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Current role of narrow band imaging in diagnosing gastric intestinal metaplasia: a systematic review and meta-analysis of its diagnostic accuracy

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Abstract

Background Gastric intestinal metaplasia (GIM) can be missed by random gastric biopsies taken during white light endoscopy. Narrow band imaging (NBI) may potentially improve the detection of GIM. However, pooled estimates from prospective studies are lacking and the diagnostic accuracy of NBI in detecting GIM needs to be more precisely defined. The aim of this systematic review and meta-analysis was to study the diagnostic performance of NBI in detecting GIM.

Methods PubMed/Medline and EMBASE were screened for studies examining GIM in relation to NBI. Data from each study were extracted and calculations of pooled sensitivity, specificity, likelihood ratios, diagnostic odds ratios (DORs), and areas under the curve (AUCs) were performed. Fixed or random effects models, were used as appropriate, depending on the presence of significant heterogeneity.

Results We included 11 eligible studies in the meta-analysis, comprising 1672 patients. NBI showed a pooled sensitivity of 80% (95% confidence interval [CI] 69-87), specificity of 93% (95%CI 85-97), DOR 48 (95%CI 20-121), and AUC of 0.93 (95%CI 0.91-0.95) in detecting GIM.

Conclusions This meta-analysis showed that NBI is a reliable endoscopic means of detecting GIM. NBI with magnification performed better than NBI without magnification. However, better designed prospective studies are needed to precisely determine the diagnostic role of NBI, especially in high-risk populations where early detection of GIM can impact gastric cancer prevention and survival.

Keywords Narrow band imaging, gastric intestinal metaplasia, diagnostic accuracy, meta-analysis

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Introduction

Gastric cancer (GC) is one of the major cancer burdens globally [1]. Despite the fact that the trend in death rates is decreasing, GC still has a poor prognosis and few therapeutic options are efficacious, particularly in advanced stages of the disease. It is now well established that GC pathogenesis is a multifactorial process, in which *Helicobacter pylori*, environmental and host factors may play significant roles [2]. It is a multistep process that includes the sequential development of chronic gastritis, followed by gastric mucosal atrophy, gastric intestinal metaplasia (GIM), dysplasia, and ultimately adenocarcinoma [2-4]. GIM is generally considered as a pre-cancerous lesion in the gastric mucosa. However, when white light endoscopy (WLE) is used, the detection of GIM requires biopsies for proper histology assessment. Fortunately, the detection of GIM is possible using improved endoscopic techniques [5].

Narrow band imaging (NBI) involves optical image enhancement that uses 2 short wavelength light beams, 415 nm (blue) and 540 nm (green) [6]. It is an endoscopic technique that can provide enhanced visualization of the micro-surface structure and microvascular architecture of subjacent microvascular patterns [7]. Consequently, studies have examined the association between the appearance of the mucosa observed with NBI and pathology [8-10]. In particular, the combination of NBI with magnification is of importance,

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Conflict of Interest: None

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since it facilitates the detection of the characteristic light blue crest, thus increasing the possibility of diagnosing GIM [11].

So far, there have been 2 meta-analyses addressing the role of NBI in diagnosing GIM. One was published some years ago (2014) [12] and the other was a pairwise meta-analysis comparing NBI to WLE, expressing the comparison results as odds ratios and not addressing the diagnostic accuracy [13]. Therefore, the aim of this systematic review and diagnostic accuracy meta-analysis was to evaluate the current diagnostic accuracy of NBI in detecting GIM.

Materials and methods

Selection criteria

We strictly followed the PRISMA guidelines for systematic reviews [14] and potentially eligible studies for the meta-analysis were selected by applying the following inclusion criteria: (a) they were written in the English language; and (b) they contained data that were appropriate for the construction of 2-by-2 contingency tables for calculations of NBI diagnostic accuracy parameters. When the same data were reported in 2 studies the more informative study was selected. QUADAS-2 evaluation was used for quality estimation of the eligible studies [15].

Identification of studies and data extraction

We searched PubMed/MEDLINE and EMBASE databases for suitable studies comparing the endoscopic diagnosis of GIM with histology (Fig. 1). We used the following search terms: *"NBI"[All Fields] AND ("intestinalization"[All Fields] OR "intestinalized"[All Fields] OR "intestinally"[All Fields] OR "intestinals"[All Fields] OR "intestine s"[All Fields] OR "intestines"[MeSH Terms] OR "intestines"[All Fields] OR "intestinal"[All Fields] OR "intestine"[All Fields]) AND ("metaplasia"[MeSH Terms] OR "metaplasia"[All Fields] OR "metaplasias"[All Fields]) AND ("sensitivity and specificity"[MeSH Terms] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity and specificity"[All Fields] OR ("sensitivity"[All Fields] AND "specificity"[All Fields]) OR "sensitivity specificity"[All Fields]) AND ("diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnostic"[All Fields] OR "diagnostical"[All Fields] OR "diagnostically"[All Fields] OR "diagnostics"[All Fields]) AND ("accuracies"[All Fields] OR "accuracy"[All Fields])*. We searched until the end of September 2022. All selected studies were further screened, searching for more appropriate studies. Data from each study were extracted independently by the 2 authors and any disagreement was settled by discussion.

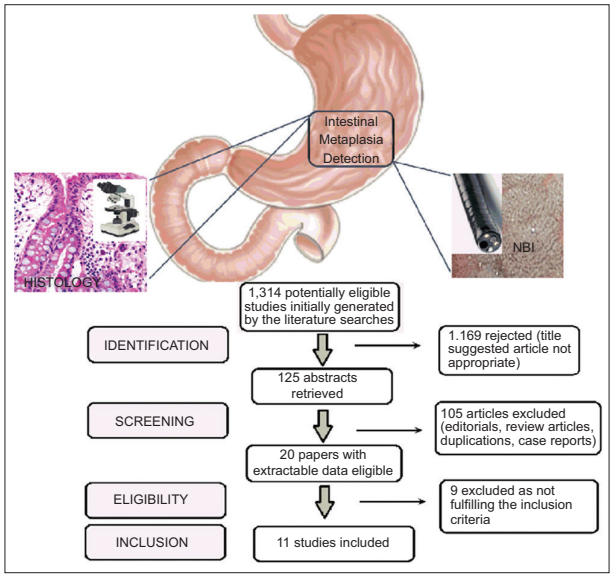

Figure 1 Flow chart describing the identification, screening, eligibility and inclusion of the studies in this meta-analysis

Statistical analysis

For statistical analysis we followed a methodology described previously [16]. In brief, pooled data concerning all NBI diagnostic accuracy parameters, i.e., sensitivity, specificity and in addition positive and negative likelihood ratios (LR), diagnostic odds ratios (DOR) and AUCs, with 95% confidence intervals (CIs), were derived by computing data obtained from the individual studies and constructing 2-by-2 contingency tables. For calculations we used the fixed-effects model (Mantel and Haenszel method) [17]. When significant heterogeneity was present, we used the random-effects model (DerSimonian and Laird method) [18]. Forest plots were constructed for visual display of individual and pooled data. In addition, the results of the individual studies were displayed in a receiver operating characteristic (ROC) graph, illustrating the distribution of sensitivities and specificities. Additionally, a weighted symmetric summary ROC (sROC) curve was derived, with calculation of the relevant areas under the curve (AUC). The AUC in accurate tests approaches 1 and in poor tests is close to 0.5 [19-21]. The heterogeneity between studies was estimated using the Cochran Q-test, and the inconsistency index I squared (I^2) was used to quantify the degree of heterogeneity [22]. When the Q-test provided a P-value of less than 0.1 and the I^2 was more than 50 [23], then heterogeneity was considered to be present, and further sensitivity-subgroup analyses were performed in addition to the random-effects model. The possibility of publication bias was examined using Deeks' funnel plot, with a superimposed regression line [24]. All analyses were performed with Stata software (version 13.0, College Station, TX) using the MIDAS command and Meta-DiSc software [21].

Results

Study characteristics and descriptive assessment

Fig. 1 shows the flow chart describing the process of study selection. Of 1314 titles initially generated by the literature

searches, 11 prospective cohort studies in adult patients [25-35] were found eligible for meta-analysis. These studies included a total of 1672 patients whose NBI endoscopy GIM findings were compared to the gold standard, i.e., histology. The main characteristics of the 11 included studies are shown in Table 1. The quality assessment of the included studies according to the QUADAS-2 evaluation is shown in Supplementary Fig. 1.

NBI diagnostic performance

In view of the significant heterogeneity found for both the sensitivity and the specificity, with respective heterogeneity values of Q-test=49.63, d.f.=10, P<0.001, I^2=79.85% and Q-test=39.87, d.f.=10, P<0.001, I^2=74.92%, the random-effects analysis was used throughout the calculations. The pooled data showed that NBI had a sensitivity of 80% (95%CI 69-87%) and a specificity of 93% (95%CI 85-97%), with respective forest plots shown in Fig. 2.

The corresponding ROC plot with sROC is displayed in Fig. 3A, showing an AUC of 0.93 (0.91-0.95). The possibility of publication bias was explored using Deek's funnel plot asymmetry test with a superimposed regression line, as shown in Fig. 3B. There was no significant evidence of publication bias (P=0.88 for the slope coefficient). In addition, the bivariate boxplot is shown in Fig. 3C, where most studies are clustered within the median distribution with some outliers, indirectly suggesting the magnitude of the heterogeneity. The relevant LR scattergram is shown in Fig. 3D and provides the summary point of LRs obtained as functions of mean sensitivity and specificity.

In exploring the reasons for the significant heterogeneity found among studies, further analyses (sensitivity analyses) were conducted. These are shown in Fig. 4A-D, depicting the residual-based goodness-of-fit, the bivariate normality, the influence analysis and the outlier detection, respectively. These analyses identified 3 outlier studies that contributed to the significant heterogeneity found. Fig. 5A shows the respective Fagan's nomogram providing 73% post-test probability of GIM after an NBI-positive result and only a 5% post-test probability after an NBI-negative result. The relevant probability modifying plot is shown in Fig. 5B, with a positive LR 10.63 (95%CI 5.07-22.32) and negative LR 0.22 (95%CI 0.14-0.34). These results give a 90% (95%CI 86-95%) positive predictive value (PPV) and an 80% (95%CI 76-84%) negative predictive value (NPV).

Subgroup analysis

Given the significant heterogeneity found, in addition to sensitivity analyses, subgroup analysis was performed according to the NBI modality used, i.e., with and without magnification. NBI with magnification was used in 6 studies [25,28-30,34,35], whereas 5 studies [26,27,31-33] used NBI without magnification. The pooled data (random-effects analysis) showed that NBI with magnification performed better than NBI without magnification (Table 2). For NBI with magnification, sensitivity (95%CI), specificity, LR positive, LR negative, DOR, ROC area, PPV and NPV were 0.85 (95%CI 0.74-0.92), 0.93 (95%CI 0.86-0.97), 11.97 (95%CI 5.69-25.21), 0.16 (95%CI 0.09-0.30), 75 (95%CI 24-239), 0.95 (95%CI

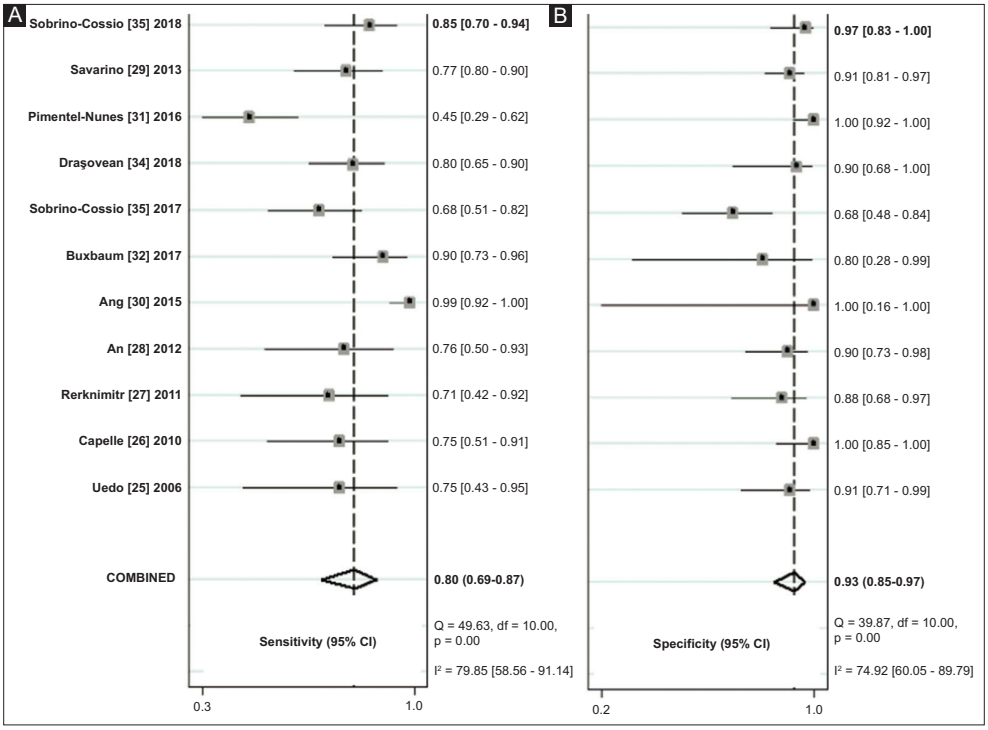

Figure 2 Forest plot showing sensitivities (A) and specificities (B) with corresponding heterogeneity statistics
CI, confidence interval

Table 1 Main characteristics of the studies included in the meta-analysis

Author year [ref.]	Study design	Study population	Gastric preparation	Study protocol/intervention	Additional endoscopic findings
Uedo 2006 [25]	Prospective study	107 patients	40-100 mL of 0.04% simethicone (activated dimethicone) solution	WLE to exclude obvious lesions followed by NBI-ME; LBC was defined as a fine, blue-white line on the crests of the epithelial surface/gyri; LBC graded as less than 20%, 20±80%, and more than 80% of an image field.	N/A
Capelle 2010 [26]	Prospective study	43 patients	N/A	WLE to exclude obvious lesions followed by NBI; NBI suspicious lesions for IM defined as bluish-whitish areas with an irregular mucosal pattern.	N/A
Rerknimitr 2011 [27]	Prospective study	38 patients	Simethicone solution	All patients underwent, 1 year apart, 2 upper endoscopies with NBI targeted biopsy; endoscopic criteria (LBC, VP, and LLC) compared with standard histology.	N/A
An 2012 [28]	Prospective study	47 patients	N/A	WLE to exclude obvious lesions followed by NBI-ME; MTB was defined as an enclosing, white turbid band on the epithelial surface/gyri, and LBC as a fine, blue-white line on the crest of the epithelial surface/gyri.	N/A
Savarino 2013 [29]	Prospective study	100 patients	66.6 mg of simethicone diluted in 40 mL of water (additional 30-60 mL of the simethicone solution, if poor visualization persisted)	WLE to exclude obvious lesions followed by NBI and NBI-ME; LBC graded as less than 20%, 20±80%, and more than 80% of an image field.	N/A
Ang 2012 [30]	Prospective study	458 patients	N/A	Patients randomized to undergo either NBI or HD-WLE; IM was diagnosed on HD-WLE on the basis of whitish color change with plaques, patches, or homogeneous discoloration on the gastric mucosa; IM diagnosed on NBI on the basis of LBC and villous morphology. The sequence of endoscopic evaluation was WLE followed by NBI. Focal lesions were re-examined by NBI-ME. The incremental diagnostic yield of NBI over WLE and ability of NBI-ME to differentiate gastric mucosal pathology were analyzed.	N/A
Pimentel-Nunes 2016 [31]	Prospective study	238 patients	N/A	HR-WLE and HR-NBI endoscopy performed; mucosal pattern, LBC, WOS, vascular pattern, vascular thickness, vascular density and VVD recorded.	N/A
Buxbaum 2017 [32]	Prospective study	112 patients	None	HR-WLE to exclude obvious lesions followed by NBI by a second endoscopist blinded to HR-WLE findings; features suggestive of IM included a well-delineated tubulovillous or ridge glandular pattern and/or a LBC sign.	N/A
Sha 2017 [33]	Prospective study	132 patients	Acetic acid diluted with water (0.6%) used for AA-NBI	Conventional WLE, NBI and AA-NBI performed in all patients during a single procedure; suspicious IM lesions defined as whitish patches with a regular mucosal pattern.	N/A
Drașovean 2018 [34]	Prospective study	59 patients	N/A	NBI-ME performed; IM endoscopic diagnosis established by subsequent evaluation of pit pattern of the mucosal and vascular patterns (Type A: areas presenting either a tubulovillous mucosal pattern with regular microvessels or the LBC sign; Type B: areas with SECN disappearance; Type C: areas showing IMP and/or IVP).	N/A
Sobrino-Cossío 2018 [35]	Prospective study	338 patients	N/A	NBI using 1.5 × electronic zoom endoscopy (with no high magnification) to diagnose IM; WOS and LBC recorded.	N/A

WLE, white-light endoscopy; NBI, narrow band imaging; ME, magnifying endoscopy; LBC, light blue crest; N/A, not available; IM, intestinal metaplasia; VP, villous pattern; LLC, large long crest; MTB, marginal turbid band; HD, high definition; HR, high resolution; VVD, variable vascular density; AA, acetic acid; IMP, irregular mucosal pattern; IVP, irregular vascular pattern; WOS, white opaque substance

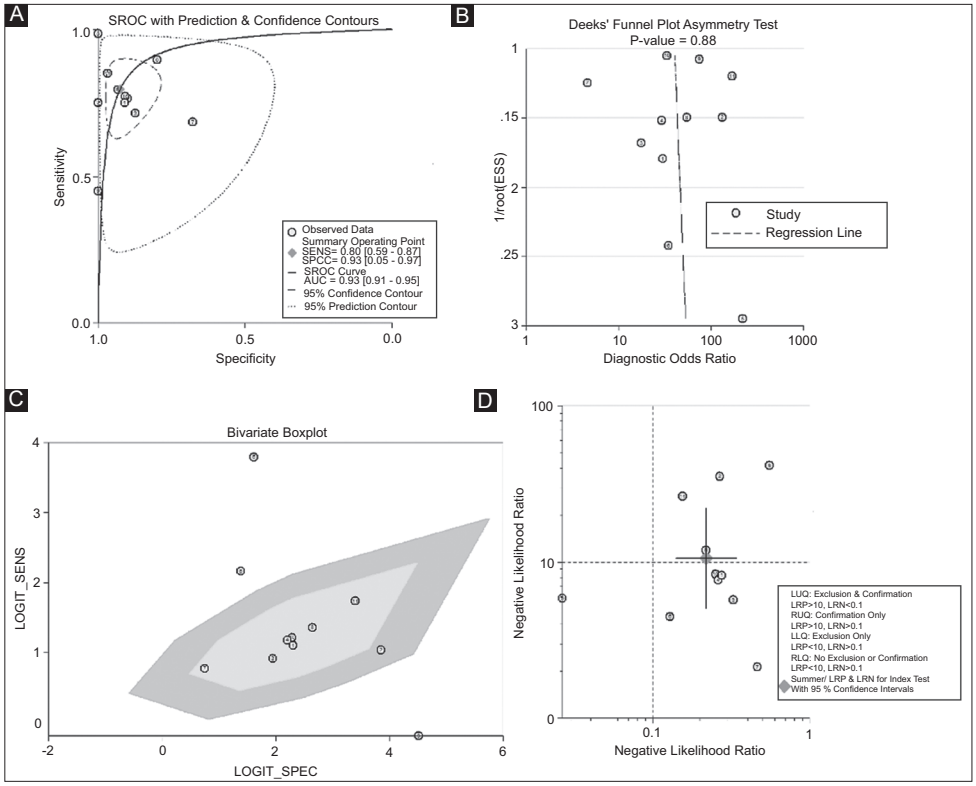

Figure 3 (A) Weighted symmetric summary receiver operating curve (sROC), with 95% confidence intervals and prediction regions around mean operating sensitivity and specificity point. (B) Deeks' funnel plot, with superimposed regression line. No evidence of publication bias. (C) Bivariate box plot, with most studies clustering within the median distribution and some outliers indirectly suggesting the existence of heterogeneity. (D) Likelihood ratio scattergram

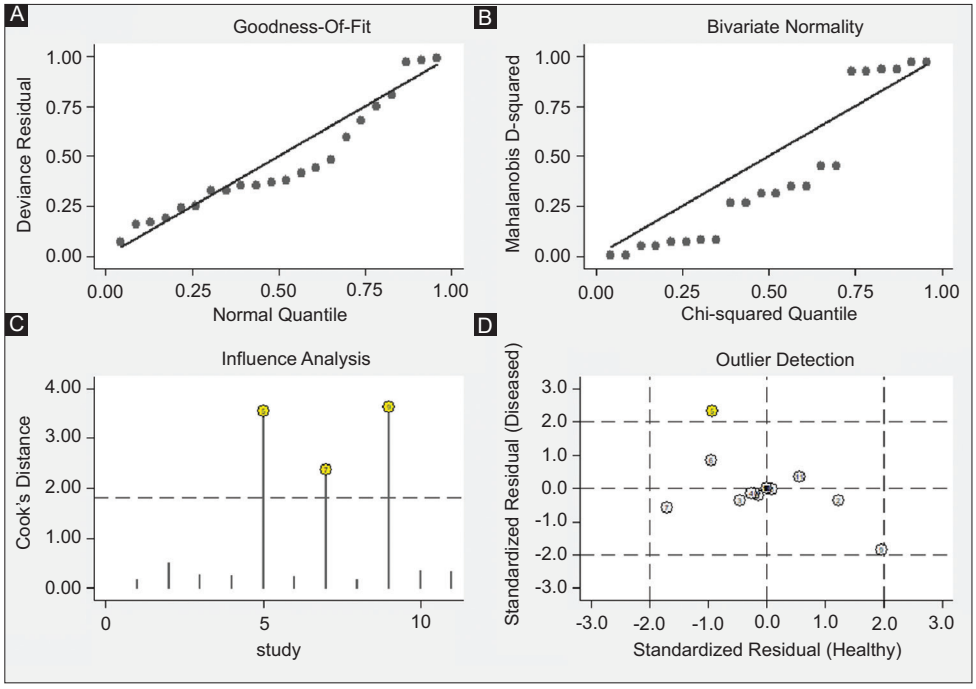

Figure 4 Sensitivity analyses, with graphical depiction of: (A) residual-based goodness-of-fit, (B) bivariate normality, (C) influence analyses, (D) outlier detection analyses

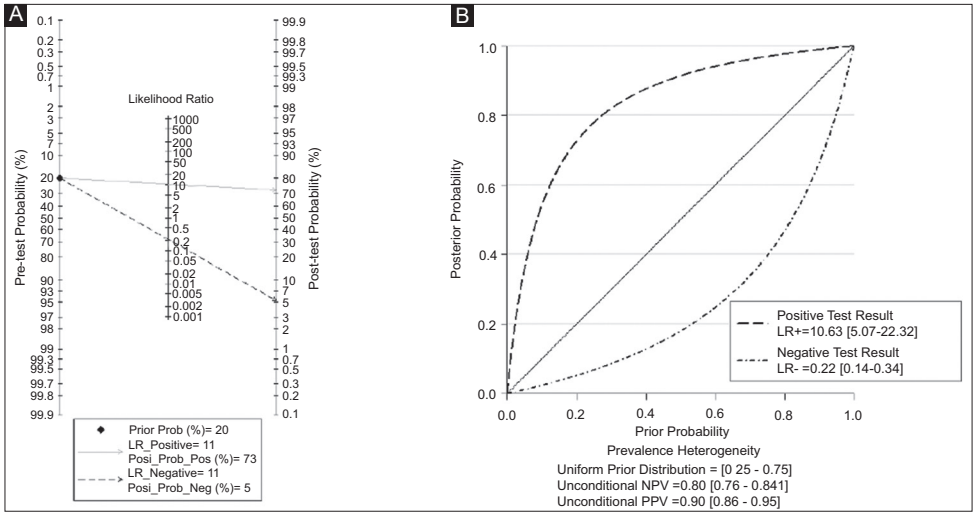

Figure 5 (A) Fagan's nomogram showing pre-test and post-test probabilities with relevant likelihood ratios. (B) Probability modifying plot

Table 2 NBI sensitivity, specificity, LR positive, LR negative, DOR, ROC area, PPV, NPV in all included studies and the 2 subgroups, i.e., with and without magnification

Parameter	All included studies with and without NBI magnification (n=11)	Studies with NBI magnification (n=6)	Studies without NBI magnification (n=5)
Sensitivity (95%CI)	0.80 (0.69-0.87)	0.85 (0.74-0.92)	0.70 (0.55-0.82)
Specificity (95%CI)	0.93 (0.85-0.97)	0.93 (0.86-0.97)	0.94 (0.66-0.99)
LR positive (95%CI)	10.63 (5.07-22.32)	11.97 (5.69-25.21)	12.24 (1.74-86.11)
LR negative (95%CI)	0.22 (0.14-0.34)	0.16 (0.09-0.30)	0.31 (0.20-0.49)
DOR (95%CI)	48 (20-121)	75 (24-239)	39 (5-277)
ROC area (95%CI)	0.93 (0.91-0.95)	0.95 (0.93-0.97)	0.84 (0.81-0.87)
PPV (95%CI)	0.90 (0.86-0.95)	0.91 (0.87-0.95)	0.91 (0.84-0.98)
NPV (95%CI)	0.80 (0.76-0.84)	0.85 (0.81-0.88)	0.74 (0.69-0.80)

LR, likelihood ratio; DOR, diagnostic odds ratio; ROC, receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value; NBI, narrow band imaging; CI, confidence interval

0.93-0.97), 0.91 (95%CI 0.87-0.95), 0.85 (95%CI 0.81-0.88), respectively. For NBI without magnification the respective values were 0.70 (95%CI 0.55-0.82), 0.94 (95%CI 0.66-0.99), 12.24 (95%CI 1.74-86.11), 0.31 (95%CI 0.20-0.49), 39 (95%CI 5-277), 0.84 (95%CI 0.81-0.87), 0.91 (95%CI 0.84-0.98), 0.74 (95%CI 0.69-0.80).

Discussion

GC is the third leading cause of cancer deaths worldwide, with 1,033,701 new cases diagnosed globally in 2018 [1]. GIM has been associated with an increased risk for GC and may represent the histological step before the development of dysplasia [36]. Furthermore, it has been considered as a specific marker to identify patients who might benefit from surveillance. The ability to identify precursor lesions on gastric biopsies has led to interest in developing screening and surveillance strategies for the early detection and prevention of GC. Various endoscopic techniques have been developed for diagnosing mucosal lesions, but not all of them are widely available. In standard or high definition WLE, the shorter wavelength can only penetrate superficial mucosa, which limits the ability to evaluate the mucosa in detail. Therefore, WLE does not provide mucosal or microvascular details and, as GIM does not manifest easily detectable lesions, it can be missed when WLE is used alone. Hence, endoscopists usually rely only on random biopsies for the detection of GIM.

The NBI endoscopic technique is based on a modification of the spectral characteristics of the optical filter in the light source, leading to improved visibility of mucosal structures. In addition, NBI does not require tedious patient preparation, as in other modalities such as chromoendoscopy, and it can be used easily by switching on a filter on the endoscope during endoscopy. Consequently, NBI has made possible the detection of mucosal changes that precede malignant changes, such as GIM [6]. In particular, the presence of a blue-white line on the crests of the epithelial surface of the gastric mucosa (the

so called "light blue crest" sign) on NBI with magnification has high sensitivity and specificity for GIM [11,25,27-30,35]. Therefore, detection of light blue crest lesions on NBI can enhance the GIM detection rate.

This study addressed the accuracy of NBI in diagnosing GIM, taking into account all the available published evidence regarding the diagnostic performance of NBI in comparison to histology, and the results showed that good diagnostic accuracy was achieved. Thus, the pooled sensitivity was 80% (95%CI 69-87), the pooled specificity was 93% (95%CI 85-97) and the relevant AUC was 0.93 (95%CI 0.91-0.95) in detecting GIM. These data indicate a good diagnostic accuracy for NBI in diagnosing GIM. When we split the whole group of included studies according to the NBI modality used, i.e., with and without magnification, we found that NBI with magnification performed better than NBA in the whole group and the group without NBI magnification, with values for sensitivity, specificity and AUC 0.85 (95%CI 0.74-0.92), 0.93 (95%CI 0.86-0.97), and 0.95 (95%CI 0.93-0.97), respectively.

The ability to identify precursor lesions, such as GIM, on gastric biopsies has led to interest in developing screening and surveillance strategies for the early detection and prevention of GC. Histology is currently considered to be the gold standard diagnostic tool in diagnosing GIM. However, GIM lesions can be missed by random biopsy sampling, since their distribution in various parts of the stomach can be patchy. In addition, histology can carry a financial burden. Consequently, identification of GIM lesions, especially by NBI endoscopy, can be of great diagnostic importance in daily clinical practice, since this endoscopic technique is spreading and endoscopists' expertise in detecting GIM is improving, which could overcome the need for histology.

The lack of publication bias strengthens the results of this meta-analysis. However, the study has some limitations. Thus, significant heterogeneity was observed among studies. This could be due to a number of factors related to the NBI examination itself, since it is operator dependent and can therefore vary between operators and centers. Moreover, the NBI modality, i.e., NBI with and without magnification, could be of importance. Indeed, when we split the whole group according to the NBI modality used, we found that NBI with magnification performed better than NBI without magnification. Furthermore, the heterogeneity found may be related to the quality of selected studies. Consequently, more data from high quality multicenter studies are necessary to further evaluate whether NBI stands as an accurate endoscopic diagnostic tool in detecting GIM and thus overcoming histology. Finally, an additional limitation might be related to the fact that we included only studies published in English; therefore, language bias may exist.

In conclusion, this meta-analysis showed that NBI is an accurate and useful tool to diagnose GIM. NBI with magnification performed better than NBI without magnification and therefore it should be preferred. However, as only a few studies were available, more high-quality trials are warranted to further evaluate the actual diagnostic accuracy and clinical relevance of NBI for diagnosing GIM.

Summary Box

What is already known:

- Gastric intestinal metaplasia (GIM) is generally considered as a precancerous lesion in the gastric mucosa
- Using white light endoscopy, GIM detection requires biopsies for a proper histological assessment
- Narrow band imaging (NBI) enhances visualization of microvascular architecture and micro-surface structure between the epithelial surface and subjacent vascular pattern with increased likelihood of detecting GIM

What the new findings are:

- NBI is an accurate and useful endoscopic diagnostic tool in detecting GIM thereby avoiding the need for histology
- NBI with magnification performed better than NBI without magnification and it should be preferred

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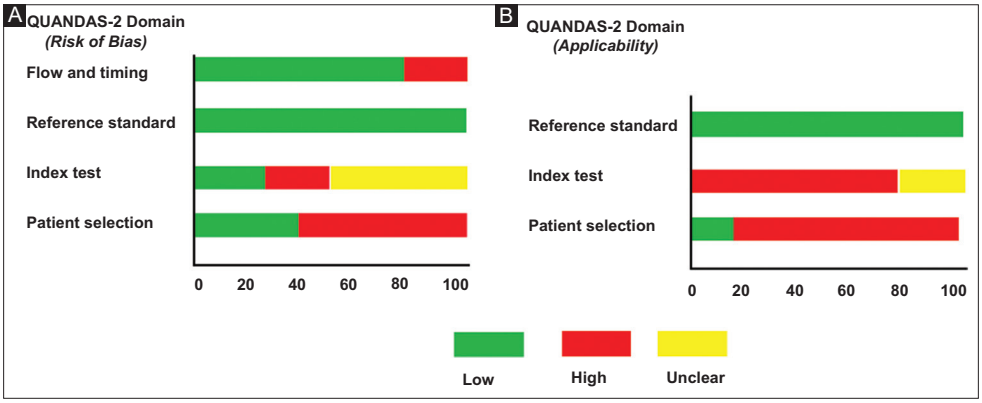
Supplementary material



Supplementary Figure 1 (A) Proportion of studies (%) with low, high or unclear risk of bias. (B) Proportion of studies (%) with low, high or unclear concerns regarding applicability