle. We then further calculated incidence of *H. pylori* infection in different parts of the stomach, and investigated the respective pathological changes. Of 107 patients with *H. pylori* infection in the stomach, there were 64 patients (59.8%) with *H. pylori* infection only in the gastric antrum, nine (8.4%) with *H. pylori* infection only in the gastric body, and 34 (31.2%) with *H. pylori* infection in both the gastric body and antrum (► **Table 3**). Intestinal metaplasia and atrophy occurred more often in the gastric antrum than in the gastric body. Typical color changes under LCI were highly consistent with the pathology (purple for intestinal metaplasia, $P=0.025$; diffusive red for inflammation, $P=0.016$). In addition, we validated LCI staging by comparing WLE staging in terms of its correlation with pathological staging. LCI had higher consistency with pathological staging than did WLE staging. However, 16 patients could not be staged by LCI (LCI Stage X), 12 of whom could not be staged by pathology due to atypical pathological changes (pathological Stage X). All of the patients were older than age 30 year, and no other special demographical and clinical characteristics were detected.

There were limitations in our study. First, patients who had ever undergone *H. pylori* eradication therapy were excluded. Thus, our staging method could not be used for them. Second, our conclusion was obtained based on the findings in a patient cohort, which may be further validated in a large-scale clinical trial. The main limitation in this study was that the role of LCI in surveillance of patients with *H. pylori* infection was not examined. Follow-ups will be further investigated in future research. It was expected that the endoscopic and histological features could help screen for gastric mucosal changes after eradication of *H. pylori* infection [31, 32].

Conclusion

From this multicenter RCT, we conclude that LCI has higher diagnostic efficacy for evaluating *H. pylori* infection in the stomach than does WLE, and this new endoscopic technique can be used as an effective method for quick diagnosis. Correlation analysis with pathology indicated that red ringed with purple observed under LCI could predict presence of *H. pylori* infection. In addition, this staging system can help clarify development of *H. pylori* infection in the stomach, which might have benefits for clinical management of such disease.

Competing interests

None

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