

Review Article

Efficacy of magnifying endoscopy combined with narrowband imaging in detection of early gastric cancer: a systematic evaluation and meta-analysis

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Abstract: Objective: To systematically evaluate the diagnostic accuracy of magnifying endoscopy combined with narrowband imaging (ME-NBI) in detecting early gastric cancer (EGC) and to provide a scientific basis for its clinical utility. Methods: Literature published before May 2024 that utilized ME-NBI for diagnosing EGC was searched across PubMed, EMBASE, The Cochrane Library, Web of Science, and major Chinese databases. Included studies were cohort studies or randomized controlled trials, and their quality was assessed using the QUADAS-2 framework. Meta-analysis was conducted using Stata 17 software to calculate diagnostic indicators such as sensitivity, specificity, and area under the curve (AUC). Heterogeneity was explored through Spearman's correlation coefficient, I^2 statistics, subgroup analysis, and meta-regression analysis. Publication bias was assessed with Deeks' funnel plot. Results: Twenty studies involving 7,770 patients and 7,917 lesions were included. The pooled sensitivity of ME-NBI for diagnosing EGC was 0.86 (95% CI: 0.80-0.90), specificity was 0.92 (95% CI: 0.86-0.96), and the AUC was 0.94 (95% CI: 0.91-0.96), demonstrating high diagnostic accuracy. Subgroup analysis revealed lower sensitivity in multi-center studies. Excised samples had similar sensitivity to biopsy samples but differed in specificity. Publication bias was detected ($P=0.01$), but sensitivity analysis corrected for this, maintaining high combined sensitivity, specificity, and AUC. Conclusion: ME-NBI is a highly accurate and reliable diagnostic tool for EGC. Despite have some bias and heterogeneity, this was effectively addressed through sensitivity and subgroup analyses. ME-NBI should be considered a preferred method for EGC screening and diagnosis in clinical practice.

Keywords: Magnifying endoscopy, early gastric cancer, sensitivity and specificity, diagnostic performance, meta-analysis

Introduction

Gastric cancer is the fifth most common cancer globally and one of the top four causes of cancer-related deaths, accounting for 7.7% of all cancer fatalities. The 5-year survival rate for gastric cancer is approximately 30% [1]. Early gastric cancer (EGC) refers to tumors confined to the mucosa and submucosa, with a significantly higher 5-year survival rate of around 90% compared to advanced gastric cancer [2]. Therefore, early diagnosis and treatment are essential for improving patient outcomes. However, detecting EGC is challenging, as it often presents without obvious symptoms, leading to diagnosis at more advanced stages when distant metastasis may already be present.

Digestive endoscopy is the gold standard for diagnosing EGC. Endoscopic techniques are widely used in diagnosing and treating gastrointestinal cancers. Magnifying endoscopy, which incorporates a zoom lens into standard endoscopy, magnifies the histological image of the gastrointestinal tract, revealing changes in the mucosal microstructure and even allowing cytological observation [3]. Narrowband imaging (NBI) is an emerging endoscopic technology that enhances the visualization of microvessels and microstructures within different layers of the gastrointestinal mucosa, aiding in the detection of early cancers and precancerous lesions and enabling precise biopsies [4].

In order to improve the identification of early gastrointestinal cancers, magnifying endosco-

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py combined with narrow band imaging (ME-NBI) has been developed. ME-NBI enhances the morphological details of the mucosal surface, allowing clear observation of gland duct openings and the microvascular structure [5]. Studies [6-8] have demonstrated that ME-NBI offers significant advantages over traditional endoscopy in detecting early cancer, delineating its extent, and identifying tissue types in the upper digestive tract. It has become the preferred tool for diagnosing early gastrointestinal cancers. This study systematically evaluates the diagnostic value of ME-NBI in detecting EGC to guide its clinical application.

Data and methods

PROSPERO registration

This study has been registered in PROSPERO (registration number: CRD42024571695).

Literature inclusion and exclusion criteria

Inclusion criteria: Cohort studies or randomized controlled trials. Studies using ME-NBI for diagnosis of EGC, with pathological histological examination as the gold standard. Studies providing data or allowing calculation of true positives, false positives, false negatives, and true negatives.

Exclusion criteria: Non-English and non-Chinese literature, and duplicate publications. Reviews, conference abstracts, case reports, experience summaries, animal studies, etc. Studies from which useful data cannot be extracted or for which the full text was unavailable.

Literature search

A comprehensive search was conducted using both subject and free terms across PubMed, EMBASE, The Cochrane Library, Web of Science, and major Chinese databases (Wanfang, China Science and Technology Journal Database). The search focused on studies published up to May 2024 that investigated the diagnosis of gastric cancer using ME-NBI.

Search terms: English: magnifying endoscopy, narrow band imaging, early gastric cancer, gastric neoplasia, endoscopic diagnosis. Chinese: magnifying endoscopy, narrow band imaging,

early gastric cancer, gastric tumor, endoscopic diagnosis.

Search strategies: PubMed: (("Endoscopy, Digestive System"[Mesh] OR "Endoscopy, Gastrointestinal"[Mesh]) AND "Narrow Band Imaging"[Mesh]) AND ("Stomach Neoplasms"[Mesh] OR "gastric cancer" OR "gastric carcinoma" OR "gastric tumor").

Embase: ('stomach tumor'/exp/mj OR 'gastric mass (tumor)' OR 'gastric masses (tumor)' OR 'gastric neoplasia' OR 'gastric neoplasm' OR 'gastric subepithelial tumor' OR 'gastric tumor' OR 'gastric tumorigenesis' OR 'gastric tumour' OR 'mucosa tumor, stomach' OR 'mucosa tumour, stomach' OR 'neoplasia of the stomach' OR 'neoplasm of the stomach' OR 'neoplasms of the stomach' OR 'neoplastic gastric' OR 'neoplastic stomach' OR 'stomach mucosa tumor' OR 'stomach mucosa tumour' OR 'stomach neoplasia' OR 'stomach neoplasm' OR 'stomach neoplasms' OR 'stomach tumor' OR 'stomach tumorigenesis' OR 'stomach tumour' OR 'stomach ulcerated tumor' OR 'stomach ulcerated tumour' OR 'stomach ulcerating tumor' OR 'stomach ulcerating tumour' OR 'tumor of the gastric' OR 'tumor of the stomach' OR 'tumor, stomach mucosa' OR 'tumour of the gastric' OR 'tumour of the stomach' OR 'tumour, stomach mucosa') AND ('narrow band imaging'/exp/mj OR 'nbi (narrow band imaging)' OR 'narrow band imaging' OR 'narrowband imaging') AND ('magnifying endoscopy'/exp/mj OR 'magnification endoscopy' OR 'magnifying endoscopy') AND ('sensitivity and specificity'/exp/mj OR 'sensitivity and specificity' OR 'specificity and sensitivity').

The Cochrane Library: #1. MeSH descriptor: [Stomach Neoplasms] explode all trees; #2. MeSH descriptor: [Endoscopy, Gastrointestinal] explode all trees; #3. MeSH descriptor: [Endoscopy, Digestive System] explode all trees; #4. MeSH descriptor: [Narrow Band Imaging] explode all trees; #5. (gastric cancer):ti,ab,kw (Word variations have been searched); #6. (gastric carcinoma):ti,ab,kw (Word variations have been searched); #7. (gastric tumor):ti,ab,kw (Word variations have been searched); #8. (magnifying endoscopy):ti,ab,kw (Word variations have been searched); #9. #1 OR #5 OR #6 OR #7; #10. #2 OR #3; #11. #4 OR #8; #12. #9 AND #10; #13. #12 AND #11.

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Web of Science: TS= (Endoscopy) AND TS= (Narrow Band Imaging) AND (TS= (Stomach Neoplasms) OR TS= (gastric cancer) OR TS= (gastric carcinoma) OR TS= (gastric tumor)).

Literature screening and data extraction

Two physicians (Hong-Mei Zhu, Shi-Yi Wang) independently screened the literature, extracted the data, and cross-checked it. Any disagreements were resolved by a third physician or through group discussion. Data extracted from each study included: first author's name, year of publication, country/region, study type, multicenter status, endoscopic equipment used, real-time diagnosis, specimen collection method, number of endoscopists, number of patients, number of lesions, and number of cancerous lesions.

Quality evaluation of included studies

Two physicians (Hong-Mei Zhu, Shi-Yi Wang) assessed the quality of the included studies using the QUADAS-2 assessment framework. Disagreements were resolved by a third physician or group discussion. The evaluation framework covered four key areas: patient selection, indicator testing, reference standards, and process and timing. The first three areas are particularly important for clinical applicability. Each section was rated for risk of bias as high, low, or unclear.

Statistical analysis

Statistical analysis was conducted using Stata 17 software. Diagnostic outcomes were classified as true positive (TP), false positive (FP), false negative (FN) and true negative (TN). Combined diagnostic indicators calculated included diagnostic odds ratio (DOR), sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and area under the receiver operating characteristic curve (AUC). Sensitivity was defined as the proportion of true positive cases among all positive cases (TP + FN), and specificity as the proportion of true negative cases among all negative cases (TN + FP). True positive cases refer to correctly diagnosed EGC, false negatives to actual EGC not diagnosed, true negatives to correctly diagnosed non-cancerous cases, and false positives to non-cancerous cases misdiagnosed as EGC.

Spearman's correlation coefficient was used to detect a threshold effect, while I^2 statistics quantified heterogeneity between studies. Significant heterogeneity was indicated by I^2 values $\geq 50\%$. A fixed-effect model was used in the absence of heterogeneity, while a random-effects model was applied in the presence of significant heterogeneity. Sources of heterogeneity were explored through subgroup analysis and meta-regression analysis. Publication bias was assessed using Deeks' funnel plot, and if detected, sensitivity analysis was performed to explore potential causes. A p -value < 0.05 was considered statistically significant.

Results

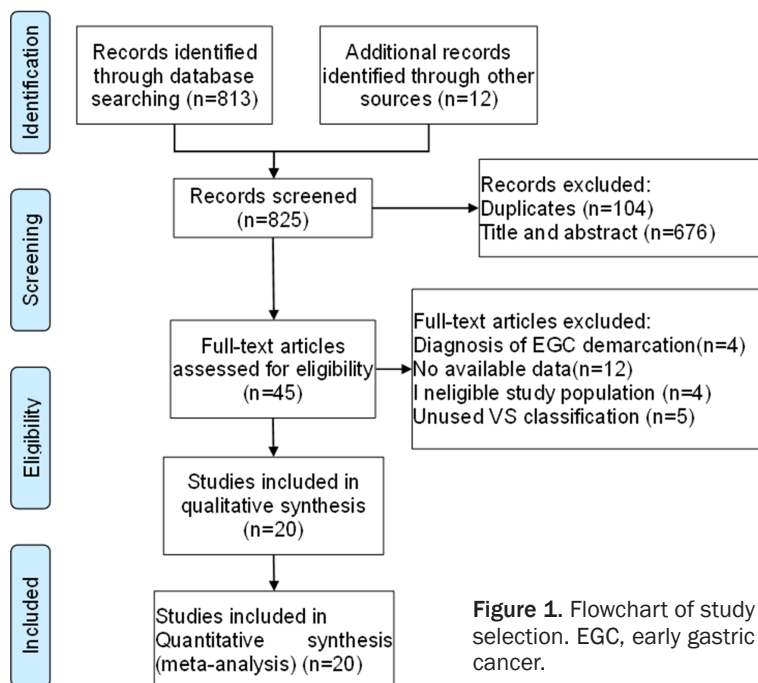
Screening results and quality evaluation

A total of 813 articles were identified through database searches. After removing duplicates using NoteExpress and excluding irrelevant articles by reviewing titles and abstracts, 20 articles were retained for full-text analysis, including 12 retrospective and 8 prospective studies. These studies encompassed 7,770 patients and 7,917 lesions. Basic characteristics of the included studies, such as author, publication year, country/region, study type, multicenter status, endoscopic equipment, real-time diagnosis, specimen collection, number of endoscopists, patients, lesions, and cancerous lesions (**Figure 1**), are summarized in **Table 1**. Risk of bias and clinical applicability were assessed, with results presented in **Table 2**.

Meta-analysis results

Overall diagnostic efficacy: Twenty studies involving 1,129 positive and 6,788 negative cases were included. Sensitivity variation across studies (ICC SEN) was estimated at 0.15 (95% CI: 0.03-0.27), and specificity variation (ICC SPE) was 0.39 (95% CI: 0.23-0.55), indicating some variability across studies. However, heterogeneity analysis (LRT Q and LRT I^2) showed that between-study heterogeneity was not due to threshold effects (only 1%). The PLR was 10.9 (95% CI: 5.9-20.1), indicating a significantly increased likelihood of disease when the test was positive. The NLR was 0.16 (95% CI: 0.11-0.22), suggesting a high probability of absence of disease when the test was nega-

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ticenter studies showed lower sensitivity (0.73, 95% CI: 0.57-0.88). Resection samples had sensitivities of 0.86 (95% CI: 0.77-0.94) and 0.86 (95% CI: 0.80-0.92). However, regression analysis revealed a statistically significant difference in sensitivity between these groups ($P=0.01$). Additionally, specificity was lower in resection samples (0.74, 95% CI: 0.58-0.90) compared to biopsy samples (0.96, 95% CI: 0.94-0.98), with this difference being statistically significant ($P<0.05$). For other subgroup comparisons, numerical differences were observed, but they were not statistically significant ($P>0.05$).

tive. As shown in **Figure 2**, the pooled sensitivity was 0.86 (95% CI: 0.80-0.90) and specificity was 0.92 (95% CI: 0.86-0.96).

The area under the curve (AUC) was 0.94 (95% CI: 0.91-0.96) (**Figure 3**), and the combined DOR was 69.9 (95% CI: 33-147).

Results of the regression analysis

Subgroup analysis assessed the impact of various parameters on diagnostic performance. The LRT Chi^2 values, p -values, and I^2 heterogeneity for multicenter studies, prospective studies, real-time diagnosis, resection, lesion size (>20 mm), and number of lesions (>400) are summarized (**Table 3**). The LRT Chi^2 value for multicenter studies was 5.49 ($P=0.06$), with moderate heterogeneity ($I^2=64\%$, 95% CI: 18%-100%). For prospective studies, the LRT Chi^2 value was 4.56 ($P=0.10$), with significant heterogeneity ($I^2=56\%$). Real-time assessment showed low heterogeneity ($I^2=0\%$). The heterogeneity for resection specimens was highly significant (LRT $\text{Chi}^2=12.19$, $P<0.01$, $I^2=84\%$, 95% CI: 65%-100%). Studies with lesions >20 mm showed lower heterogeneity ($I^2=36\%$), while studies with lesions >400 exhibited higher heterogeneity (LRT $\text{Chi}^2=7.78$, $P=0.02$, $I^2=74\%$, 95% CI: 43%-100%).

The sensitivity and specificity from the subgroup analysis are shown in **Figure 4**. Mul-

Figure 5A shows the publication bias in studies using ME-NBI to diagnose EGC ($P=0.01$). Sensitivity analysis indicated that excluding the work by Yu et al. [17] eliminated publication bias ($P=0.37$, **Figure 5B**). After excluding this study, the pooled sensitivity was 0.86 (95% CI: 0.79-0.90), specificity was 0.91 (95% CI: 0.84-0.95), AUC was 0.94 (95% CI: 0.91-0.95), and DOR was 63 (95% CI: 29-133).

Discussion

As an advanced endoscopic technique, ME-NBI aims to improve the diagnostic accuracy of early digestive tract cancers and has the potential to replace conventional endoscopic biopsy. This technique enables endoscopists to make more accurate diagnoses by providing clearer images of microvascular and microsurface structures. In the 20 included studies, ME-NBI demonstrated high diagnostic performance in diagnosing EGC, with a pooled sensitivity of 0.86 and specificity of 0.92, indicating high accuracy and a low rate of misdiagnosis.

There is expert consensus that in the NBI-ME mode, a final pathological upgrade should be considered if a lesion exhibits well-defined borders or surface microstructural abnormalities [29]. This underscores the potential of NBI-ME technology in identifying precancerous lesions and early cancers. A meta-analysis also showed

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Table 1. Characteristics of the included studies

Study	Country	Type	Multi-center	Endoscopy equipment	Real-time diagnosis	Specimen	No. of endoscopists	No. of patient	No. of lesions	No. of cancerous lesion
Umeda 2023 [9]	Japan	Retrospective	N	Olympus	Y	Resected	2	125	142	58
Yoo 2023 [10]	South Korea	Retrospective	Y	Olympus	Y	Resected	3	24	24	15
Tamura 2022 [11]	Japan	Retrospective	N	Olympus	N	Resected	14	100	100	50
Zhang 2021 [12]	China	Retrospective	N	NA	Y	Biopsied	2	837	882	79
Teng 2019 [13]	China	Retrospective	N	NA	Y	Biopsied	2	301	301	130
Dohi 2017 [14]	Japan	Prospective	N	Fujifilm	Y	Biopsied	4	530	127	32
Nonaka 2016 [15]	Japan	Retrospective	N	NA	N	Resected	3	91	100	79
Gong 2015 [16]	China	Prospective	N	Olympus	Y	Biopsied	1	82	86	40
Yu 2015 [17]	China	Prospective	Y	Olympus	N	Biopsied	4	3616	3675	257
Zheng 2015 [18]	China	Prospective	N	Olympus	Y	Biopsied	1	123	123	48
Fujiwara 2014 [19]	Japan	Retrospective	N	Olympus	N	Resected	2	99	103	32
Liu 2014 [20]	China	Prospective	N	Olympus	Y	Biopsied	2	90	207	15
Tao 2014 [21]	China	Retrospective	N	Olympus	N	Biopsied	4	508	643	24
Yamada 2014 [22]	Japan	Prospective	Y	Olympus	Y	Biopsied	31	362	353	20
Yao 2014 [23]	Japan	Prospective	Y	Olympus	Y	Biopsied	20	310	371	20
Maki 2013 [24]	Japan	Retrospective	N	Olympus	Y	Resected	2	93	93	61
Li 2012 [25]	China	Prospective	N	Olympus	Y	Resected/Biopsied	2	146	164	52
Zhang 2011 [26]	China	Retrospective	N	Olympus	Y	Biopsied	NA	122	122	48
Kato 2010 [27]	Japan	Prospective	N	Olympus	Y	Biopsied	NA	111	201	14
Kaise 2009 [28]	Japan	Retrospective	N	Olympus	Y	Biopsied	11	100	100	55

NA, Not available.

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Table 2. Quality assessment of studies using QUADAS-2

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standards	Flow and Timing	Patient Selection	Index Test	Reference Standards
Umeda 2023 [9]	Low	Low	Low	Low	Low	Low	Low
Yoo 2023 [10]	Low	Low	Low	Low	Low	Low	Low
Tamura 2022 [11]	Unclear	Low	Low	Unclear	Low	Low	Low
Zhang 2021 [12]	Low	Low	Low	Unclear	Low	Low	Low
Teng 2019 [13]	Low	Low	Low	Unclear	Low	Low	Low
Dohi 2017 [14]	Low	Low	Low	Low	Low	Low	Low
Nonaka 2016 [15]	Low	Low	Low	Low	Low	Low	Low
Gong 2015 [16]	Low	Low	Low	Low	Low	Low	Low
Yu 2015 [17]	Low	Low	Low	Low	Low	Low	Low
Zheng 2015 [18]	Low	Low	Low	Low	Low	Low	Low
Fujiwara 2014 [19]	Low	Low	Low	Unclear	Low	Low	Low
Liu 2014 [20]	Low	Low	Low	Low	Low	Low	Low
Tao 2014 [21]	Low	Low	Low	Unclear	Unclear	Low	Low
Yamada 2014 [22]	Low	Low	Low	Low	Low	Low	Low
Yao 2014 [23]	Low	Low	Low	Low	Low	Low	Low
Maki 2013 [24]	Low	Low	Low	Low	Low	Low	Low
Li 2012 [25]	Low	Low	Low	Unclear	Low	Low	Low
Zhang 2011 [26]	Unclear	Low	Low	Unclear	Unclear	Low	Low
Kato 2010 [27]	Low	Low	Low	Unclear	Low	Low	Low
Kaise 2009 [28]	Unclear	Low	Low	Unclear	Low	Low	Low

that ME-NBI has a higher diagnostic value for EGC than conventional white-light endoscopy (WLI), with higher accuracy for ME-NBI compared to M-WLI (OR of ME-NBI: 2.56, 95% CI: 2.13-3.13; OR of M-WLI: 1.43, 95% CI: 1.12-1.85) [30].

Tamura et al. [11] used C-WLI and C-WLI + M-NBI to diagnose 100 cases of adenoma or cancer based on size (<20 mm), shape (depressed or non-depressed), and color (red or non-red). They found that the sensitivity for cancer diagnosis was significantly higher with C-WLI + M-NBI compared to C-WLI alone (79.9% vs. 71.6%), as was the negative predictive value (65.2% vs. 60.1%), although specificity, accuracy, and positive predictive values did not differ significantly.

Yao et al. [3] developed a VS classification system to diagnose gastric cancer by observing microvessels and microsurface morphology in NBI-ME mode, demonstrating the superiority of NBI-ME in distinguishing cancer from non-cancerous lesions in multiple studies. Additionally, Doyama et al. [31] described white spherical lesions <1 mm in diameter, known as white

globe appearance (WGA), which are present below the intraepithelial microvessels. WGA reflects intraglandular necrotic debris, indicative of glandular structures. It is present in differentiated gastric cancers but not in undifferentiated EGC, with a prevalence of 20% in EGC, 0% in low-grade adenomas, and 2.5% in non-cancerous lesions. Thus, WGA can help distinguish differentiated gastric cancer from non-cancerous lesions such as low-grade adenomas and gastritis.

However, diagnosing endoscopic EGC requires extensive experience and clinical practice, which many endoscopists currently lack.

Subgroup analysis showed that sensitivity in multicenter studies was slightly lower than in single-center studies, possibly due to differences in operational techniques and patient populations. Variations in expertise among researchers at different centers can lead to inconsistencies in data collection, processing, and interpretation, affecting sensitivity. Additionally, the patient population in multicenter studies may be more diverse, with variations in age, gender, and disease severity. Coordinating

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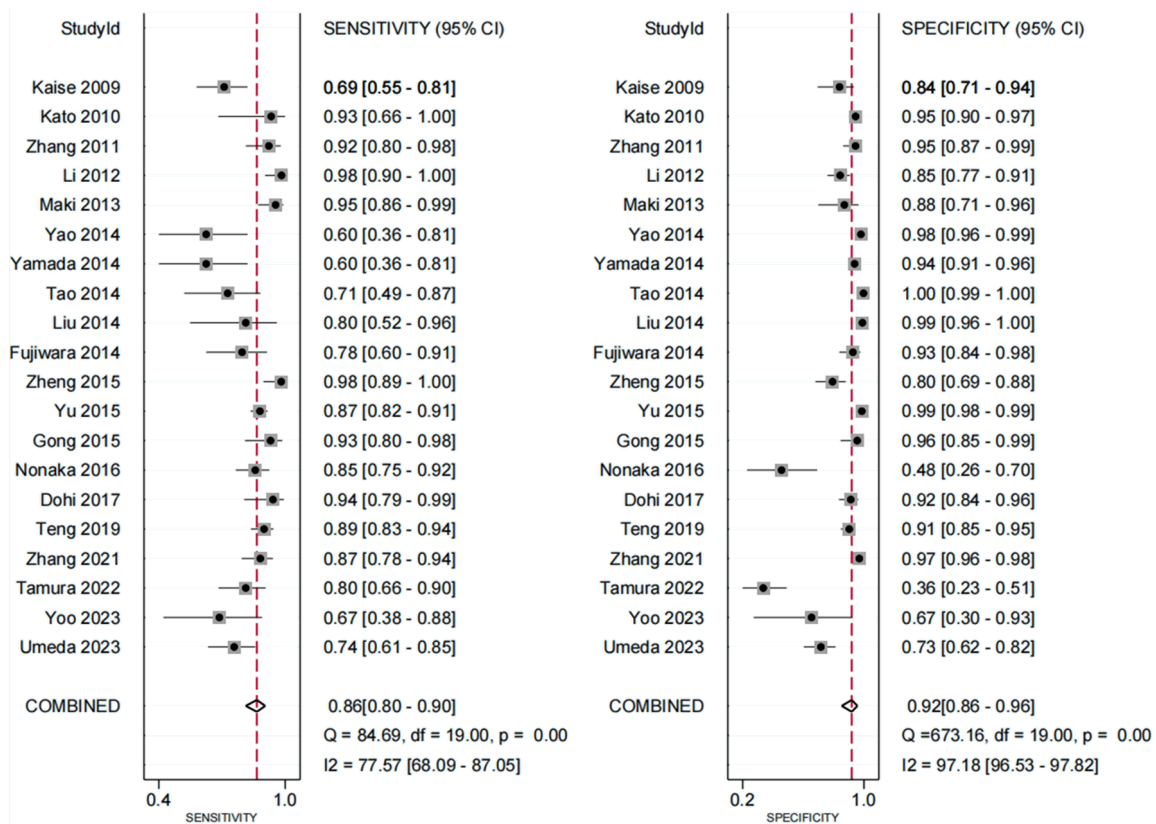


Figure 2. Forest plot of sensitivity and specificity in the diagnosis of early gastric cancer by ME-NBI. ME-NBI, magnifying endoscopy combined with narrowband imaging.

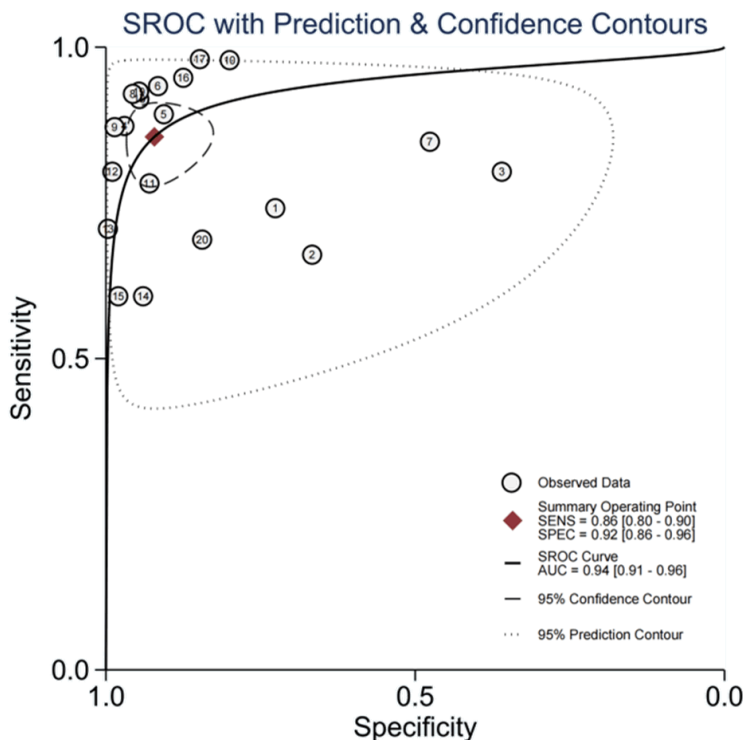


Figure 3. Summary receiver operator characteristic (SROC) curve in the diagnosis of early gastric cancer by ME-NBI. SENS = sensitivity, SPEC = specificity, AUC = area under the receiver operating characteristic curve. Numbers 1 to 20 represent the study arms (Umeda 2023, Yoo 2023, Tamura 2022, Zhang 2021, Teng 2019, Dohi 2017, Nonaka 2016, Gong 2015, Yu 2015, Zheng 2015, Fujiwara 2014, Liu 2014, Tao 2014, Yamada 2014, Yao 2014, Maki 2013, Li 2012, Zhang 2011, Kato 2010 and Kaise 2009). ME-NBI, magnifying endoscopy combined with narrowband imaging.

research resources and processes across multiple centers introduces more variables and uncertainties, reducing the stability of the results. Enhancing standardization in study design and management is crucial to

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Table 3. Subgroup analysis of the diagnostic accuracy of ME-NBI in identifying cancerous and noncancerous gastric lesions

Parameter	No. of studies	LRTChi2	P	I ² % (95% CI)	
Center	Multi	4	5.49	0.06	64 (18-100)
	Single	16			
Type	Prospective	9	4.56	0.1	56 (1-100)
	Retrospective	11			
Assessment	Real-time	15	0.89	0.64	0 (0-100)
	Post-procedure	5			
Specimen	Resected	7	12.19	<0.001	84 (65-100)
	Biopsied	13			
Lesion size	>20 mm	4	3.13	0.21	36 (0-100)
	≤20 mm	16			
Number of lesions	>400	3	7.78	0.02	74 (43-100)
	≤400	17			

CI, confidence interval; ME-NBI, magnifying endoscopy combined with narrowband imaging.

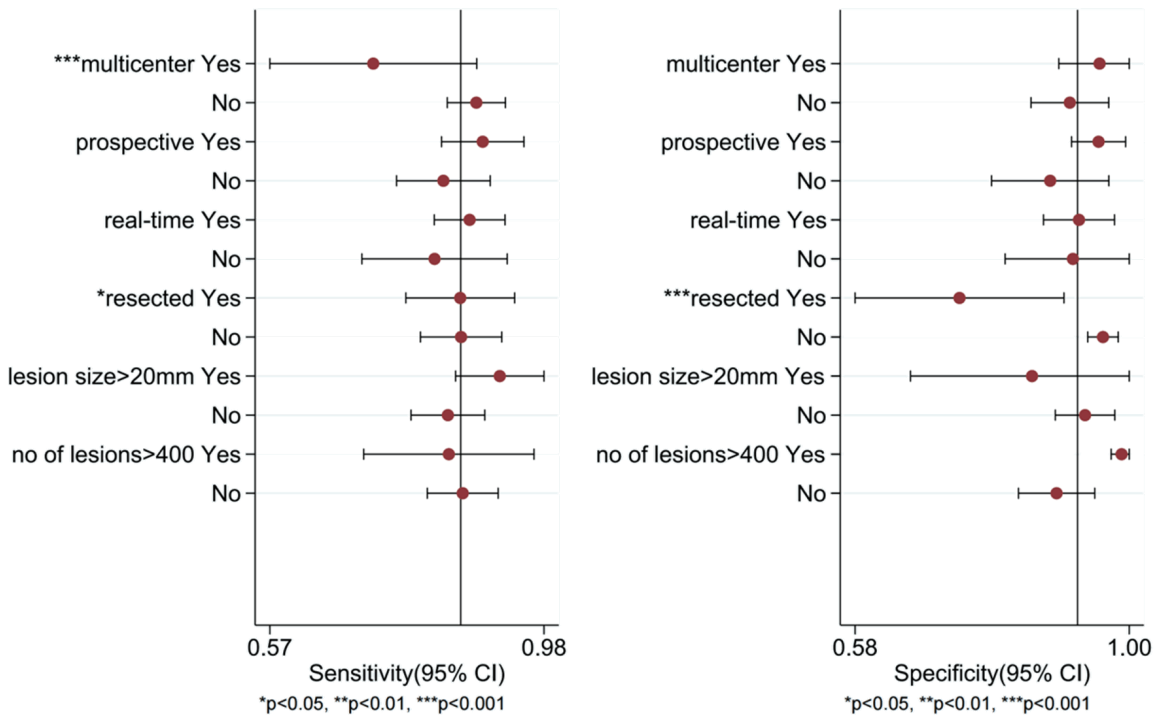


Figure 4. Meta regression and forest plot displaying the sensitivity and specificity in early gastric cancer subgroups.

minimize the impact of these differences. Moreover, the similarity in sensitivity between resection and biopsy samples indicates that ME-NBI maintains a high detection rate across different sample types. However, the lower specificity of resection samples suggests the possible influence of non-specific lesions or pathological changes [32]. The Deeks funnel plot indicated potential publication bias, which

was significantly reduced after excluding specific studies in the sensitivity analysis. The large sample size in one study (over 3,000 cases) may have skewed the overall results.

The meta-analysis on the use of ME-NBI for diagnosing EGC, while promising, has limitations that could impact its findings and generalizability. Key issues include the heavy reli-

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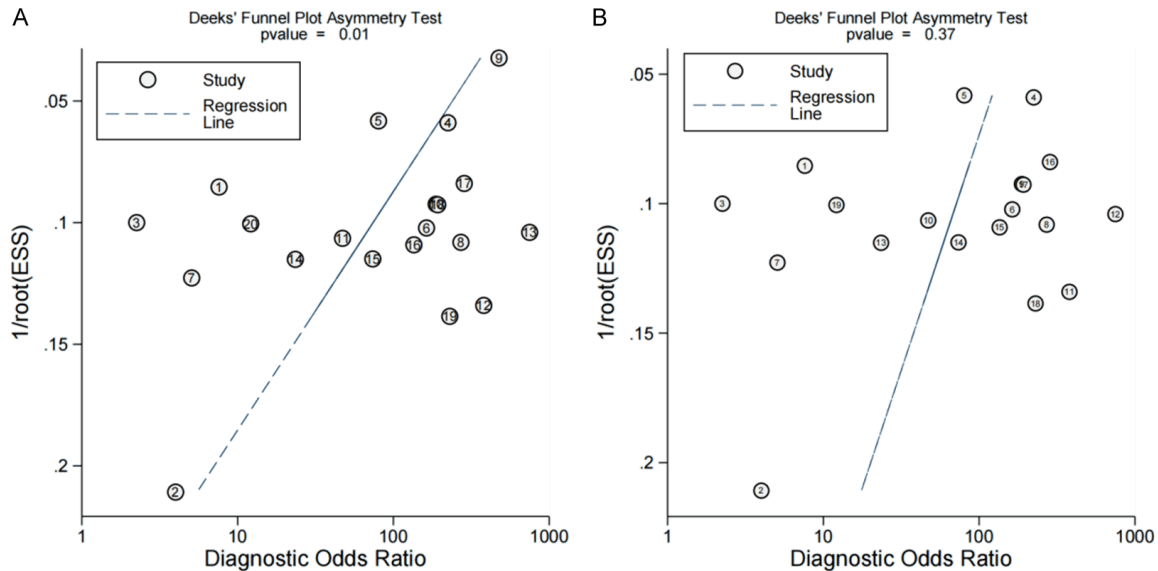


Figure 5. Funnel plot of publication bias for Deeks. A: The funnel plot indicates significant publication bias ($P=0.01$), suggesting potential bias in study results due to publication strategies. B: After sensitivity analysis, excluding the study by Yu et al., the funnel plot shows that publication bias is no longer significant ($P=0.37$)

ance on endoscopist expertise, variability in operational techniques across centers, and heterogeneity in patient populations in multi-center studies. These factors underscore the need for standardized study design and management to mitigate their effects. Additionally, potential publication bias was partially addressed through sensitivity analysis, but the large sample size in one study may have influenced the overall analysis. The low specificity of resection samples suggests possible misdiagnosis due to non-specific lesions or pathological changes. Subgroup analysis revealed slightly lower sensitivity in multicenter studies, and using WGA as a distinguishing feature has its limitations. These factors should be carefully considered when interpreting the results and assessing the applicability of ME-NBI in clinical settings.

In conclusion, white-light endoscopy detection of EGC is challenging and lacks clear endoscopic features. While many descriptions of ME-NBI in EGC diagnosis are useful and contribute to EGC detection, the sensitivity of ME-NBI has not significantly improved compared to conventional C-WLI. This indicates that relying solely on ME-NBI for diagnosis may be limited, and regular follow-up may be required for patients diagnosed with adenoma using ME-NBI.

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Disclosure of conflict of interest

None.

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