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Clinical usefulness of linked color imaging in identifying *Helicobacter pylori* infection: A systematic review and meta-analysis

Zhang Y *et al*. LCI benefits *H. pylori* diagnosis

Abstract

BACKGROUND

Accurate diagnosis of *Helicobacter pylori* (*H. pylori*) infection status is a crucial premise for eradication therapy, as well as evaluation of risk for gastric cancer. Recent progress on imaging enhancement endoscopy (IEE) made it possible to not only detect precancerous lesions and early gastrointestinal cancers but also to predict *H. pylori* infection in real time. As a novel IEE modality, linked color imaging (LCI) has exhibited its value on diagnosis of lesions of gastric mucosa through emphasizing minor differences of color tone.

AIM

To compare the efficacy of LCI for *H. pylori* active infection *vs* conventional white light imaging (WLI).

METHODS

PubMed, Embase, Embase and Cochrane Library were searched up to the end of April 11, 2022. The random-effects model was adopted to calculate the diagnostic efficacy of LCI and WLI. The calculation of sensitivity, specificity, and likelihood ratios were performed; symmetric receiver operator characteristic (SROC) curves and the areas under the SROC curves were computed. Quality of the included studies was chosen to assess using the quality assessment of diagnostic accuracy studies-2 tool.

RESULTS

Seven original studies were included in this study. The pooled sensitivity, specificity, positive likelihood rate, and negative likelihood rate of LCI for the diagnosis of *H. pylori* infection of gastric mucosa were 0.85 [95% confidence interval (CI): 0.76-0.92], 0.82 (95%CI: 0.78-0.85), 4.71 (95%CI: 3.7-5.9), and 0.18 (95%CI: 0.10-0.31) respectively, with diagnostic odds ratio = 26 (95%CI: 13-52), SROC = 0.87 (95%CI: 0.84-0.90), which showed superiority of diagnostic efficacy compared to WLI.

CONCLUSION

Our results showed LCI can improve efficacy of diagnosis on *H. pylori* infection, which represents a useful endoscopic evaluation modality for clinical practice.

Key Words: *Helicobacter pylori* infection; Endoscopic diagnosis; Linked color imaging; Gastric cancer; Meta-analysis

Zhang Y, Wang JZ, Bai X, Zhang PL, Guo Q. Clinical usefulness of linked color imaging in identifying *Helicobacter pylori* infection: A systematic review and meta-analysis. *World J Gastrointest Endosc* 2023; In press

Core Tip: As a novel imaging enhancement endoscopy modality, linked color imaging (LCI) has exhibited its value on diagnosis of lesions of gastric mucosa through emphasizing minor differences of color tone. In this meta-analysis enrolled seven clinical trials, we showed LCI can improve efficacy of diagnosis on *Helicobacter pylori* infection compared with white light endoscopy, which represents a useful endoscopic evaluation modality for clinical practice.

INTRODUCTION

Growing evidences has supported the predominant role of *Helicobacter pylori* (*H. pylori*) infection in development of gastric cancer, since World Health Organization designated *H. pylori* a type 1 carcinogen in 1993. It has been widely accepted that *H. pylori* infection leads to the progressive way from chronic atrophic gastritis, intestinal metaplasia, to dysplasia[1]. Moreover, prolonged infection with *H. pylori* cause inflammation, abnormal cell proliferation, release of bacterial virulence factors, and nitrate reduction, all of which contribute to the development of gastric cancer[1]. Recent random controlled trials and meta-analysis have verified that *H. pylori* eradication therapy appears to reduce new-onset gastric cancer[2-5]. Therefore, from the perspective of clinical practice, it

is important to make diagnosis accurately of active *H. pylori* infection by endoscopic observation with the prevalence of gastroscopy screening in population.

The Kyoto classification of gastritis was advocated in 2013 to evaluate the gastric background mucosa by endoscopic features, eventually to assess the risk of developing gastric cancer[6,7]. Some typical endoscopic findings of gastric mucosa have been literally associated to active *H. pylori* infection, including diffuse redness, gooseflesh-like nodularity in antrum, and enlarged folds, while regular arrangement of collecting venules presents a sign of non-infection status of *H. pylori*[8-10]. With the advances of endoscopic techniques, it is feasible to make diagnosis of presence or absence of active *H. pylori* infection of stomach by using conventional white light imaging (WLI) and imaging enhancement endoscopy (IEE).

Linked color imaging (LCI) is a novel mode of IEE recently launched by FUJIFILM Corporation (Tokyo, Japan), which uses a color tone like WLI by emphasizing minute differences in mucosal colors[11]. In common, mucosal lesions seen in red or white by WLI get redder or whiter under LCI endoscopy, thereby making the lesions more visible during screening. Growing studies have demonstrated that LCI endoscopy can obviously improve the visibility of diffuse redness, map-like redness as well as atrophy and intestinal metaplasia, thus showing the reliability of LCI in recognition of gastritis and early gastric cancer[12-14]. Meanwhile, studies have also conducted to evaluate the diagnostic effect of LCI endoscopy on *H. pylori* infection status. *H. pylori* infected mucosa is redder than other uninfected areas due to post-inflammatory congestion and oedema[15]. Compared to WLI, this difference in coloration was amplified by LCI, which may lead to easier identification of lesions suspected of *H. pylori* infection by the endoscopist, increasing the accuracy of the diagnosis for *H. pylori* infection. However, the difference between WLI and LCI for *H. pylori* diagnostic rates remains unknown. Hence in current study, we aim to assess the diagnostic value of LCI for *H. pylori* active compared to WLI by performing a meta-analysis, to provide evidences for extending the clinical application of LCI endoscopy.

MATERIALS AND METHODS

Literature search strategy

Online English literatures were searched using electronic literature databases including PubMed, Embase, Cochrane and Web of Science. The cut-off time of the articles published was set on April 15, 2022. The keywords used in literature search were "linked color imaging" and "*Helicobacter pylori* infection" as well as their corresponding abbreviations.

Study inclusion and exclusion

Literature reviews, letters, meeting abstracts, case reports were not included. In addition, duplicated data records were also excluded. In all included studies, the diagnosis of *H. pylori* active infection under LCI endoscopy was eventually determined by rapid urease test which is the most common test for diagnosis of *H. pylori* infection. There were no restrictions in terms of the age or sex of study participants.

Data extraction and quality assessment

Data extracted from each study mainly included the following information: First author, year of publication, country, study design, object of research, number of cases, endoscopic system, and test parameters (true positive, false positive, false negative, and true negative). The first and second authors screened the enrolled studies and extracted relevant data. When critical data was not clearly stated, it would be resolved through discussion with the corresponding author.

Risk of bias assessment

The quality assessment tool of diagnostic tests, the quality assessment of diagnostic accuracy studies-2 was used to evaluate the risk of bias[16]. The scale comprises assessment of risk of bias and applicability. The risk-of-bias assessment is composed of patient selection, evaluated tests, the criterion and patient flow and progress. The

applicability assessment included 3 aspects: Patient selection, evaluated tests and the golden criterion. In each aspect, the of bias was defined as "high", "low", or "unclear".

Statistical analysis

The "midas" command of Stata 15.0 (StataCorp LLC, College Station, TX) was used to fit the two-variable mixed-effect model, and the point estimates of the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic ratio and their corresponding 95% confidence interval (CI) in each group were combined to draw the comprehensive subject working characteristics [symmetric receiver operator characteristic (SROC)], area under the curve (AUC) and its 95%CI were calculated. The Deek's funnel plot was used to determine publication bias, and Q statistics and I^2 statistics were used to determine whether there was heterogeneity between studies. Levels of 0%-25%, 26%-50%, 51%-75% and more than 75% indicate insignificant, low, moderate, and high heterogeneity respectively. $P < 0.05$ was considered statistically significant.

RESULTS

Searched literatures and bias risk

We initially searched 94 articles including 25 in PubMed, 16 in Embase, 19 in Cochrane, and 34 in Web of Science. Careful review of the title and abstract and full-text reading were performed independently by two reviewers and the Kappa value was calculated as 0.849. Finally, 7 research articles were selected[17-23] (Table 1). Of them, two studies evaluated the diagnostic effect of LCI by computer-aided diagnosis system (CAD) and artificial intelligence (AI) but not by endoscopist. The specific literature screening process for the included studies is shown in Figure 1. The assessment of bias risk is shown in Figure 2. Of the seven included studies, two were case-free, so there was some bias on patient selection. In addition, in the study performed by Sun *et al*[21], both measures were tested interchangeably in the same group, and the outcome data were not completely distinguished.

WLI has moderate effect on detecting active H. pylori infection of gastric mucosa

For the overall detection effect on active *H. pylori* infection in the enrolled studies, WLI endoscopy had a moderate effect of diagnosis with a heterogeneity (I^2 = 97) by pooled sensitivity = 0.63 (95%CI: 0.46-0.77) (Figure 3A), pooled specificity = 0.73 (95%CI: 0.66-0.78) (Figure 3B), positive likelihood rate (PLR) = 2.32 (95%CI: 1.8-3.0) (Figure 3C, Supplementary Figure 1C), and negative likelihood rate (NLR) = 0.51 (95%CI: 0.34-0.76) (Figure 3C, Supplementary Figure 1C). The posterior probability was calculated by plotting Fagan diagram assuming the anterior probability was 50%. When *H. pylori* infection was diagnosed based on WLI, the probability of confirming *H. pylori* infection was 70%. In the case of negative results, the probability of *H. pylori* infection was 34% (Figure 3C). In addition, the diagnostic odds ratio (DOR) was 5 (95%CI: 2-9), and SROC was 0.75 (95%CI: 0.71-0.78) (Figure 3D). The Deeks' funnel plot was used to evaluate publication bias. The *P* value was calculated as 0.12 which indicates the risk of publication bias is not significant (Supplementary Figure 1A). The high heterogeneity existed among the studies with I^2 = 97 (95%CI: 94-99). The further bivariate box-type diagram showed that two of the seven included studies (10 groups) fell outside the box-type diagram suggesting the two studies might be the main source of heterogeneity, The high heterogeneity of the enrolled publications may be caused by the small sample size, study type and study population (Supplementary Figure 1B).

LCI exhibits better diagnostic value of H. pylori infection compared to WLI

The sensitivity, specificity, PLR, and NLR of LCI endoscopy for the diagnosis of *H. pylori* infection of gastric mucosa were 0.85 (95%CI: 0.76-0.92) (Figure 4A), 0.82 (95%CI: 0.78-0.85) (Figure 4B), 4.71 (95%CI: 3.7-5.9) (Figure 4C, Supplementary Figure 2C), and 0.18 (95%CI: 0.10-0.31) (Figure 4C, Supplementary Figure 2C) respectively. The posterior probability was calculated by plotting the Fagan diagram assuming the anterior probability to be 50%. When *H. pylori* infection was diagnosed based on LCI, the probability of diagnosis of *H. pylori* infection was 82%. In the negative case, the

probability of *H. pylori* infection was 15% (Figure 4C). Moreover, the DOR was 26 (95%CI: 13-52), and SROC was 0.87 (95%CI: 0.84-0.90) (Figure 4D). The high heterogeneity of this analysis was 90 (95%CI: 80-100). We calculated the *P* value as 0.72 indicating an insignificant risk of publication bias. The higher heterogeneity existed among the studies with I^2 = 90 (95%CI: 80-100). The bivariate box-type diagram showed that one study of the seven included studies (10 groups) fell outside the box-type diagram (Supplementary Figure 2A), suggesting that this one study might be the main source of heterogeneity (Supplementary Figure 2B). The results indicate LCI has significant superiority over WLI when they are used in diagnosis of *H. pylori* infection.

DISCUSSION

Diagnosis of the status of *H. pylori* infection represents a crucial step in prior to assess the risk of atrophy, intestinal metaplasia and *H. pylori* associated gastric cancer, according to current consensual strategy on prevention and treatment of gastric cancer. However, the endoscopic diagnosis of *H. pylori* associated gastritis does not often correspond with the histological findings in clinical practice[24]. Previous studies have disclosed that the accuracy of endoscopic diagnosis of *H. pylori* infection ranged from 64% to 71% based on the endoscopic appearance alone[19,25]. This moderate accuracy of diagnosis suggests that endoscopy may not be definitive method, but can be important part of comprehensive diagnosis with other invasive or noninvasive tests such as biopsy based rapid urease test or urea breath test.

In the past decades, image enhancement technique upgraded the conventional endoscopy to an indispensable test for diagnosis of gastrointestinal diseases including early malignancies. Emerged researches have demonstrated that various types of IEEs such as blue laser imaging, narrow band imaging and LCI can improve accuracy of diagnosis on *H. pylori* infection status[20,26-28]. As the latest IEE technique, LCI endoscopy can theoretically highlight the color tone of mucosa thus facilitating the visuality of endoscopic features for active infection of *H. pylori*, such as diffuse redness, mucosal edema, hemorrhagic spots, enlarged folds, and gooseflesh-like nodularity[29].

Correspondingly, growing evidences have emerged that LCI endoscopy significantly improves recognition of *H. pylori* associated changes of mucosa to help making diagnosis of *H. pylori* infection more accurately than conventional WLI endoscopy[18-23].

The combined accuracy of LCI endoscopy on diagnosis of *H. pylori* active infection concluded by our meta-analysis, is obviously higher than that of conventional WLI endoscopy, which is demonstrated by 0.85 (95%CI: 0.76-0.92) of sensitivity, 0.82 (95%CI: 0.78-0.85) of specificity, 4.71 (95%CI: 3.7-5.9) of PLR, and 0.18 (95%CI: 0.10-0.31) of NLR, with the AUC being 0.87. Although this accuracy is not high enough, it apparently indicates the advantage of LCI endoscopy before patients with suspected *H. pylori* infection are subjected to invasive tests. Moreover, it has been elucidated that LCI endoscopy not only have good efficacy on diagnosis of current *H. pylori* infection, but also superior in diagnosis of other abnormalities of *H. pylori* associated gastritis, such as gastric intestinal metaplasia and atrophy[14,30,31]. Some most recent studies have further demonstrated better effects of LCI endoscopy, in comparison with WLI endoscopy or indigo carmine chromoendoscopy, on identifying featured mucosal appearances after successful *H. pylori* eradication, thus facilitating to recognize early gastric cancer[32-34]. Therefore, LCI endoscopy is exhibiting the potential as an important alternative modality of endoscopy for gastrointestinal disease screening in future, or at least, as a feasible supplementary method of WLI endoscopy-based screening strategy.

Our analysis had several limitations that may have influence on the results. Firstly, there haven't been insufficient original studies related to the diagnosis efficacy of LCI on *H. pylori* infection. The selected studies in our analysis were almost performed in single center, and enrolled relatively small size of patient samples, which restrict further subgroups analysis based on variables. Secondly, these enrolled studies performed different tests to make definite diagnosis of *H. pylori* infection after LCI endoscopy, such as biopsy based histological staining or rapid urease test, urea breath test, and serological test. Thirdly, two studies of Nakashima *et al*[17,18] proposed inconsistent diagnosis accuracy of LCI on *H. pylori* infection, when using AI or CAD instead of endoscopists, that was 96.7% of sensitivity, 83.3% of specificity, 0.95 of AUC for AI, and

62.5% of sensitivity, 92.5% of specificity, 0.82 of AUC for CAD. These problems mentioned above may bring heterogeneity of the analysis and further lead to instability of the results.

CONCLUSION

Summarily, as a novel technique of image enhancement endoscopy, growing evidences have proved that LCI can significantly improve accuracy of diagnosis on *H. pylori* infection, as well as *H. pylori* associated changes of gastric mucosa, including atrophy and gastric intestinal metaplasia. Moreover, by emphasizing the difference of color tone between lesion and surrounding normal mucosa, LCI also shows promising usefulness in detecting early gastric cancer. Combined with current knowledge, it is anticipated to use LCI endoscopy alone for detection of gastric diseases instead of WLI endoscopy in future, while a screening strategy of LCI followed by magnifying IEEs may theoretically have better clinical prospects for early cancer detection.

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