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*Review Article*

# Hesitate between confocal laser endomicroscopy and narrow-band imaging: how to choose a better method in the detection of focal precancerous state of gastric cancer

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**Abstract:** Background: With a high incidence globally, deaths form gastric cancer (GC) are not rare. Early diagnosis is crucial to ameliorate its prognosis. Confocal laser endomicroscopy (CLE) and narrow band imaging (NBI) have been extensively applied in gastroscopy, particularly when it comes to the detection and management of premalignant gastric lesion. Our meta-analysis intends to appraise the diagnostic capability and compare the efficacy of NBI and CLE for focal precancerous state of gastric cancer. Methods: We performed a literature search up to November 5, 2020 in online databases and major conferences. Two investigators assessed the methodological bias by QUADAS-2, followed by sophisticated study selection and data exaction to make a comparison between sensitivity, specificity, positive and negative likelihood values, and diagnostic odds ratio. A symmetric summary receiver-operating curve (sROC) and its area under the curve (AUC) were used to estimate threshold effect. Additionally, we evaluated the publication bias by Deeks' asymmetry test. Results and conclusions: Four studies involved 248 patients and 526 lesions. In analysis drawn from every lesion, the NBI's pooled sensitivity and specificity were 87% (95% CI: 0.80-0.92) and 85% (95% CI: 0.75-0.91), and those of CLE were 90% (95% CI: 0.85-0.91) and 87% (95% CI: 0.83-0.91). CLE illustrated that the pooled two were slightly higher than NBI when compared at the level of every lesion. The AUC for NBI and CLE was 0.92 (0.90-0.94) and 0.95 (0.92-0.96), and there might be a threshold effect, according to the shoulder-like distribution of scatter points in the sROC. We did not find obvious publication bias in our meta-analysis.

**Keywords:** Focal precancerous state of gastric cancer, early diagnosis, confocal laser endomicroscopy, narrow-band imaging, meta-analysis

## Introduction

Gastric cancer (GC) has joined the front rank (6th) of the most commonly diagnosed cancer and the second most common cause of cancer-related death globally [1]. Although its incidence is decreasing, its median survival time which has remained poor for less than 2 years is still not optimistic [2]. More than 60 percent of patients (63%) with GC have locally advanced stages, which lead to an unsatisfied prognosis after first-line treatment [3]. The presence of premalignant changes commonly called precancerous conditions of GC, including gastric intestinal metaplasia (GIM), gastric atrophy (GA), intraepithelial neoplasia (IN), and dysplasia, et cetera, are significant risk factors for GC development, in line with the generally accepted multistep model of gastric carcinogenesis [4]. Therefore, identified as secondary prevention strategies, detection and scrutiny of patients with these precancerous conditions

when it's early, could eventually reduce mortality rates and prolong survival time for gastric cancer patients [5]. According to the fact that this stage has close correlation with the occurrence of early gastric cancer (EGC), its diagnosis needs to be accurate and effective, but on the contrary, the treatment for both is widely divergent. Hence, we consider that this stage should be given a new definition: focal precancerous state of gastric cancer.

As the CSCO recommended presently, endoscopy is the core for diagnosis and management of EGC (Evidence 1A), as well as a crucial tool for biopsy of target lesions [6]. While conventional white-light endoscopy (C-WLE) has been looked upon as the basic endoscopic examination to identify questionable lesions, it is hard to measure up a high diagnostic efficacy of premalignant changes in most cases yet [7]. Conducted between 2009 and 2014, previous studies found that the sensitivity of C-WLE in EGC's diagnosis varied from 33% to 75% and specificity from 57.0% to 93.8% [8-13]. Against such background, making an accurate and stable diagnosis from the microscopic view with the help of endoscope is the ultimate objective of the evolution of endoscopic technology. As recent advances, some new image-enhancement endoscopic techniques have been extensively applied to clinical diagnosis. Recommended in consensus of experts on screening process of early gastric cancer in China (2017, Shanghai), it is easier to detect precancerous gastric lesions and GC, for example, by magnifying endoscopy, narrow-band imaging (NBI) and confocal laser endomicroscopy (CLE). Whereas there is no clear tendency to choose a more proposed approach. In order to enhance the diagnostic accuracy of focal precancerous state of gastric cancer, it is still a problem demanding prompt solution which endoscopic technique is the most accurate diagnostic method.

NBI, with high-resolution and wide-field endoscopic images, has been extensively used for the detection of focal precancerous state of gastric cancer. It is mainly characterized by the ability to enhance visualization of superficial mucosa, including microvascular patterns and microsurface structures [14, 15]. Beyond that, NBI also has shown its improvement of the diagnostic value in the detection of precancerous and early neoplastic lesions, which could be magnified combined with magnification endoscopy (ME-NBI) [16-18]. Additionally, a latest endoscopic technique, the combination application of C-WLE and CLE, has been applied for detection of some gastrointestinal diseases. It could be divided into two categories: endoscope-based CLE (e-CLE) and probe-based CLE (p-CLE) [19, 20]. This efficient endoscopic technique has advantages that not only can observe macroscopic and microscopic appearances of the gastrointestinal mucosa simultaneously, but also take high diagnosis validity into account [21, 22]. In accordance with previous studies, ME-NBI was excellent for detecting EGC successfully, with success ratio reaching 90% and 100%, respectively [23]. Another study showed that CLE may be beneficial to the diagnosis of EGC by detecting subsurface microstructure, which could be basis for further use in clinical practice with reliability and accuracy, whereas it did not have significant statistical difference from ME-NBI [24].

Generally speaking, those endoscopic techniques of NBI and CLE, with the superiorities of providing valuable information, should be put in application to evaluating the focal precancerous state of gastric cancer. However, it is still in the absence of proof from the significant difference between NBI and CLE for the patients with focal precancerous state of gastric cancer, making it unclear whether or not there is distinct advantage in practice between NBI and CLE clinically. To determine the better utility between NBI and CLE, systematic review and meta-analysis were performed to estimate the diagnostic efficacy of within-lesion differences between these two endoscopic techniques.

## Methods

Our meta-analysis was performed in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Meanwhile, we have already completed the registration of this article at International Prospective Register of Systematic Reviews (ID: CRD42020152450).

### *Literature search and study selection*

Two independent authors performed a literature search from online databases like PubMed,

from inception to November 5, 2020. In the searching procedure, authors followed the principle of combining the following terms: stomach neoplasms, gastric polyps, precancerous condition, gastric stump, atrophic gastritis, gastric mucosa, epithelial dysplasia, metaplasia and CLE and NBI and randomized controlled trial (Supplementary Method 1). Giving consideration to that recent research may not have been delivered, we also searched the abstracts and conference contents of three major international conferences of DDW, CGC and ACG. In the condition of duplicate publications, only the most complete and up-to-date article of the study was put in acquisition for double-check.

Clinical trials included must meet the criteria as follows: (1) True-negative (TN), false-negative (FN), true-positive (TP) and false-positive (FP) patients with focal precancerous state of gastric cancer must be provided in studies to make assessment of the diagnostic efficacy of NBI and CLE in this population; (2) Comparison in groups of NBI versus CLE was set and reported in studies; (3) Results provided effective and quantitative data to build diagnostic 2×2 contingency tables of NBI and CLE, containing TN, FN, TP and FP; (4) In included studies, histological biopsy as a standard criterion (gold standard) for lesions diagnosis should be applied in pathological examination of gastric tissue in participants. For sure, only those were included, if there were more publications from the same population at different period, or cases were mixed in different publications, then the information we collected can be called comprehensive. Our kick-out condition of articles is also listed below: (1) The article is case report, review, meta-analysis, animal or in vitro study; (2) Articles were published without full text, only as meeting abstracts; (3) Articles failed to provide data including sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio to calculate diagnostic efficacy at the same time. EndNote (version X9) was used to perform citations for the purpose of facilitating management. Two independent reviewers retrieved title and abstracts of studies at the beginning. For the sake of checking whether the studies' eligibility was consistent with inclusion criteria, we conducted further exploration of full texts.

*Data extraction and methodological bias assessment*

Two investigators implemented data extraction independently. They extracted data from the study included country, first author, publication date, study design, median age, number of centers, number of enrolled patients, patient sex ratio, number of lesions examined, and type of CLE and NBI. If available, data were extracted for each patient and each lesion. Additionally, we didn't miss any supplementary materials to refrain from neglecting relevant data in appendix from each article. Consensus was reached by discussion and solution by all reviewers, if there were any discrepancies between them.

Giving an assessment of patient selection including four key domains, i.e., patients' flow in the study, index test, reference standard, and index tests' time and reference standard (flow and timing), the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) of studies was applied to evaluate all studies' quality by Review Manager (RevMan) 5.3. Two independent investigators subjectively examined and scored the risk of bias as high, low, or unclear in each trial. All divergences about bias assessment got resolved as those in the last part.

*Statistical analysis*

To summarize and visualize odd ratios (ORs) with 95% confidence intervals (CIs) for all studies involved, we calculated the sensitivity, specificity, positive and negative likelihood values (PLR and NLR), and diagnostic odds ratio (DOR) separately by pooling the data and constructing the forest plots with Stata 15. We used the Q test to detect threshold-independent heterogeneity. In the application of this statistical method, we considered $P<0.10$ to be significant heterogeneity. Moreover, three fixed knots were set at 25%, 50% and 75% from $I^2$ test as predefined indicators of mild, moderate and high heterogeneity, respectively. We calculated pooled data via a random-effects model for the studies whose test showed $I^2>50\%$ or $P<0.10$. If not, we had another fixed-effects model to compute and analyse them. What's more, meta-regression and subgroup analysis were performed in order to explore the potential sources

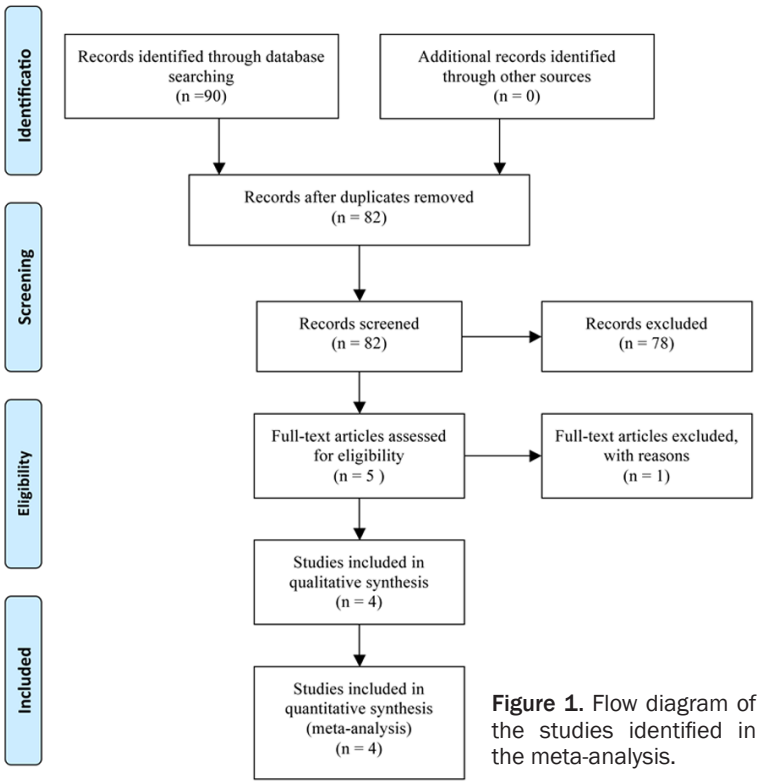


**Figure 1.** Flow diagram of the studies identified in the meta-analysis.

of heterogeneity among these studies. Threshold analysis was executed by drawing a weighted symmetric summary receiver-operating curve (sROC) and calculating the area under the curve (AUC). Funnel plot asymmetry test was conducted to assess publication bias with $P<0.05$ indicating statistical significance.

## Results

### *Description of the included studies*

Totally 8 publications were weeded out of 90 relevant documents from manual retrieval sources like online database during duplicate checking. Among 82 potentially relevant studies identified by initial search, after screening both abstract and full text of references, 4 studies (Wang 2012 [25], Gong 2015 [26], Lim 2013 [24], Liu 2015 [27]) with a total of 248 patients and 526 lesions involved, reported comparisons between NBI and CLE in detecting focal precancerous state of gastric cancer. **Figure 1** shows the selection process, and **Table 1** includes the main characteristics of four. Four eligible studies involving 248 patients reported the diagnostic efficacy of NBI and CLE but without reported data at an average level. Within a finite range of four RCTs, only one study was conducted in multiple centers, while inversely others in a single center. Two available CLE systems (eCLE and pCLE) were used for diagnosis, and to be specific, three of the studies used eCLE and one used pCLE.

### *Assessment of methodological bias*

Using QUADAS-2 for quality assessment, we recorded the test results all in Supplementary Table 1 and Supplementary Figure 1. Overviewing the included studies, the majority in our meta-analysis had high quality. One had high risk while another had ambiguous risk of bias in patient selection since some of them had been confirmed with focal precancerous state of gastric cancer before CLE and NBI, which had inappropriate inclusion in the meantime. In the study of Gong 2015 and Wang 2012, some patients were eliminated from the final analysis because there was no adequate explanation, and in other words, it suggested an unclear risk of bias in patient flow.

### *The value of NBI in the diagnosis of focal precancerous state of gastric cancer*

Four studies with a total of 248 patients reported 526 lesions. The NBI's diagnostic efficacy for focal precancerous state of gastric cancer lesions is assessed in each study (**Table 2**). As shown in **Figure 2A**, all the studies showed moderate heterogeneity in both sensitivity ($I^2$=52.05%) and specificity ($I^2$=70.50%) analysis. Authors comprehensively evaluated the efficacy of each study on NBI in the diagnosis of GC lesion under the application of the random-effects model. The pooled sensitivity and specificity were 87% (95% CI: 0.80-0.92) and 85% (95% CI: 0.75-0.91), respectively. No remarkable difference between the methods was suggested under the circumstance that positive likelihood ratio and negative likelihood ratio for diagnosing EGC by NBI were 5.9 (95% CI: 3.3-

**Table 1.** Characteristics of the included studies

| Study | Country | Number of patients (n) | Lesions examined (n) | Age (yr) | M/F | Endoscopists (n) | | Pathologist (n) | Type | | Endoscopic System Used | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | NBI | CLE | | CLE | NBI | CLE | NBI |
| Wang, 2012 | China | 59 | 62 | 63.1 | 44/15 | 1 | 2 | 2 | eCLE | ME-NBI | EC-3870K (OptiScan) | GIF-H260Z (Olympus) |
| Gong, 2015 | China | 82 | 86 | 59.3 | 58/24 | 2 | 1 | 2 | eCLE | ME-NBI | EG-3870CIK (Pentax) | GIF-H260Z (Olympus) |
| Lim, 2013 | Singapore | 20 | 125 | 62.5 | 15/5 | 1 | 1 | 2 | pCLE | ME-NBI | Cellvizio-GI (Mauna Kea Technologies) | GIF-FQ260Z (Olympus) |
| Liu, 2015 | China | 87 | 253 | 49.8 | 48/39 | 1 | 1 | 1 | eCLE | ME-NBI | EC-3870K (OptiScan) | GIF-H260Z/GIF-Q240Z (Olympus) |

Footnotes: M/F, male to female; NM, not mentioned; eCLE, endoscope-based CLE; pCLE, probe-based CLE.

**Table 2.** Results of the individual studies retrieved from 2*2 tables

| Study | NBI | | | | | CLE | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | TP:FN | FP:TN | Sensitivity | Specificity | DOR | TP:FN | FP:TN | Sensitivity | Specificity | DOR |
| Wang, 2012 | 20/6 | 5/27 | 0.77 (0.56, 0.91) | 0.84 (0.67, 0.95) | 18.00 (4.81, 67.39) | 22/4 | 3/29 | 0.85 (0.65, 0.96) | 0.91 (0.75, 0.98) | 53.17 (10.77, 262.34) |
| Gong, 2015 | 33/3 | 2/42 | 0.92 (0.78, 0.98) | 0.95 (0.85, 0.99) | 231.00 (36.45, 1463.80) | 36/4 | 3/43 | 0.90 (0.76, 0.97) | 0.93 (0.82, 0.99) | 129.00 (27.08, 614.54) |
| Lim, 2013 | 60/6 | 9/50 | 0.91 (0.81, 0.97) | 0.85 (0.73, 0.93) | 55.56 (18.51, 166.74) | 57/9 | 10/49 | 0.86 (0.76, 0.94) | 0.83 (0.71, 0.92) | 31.03 (11.67, 82.53) |
| Liu, 2015 | 108/22 | 29/94 | 0.83 (0.76, 0.89) | 0.76 (0.68, 0.84) | 15.91 (8.57, 29.56) | 120/10 | 17/106 | 0.92 (0.86, 0.96) | 0.86 (0.79, 0.92) | 74.82 (32.84, 170.50) |

Footnotes: DOR, diagnostic odds ratio; FN, false negative; FP, false positive; NLR, negative likelihood ratio; PLR, positive likelihood ratio; TN, true negative; TP, true positive.

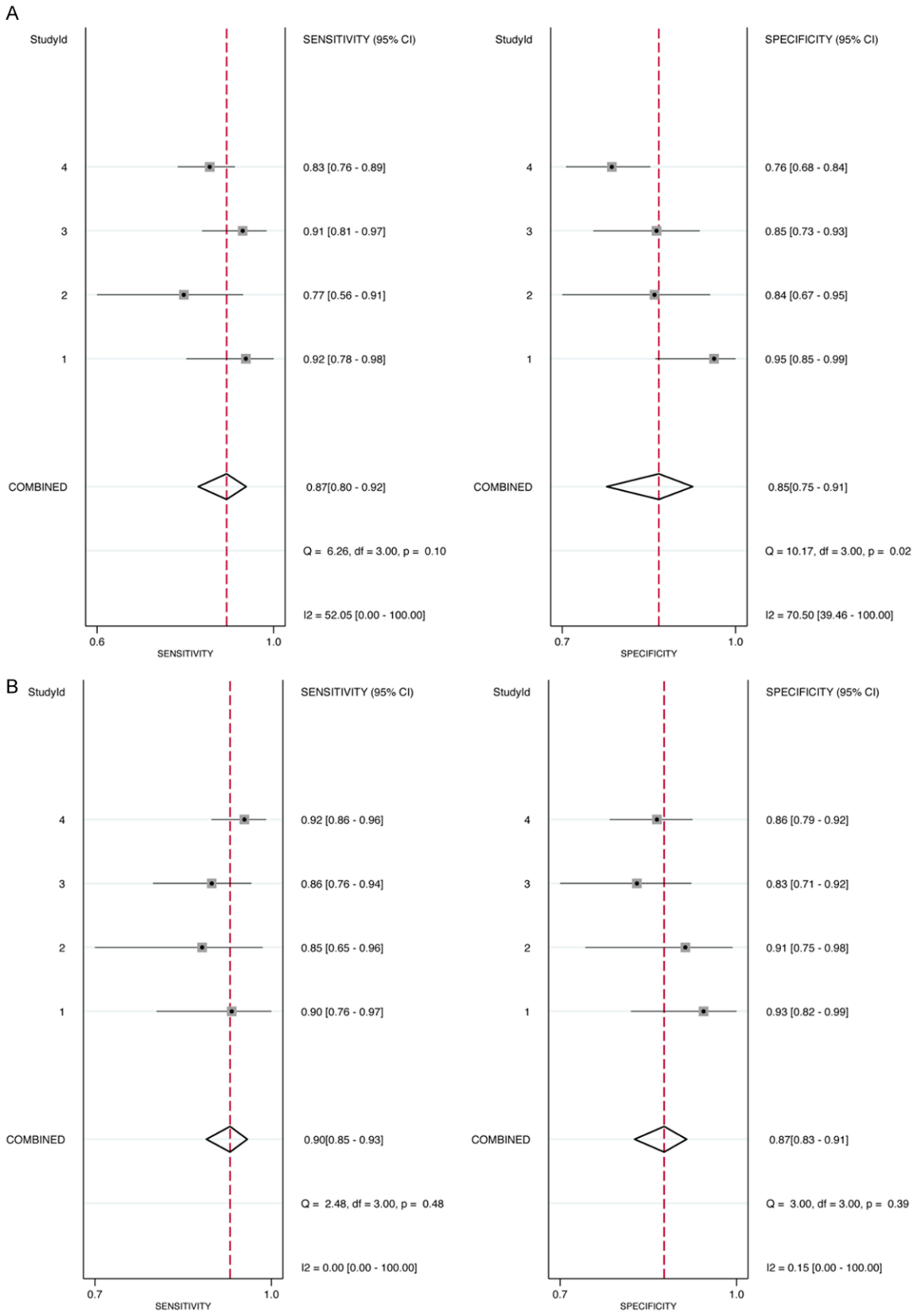


**Figure 2.** Forest plot of diagnostic performance of NBI (A) and CLE (B) for focal precancerous state of gastric cancer in a per-lesion analysis.

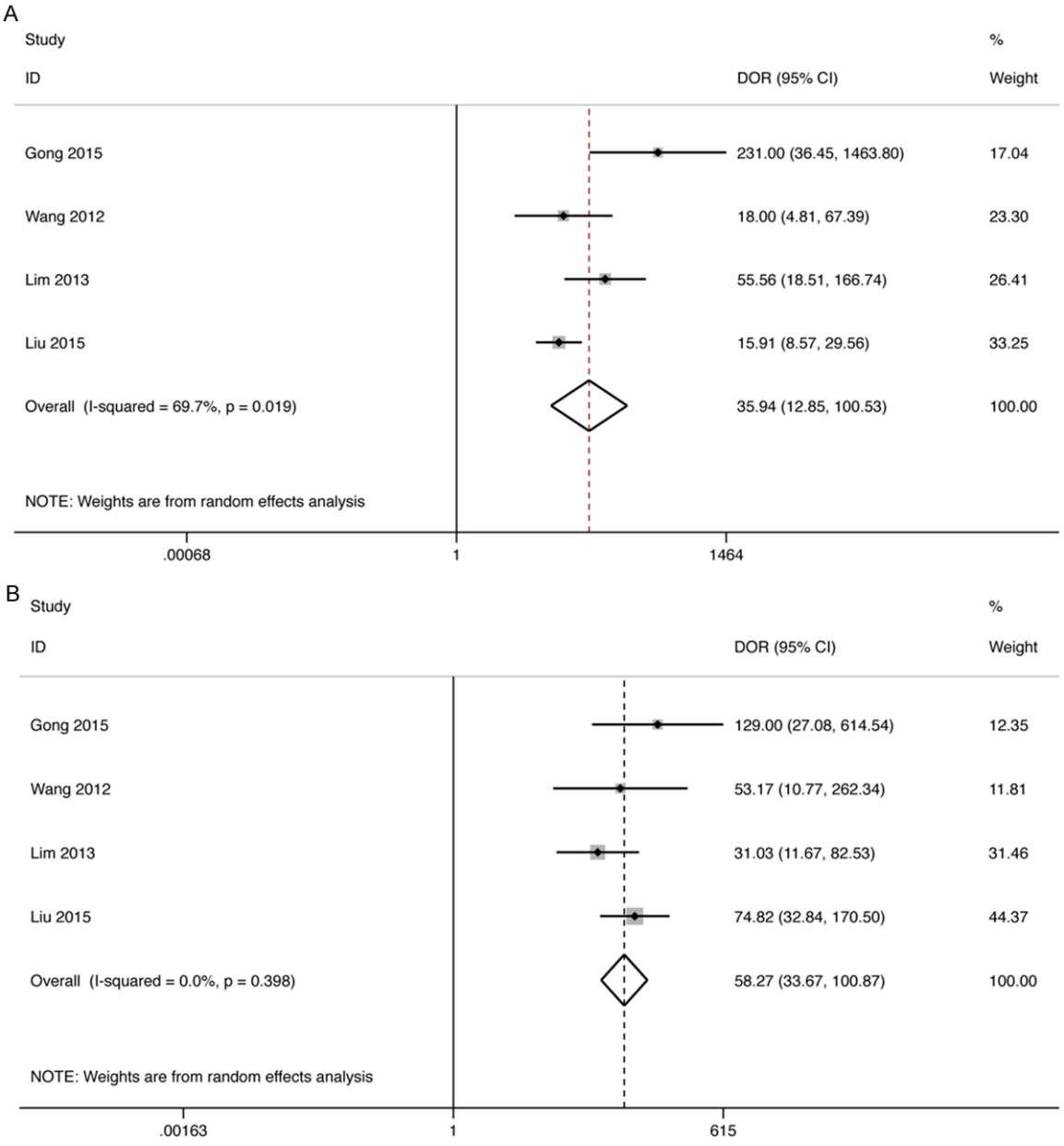


**Figure 3.** Forest diagnostic odds ratio (DOR) of NBI (A) and CLE (B).

10.3) and 0.15 (95% CI: 0.09-0.25), and the DOR was 35.94 (12.85-100.53, $I^2$=69.7%) (**Figure 3A**). The AUC for sROC was 0.92 (0.90-0.94), and there might be a tendency towards a threshold effect, since scatter points in the sROC were shoulder distributed (**Figure 4A**).

*The value of CLE in the diagnosis of focal precancerous state of gastric cancer*

Four studies with 248 patients reported CLE analysis in 526 lesions. The data was analyzed to estimate the diagnostic performance of CLE for focal precancerous state of gastric cancer lesions (**Table 2**). Similar to NBI (**Figure 2B**), pooled sensitivity of CLE to diagnosing focal precancerous state of gastric cancer was 90% (95% CI, 0.85-0.91, $I^2$=0.0%), while specificity, without any heterogeneity, was 87% (95% CI: 0.83-0.91, $I^2$=0.0%). Positive likelihood ratio of CLE for diagnosing EGC was 7.12 (95% CI: 5.1-9.7), and the negative one was 0.12 (95% CI: 0.08-0.17). These data prompted that there was no statistically distinct difference among

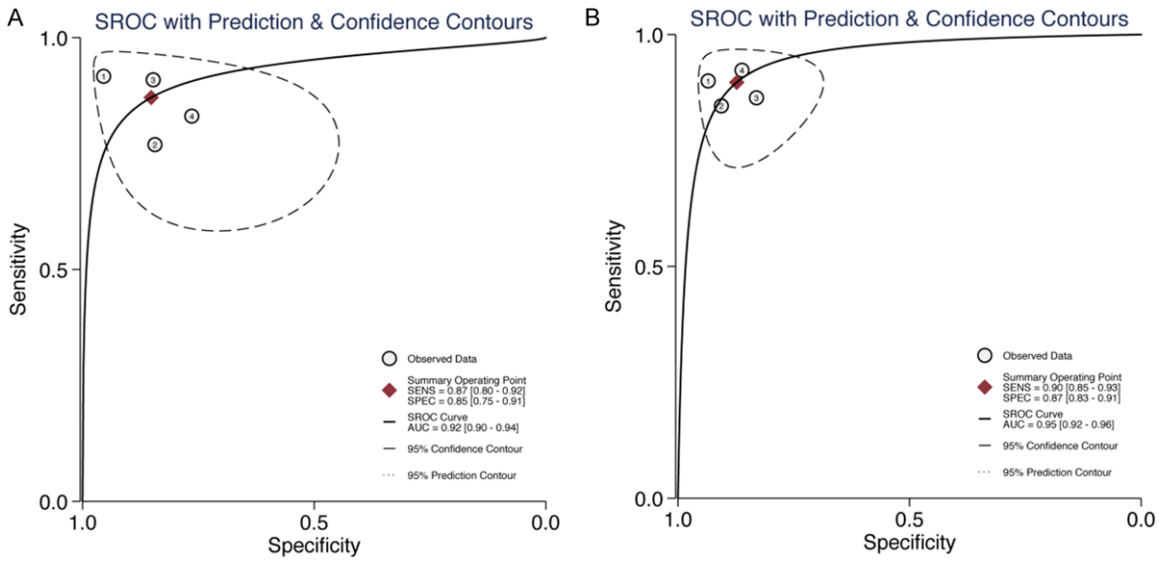


**Figure 4.** The summary receiver operating characteristic (sROC) with 95% confidence interval of NBI (A) and CLE (B) in a per-lesion analysis. AUC, area under the curve.

the methods. The DOR was 58.27 (33.67-100.87, $I^2$=0.0%) (**Figure 3B**). The AUC was 0.95 (0.92-0.96) for sROC, and in the sROC, scatter points distributed in a shoulder-like form, which showed that a threshold effect exists among the included studies (**Figure 4B**).

*Publication bias*

There was no significant asymmetry displayed according to NBI and CLE ($P$=0.44 and $P$=0.93) by Deeks' funnel plot, indicating that under the application of NBI and CLE, diagnostic accuracies for the per-lesion analysis was without significant publication bias as shown in Supplementary Figure 2.

## Discussion

From our study, the findings were as what follows. At per-patient level, NBI has excellent diagnostic veracity as well as CLE. Whereas, at the per-lesion level, CLE has shown the slightly higher pooled sensitivity and specificity than NBI (90% vs. 87% and 87% vs. 85%). Moreover, it seems that it still remains a risk of bias in patient selection and flow and timing, mainly on account of the fact that 3 of the 4 studies include patients with suspicious lesions or high risk of gastric cancer. Furthermore, NBI has shown its value of differential diagnosis for lesions with relatively low sensitivity and high specificity in clinical tests.

The occurrence of GC is a process with multiple factors involving many sequential development stages: chronic active gastritis, chronic atrophic gastritis, intestinal metaplasia, dysplasia (alias intraepithelial neoplasia), and finally invasive carcinoma [4, 28]. The progressive severity of the lesions significantly increases the risk of leading to GC. Accordingly, we set a new definition called 'Focal precancerous state of gastric cancer', including GA, GIM and IN, which progressively gives rise to the gastric cancer, but without a need for conventional and traditional surgical resection. In order to decrease the fatality rate of gastric cancer, recognizing high-risk patients with focal precancerous state of gastric cancer may be the most effective methods. Likewise, improving the detection rate before cancer establishes works.

Performed as Evidence 1A, endoscope with the determination of the nature and location of the lesion can accurately identify individuals at greatest risk and make a precise proposal for establishing personalized strategy for secondary prevention of GC [6, 29]. A full systematic as well as high-quality endoscopy protocol of the stomach combined with histopathological biopsy sampling is required to detect GA, GIM, dysplasia, IN and EGC, especially taking post-endoscopy GC rates of 11.3% into consideration [30]. However, focal precancerous state of gastric cancer is of general difficulties to be

detected, because of the lack of specific manifestations under ordinary gastroscopy, which usually leads to a high mortality rate for GC. Therefore, image-enhanced endoscopy (IEE) is recommended to be used as the best imaging modality to detect and risk-stratify according to British Society of Gastroenterology guidelines (evidence level: moderate quality; grade of recommendation: strong; level of agreement: 100%) [31]. Recently, with the development of NBI and CLE, doctors can determine the nature and location of lesions, and this became an important breakthrough in the history of IEE. It can not only provide direct observation on the focus, make quick determination of the nature and location of the lesion, but also carry effective launch of targeted biopsy, and make a judgment for the later treatment plan.

By using optic digital methods, NBI is able to visualize the microvascular pattern, the mucosal surface architecture can be enhanced as well, and in the same way, enhancement of endoscopic images can also be achieved [32]. It showed widely available, simple and convenient features without staining, and besides, it can display both vascular and mucosal modes and inspect the whole endoscopic field [33]. According to data from the research, the diagnostic efficacy of NBI in EGC and precancerous lesions showed obvious superiority contrasted with that of C-WLE and chromo endoscopy (CE) [16]. What's more important, it allows to differentiate between benign lesion and malignant lesion and predict the risk of invasive cancer [32]. Whereas, false-negative results is expected to appear. Its root cause lies in the NBI's limited resolution and its weakness in detecting cell-level lesions [34].

CLE, including eCLE and pCLE, is promised as a technique for the mucosal surface and the immediate subsurface area examination [35]. Compared with others, the dominance of CLE over other optical techniques is that it can observe not only the surface structure of the epithelium, but also the deep structure of the mucosa by means of tomographic imaging. Clinically, CLE has the ability to accurately determine the edge contour of the lesion area, which shows a much better performance than C-WLE [36, 37]. Whereas, as the point technique with poor range of motion at the head of the endoscopy, CLE was usually used for lesions within a small field of view, but not for surveillance of large areas [20]. Moreover, CLE may result in allergy for requiring intravenous injection of fluorescent reagents. There are some limiting factors of CLE clinically, for example, economic cost and availability of endoscopic physicians and hospitals, due to the high price of purchasing and maintaining, and also the requirement of high kill level of the endoscopic physicians.

Currently, NBI and CLE have shown high accuracy for the diagnosis of focal precancerous state of gastric cancer, and both of them are also widely used in clinical practice. Although NBI and CLE are compared by many studies with C-WLE, seldom of them have direct comparisons of these two endoscopic diagnostic methods. According to our understanding, our study is the first one focusing on systematic evaluation of the diagnostic efficacy of NBI and CLE for focal precancerous state of gastric cancer by meta-analysis.

The findings from our study were that patients could receive benefit from both NBI and CLE for diagnosis at per-patient level, while CLE showed higher sensitivity and specificity than those of NBI at the per-lesion level. Moreover, Song et al. suggested that, based on per-lesion level, the sensitivity and specificity of NBI were separately manifested as 0.69 (0.63-0.74) and 0.91 (0.87-0.94) [38]. From the result of Ying's meta-analysis, the pooled sensitivity and specificity were 0.64 (0.52-0.75) and 0.96 (0.95-0.98) [39]. CLE showed higher sensitivity (96.7% vs. 69.0%) than NBI. On a per-lesion basis, CLE has similar specificity (94% vs. 91%) as well as similar AUC (99% vs. 90%), compared to NBI [38]. Li et al. came to the same conclusion that CLE showed higher values in sensitivity (88.9%), specificity (99.3%) and accuracy (98.8%) than C-WLE in application to identify GC or HGIN lesions [40]. The sensitivity, specificity, and accuracy of diagnosing tumorigenesis (including LGIN, HGIN and GC) were respectively 92.13%, 99.50% and 99.15% [41]. Zhang and his colleagues reported that the pooled sensitivity, specificity and AUC of CLE were 81% (95% CI: 0.75-0.85), 98% (95% CI: 0.97-0.98), and 0.9204, respectively for the diagnosis of GIN lesions [21].

Undeniably, there was heterogeneity in our meta-analysis, which shows a similarity to other

studies with a high degree of heterogeneity [38, 42]. It was known to us that experiences did have an impact on the diagnostic efficacy of NBI for focal precancerous state of gastric cancer [43, 44]. Although NBI has the ability to help to make a differential diagnosis between EGC and gastritis, there will still be some limitations [8, 45]. Microvascular patterns and irregularity of the microsurface can be found by the NBI, especially when focusing on cancerous tissue spared by overlying non-neoplastic epithelium [38]. Particularly, for patients with the emergence of EGC after the eradication of Helicobacter pylori, doctors will easily ignore even if using ME-NBI [46]. Moreover, NBI technology works on the basis of high reflectivity of mucosal surface and the fact that hemoglobin has a strong absorption capacity of narrow band light. When observing the lesions, the normal judgment of NBI may be affected by the bile and blood on superficies of them [47, 48]. There are a variety of classification standards of NBI widely applied as the diagnostic criteria for ME-NBI diagnosis of focal precancerous state of gastric cancer. The "VS classification" criterion set by Yao et al. is one of them, and it indicates the presence of a lesion with the boundary, an abnormal vascular network on the microsurface, or an unusual change on superficies of the microstructure [49, 50]. Currently, there are many other criteria like "MV-FMS classification" [51], "ABC classification" [52, 53], and "LBC classification" [54]. Relatively speaking, the diagnostic criteria of CLE, which can be exploited to observe the structure of gastric mucosa at cellular and subcellular level in vivo, is stricter than NBI owing to microscopic visualization of the gastrointestinal structures. An analogous diagnostic criteria put forward by Guo and his colleagues was adopted by all studies, that in CLE the GIM can be diagnosed with the existence of the following features in the image: columnar absorptive cells, goblet cells, and villiform shape of foveolar epithelium [55]. Hence, the diagnostic criteria of CLE on focal precancerous state of gastric cancer correspond well with histopathologic criteria.

However, there are several limitations in our research. First, we should interpret the results in our meta-analysis with caution on account of the limited studies and little sample size. We have an urgent demand for further analysis with qualified data and that from multi-center studies to evaluate the effectiveness and superiority of NBI and CLE in the detection of focal precancerous state of gastric cancer. Second, the overall outcomes may not be representative of all populations because the included RCTs were from small cohorts of patients from single centers of China or Singapore. Third, even though we adopted a random-effects model, heterogeneity remained in certain major outcomes. Heterogeneity mainly comes from different patient characteristics, inclusion criterion and exclusion criterion, presence of observers' experience bias and so on. And between NBI and CLE, our further comparison was prevented by incomparable baselines. Beyond that, performing subgroup and meta-regression analysis failed to research possible sources of NBI heterogeneity among studies for only four RCTs included. Finally, data from different studies might be under the influence of variable experiences of endoscopists during the usage of NBI and CLE, and our research did not clearly describe the experience level of the endoscopists.

## Conclusions

This meta-analysis has demonstrated that, NBI and CLE both have outstanding diagnostic efficacy, while the CLE's pooled sensitivity and specificity were slightly higher than those of NBI at the per-lesion level (90% vs. 87% and 87% vs. 85%). Nevertheless, in account of that only a few studies were available, and we think that more high-quality trials shall be updated and further investigated.

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## Disclosure of conflict of interest

None.

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## References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.

[2] Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Niksic M, Bonaventure A, Valkov M, Johnson CJ, Esteve J, Ogunbiyi OJ, Azevedo ESG, Chen WQ, Eser S, Engholm G, Stiller CA, Monnereau A, Woods RR, Visser O, Lim GH, Aitken J, Weir HK and Coleman MP; CONCORD Working Group. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 2018; 391: 1023-1075.

[3] Song Z, Wu Y, Yang J, Yang D and Fang X. Progress in the treatment of advanced gastric cancer. Tumour Biol 2017; 39: 1010428317714626.

[4] Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on cancer epidemiology and prevention. Cancer Res 1992; 52: 6735-6740.

[5] Santaballa A, Pinto A, Balanya RP, Ramirez Merino N, Martin IR, Grau SS, Fombella JPB, Cano JM, Gonzalez CH and Bayo J. SEOM clinical guideline for secondary prevention (2019). Clin Transl Oncol 2020; 22: 187-192.

[6] Wang FH, Shen L, Li J, Zhou ZW, Liang H, Zhang XT, Tang L, Xin Y, Jin J, Zhang YJ, Yuan XL, Liu TS, Li GX, Wu Q, Xu HM, Ji JF, Li YF, Wang X, Yu S, Liu H, Guan WL and Xu RH. The Chinese Society of Clinical Oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer. Cancer Commun (Lond) 2019; 39: 10.

[7] Horiguchi N, Tahara T, Kawamura T, Okubo M, Tahara S, Nagasaka M, Nakagawa Y, Shibata T and Ohmiya N. A comparative study of white light endoscopy, chromoendoscopy and magnifying endoscopy with narrow band imaging in the diagnosis of early gastric cancer after helicobacter pylori eradication. J Gastrointestin Liver Dis 2017; 26: 357-362.

[8] Ezoe Y, Muto M, Uedo N, Doyama H, Yao K, Oda I, Kaneko K, Kawahara Y, Yokoi C, Sugiura Y, Ishikawa H, Takeuchi Y, Kaneko Y and Saito Y. Magnifying narrowband imaging is more accurate than conventional white-light imaging in diagnosis of gastric mucosal cancer. Gastroenterology 2011; 141: 2017-2025, e2013.

[9] Tao G, Xing-Hua L, Ai-Ming Y, Wei-Xun Z, Fang Y, Xi W, Li-Yin W, Chong-Mei L, Gui-Jun F, Hui-Jun S, Dong-Sheng W, Yue L, Xiao-Qing L and Jia-Ming Q. Enhanced magnifying endoscopy for differential diagnosis of superficial gastric lesions identified with white-light endoscopy. Gastric Cancer 2014; 17: 122-129.

[10] Maki S, Yao K, Nagahama T, Beppu T, Hisabe T, Takaki Y, Hirai F, Matsui T, Tanabe H and Iwashita A. Magnifying endoscopy with narrow-band imaging is useful in the differential diagnosis between low-grade adenoma and early cancer of superficial elevated gastric lesions. Gastric Cancer 2013; 16: 140-146.

[11] Miwa K, Doyama H, Ito R, Nakanishi H, Hirano K, Inagaki S, Tominaga K, Yoshida N, Takemura K, Yamada S, Kaneko Y, Katayanagi K, Kurumaya H, Okada T and Yamagishi M. Can magnifying endoscopy with narrow band imaging be useful for low grade adenomas in preoperative biopsy specimens? Gastric Cancer 2012; 15: 170-178.

[12] Ezoe Y, Muto M, Horimatsu T, Minashi K, Yano T, Sano Y, Chiba T and Ohtsu A. Magnifying narrow-band imaging versus magnifying white-light imaging for the differential diagnosis of gastric small depressive lesions: a prospective study. Gastrointest Endosc 2010; 71: 477-484.

[13] Kato M, Kaise M, Yonezawa J, Toyoizumi H, Yoshimura N, Yoshida Y, Kawamura M and Tajiri H. Magnifying endoscopy with narrow-band imaging achieves superior accuracy in the differential diagnosis of superficial gastric lesions identified with white-light endoscopy: a prospective study. Gastrointest Endosc 2010; 72: 523-529.

[14] Buxbaum JL, Hormozdi D, Dinis-Ribeiro M, Lane C, Dias-Silva D, Sahakian A, Jayaram P, Pimentel-Nunes P, Shue D, Pepper M, Cho D and Laine L. Narrow-band imaging versus white light versus mapping biopsy for gastric intestinal metaplasia: a prospective blinded trial. Gastrointest Endosc 2017; 86: 857-865.

[15] Pimentel-Nunes P, Libanio D, Lage J, Abrantes D, Coimbra M, Esposito G, Hormozdi D, Pepper M, Drasovean S, White JR, Dobru D, Buxbaum J, Ragunath K, Annibale B and Dinis-Ribeiro M.

A multicenter prospective study of the real-time use of narrow-band imaging in the diagnosis of premalignant gastric conditions and lesions. Endoscopy 2016; 48: 723-730.
[16] Nagahama T, Yao K, Uedo N, Doyama H, Ueo T, Uchita K, Ishikawa H, Kanesaka T, Takeda Y, Wada K, Imamura K, Arima H and Shimokawa T. Delineation of the extent of early gastric cancer by magnifying narrow-band imaging and chromoendoscopy: a multicenter randomized controlled trial. Endoscopy 2018; 50: 566-576.
[17] Yoshimizu S, Yamamoto Y, Horiuchi Y, Omae M, Yoshio T, Ishiyama A, Hirasawa T, Tsuchida T and Fujisaki J. Diagnostic performance of routine esophagogastroduodenoscopy using magnifying endoscope with narrow-band imaging for gastric cancer. Dig Endosc 2018; 30: 71-78.
[18] Li Z, Zuo XL, Yu T, Gu XM, Zhou CJ, Li CQ, Ji R and Li YQ. Confocal laser endomicroscopy for in vivo detection of gastric intestinal metaplasia: a randomized controlled trial. Endoscopy 2014; 46: 282-290.
[19] Horiguchi N, Tahara T, Yamada H, Yoshida D, Okubo M, Nagasaka M, Nakagawa Y, Shibata T, Tsukamoto T, Kuroda M and Ohmiya N. In vivo diagnosis of early-stage gastric cancer found after Helicobacter pylori eradication using probe-based confocal laser endomicroscopy. Dig Endosc 2018; 30: 219-227.
[20] Goetz M. Characterization of lesions in the stomach: will confocal laser endomicroscopy replace the pathologist? Best Pract Res Clin Gastroenterol 2015; 29: 589-599.
[21] Zhang HP, Yang S, Chen WH, Hu TT and Lin J. The diagnostic value of confocal laser endomicroscopy for gastric cancer and precancerous lesions among Asian population: a system review and meta-analysis. Scand J Gastroenterol 2017; 52: 382-388.
[22] Zuo XL, Li Z, Li CQ, Zheng YY, Xu LD, Chen J, Lin R, Song J, Yu CH, Yue M, Zhou Q, Liu ZY and Li YQ. Probe-based endomicroscopy for in vivo detection of gastric intestinal metaplasia and neoplasia: a multicenter randomized controlled trial. Endoscopy 2017; 49: 1033-1042.
[23] Yu H, Yang AM, Lu XH, Zhou WX, Yao F, Fei GJ, Guo T, Yao LQ, He LP and Wang BM. Magnifying narrow-band imaging endoscopy is superior in diagnosis of early gastric cancer. World J Gastroenterol 2015; 21: 9156-9162.
[24] Lim LG, Yeoh KG, Srivastava S, Chan YH, Teh M and Ho KY. Comparison of probe-based confocal endomicroscopy with virtual chromoendoscopy and white-light endoscopy for diagnosis of gastric intestinal metaplasia. Surg Endosc 2013; 27: 4649-4655.
[25] Wang SF, Yang YS, Wei LX, Lu ZS, Guo MZ, Huang J, Peng LH, Sun G, Ling-Hu EQ and Meng JY. Diagnosis of gastric intraepithelial neoplasia by narrow-band imaging and confocal laser endomicroscopy. World J Gastroenterol 2012; 18: 4771-4780.
[26] Gong S, Xue HB, Ge ZZ, Dai J, Li XB, Zhao YJ, Zhang Y, Gao YJ and Song Y. Value of magnifying endoscopy with narrow-band imaging and confocal laser endomicroscopy in detecting gastric cancerous lesions. Medicine (Baltimore) 2015; 94: e1930.
[27] Liu T, Zheng H, Gong W, Chen C and Jiang B. The accuracy of confocal laser endomicroscopy, narrow band imaging, and chromoendoscopy for the detection of atrophic gastritis. J Clin Gastroenterol 2015; 49: 379-386.
[28] Correa P. Gastric cancer: overview. Gastroenterol Clin North Am 2013; 42: 211-217.
[29] Rugge M, Meggio A, Pravadelli C, Barbareschi M, Fassan M, Gentilini M, Zorzi M, Pretis G, Graham DY and Genta RM. Gastritis staging in the endoscopic follow-up for the secondary prevention of gastric cancer: a 5-year prospective study of 1755 patients. Gut 2019; 68: 11-17.
[30] Menon S and Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis. Endosc Int Open 2014; 2: E46-50.
[31] Banks M, Graham D, Jansen M, Gotoda T, Coda S, di Pietro M, Uedo N, Bhandari P, Pritchard DM, Kuipers EJ, Rodriguez-Justo M, Novelli MR, Ragunath K, Shepherd N and Dinis-Ribeiro M. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. Gut 2019; 68: 1545-1575.
[32] Gono K. Narrow band imaging: technology basis and research and development history. Clin Endosc 2015; 48: 476-480.
[33] Barbeiro S, Libanio D, Castro R, Dinis-Ribeiro M and Pimentel-Nunes P. Narrow-band imaging: clinical application in gastrointestinal endoscopy. GE Port J Gastroenterol 2018; 26: 40-53.
[34] Yao K, Doyama H, Gotoda T, Ishikawa H, Nagahama T, Yokoi C, Oda I, Machida H, Uchita K and Tabuchi M. Diagnostic performance and limitations of magnifying narrow-band imaging in screening endoscopy of early gastric cancer: a prospective multicenter feasibility study. Gastric Cancer 2014; 17: 669-679.
[35] Lee SK. Usefulness and future prospects of confocal laser endomicroscopy for gastric premalignant and malignant lesions. Clin Endosc 2015; 48: 511-515.
[36] Park CH, Kim H, Jo JH, Hahn KY, Yoon JH, Kim SY, Lee YC, Noh SH, Chung HC and Lee SK. Role of probe-based confocal laser endomicroscopy-targeted biopsy in the molecular and

histopathological study of gastric cancer. J Gastroenterol Hepatol 2019; 34: 84-91.
[37] Park JC, Park Y, Kim HK, Jo JH, Park CH, Kim EH, Jung DH, Chung H, Shin SK, Lee SK and Lee YC. Probe-based confocal laser endomicroscopy in the margin delineation of early gastric cancer for endoscopic submucosal dissection. J Gastroenterol Hepatol 2017; 32: 1046-1054.
[38] Song J, Zhang J, Wang J, Guo X, Wang J, Liu Y and Dong W. Meta-analysis: narrow band imaging for diagnosis of gastric intestinal metaplasia. PLoS One 2014; 9: e94869.
[39] Hu YY, Lian QW, Lin ZH, Zhong J, Xue M and Wang LJ. Diagnostic performance of magnifying narrow-band imaging for early gastric cancer: a meta-analysis. World J Gastroenterol 2015; 21: 7884-7894.
[40] Li WB, Zuo XL, Li CQ, Zuo F, Gu XM, Yu T, Chu CL, Zhang TG and Li YQ. Diagnostic value of confocal laser endomicroscopy for gastric superficial cancerous lesions. Gut 2011; 60: 299-306.
[41] Li Z, Zuo XL, Li CQ, Liu ZY, Ji R, Liu J, Guo J and Li YQ. New classification of gastric pit patterns and vessel architecture using probe-based confocal laser endomicroscopy. J Clin Gastroenterol 2016; 50: 23-32.
[42] Zhang Q, Wang F, Chen ZY, Wang Z, Zhi FC, Liu SD and Bai Y. Comparison of the diagnostic efficacy of white light endoscopy and magnifying endoscopy with narrow band imaging for early gastric cancer: a meta-analysis. Gastric Cancer 2016; 19: 543-552.
[43] Dias-Silva D, Pimentel-Nunes P, Magalhaes J, Magalhaes R, Veloso N, Ferreira C, Figueiredo P, Moutinho P and Dinis-Ribeiro M. The learning curve for narrow-band imaging in the diagnosis of precancerous gastric lesions by using Web-based video. Gastrointest Endosc 2014; 79: 910-920.
[44] Higashi R, Uraoka T, Kato J, Kuwaki K, Ishikawa S, Saito Y, Matsuda T, Ikematsu H, Sano Y, Suzuki S, Murakami Y and Yamamoto K. Diagnostic accuracy of narrow-band imaging and pit pattern analysis significantly improved for less-experienced endoscopists after an expanded training program. Gastrointest Endosc 2010; 72: 127-135.
[45] Yao K, Iwashita A, Tanabe H, Nagahama T, Matsui T, Ueki T, Sou S, Kikuchi Y and Yorioka M. Novel zoom endoscopy technique for diagnosis of small flat gastric cancer: a prospective, blind study. Clin Gastroenterol Hepatol 2007; 5: 869-878.
[46] Saka A, Yagi K and Nimura S. Endoscopic and histological features of gastric cancers after successful Helicobacter pylori eradication therapy. Gastric Cancer 2016; 19: 524-530.
[47] Gono K, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y and Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 2004; 9: 568-577.
[48] Kuznetsov K, Lambert R and Rey JF. Narrow-band imaging: potential and limitations. Endoscopy 2006; 38: 76-81.
[49] Yao K, Takaki Y, Matsui T, Iwashita A, Anagnostopoulos GK, Kaye P and Ragunath K. Clinical application of magnification endoscopy and narrow-band imaging in the upper gastrointestinal tract: new imaging techniques for detecting and characterizing gastrointestinal neoplasia. Gastrointest Endosc Clin N Am 2008; 18: 415-433.
[50] Yao K, Anagnostopoulos GK and Ragunath K. Magnifying endoscopy for diagnosing and delineating early gastric cancer. Endoscopy 2009; 41: 462-467.
[51] Kaise M, Kato M, Urashima M, Arai Y, Kaneyama H, Kanzazawa Y, Yonezawa J, Yoshida Y, Yoshimura N, Yamasaki T, Goda K, Imazu H, Arakawa H, Mochizuki K and Tajiri H. Magnifying endoscopy combined with narrow-band imaging for differential diagnosis of superficial depressed gastric lesions. Endoscopy 2009; 41: 310-315.
[52] Pimentel-Nunes P, Dinis-Ribeiro M, Soares JB, Marcos-Pinto R, Santos C, Rolanda C, Bastos RP, Areia M, Afonso L, Bergman J, Sharma P, Gotoda T, Henrique R and Moreira-Dias L. A multicenter validation of an endoscopic classification with narrow band imaging for gastric precancerous and cancerous lesions. Endoscopy 2012; 44: 236-246.
[53] Nakayoshi T, Tajiri H, Matsuda K, Kaise M, Ikegami M and Sasaki H. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology (including video). Endoscopy 2004; 36: 1080-1084.
[54] Uedo N, Ishihara R, Iishi H, Yamamoto S, Yamamoto S, Yamada T, Imanaka K, Takeuchi Y, Higashino K, Ishiguro S and Tatsuta M. A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. Endoscopy 2006; 38: 819-824.
[55] Guo YT, Li YQ, Yu T, Zhang TG, Zhang JN, Liu H, Liu FG, Xie XJ, Zhu Q and Zhao YA. Diagnosis of gastric intestinal metaplasia with confocal laser endomicroscopy in vivo: a prospective study. Endoscopy 2008; 40: 547-553.

**Supplementary Method 1**

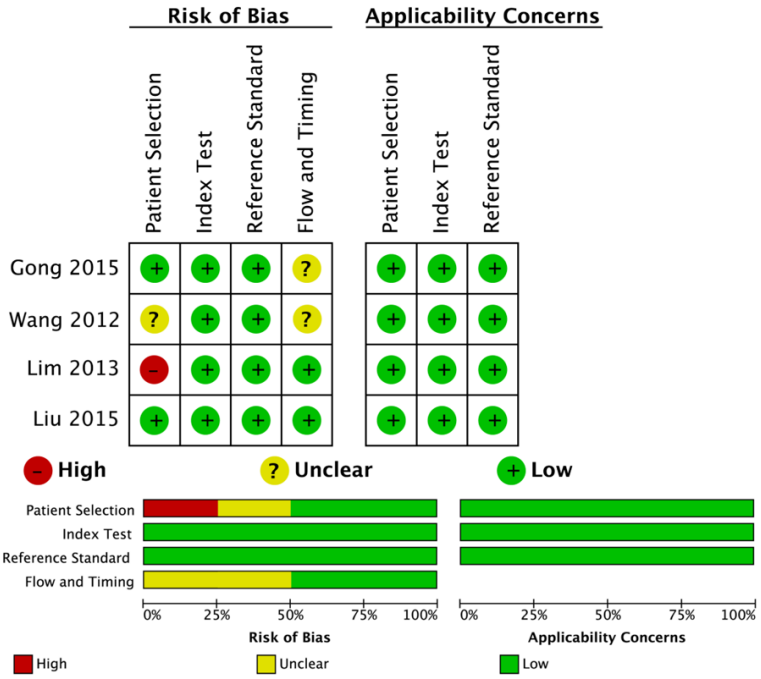
*Search strategy for PubMed*

((((((((((((((((((stomach neoplasms[MeSH Terms]) OR (((((stomach[MeSH Terms]) OR stomach[Title/Abstract]) OR gastric[Title/Abstract])) AND (((((cancer[Title/Abstract]) OR carcinoma[Title/Abstract]) OR neoplasm[Title/Abstract]) OR malignant[Title/Abstract]) OR tumor[Title/Abstract])))))) OR ((((Precancerous Conditions[MeSH Terms]) OR Precancerous lesions[Title/Abstract]) OR Preneoplastic Condition[Title/Abstract]) OR Precancerous Condition[Title/Abstract])) OR (((((Gastric Stump[MeSH Terms]) OR gastric stumps[Title/Abstract]) OR gastric remnant[Title/Abstract]) OR residual stomach[Title/Abstract]) OR remnant stump[Title/Abstract])) OR (((Gastritis, Atrophic[MeSH Terms]) OR atrophic gastritides[Title/Abstract]) OR atrophic gastritis[Title/Abstract])) OR ((Stomach Ulcer[MeSH Terms]) OR (((((stomach[MeSH Terms]) OR stomach[Title/Abstract]) OR gastric[Title/Abstract])) AND ((((ulcer[MeSH Terms]) OR ulcer[Title/Abstract]) OR anabrosis[Title/Abstract]) OR ulceration[Title/Abstract]))))) OR (((((stomach[MeSH Terms]) OR stomach[Title/Abstract]) OR gastric[Title/Abstract])) AND (((Adenoma[MeSH Terms]) OR (adenoid tumor)[Title/Abstract]) OR adenoma[Title/Abstract])))) OR (((((((((mucosa[Title/Abstract]) OR Mucous Membrane[MeSH Terms]) OR mucus membrane[Title/Abstract]) OR mucous lining[Title/Abstract])) AND ((gastric[Title/Abstract]) OR stomach[Title/Abstract])) OR (((((((gastric mucosa[Title/Abstract]) OR gastric mucosa[MeSH Terms]) OR Pyloric Glands[Title/Abstract]) OR Gastric Glands[Title/Abstract]) OR stomach lining[Title/Abstract]) OR Gastric mucous membrane[Title/Abstract]) OR tunica mucosa ventriculi[Title/Abstract]) OR Mucous Membrane[MeSH Terms])) AND ((epithelial[Title/Abstract]) OR epithelial dysplasia[MeSH Terms])) AND ((((dysplasia[Title/Abstract]) OR atypical hyperplasia[Title/Abstract])) OR Carcinoma in Situ[MeSH Terms])))) OR ((((((atypical hyperplasia[Title/Abstract]) OR dysplasia[Title/Abstract])) AND (((intestines[MeSH Terms]) OR intestines[Title/Abstract]) OR enteron[Title/Abstract])) AND ((((mucosa[Title/Abstract]) OR Mucous Membrane[MeSH Terms]) OR mucus membrane[Title/Abstract]) OR mucous lining[Title/Abstract])) AND ((((intestinal mucosa[Title/Abstract]) OR intestinal mucosa[MeSH Terms]) OR ileal mucosa[Title/Abstract]) OR intestinal mucous[Title/Abstract])))) OR (((((((((mucosa[Title/Abstract]) OR Mucous Membrane[MeSH Terms]) OR mucus membrane[Title/Abstract]) OR mucous lining[Title/Abstract])) AND ((gastric[Title/Abstract]) OR stomach[Title/Abstract])) OR (((((((gastric mucosa[Title/Abstract]) OR gastric mucosa[MeSH Terms]) OR Pyloric Glands[Title/Abstract]) OR Gastric Glands[Title/Abstract]) OR stomach lining[Title/Abstract]) OR Gastric mucous membrane[Title/Abstract]) OR tunica mucosa ventriculi[Title/Abstract]) OR Mucous Membrane[MeSH Terms])) AND ((epithelium[Title/Abstract]) OR epithelium[MeSH Terms])) AND ((Metaplasia[Title/Abstract]) OR Metaplasia[MeSH Terms])))) OR (((((polyp[Title/Abstract]) OR Polyps[Title/Abstract])) AND ((gastric[Title/Abstract]) OR stomach[Title/Abstract])) OR gastric polyps[Title/Abstract])))) AND ((((((((((((Microscopy, Confocal[MeSH Terms]) OR Confocal laser endomicroscopy[Title/Abstract]) OR Confocal Microscopy[Title/Abstract]) OR Laser Scanning Microscopy[Title/Abstract]) OR Laser Scanning Confocal Microscopy[Title/Abstract]) OR confocal laser scanning microscope[Title/Abstract]) OR reflectance confocal microscope[Title/Abstract]) OR confocal microscope[Title/Abstract]) OR laser scanning confocal microscope[Title/Abstract]) OR CLE[Title/Abstract]) OR RCM[Title/Abstract]) OR CLSM[Title/Abstract])))) AND ((((((narrow band imaging[MeSH Terms]) OR narrow band imaging[Title/Abstract]) OR Band Imaging, Narrow[Title/Abstract]) OR Imagings, Narrow Band[Title/Abstract]) OR Narrow Band Imagings[Title/Abstract])))) AND (((((((randomized controlled trial[Publication Type]) OR controlled clinical trial[Publication Type]) OR randomized[Title/Abstract]) OR placebo[Title/Abstract]) OR randomly[Title/Abstract])) NOT ((animals[MeSH Terms]) NOT ((humans[MeSH Terms]) AND animals[MeSH Terms]))).

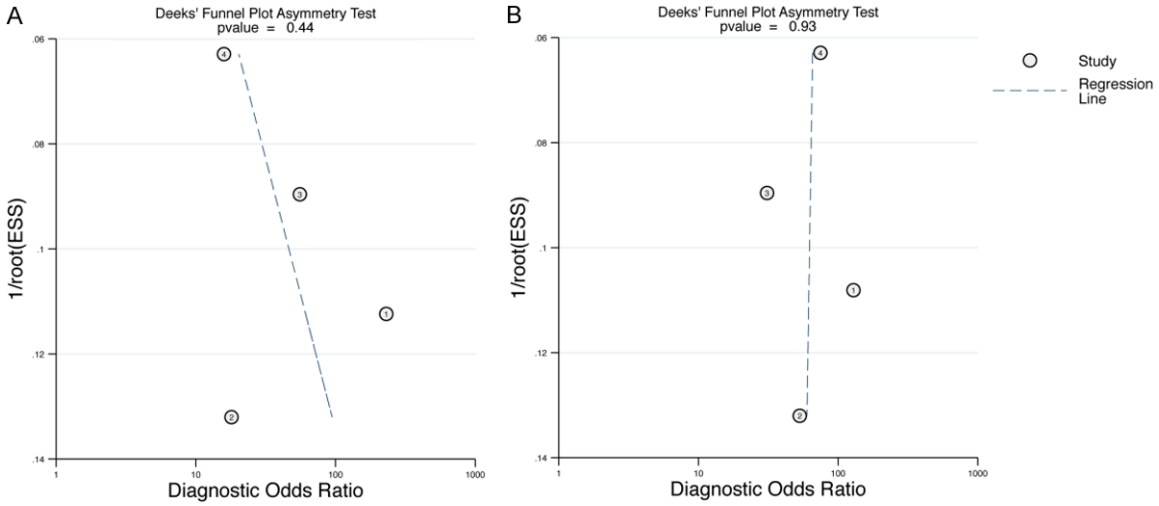
**Supplementary Table 1.** Quality assessment of the studies included for the meta-analysis (QUADAS-2)

| Study | Risk of Bias | | | | Applicability Concerns | | |
|---|---|---|---|---|---|---|---|
| | Patient Selection | Index Test | Reference Standard | Flow and Timing | Patient Selection | Index Test | Reference Standard |
| Gong, 2015 | L | L | L | U | L | L | L |
| Wang, 2012 | U | L | L | H | L | L | L |
| Lim, 2013 | H | L | L | L | L | L | L |
| Liu, 2015 | L | L | L | L | L | L | L |

Footnotes: L, Low risk; H, High risk; U, Unclear risk.




**Supplementary Figure 1.** Assessment of methodological quality according to the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).




**Supplementary Figure 2.** Results of Deeks' funnel plot asymmetry test on inverse root of effective sample size of NBI (A) and CLE (B) for visualization of publication bias. ESS, Effective sample size.