Performance of screening tests for esophageal squamous cell carcinoma: a systematic review and meta-analysis

Martin C. S. Wong, MD,[1,2,3,*] Yunyang Deng, MPhil,[1,*] Junjie Huang, PhD,[1,*] Yijun Bai, MPH,[1]
Harry H. X. Wang, PhD,[4,5] Jinqiu Yuan, PhD,[6] Lin Zhang, PhD,[2,7] Hon Chi Yip, MD,[8]
Philip Wai Yan Chiu, MD[8]

Hong Kong SAR, Beijing, Guangzhou, Guangdong, China; Scotland, United Kingdom; Melbourne, Victoria, Australia

Background and Aims: This systematic review and meta-analysis aims to compare the pooled diagnostic accuracy of the currently available esophageal squamous cell carcinoma (ESCC) screening tests.

Methods: A comprehensive literature search of Embase and Medline (up to October 31, 2020) was performed to identify eligible studies. We pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio for ESCC screening tools using a bivariate random-effects model. The summary receiver operating characteristic curves with area under the curve (AUC) were plotted for each screening test.

Results: We included 161 studies conducted in 81 research articles involving 32,209 subjects. The pooled sensitivity, specificity, and AUC of the major screening tools were respectively as follows: endoscopy (peroral endoscopy): .94 (95% confidence interval [CI], .87-.97), .92 (95% CI, .87-.95), and .97 (95% CI, .96-.99); endoscopy (transnasal endoscopy): .85 (95% CI, .70-.93), .96 (95% CI, .91-.98), and .97 (95% CI, .95-.98); microRNA: .77 (95% CI, .75-.80), .78 (95% CI, .75-.80), and .85 (95% CI, .81-.87); autoantibody: .45 (95% CI, .36-.53), .91 (95% CI, .89-.93), and .84 (95% CI, .81-.87); and cytology: .82 (95% CI, .60-.93), .97 (95% CI, .88-.99), and .97 (95% CI, .95-.98). There was high heterogeneity.

Conclusions: The diagnostic accuracy seemed to be comparable between cytology and endoscopy, whereas autoantibody and microRNAs bear potential as future noninvasive screening tools for ESCC. To reduce ESCC-related death in high-risk populations, it is important to develop a more accurate and less-invasive screening test. (Gastrointest Endosc 2022;96:197-207.)

Esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer deaths worldwide.[1] A recent global analysis showed an incidence increase in countries that span diverse geographic locations such as the Czech Republic, Spain, Norway, Japan, Thailand, the Netherlands, and Canada.[2] An increasing mortality rate was reported worldwide.[2] Esophageal cancer imposes a substantial global burden of disease with its aggressive nature and poor prognosis.[3] Most cases were diagnosed in Eastern Asia and developing nations.[4] The disability-adjusted life-years attributable to esophageal cancer has achieved an annual rate of .58 disability-adjusted life-years per 1000 people globally, where most cases (96.8%) were accounted for by years of life lost, indicating the importance of public health efforts on disease prevention and early detection.[5]

Among different esophageal cancer subtypes, esophageal squamous cell carcinoma (ESCC) initiates in the squamous cells that line the esophagus and is the most common, comprising more than 80% of all esophageal cancer cases; the other dominant pathologic subtype is esophageal adenocarcinoma, which arises from glandular cells present in the lower third of the esophagus, often where they have already transformed to intestinal cell type (Barrett's esophagus).[6] ESCC is more frequently diagnosed in Asia, East Africa, and South America, and its risk factors include tobacco smoking, alcohol drinking, and consumption of nitrogenous foods.[7] Notably, most esophageal cancers have developed distant metastasis when diagnosed, resulting in poor survival rates.[8] Early detection through screening and early diagnosis may play a significant role in improving clinical outcomes and informing cancer prevention strategies.[9] It is also important to detect high-grade dysplasia (HGD), which refers to precancerous changes in the cells of the esophagus and increases a person's risk for esophageal adenocarcinoma.[10]

Currently available ESCC screening methods are endoscopic screening tools, such as conventional white-light endoscopy, Lugol's chromoendoscopy, narrow-band imaging (NBI), endocytoscopy, and microendoscopy, and non-endoscopic screening tools, such as circulating microRNAs, blood autoantibodies, and esophageal cytology samples.[11] A cohort study examined the benefits of a 1-time screening EGD with Lugol's iodine stain followed by endoscopic eradication therapy if dysplasia was found. The study showed that the EGD screening group had lower cumulative incidences (4.17% vs 5.92%, $P < .001$) and overall mortality rates (3.35% vs 5.05%, $P < .001$) when compared with those with no screening.[12]

Although few guidelines have thus far recommended population-based screening for ESCC, expert opinions have highlighted the importance of ESCC screening in select high-risk patients.[13] Population-based ESCC screening for the general public is not currently recommended because endoscopic screening is expensive and inconvenient and no screening test has been shown to lower mortality in average-risk people.[14,15] One of the most important factors driving screening initiatives is the accuracy of existing screening tests.[16] However, evidence that synthesizes the performance of currently available screening tests for ESCC is absent. We aimed to conduct a systematic review and meta-analysis to examine the pooled diagnostic accuracy of the currently available screening tests.

METHODS

Search strategy

We performed a comprehensive literature search in Embase (from 1910 to October 31, 2020) and Medline (from 1946 to October 31, 2020) without any language limitation. The search strategies and number of articles identified at each stage are summarized in Supplementary Table 1 (available online at www.giejournal.org). The study was registered at the International Prospective Register of Systematic Reviews (PROSPERO) (registration no. CRD42021220586) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplementary Table 2, available online at www.giejournal.org).[17]

Inclusion and exclusion criteria

Inclusion criteria were studies that reported the use of screening tools for HGD and/or ESCC; included patients pathologically diagnosed with HGD and/or ESCC; and included rates of true positives, false positives, true negative, and false negatives so that 2 × 2 tables for deriving the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) could be obtained. We excluded studies that were reviews, meta-analyses, case reports, editorials, commentaries, or letter; reported duplicate data; presented esophageal cancer diagnoses without distinguishing between ESCC and esophageal adenocarcinoma; reported diagnoses of dysplasia without distinguishing between low-grade dysplasia and HGD; reported the progression of ESCC but not the diagnosis of ESCC; and assessed subjects with a prior history of ESCC.

Data extraction

Two independent reviewers extracted and cross-checked the information regarding first author's name; publication year; study design; study period; characteristics of participants; screening tools and category; specimen sites; criterion standard of the diagnosis; number of HGD and/or ESCC cases; number of healthy control subjects; rates of true positives, false positives, true negatives, and false negatives; and screening indexes (sensitivity, specificity, PLR, NLR, positive predictive value, negative predictive value, AUC, and cutoff values for positive

screening tests). If rates of true positives, false positives, true negatives, and false negatives were not available, these values were calculated based on the number of HGD and/or ESCC cases, healthy control subjects, sensitivity, and specificity. We also calculated the neoplasia detection rate (NDR), defined as the rate of HGD or ESCC detection during initial endoscopy in our study, for cross-sectional and cohort studies. We conducted an additional analysis on NDR between different screening options and areas.

Quality assessment

The quality of the included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies 2 tool,[18] which consists of 4 domains: patient selection, index test, reference standard, and flow and timing. The first 2 domains include questions about concerns about applicability, whereas the last domain assesssd the risk of bias. Bar charts were constructed to display findings from the quality assessment.

Statistical analyses

The estimates of diagnostic values (sensitivity, specificity, PLR, NLR, and DOR) and the corresponding 95% confidence intervals (CIs) were summarized according to the types of screening tools presented in forest plots. The heterogeneity of sensitivity and specificity was evaluated by the Q test and the I^2 statistic.[19] A $P < .10$ or $I^2 > 50\%$ were regarded as high heterogeneity, and random-effects models were used. We also constructed the summary receiver operating characteristic (sROC) curves of different screening tools and estimated the AUCs. Subgroup analyses, univariable meta-regression, and multivariable meta-regression were performed based on the main characteristics of the included studies to explore the potential sources of the heterogeneity. Deeks' funnel plots were used to test publication bias of all included studies and each ESCC screening tool.[20] We performed sensitivity analyses according to the goodness-of-fit, bivariate normality, influence analysis, and outlier detection. STATA 12.0 (StataCorp, College Station, Tex, USA) was used for all statistical analyses, and a 2-sided $P < .05$ was regarded as statistically significant.

RESULTS

Study selection

The literature search identified 1440 articles. Of these, we excluded 390 articles for removing duplicates and 747 that which were irrelevant to the topic of this study after the title and abstract screening. Three hundred three articles were included in the full-text screening, of which 222 articles were excluded. Finally, we included 161 studies conducted in 81 research articles (Supplementary Fig. 1 and Supplementary Tables 3 and 4, available online at www.giejournal.org).

Study characteristics and quality assessment

The main characteristics of all included studies are summarized in Supplementary Table 3. The 161 included studies (81 articles, n = 32,209) consisted of case-control (n = 127), cohort (n = 2), and cross-sectional (n = 32) studies. The studies were conducted in the Americas (Brazil), Asia (China and Japan), Europe (Switzerland and France), and the Middle East (Israel and Iran). Studies were published from 1997 to 2020 and were performed between 1995 and 2018. Among the included articles, 27 studies (n = 4159) used endoscopy as the screening tool for ESCC, 69 studies (n = 11,457) used microRNA, 55 studies (n = 12,459) used autoantibody, and 10 studies (n = 4134) used cytology.

Of the 27 studies that evaluated endoscopy, 19 studies were conducted using peroral endoscopy (POE) and 8 studies using transnasal endoscopy (TNE). The endoscopy screening methods were Lugol's iodine chromoendoscopy (LCE), white-light imaging (WLI) endoscopy, narrow-band imaging (NBI), endocytoscope, esophageal capsule endoscopy, probe-based confocal laser endomicroscopy, high-resolution microendoscopy, autofluorescence imaging video-endoscopy system, and flexible spectral imaging color enhancement. Of the 69 studies on microRNA, 57 studies detected single microRNA and 12 studies measured multiple microRNA panels or the ratio of microRNA. Fifty-one studies collected serum specimens and 18 collected plasma specimens. Quantitative, real-time, reverse transcription polymerase chain reaction was used to measure microRNA in 68 of 69 studies, whereas 1 study was based on next-generation sequencer. Of the 55 studies on autoantibody, 43 were serum-based and 12 were plasma-based.

The results of quality assessments (Quality Assessment of Diagnostic Accuracy Studies 2) are shown in bar charts (Supplementary Fig. 2, available online at www.giejournal.org). An average of 56.2% of studies were suggested to have a low risk of bias and an average of 87.4% of studies to have low levels of concern regarding applicability.

Diagnostic accuracy of the screening tests

Forest plots of the sensitivity and specificity of ESCC screening tools are shown in Figures 1 to 5. The pooled sensitivity, specificity, PLR, NLR, and DOR were respectively as follows: POE endoscopy: .94 (95% CI, .87-.97), .92 (95% CI, .87-.95), 11.7 (95% CI, 7.3-18.8), .07 (95% CI, .03-.15), and 168 (95% CI, 75-377); TNE endoscopy: .85 (95% CI, .70-.93), .96 (95% CI, .91-.98), 21.4 (95% CI, 9.6-47.7), .15 (95% CI, .07-.33), and 139 (95% CI, 44-437); microRNA: .77 (95% CI, .75-.80), .78 (95% CI, .75-.80), 3.5 (95% CI, 3.1-4.0), .29 (95% CI, .26-.32), and 12 (95% CI, 10-15); autoantibody: .45 (95% CI, .36-.53), .91 (95% CI, .89-.93), 5.1 (95% CI, 4.6-5), .61 (95% CI, .53-.70), and 8 (95% CI, 6-12); and cytology: .82 (95% CI, .60-.93), .97 (95% CI, .88-.99), 29.7 (95% CI, 7.4-119.6), .19 (95% CI, .08-.45), and 160 (95% CI, 42-610) (Table 1).
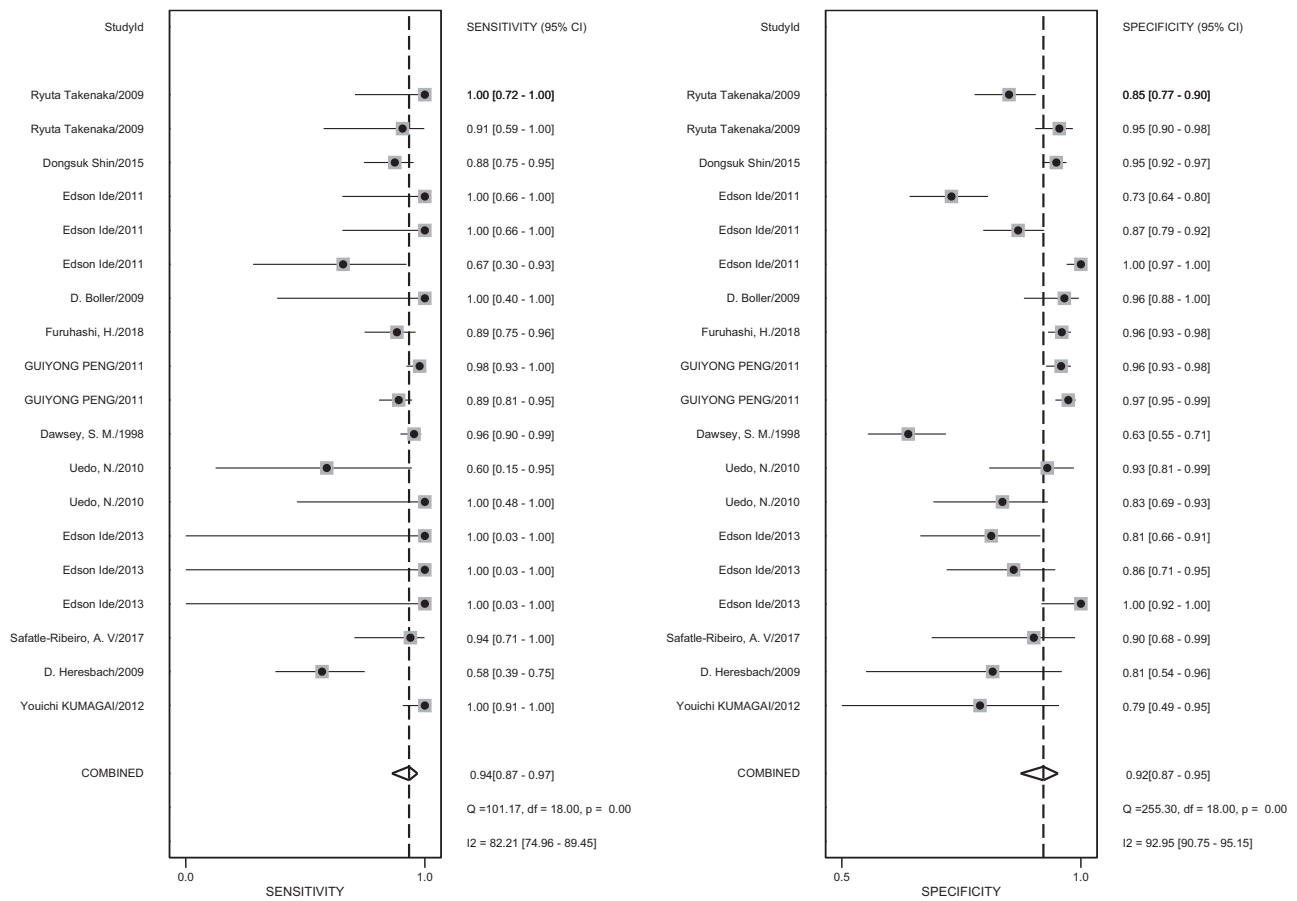
StudyId	SENSITIVITY (95% CI)
Ryuta Takenaka/2009	1.00 [0.72 - 1.00]
Ryuta Takenaka/2009	0.91 [0.59 - 1.00]
Dongsuk Shin/2015	0.88 [0.75 - 0.95]
Edson Ide/2011	1.00 [0.66 - 1.00]
Edson Ide/2011	1.00 [0.66 - 1.00]
Edson Ide/2011	0.67 [0.30 - 0.93]
D. Boller/2009	1.00 [0.40 - 1.00]
Furuhashi, H./2018	0.89 [0.75 - 0.96]
GUIYONG PENG/2011	0.98 [0.93 - 1.00]
GUIYONG PENG/2011	0.89 [0.81 - 0.95]
Dawsey, S. M./1998	0.96 [0.90 - 0.99]
Uedo, N./2010	0.60 [0.15 - 0.95]
Uedo, N./2010	1.00 [0.48 - 1.00]
Edson Ide/2013	1.00 [0.03 - 1.00]
Edson Ide/2013	1.00 [0.03 - 1.00]
Edson Ide/2013	1.00 [0.03 - 1.00]
Safatle-Ribeiro, A. V/2017	0.94 [0.71 - 1.00]
D. Heresbach/2009	0.58 [0.39 - 0.75]
Youichi KUMAGAI/2012	1.00 [0.91 - 1.00]
COMBINED	0.94 [0.87 - 0.97]

Q =101.17, df = 18.00, p = 0.00

I2 = 82.21 [74.96 - 89.45]

Studyld	SPECIFICITY (95% CI)
Ryuta Takenaka/2009	0.85 [0.77 - 0.90]
Ryuta Takenaka/2009	0.95 [0.90 - 0.98]
Dongsuk Shin/2015	0.95 [0.92 - 0.97]
Edson Ide/2011	0.73 [0.64 - 0.80]
Edson Ide/2011	0.87 [0.79 - 0.92]
Edson Ide/2011	1.00 [0.97 - 1.00]
D. Boller/2009	0.96 [0.88 - 1.00]
Furuhashi, H./2018	0.96 [0.93 - 0.98]
GUIYONG PENG/2011	0.96 [0.93 - 0.98]
GUIYONG PENG/2011	0.97 [0.95 - 0.99]
Dawsey, S. M./1998	0.63 [0.55 - 0.71]
Uedo, N./2010	0.93 [0.81 - 0.99]
Uedo, N./2010	0.83 [0.69 - 0.93]
Edson Ide/2013	0.81 [0.66 - 0.91]
Edson Ide/2013	0.86 [0.71 - 0.95]
Edson Ide/2013	1.00 [0.92 - 1.00]
Safatle-Ribeiro, A. V/2017	0.90 [0.68 - 0.99]
D. Heresbach/2009	0.81 [0.54 - 0.96]
Youichi KUMAGAI/2012	0.79 [0.49 - 0.95]
COMBINED	0.92 [0.87 - 0.95]

Q =255.30, df = 18.00, p = 0.00

I2 = 92.95 [90.75 - 95.15]

Figure 1. Forest plot of sensitivity and specificity for endoscopy (peroral endoscopy). *CI*, Confidence interval.

Supplementary Figures 3 to 7 (available online at www.giejournal.org) show the sROC curves and AUCs as .97 (95% CI, .96-99), .97 (95% CI, .95-.98), .85 (95% CI, .81-.87), .84 (95% CI, .81-.87), and .97 (95% CI, .95-.98) for POE endoscopy, TNE endoscopy, microRNA, autoantibody, and cytology, respectively.

Subgroup analyses and meta-regression

For the main subgroups of POE endoscopy, the sensitivity, specificity, PLR, NLR, DOR, and AUC were respectively as follows: LCE (POE): .96 (95% CI, .91-98), .89 (95% CI, .77-.95), 8.6 (95% CI, 4.0-18.5), .05 (95% CI, .02-.10), 180 (95% CI, 63-513), and .98 (95% CI, .96-.99); WLI (POE): .67 (95% CI, .38-.88), .99 (95% CI, .96-1.00), 32.4 (95% CI, 4.2-253.6), .37 (95% CI, .19-.70), 89 (95% CI, 10-777), and .59 (95% CI, .52-.66); and NBI (POE): .94 (95% CI, .73-.93), .93 (95% CI, .87-.96), 12.6 (95% CI, 7.2-22.2), .06 (95% CI, .01-.33), 205 (95% CI, 38-1113), and .98 (95% CI, .96-.99) (Table 1). For the main subgroups of TNE endoscopy, the sensitivity, specificity, PLR, NLR, DOR, and AUC were respectively as follows: LCE (TNE): .92 (95% CI, .81-.98), .89 (95% CI, .85-.92), 5.7 (95% CI, 1.7-19.0), .10 (95% CI, .04-

.26), and 57 (95% CI, 8-421) (AUC not available because of insufficient numbers); WLI (TNE): .59 (95% CI, .46-.71), .98 (95% CI, .96-.99), 23.4 (95% CI, 10.8-50.8), .42 (95% CI, .24-.76), 83 (95% CI, 14-495), and .99 (95% CI, .99-.99); and NBI (TNE): .86 (95% CI, .74-.94), .96 (95% CI, .93-.98), 20.6 (95% CI, 12.1-35.0), .14 (95% CI, .07-.29), and 144 (95% CI, 53-393) (AUC not available because of insufficient numbers) (Table 1).

The results of other POE endoscopy subgroups (endocytoscope, esophageal capsule endoscopy, probe-based confocal laser endomicroscopy, high-resolution microendoscopy, and autofluorescence imaging video-endoscopy system) and the TNE endoscopy subgroup (flexible spectral imaging color enhancement) can be found in Table 1. Several screening methods had no false negatives and had insufficient studies, so that the NLR, DOR, and AUC could not be calculated. For microRNA, the sensitivity, specificity, PLR, NLR, DOR, and AUC were .79 (95% CI, .76-.81), .78 (95% CI, .75-80), 3.5 (95% CI, 3.1-3.9), .28 (95% CI, .25-.31), 13 (95% CI, 10-15), and .85 (95% CI, .81-.88) for serum and .75 (95% CI, .68-.80), .80 (95% CI, .73-.85), 3.7 (95% CI, 2.6-5.3), .32 (95% CI, .24-.42), 12 (95% CI, 6-22), and .84 (95% CI, .80-.87) for
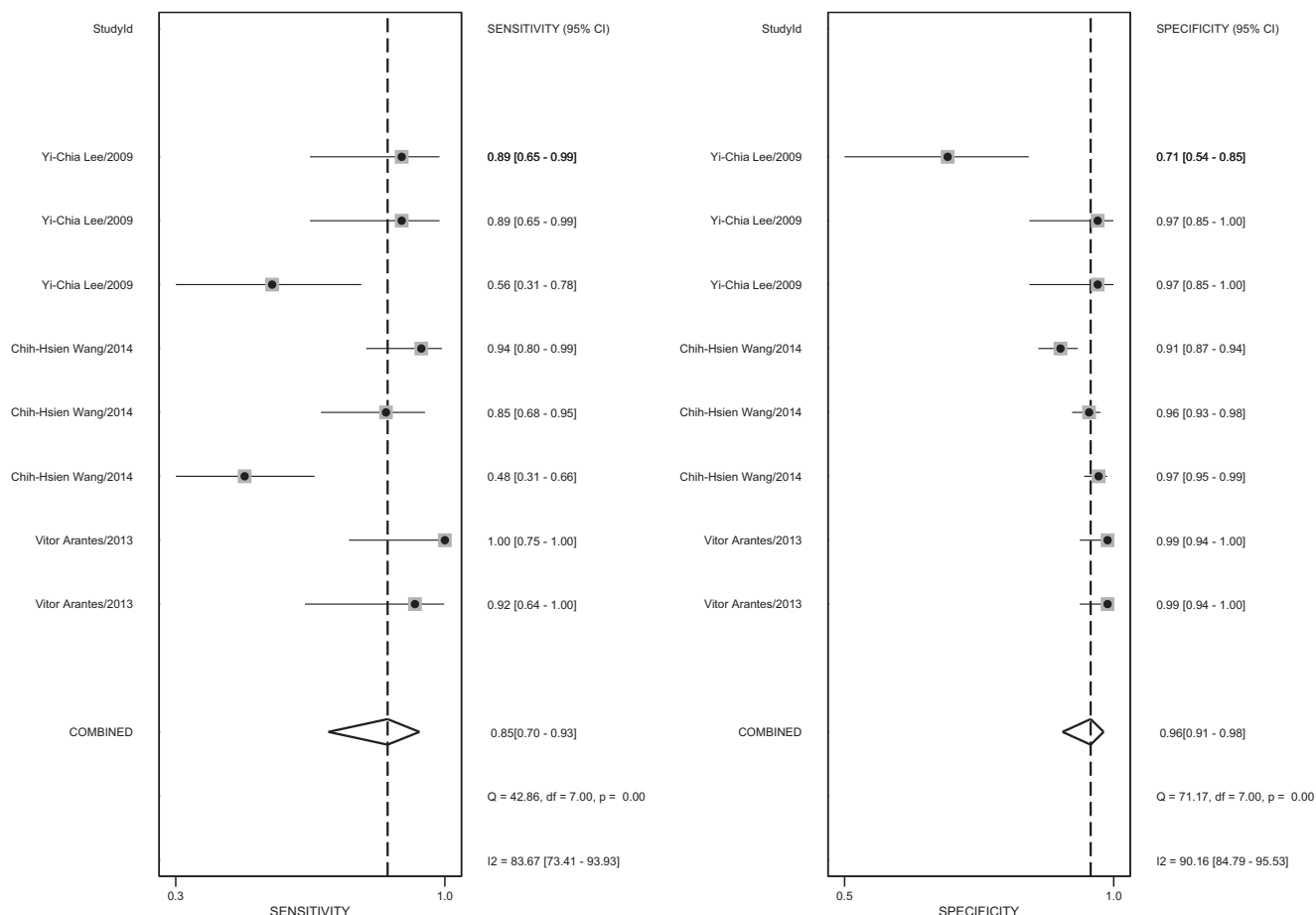
Figure 2. Forest plot of sensitivity and specificity for endoscopy (transnasal endoscopy). *CI,* Confidence interval.

plasma (Table 1). For autoantibody, the sensitivity, specificity, PLR, NLR, DOR, and AUC were .52 (95% CI, .43-.61), .92 (95% CI, .88-.94), 6.1 (95% CI, 4.5-8.2), .53 (95% CI, .44-.63), 12 (95% CI, 8-17), and .84 (95% CI, .81-.87) for serum and .22 (95% CI, .14-.33), .92 (95% CI, .90-.93), 2.6 (95% CI, 1.8-3.9), .85 (95% CI, .76-.95), 3 (95% CI, 2-5), and .89 (95% CI, .86-.91) for plasma (Table 1).

The results of the meta-regression showed that for POE endoscopy, the between-study heterogeneity was attributed to screening methods (WLI or not), countries (Israel or not), and participants' age. For TNE endoscopy, heterogeneity came from screening methods (WLI and LCE), countries (China or Brazil), and study periods (between 2010 and 2015 or not). For microRNA and autoantibody, the potential sources of heterogeneity were specimen origins (serum or plasma), countries (China or Japan), study periods (2005-2009, 2010-2014, or 2015-2019), and age. For cytology samples, they were countries (Brazil, China, Korea, or Switzerland), study periods (1995-1999, 2005-2009, 2010-2014, or 2015-2019), and age (Supplementary Figs. 8-12 and Supplementary Tables 5-9, available online at www.giejournal.org).

Publication bias

Deeks' funnel plot asymmetry test showed that *P* values of POE endoscopy, TNE endoscopy, microRNA, autoantibody, and cytology were .15, .41, .15, .05, and .62, respectively (Supplementary Figs. 13-17, available online at www.giejournal.org). Moreover, no publication bias was found for POE endoscopy subgroups (*P* values of LCE and NBI were .52 and .18, respectively), micro-RNA subgroups (*P* values of serum and plasma were .94 and .05, respectively), and autoantibody subgroups (*P* values of serum and plasma were .18 and .94, respectively) (Table 1).

Sensitivity analysis

Influence analyses and outlier detections identified 3, 1, 7, 4, and 0 outlier studies for POE endoscopy, TNE endoscopy, microRNA, autoantibody, and cytology, respectively (Supplementary Figs. 18-22, available online at www.giejournal.org). The pooled sensitivity, specificity, PLR, NLR, DOR, and AUC did not change significantly after excluding these outliers (Table 1, Supplementary Table 10, available online at www. giejournal.org).
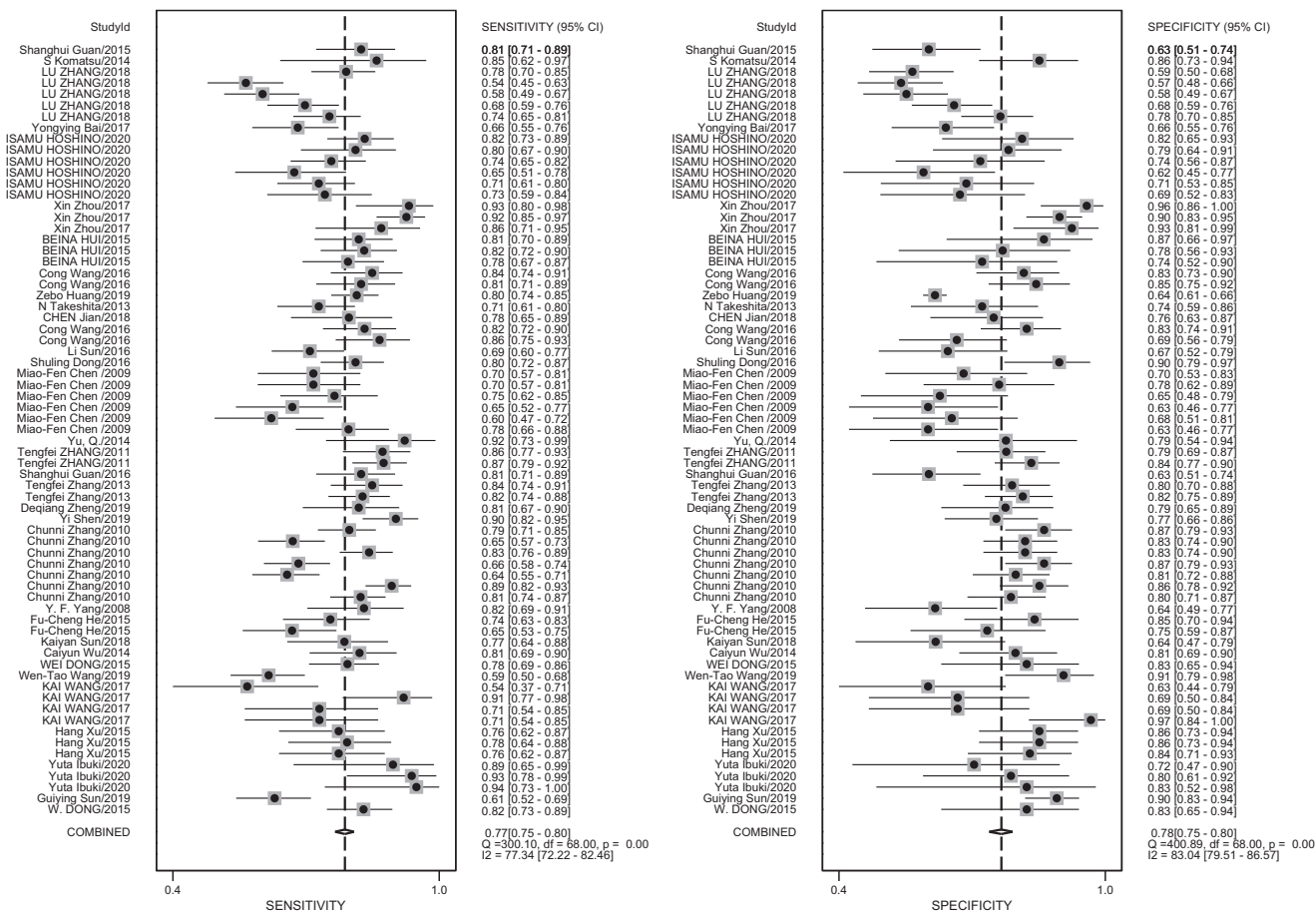
Figure 3. Forest plot of sensitivity and specificity for microRNA. *CI,* Confidence interval.

Neoplasia detection rate

Thirty-three cross-sectional or cohort studies were included in the calculation of NDR. Based on individual studies (Supplementary Table 11, available online at www.giejournal.org), the NDRs ranged from .5% to 63.6%. Based on screening methods (Supplementary Table 12, available online at www.giejournal.org), 18, 8, and 7 studies were included for POE endoscopy, TNE endoscopy, and cytology, respectively. The NDR was the highest for studies on cytology (40.2%), followed by POE endoscopy (24.5%) and TNE endoscopy (14.7%). Based on countries or regions (Supplementary Table 13, available online at www.giejournal.org), the NDR was the highest in studies from Israel (44.7%), followed by China (36.9%), Brazil (23.7%), Japan (15.7%), Switzerland (7.4%), and Iran (7.2%).

DISCUSSION

Summary of major findings

This systematic review and meta-analysis of 186 studies involving 35,793 subjects examined the accuracy of currently available screening tests for ESCC. For endoscopy, the diagnostic accuracy of image-enhanced endoscopy including LCE and NBI was higher than that of WLI endoscopy. The diagnostic accuracy of cytology seemed to be comparable with that of endoscopy and can be managed in primary care settings. Despite the findings that the diagnostic performance of autoantibody and microRNAs was not good overall, autoantibody and microRNA have potential as noninvasive screening tools for ESCC in certain population groups.

Explanations and comparison with existing literature

Effectiveness of screening ESCC for high-risk populations. The objective of screening for ESCC is to improve survival through curative treatment by detecting HGD and early-stage ESCC in asymptomatic individuals. Previous studies showed that ESCC endoscopic screening programs were effective in reducing mortality among populations at higher risk of ESCC. According to a 10-year follow-up study from China, a community-based chromoendoscopy screening program was associated with a 33% reduced risk of ESCC-related death among individuals
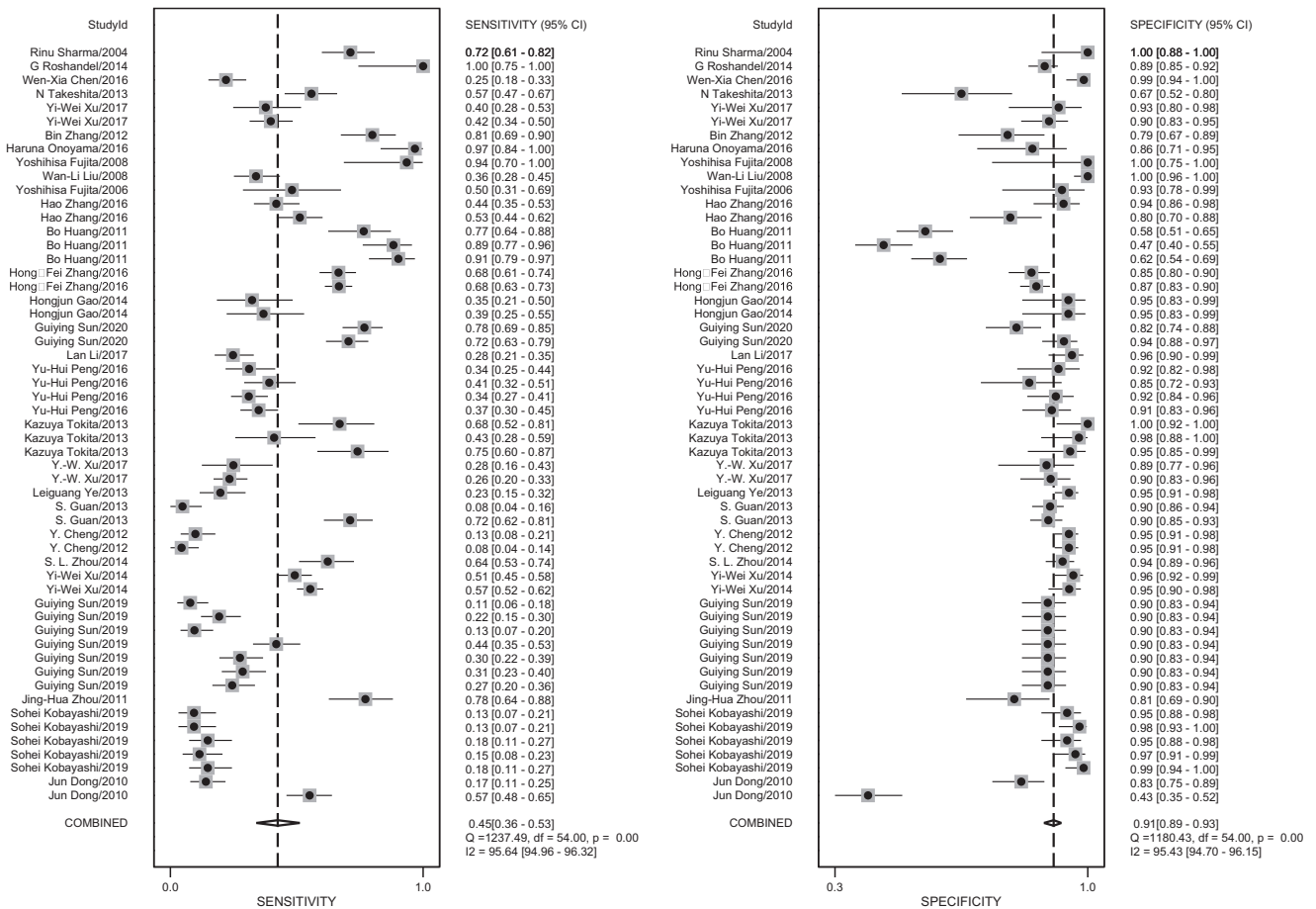
Figure 4. Forest plot of sensitivity and specificity for autoantibody. *CI*, Confidence interval.

aged 40 to 69 years from endemic regions.[12] Similar findings were reported from other cohort studies in regions with a higher risk of ESCC.[21,22] As for the lower risk regions of ESCC, evidence has demonstrated the effectiveness of screening in improving survival for patients with specific diseases associated with a higher risk of ESCC. A better prognosis of 5-year survival in secondary ESCC detected on screening was observed among patients with head-and-neck cancers.[23] An improved overall survival from ESCC was also indicated from yearly endoscopic screening among subjects with tylosis.[24]

Endoscopy. Endoscopy is a traditional tool for ESCC screening and has a heterogeneously broad spectrum of technology. Our pooled analysis showed that the diagnostic accuracy of LCE and NBI seemed to be high. Despite the high accuracy of conventional WLI in ESCC detection, it is less sensitive for detecting squamous dysplasia, which demonstrates only subtle vascular changes compared with normal squamous mucosa.[25] Instead, LCE has now become the standard test for detecting squamous dysplasia given its ability to highlight areas of abnormality. LCE has the ability to show lesions that were not visible by WLI

endoscopy.[26-28] It was reported that conventional WLI can only identify approximately half of all squamous dysplasia detected by LCE,[27] which is consistent with our findings that the sensitivity of LCE seems to be higher than that of WLI. Although LCE is the current standard modality for ESCC screening, screening participants can develop allergic reactions to the iodine,[29] and the specificity is lower for detecting squamous dysplasia. LCE is also limited in low-income regions like Africa where there are high incidences and mortality rates for ESCC.[30] NBI shows a clearer appearance of mucosal patterns and capillary networks.[31] A study found that NBI had an improved specificity compared with LCE,[32] which was also observed in our results, although the difference is not statistically significant. Despite its accuracy, the application of NBI is associated with an increased medical cost of equipment and time for training because it depends heavily on the experience of the operator.[33]

Cytology. Screening for squamous dysplasia and ESCC by endoscopy is expensive, requiring expertise in endoscopy. People in less-developed regions, such as Asia and
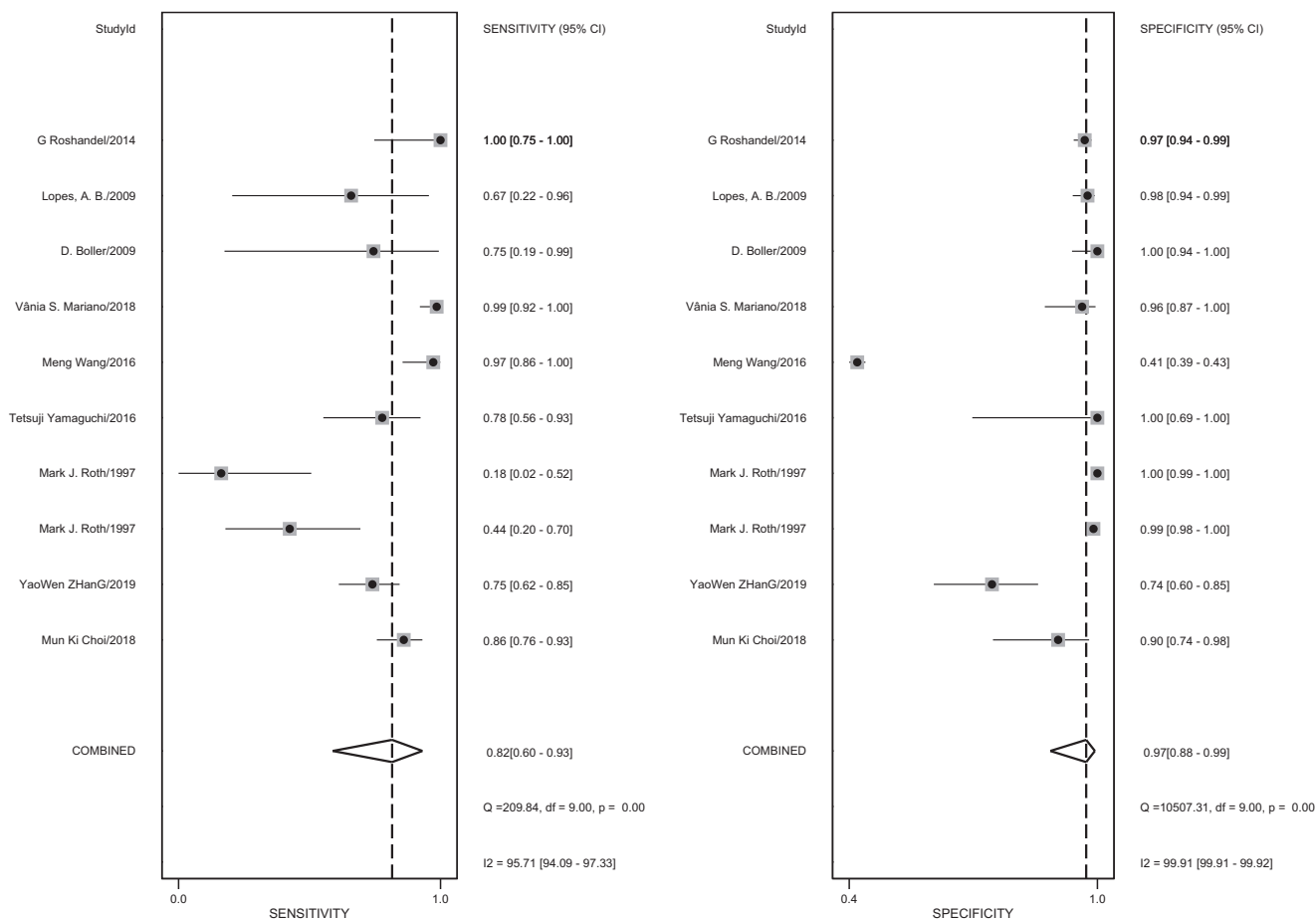
Figure 5. Forest plot of sensitivity and specificity for cytology. *CI*, Confidence interval.

Africa, may have limited access to endoscopic resources. Studies have explored less-expensive tests for ESCC screening using nonendoscopic cytology sampling devices, including a brush, sponge, or balloon attached to a string or cannula.[34,35] We found in our analysis that the diagnostic accuracy of cytology sampling (sensitivity, .82; specificity, .97; AUC, .97) seemed to be high. Because cytology is less expensive and can be managed in primary care settings without sedation, it could be a feasible tool for ESCC screening, especially in less-developed regions.[36] In a study of more than 300 participants receiving a swallowed sponge for ESCC screening, the results showed an optimal sensitivity (100%) and specificity (97%) for detecting squamous dysplasia.[37] The study demonstrated cytosponge as an effective and safe modality for ESCC screening. However, the cytology sampling devices for ESCC screening are hard to swallow and may lead to suboptimal compliance.[11]

It was reported that the value of cytology as a screening tool was enhanced by combining it with other biomarkers. In this study, most studies we included separately assessed the diagnostic values of cytology and other biomarkers. Only 2 studies performed relevant research. One study

(reference 10 in Supplementary Table 4, available online at www.giejournal.org) tested the diagnostic values of LCE combined with brush cytology and found brush cytology had no additional benefit in LCE.[38] Another study (reference 73 in Supplementary Table 4) combined sponge cytology with p53 as a screening tool and found increased diagnostic values compared with using sponge cytology alone.[37] Further studies are recommended to combine cytology with other biomarkers to enhance the screening performance.

Autoantibody and microRNA. Less-invasive tests, including autoantibodies and microRNAs, have been proposed for potential use in ESCC screening.[39] Because of their stability in blood, antibodies to cancer-associated antigens have been used as biomarkers for malignancy.[40] Anti-p53 is a widely studied tumor-associated autoantibody and can be noninvasively detected in blood.[41] However, sensitivity is suboptimal for a single autoantibody biomarker.[42] A study showed the sensitivity of anti-p53 for detecting cancer ranged from 15% to 60%.[43] We also found an overall low sensitivity (.45) of the autoantibody in detecting squamous dysplasia and ESCC despite an observed high specificity (.91).

TABLE 1. Summary estimates of diagnostic values and the 95% CI

Screening methods	Sensitivity	Specificity	PLR	NLR*	DOR*	AUC†	P‡	I²§
Endoscopy (N=27/4159)								
POE (N=19/2771)	.94 (0.87,0.97)	.92 (0.87,0.95)	11.7 (7.3,18.8)	.07 (0.03,0.15)	168 (75,377)	.97 (0.96,0.99)	.15	82.2/93.0
LIC (POE) (N=7/1340)	.96 (0.91,0.98)	.89 (0.77,0.95)	8.6 (4.0,18.5)	.05 (0.02,0.10)	180 (63,513)	.98 (0.96,0.99)	.52	58.4/96.0
WLI (POE) (N=3/219)	.67 (0.38,0.88)	.99 (0.96,1.00)	32.4 (4.2,253.6)	.37 (0.19,0.70)	89 (10,777)	.59 (0.52,0.66)	NA	.00/79.3
NBI (POE) (N=4/653)	.94 (0.73,0.93)	.93 (0.87,0.96)	12.6 (7.2,22.2)	.06 (0.01,0.33)	205 (38,1113)	.98 (0.96,0.99)	.18	.00/80.5
EC (POE) (N=1/53)	1.00 (0.89,1.00)	.79 (0.49,0.94)	4.7 (1.7,12.7)	NA	NA	NA	NA	NA
ECE (POE) (N=1/47)	.58 (0.39,0.75)	.81 (0.54,0.95)	3.10 (1.07,8.96)	.52 (0.33,0.80)	6 (5,7)	NA	NA	NA
PBCLE (POE) (N=1/37)	.94 (0.69,1.00)	.90 (0.67,0.98)	9.41 (2.51,35.2)	.07 (0.01,0.44)	144 (141,146)	NA	NA	NA
HRME (POE) (N=1/375)	.88 (0.75,0.95)	.95 (0.92,0.97)	16.8 (10.5,27.0)	.13 (0.06,0.27)	128 (127,129)	NA	NA	NA
AIVS (POE) (N=1/47)	1.00 (0.46,1.00)	.83 (0.68,0.92)	6.0 (3.05,11.8)	NA	NA	NA	NA	NA
TNE (N=8/1388)	.85 (0.70,0.93)	.96 (0.91,0.98)	21.4 (9.6,47.7)	.15 (0.07,0.33)	139 (44,437)	.97 (.95,.98)	.41	83.7/90.2
LIC (TNE) (N=2/392)	.92 (0.81,0.98)	.89 (0.85,0.92)	5.7 (1.7,19.0)	.10 (0.04,0.26)	57 (8,421)	NA	NA	.00/89.1
WLI (TNE) (N=3/498)	.59 (0.46,0.71)	.98 (0.96,0.99)	23.4 (10.8,50.8)	.42 (0.24,0.76)	83 (14,495)	.99 (.99,.99)	NA	77.7/0.00
NBI (TNE) (N=2/392)	.86 (0.74,0.94)	.96 (0.93,0.98)	20.6 (12.1,35.0)	.14 (0.07,0.29)	144 (53,393)	NA	NA	.00/0.00
FICE (TNE) (N=1/106)	1.00 (0.72,1.00)	.99 (0.93,1.00)	93.0 (13.2,653.3)	NA	NA	NA	NA	NA
MicroRNA (N=69/11457)	.77 (0.75,0.80)	.78 (0.75,0.80)	3.5 (3.1,4.0)	.29 (0.26,0.32)	12 (10,15)	.85 (0.81,0.87)	.15	77.3/83.0
Serum (N=51/8444)	.79 (0.76,0.81)	.78 (0.75,0.80)	3.5 (3.1,3.9)	.28 (0.25,0.31)	13 (10,15)	.85 (0.81,0.88)	.94	66.3/79.1
Plasma (N=18/3013)	.75 (0.68,0.80)	.80 (0.73,0.85)	3.7 (2.6,5.3)	.32 (0.24,0.42)	12 (6,22)	.84 (0.80,0.87)	.05	86.1/89.5
Autoantibody (N=55/12459)	.45 (0.36,0.53)	.91 (0.89,0.93)	5.1 (4.0,6.5)	.61 (0.53,0.70)	8 (6,12)	.84 (0.81,0.87)	.05	95.6/95.4
Serum (N=43/9050)	.52 (0.43,0.61)	.92 (0.88,0.94)	6.1 (4.5,8.2)	.53 (0.44,0.63)	12 (8,17)	.84 (0.81,0.87)	.18	94.9/95.5
Plasma (N=12/3409)	.22 (0.14,0.33)	.92 (0.90,0.93)	2.6 (1.8,3.9)	.85 (0.76,0.95)	3 (2,5)	.89 (0.86,0.91)	.94	94.8/42.1
Cytology (N=10/4134)	.82 (0.60,0.93)	.97 (0.88,0.99)	29.7 (7.4,119.6)	.19 (0.08,0.45)	160 (42,610)	.97 (0.95,0.98)	.62	95.7/99.9

CI, Confidence interval; *PLR*, positive likelihood ratio; *NLR*, negative likelihood ratio; *DOR*, diagnostic odds ratio; *AUC*, area under curve; *N*, number of studies/number of participants; *POE*, peroral endoscopy; *LIC*, lugol's iodine chromoendoscopy; *WLI*, white-light imaging endoscopy; *NBI*, narrow-band imaging; *EC*, endocytoscope; *ECE*, esophageal capsule endoscopy; *PBCLE*, probe-based confocal laser endomicroscopy; *HRME*, high-resolution microendoscopy; *AIVS*, autofluorescence imaging videoendoscopy system; *TNE*, transnasal endoscopy; *FICE*, flexible spectral imaging color enhancement; *NA*, not applicable.
*Several screening methods had zero number of false negative so the NLR and DOR cannot be calculated.
†Several screening methods had insufficient studies so the AUC cannot be calculated.
‡P: P-value of Deeks' Funnel Plot Asymmetry Test. Several screening methods had insufficient studies so this index cannot be calculated.
§I²: I² of sensitivity/I² of specificity. Several screening methods had insufficient studies so this index cannot be calculated.

Similar results were identified for microRNAs. MicroRNA is noncoding RNA that binds to target messenger RNAs, resulting in degradation or inhibition of RNA, which are abundantly and stably expressed and can be detected consistently in serum.[44] A meta-analysis of 27 studies estimated the pooled sensitivity and specificity of microRNAs for ESCC screening to be .80 and .81, respectively.[45] Our study included significantly more studies (n = 69) for analysis and found a slightly lower sensitivity (.77) and specificity (.78). Despite the suboptimal diagnostic performance of autoantibodies and microRNAs, further developments, such as the discovery of novel biomarkers or combination of different tests, could be used to increase their diagnostic accuracy.[46]

Limitations

Although this systematic review and meta-analysis is comprehensive and shows promising findings, several limitations should be addressed. First, selection bias may exist because the number of studies is limited for some subgroups. Unpublished reports and gray literature may have been missed despite a comprehensive search strategy adopted in the current study. The number of studies is small (n = 10) for the analysis for cytology. More studies need to be conducted to confirm their finding. Second, endoscopy is an operator-dependent procedure. The histopathologic classification relied on the detection of dysplasia by endoscopy. Participants without suspicious dysplasia detected by endoscopy were regarded as not having the disease. The criteria for histopathologic classification may also vary across included studies. Third, we did not look at the dysplasia rates for different studies. Future research could be done to evaluate how they affect the performance of different screening tools. Last but not least, the high level of between-study heterogeneity may be attributable to participants' age, countries, study periods, and specimen origins.

Conclusion

Endoscopy and cytology had high diagnostic accuracy, whereas autoantibody and microRNAs bear potential as future noninvasive screening tools for ESCC. To reduce ESCC-related death in high-risk populations, it is important to develop a more-accurate and less-invasive screening test. Further studies are required to evaluate the acceptability and cost-effectiveness of different screening tools for ESCC in different population subgroups.

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1440 articles identified from literature search
- 1057 from Embase
- 367 from MEDLINE
- 16 from the references of included studies and other relevant reviews

1050 articles remain after removing duplicates

747 articles were excluded in titles and abstracts screening

303 articles were included in full-text screening

222 articles were excluded:
9 articles cannot distinguish ESCC and EAC
5 articles cannot distinguish LGD and HGD/ESCC
16 articles only detected the progression of ESCC
178 articles did not have sufficient information
14 articles had subjects with a history of ESCC

161 studies in 81 articles were included in Meta-analysis

ESCC, Esophageal Squamous Cell Carcinoma; EAC, Esophageal Adenocarcinoma; LGD, low-grade dysplasia; HGD,high-grade dysplasia

Supplementary Figure 1. Flow diagram of the literature search.
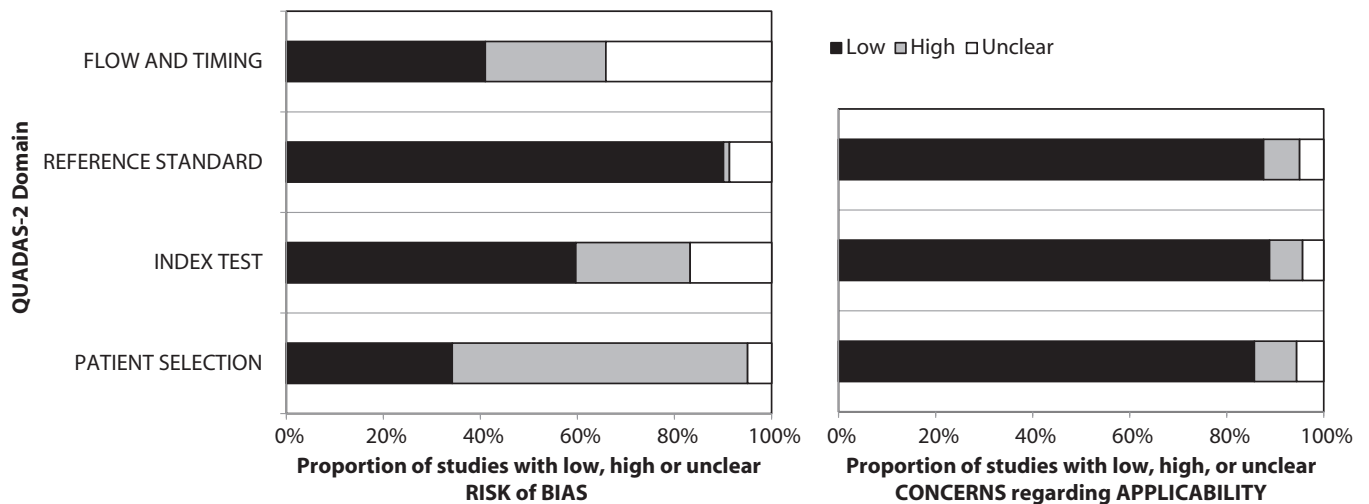
Supplementary Figure 2. Quality assessment of included studies. *QUADAS-2*, Quality Assessment of Diagnostic Accuracy Studies 2.
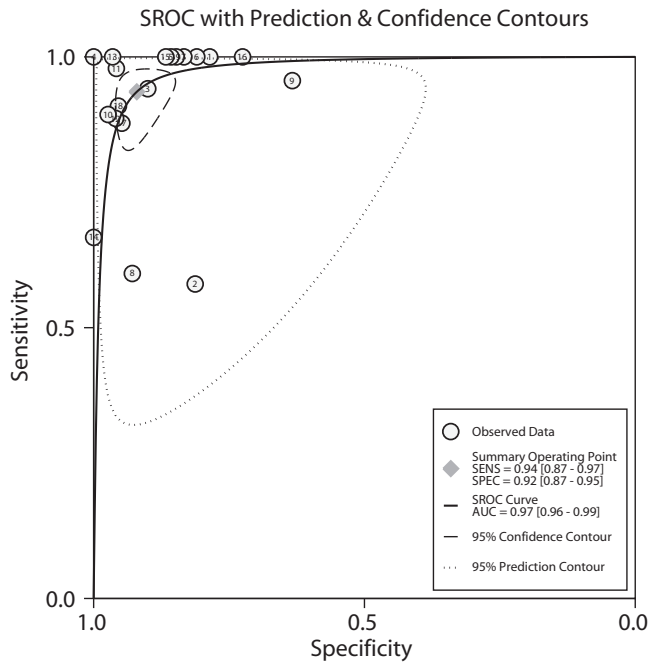
Supplementary Figure 3. Summary receiver-operating characteristic curve for endoscopy (peroral endoscopy). *SROC,* Summary receiver-operating characteristic; *AUC,* area under the curve; *SENS,* sensitivity; *SPEC,* specificity.
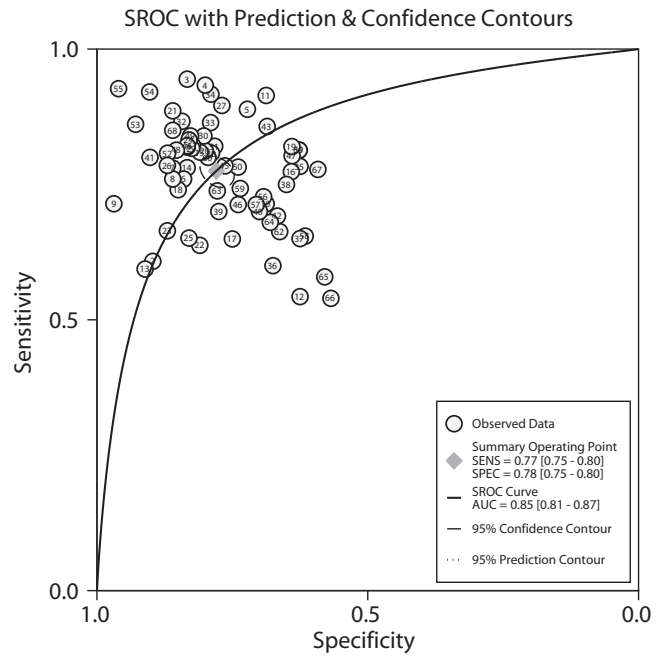
Supplementary Figure 5. Summary receiver-operating characteristic curve for microRNA. *SROC,* Summary receiver-operating characteristic; *AUC,* area under the curve; *SENS,* sensitivity; *SPEC,* specificity.
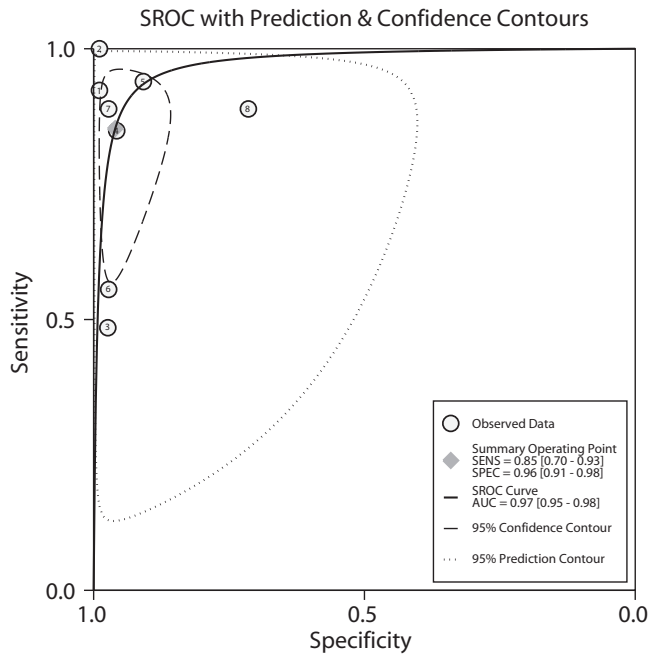
Supplementary Figure 4. Summary receiver-operating characteristic curve for endoscopy (transnasal endoscopy). *SROC,* Summary receiver-operating characteristic; *AUC,* area under the curve; *SENS,* sensitivity; *SPEC,* specificity.
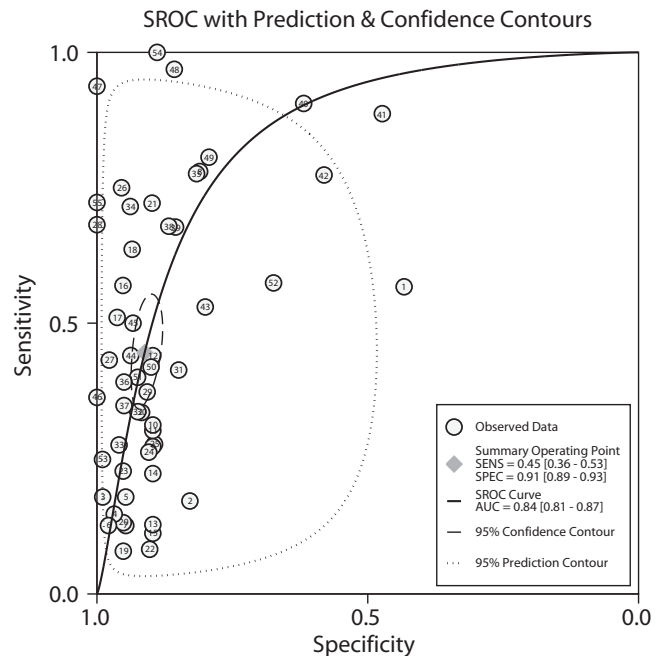
Supplementary Figure 6. Summary receiver-operating characteristic curve for autoantibody. *SROC,* Summary receiver-operating characteristic; *AUC,* area under the curve; *SENS,* sensitivity; *SPEC,* specificity.
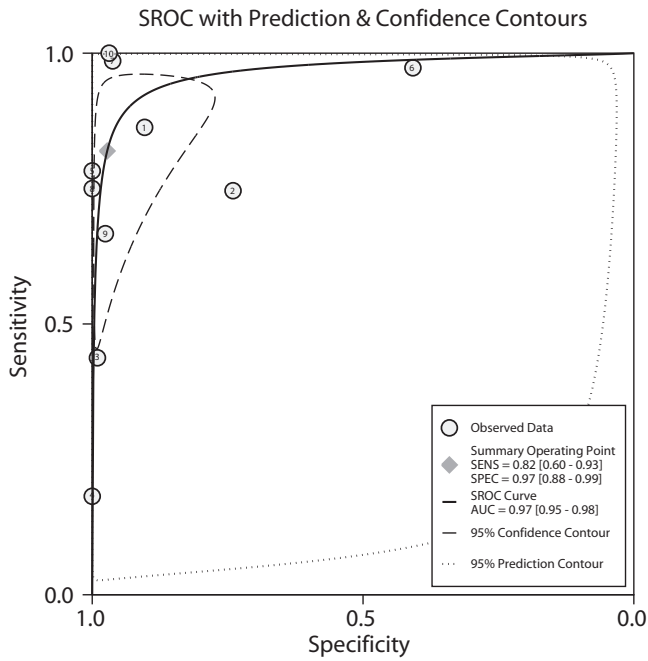
Supplementary Figure 7. Summary receiver-operating characteristic curve for cytology. *SROC*, Summary receiver-operating characteristic; *AUC*, area under the curve; *SENS*, sensitivity; *SPEC*, specificity.

WLI, White-light imaging endoscopy; POE, Per-oral endoscopy; NBI, Narrow-Band Imaging; LIC, Lugol's iodine chromoendoscopy; cs, cross-sectional study.
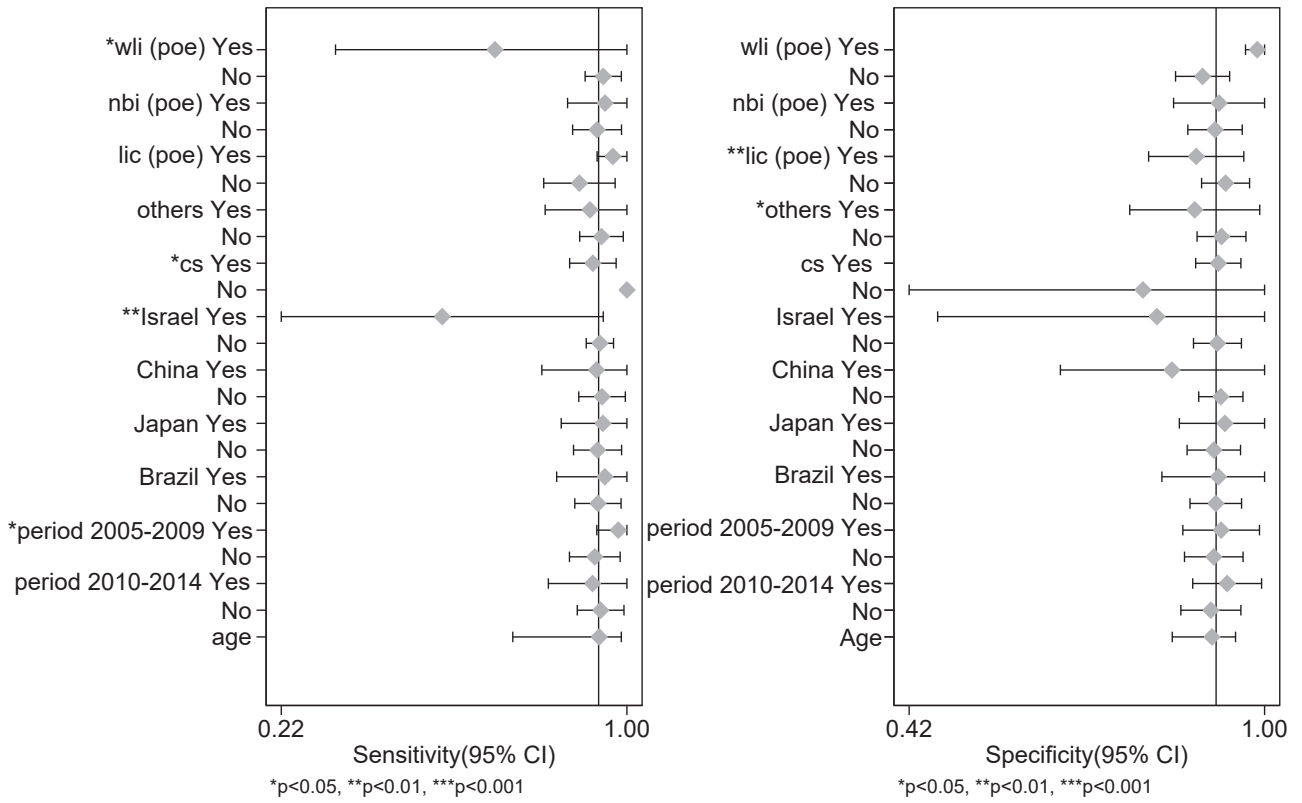
Supplementary Figure 8. Meta-regression of endoscopy (peroral endoscopy). *CI*, Confidence interval.
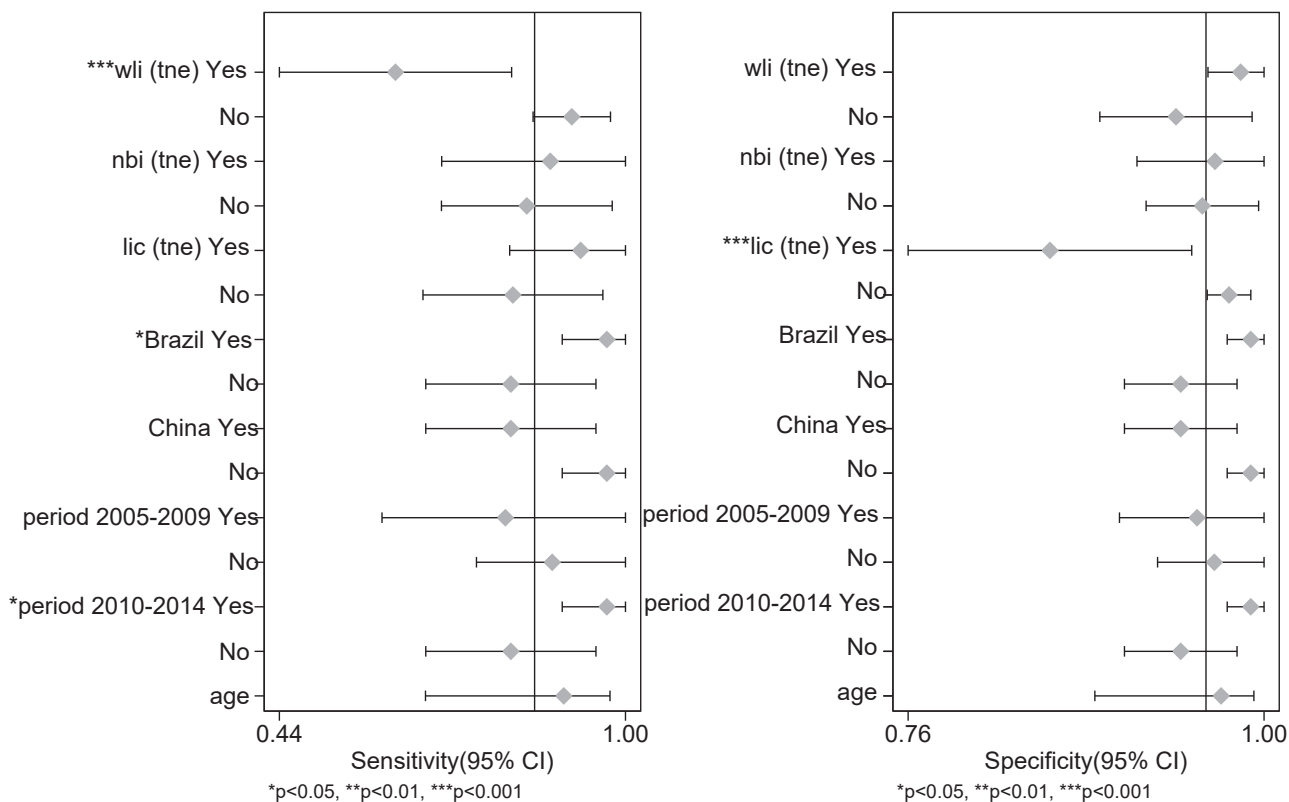
WLI, White-light imaging endoscopy; TNE, Transnasal endoscopy; NBI, Narrow-Band Imaging; LIC, Lugol's iodine chromoendoscopy.

Supplementary Figure 9. Meta-regression of endoscopy (transnasal endoscopy). *CI,* Confidence interval.
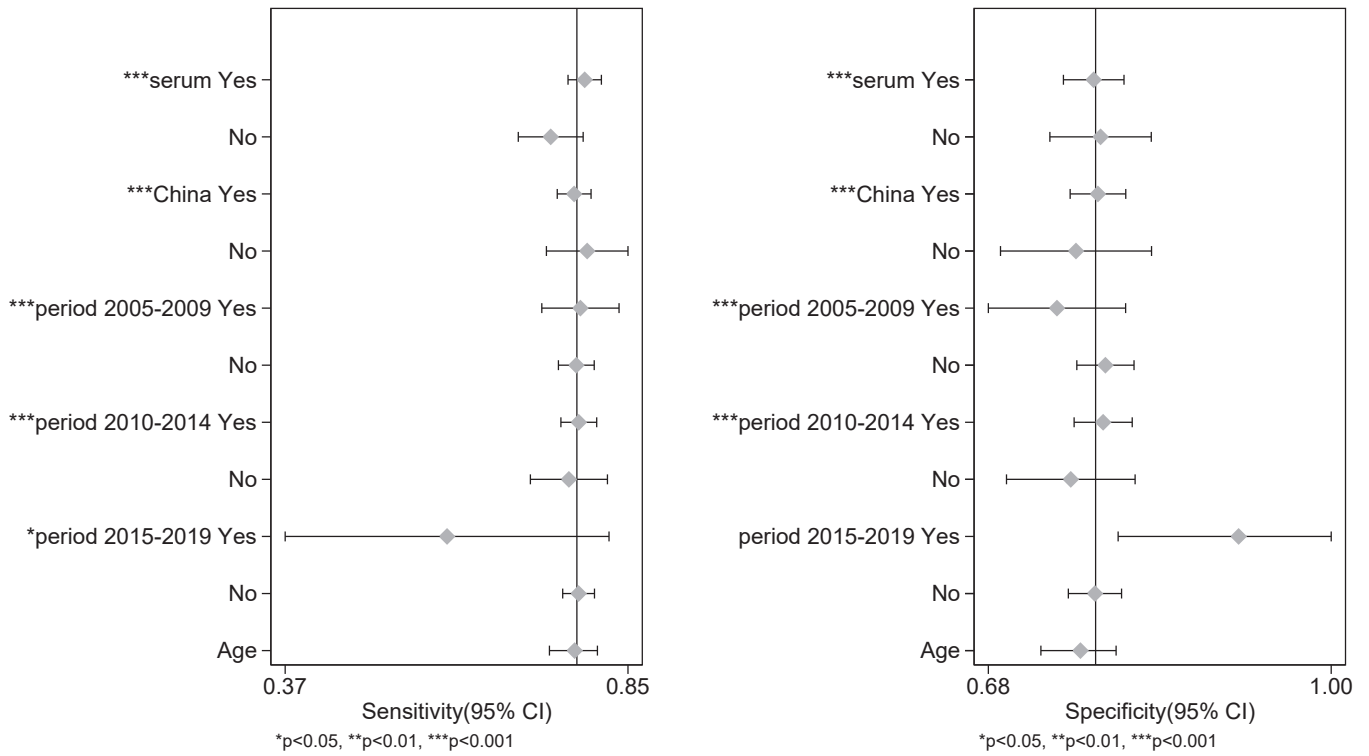
Supplementary Figure 10. Meta-regression of microRNA. *CI*, Confidence interval.
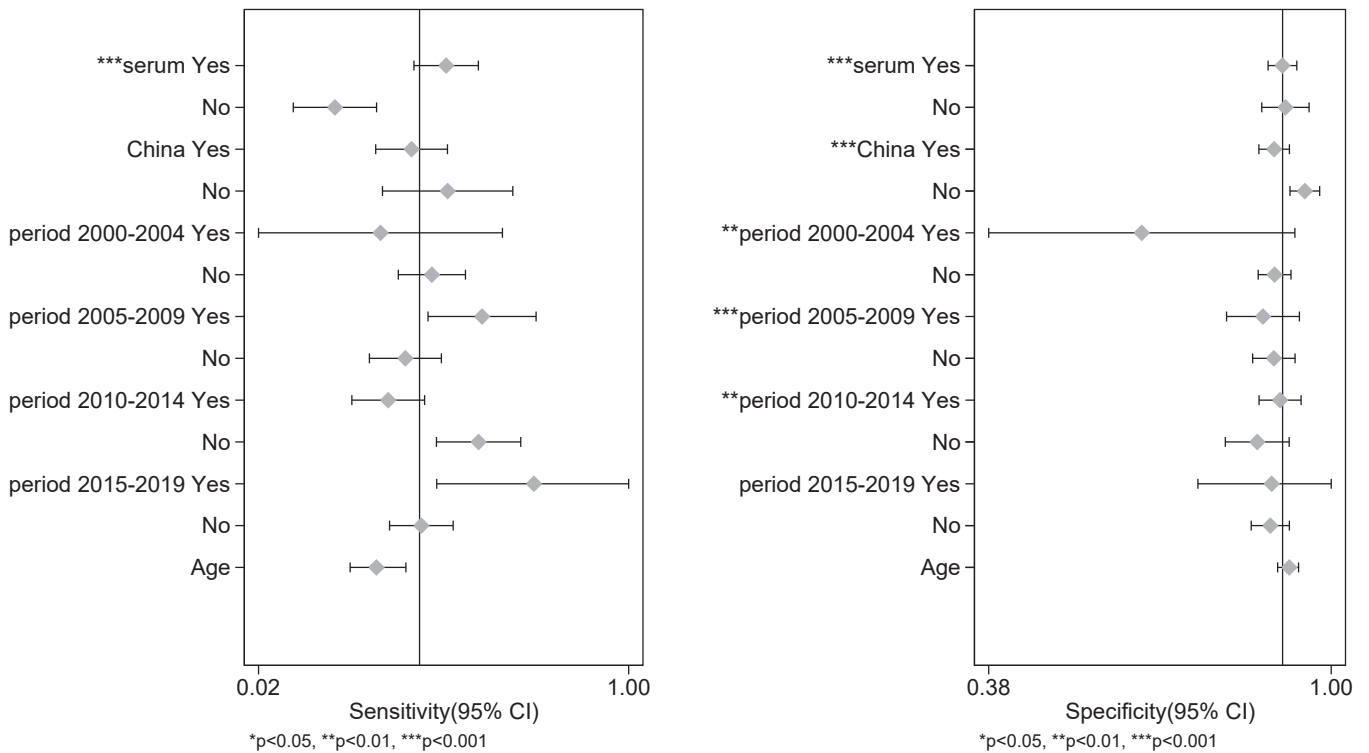
Supplementary Figure 11. Meta-regression of autoantibody. *CI*, Confidence interval.
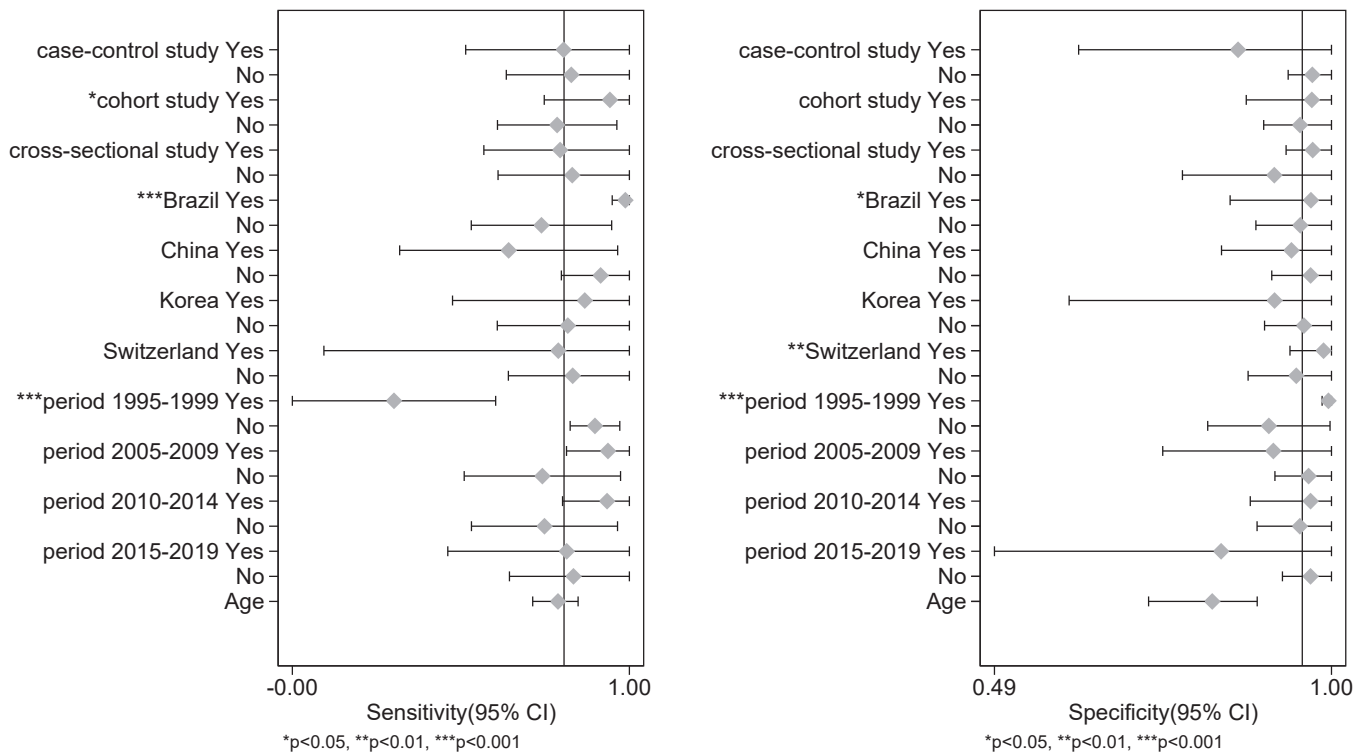
Supplementary Figure 12. Meta-regression of cytology. *CI*, Confidence interval.
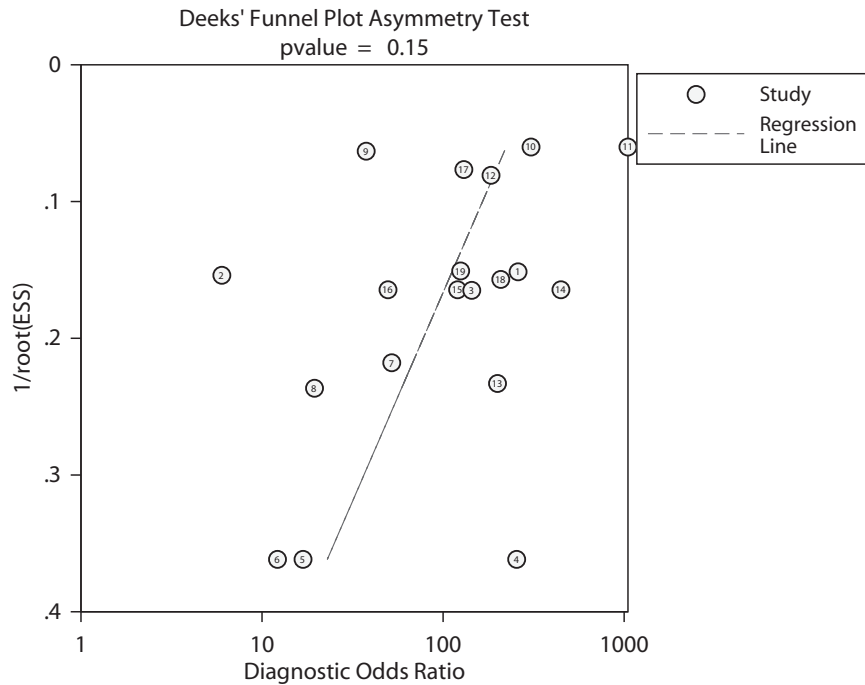
Supplementary Figure 13. Deeks' funnel plots of endoscopy (peroral endoscopy). *ESS*, Effective sample size.
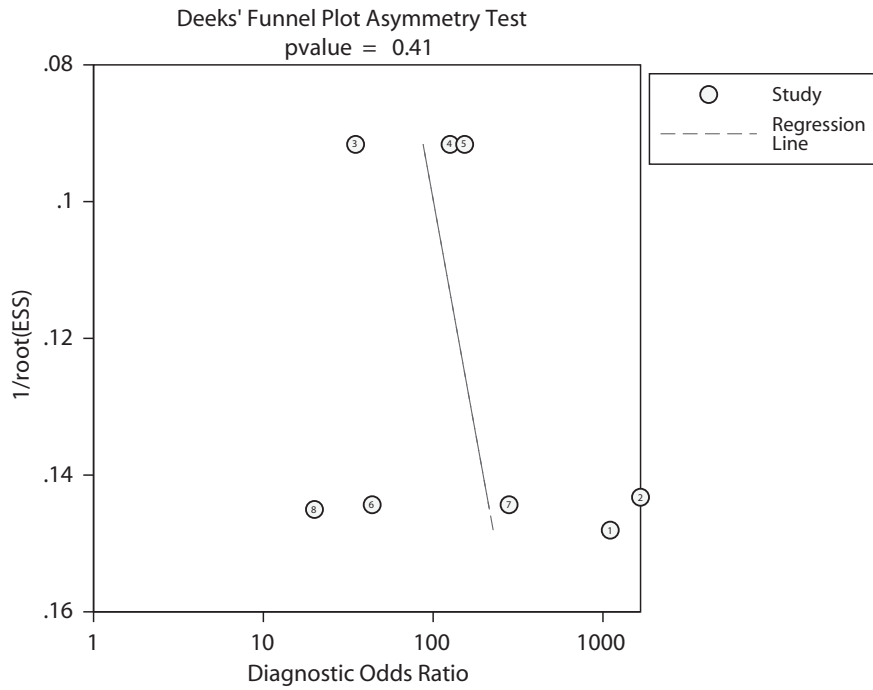
Supplementary Figure 14. Deeks' funnel plots of endoscopy (transnasal endoscopy). *ESS*, Effective sample size.
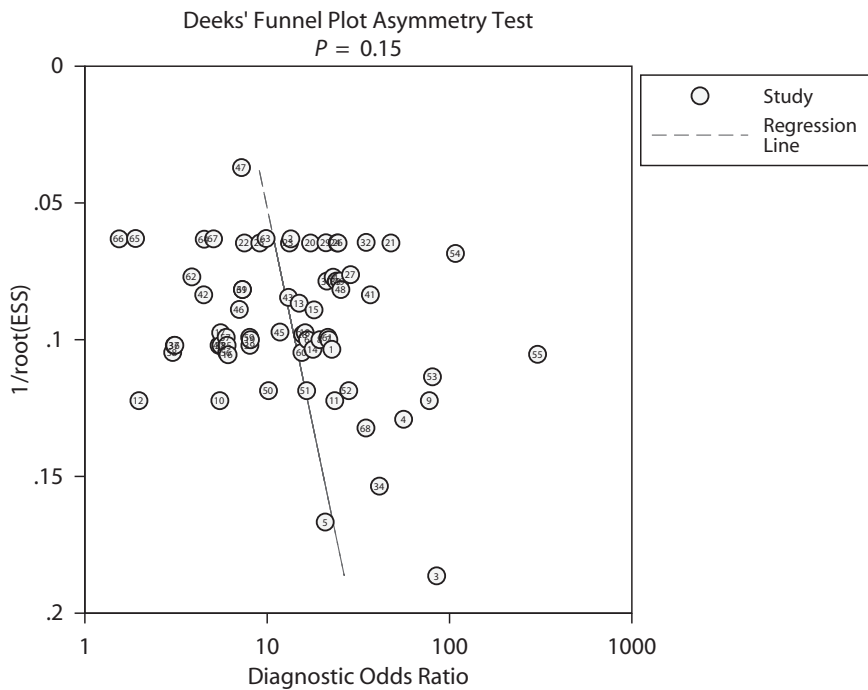
Supplementary Figure 15. Deeks' funnel plots of microRNA. *ESS*, Effective sample size.
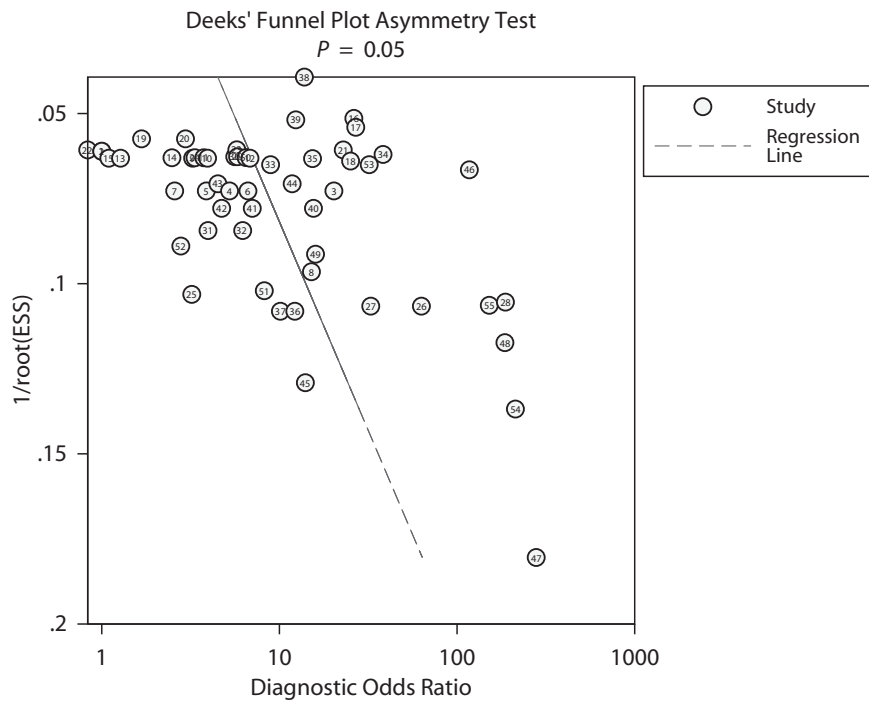
Supplementary Figure 16. Deeks' funnel plots of autoantibody. *ESS,* Effective sample size.
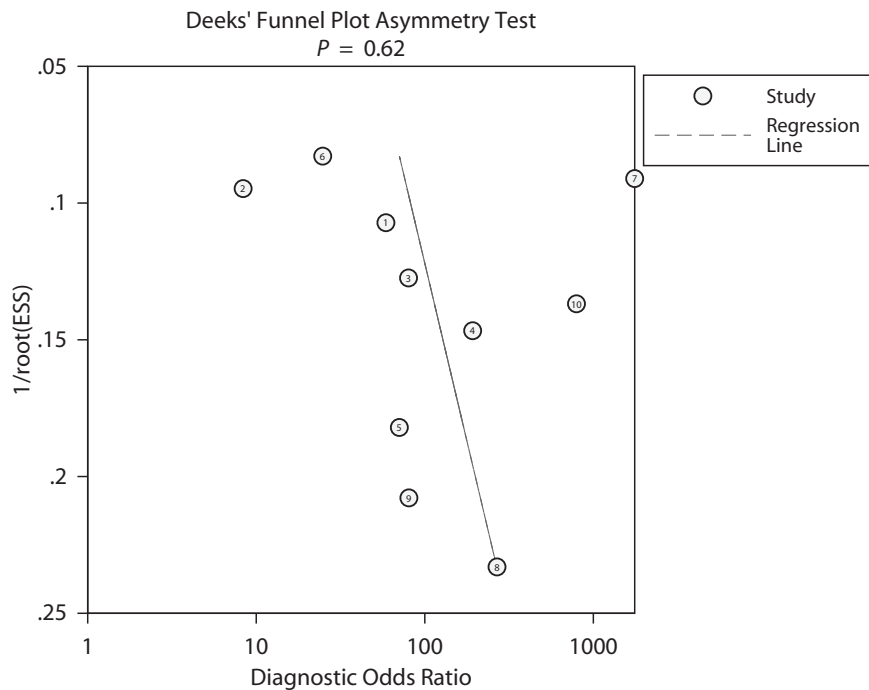
Supplementary Figure 17. Deeks' funnel plots of cytology. *ESS,* Effective sample size.
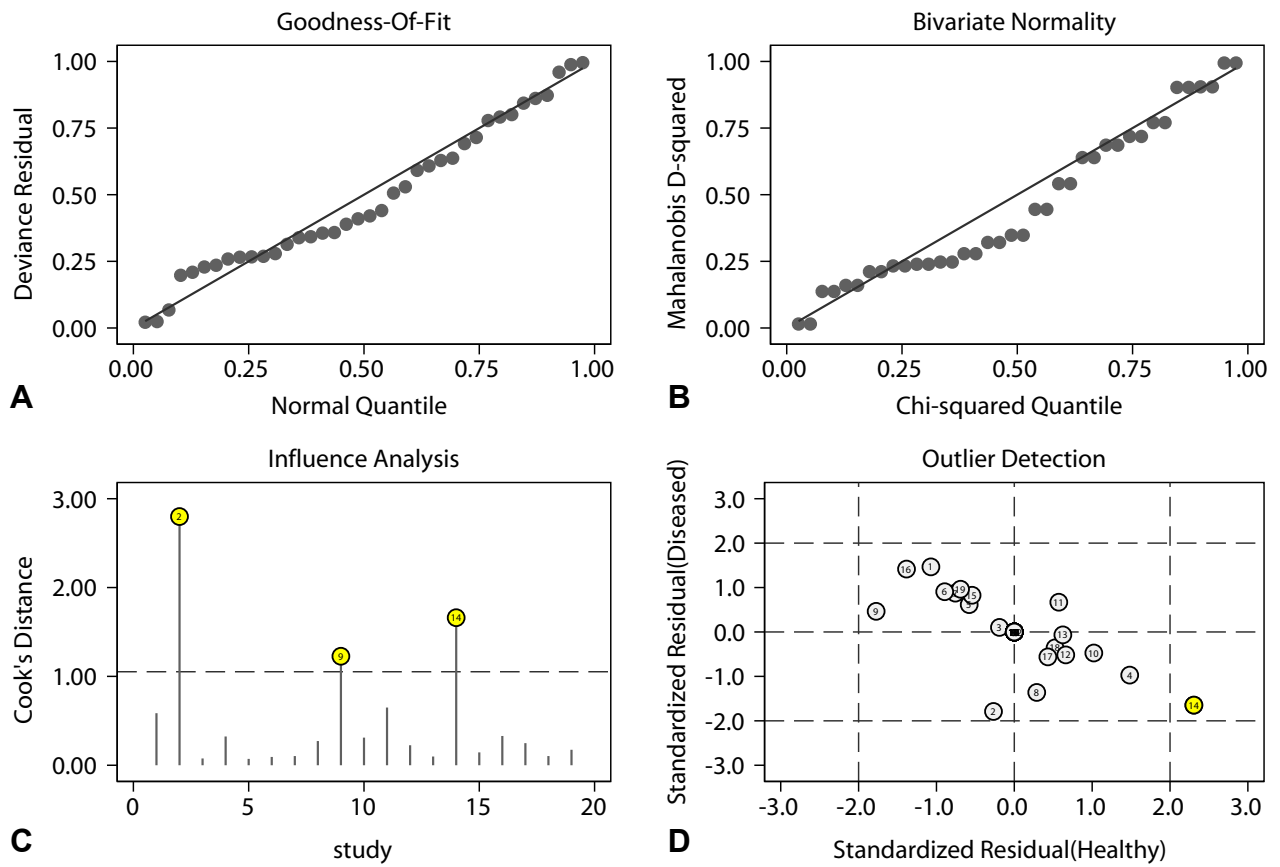
Supplementary Figure 18. Sensitivity analyses of endoscopy (peroral endoscopy).
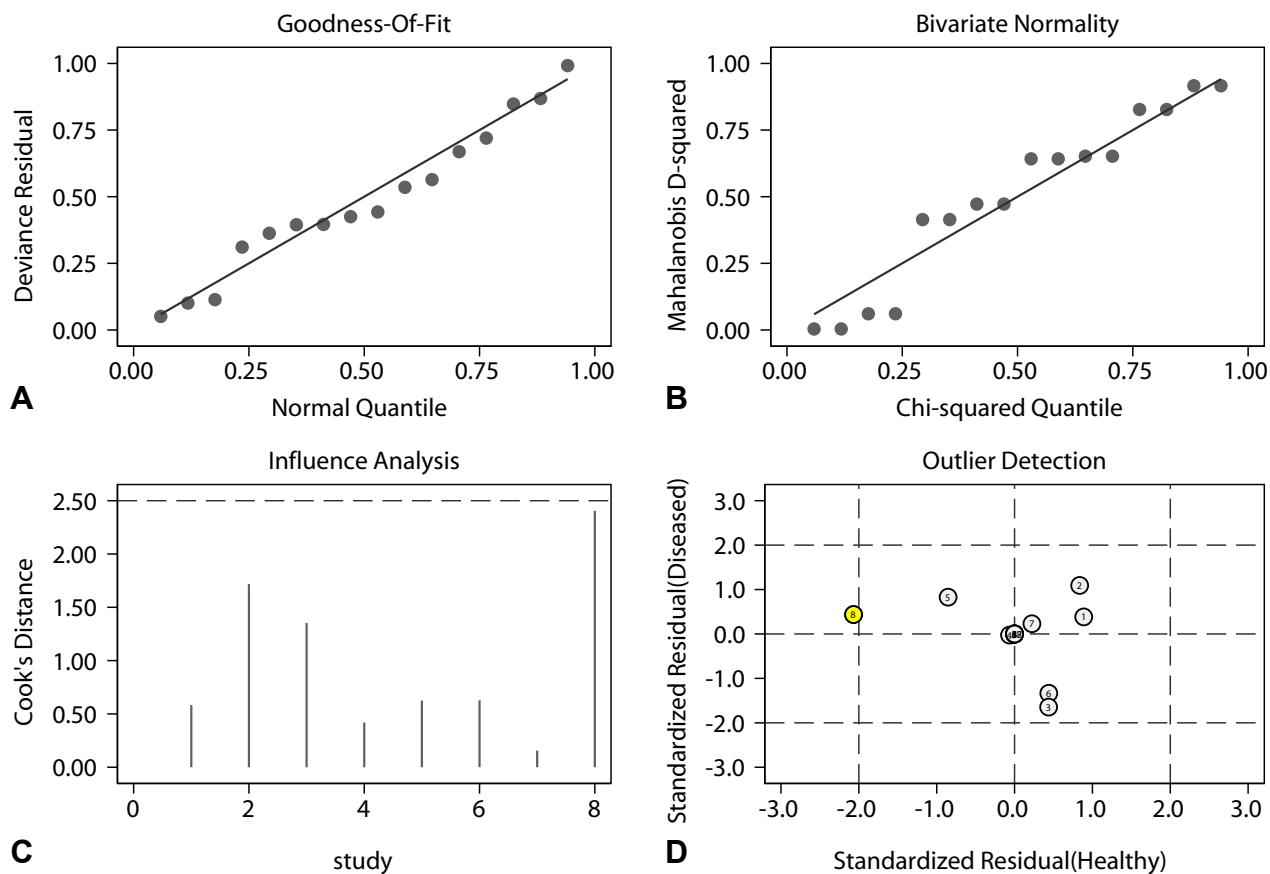
Supplementary Figure 19. Sensitivity analyses of endoscopy (transnasal endoscopy).
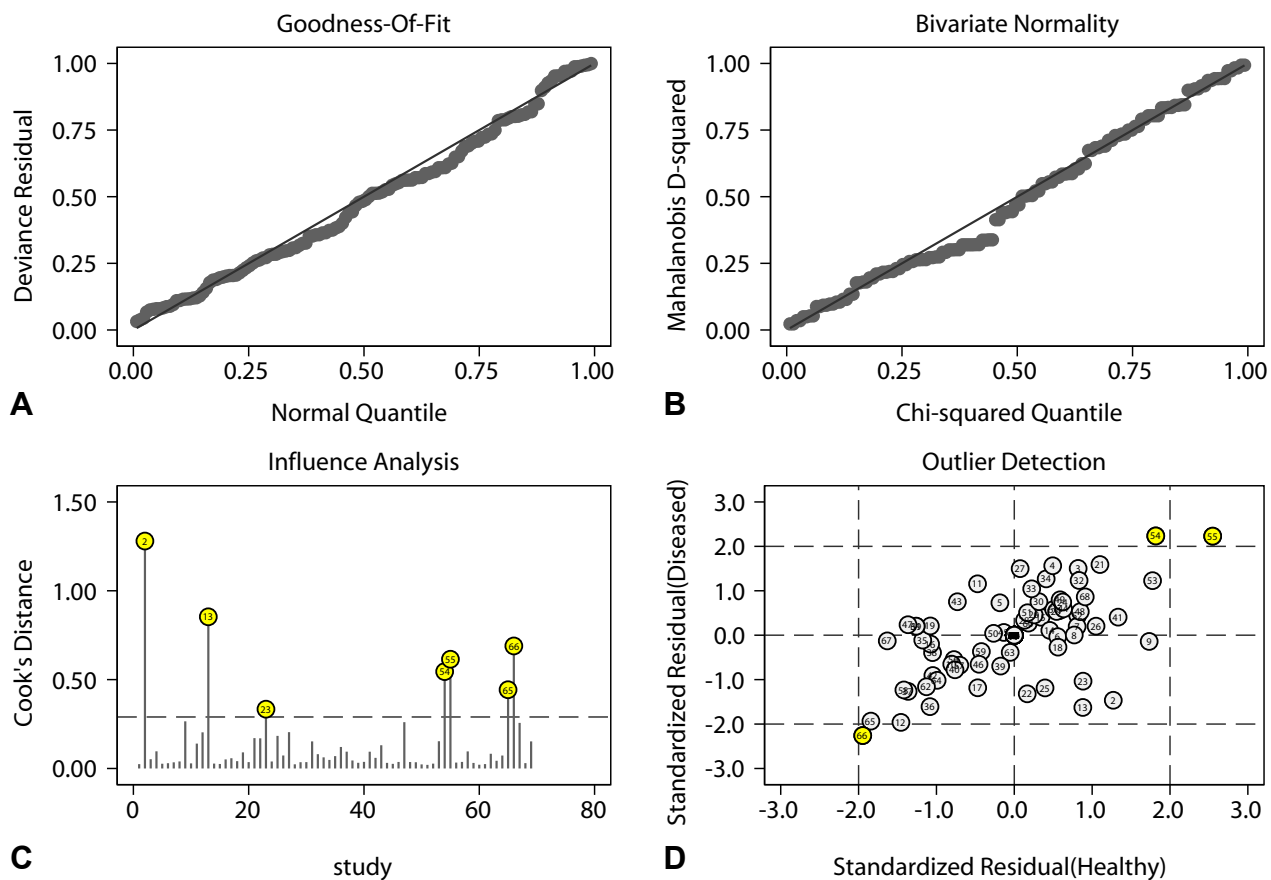
Supplementary Figure 20. Sensitivity analyses of microRNA.
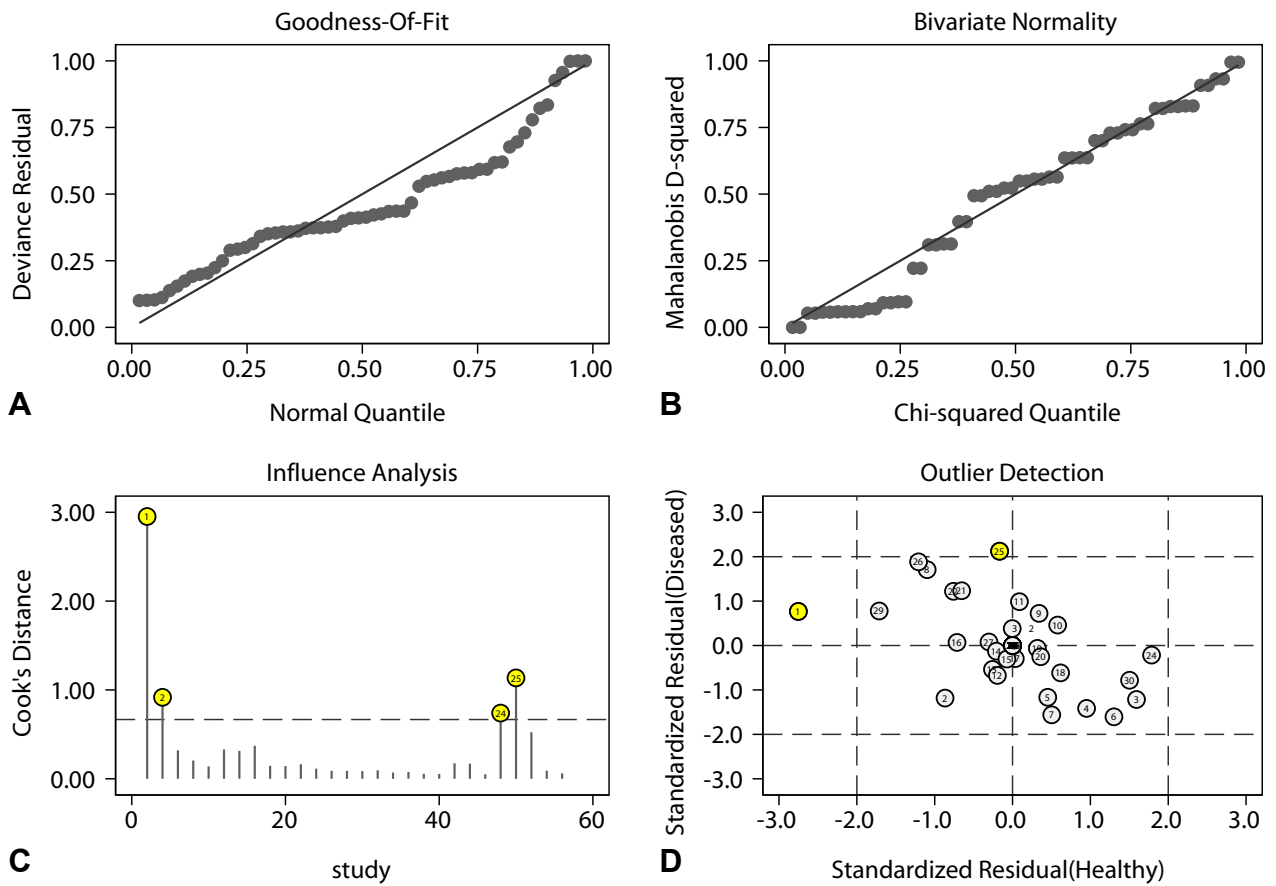
Supplementary Figure 21. Sensitivity analyses of autoantibody.
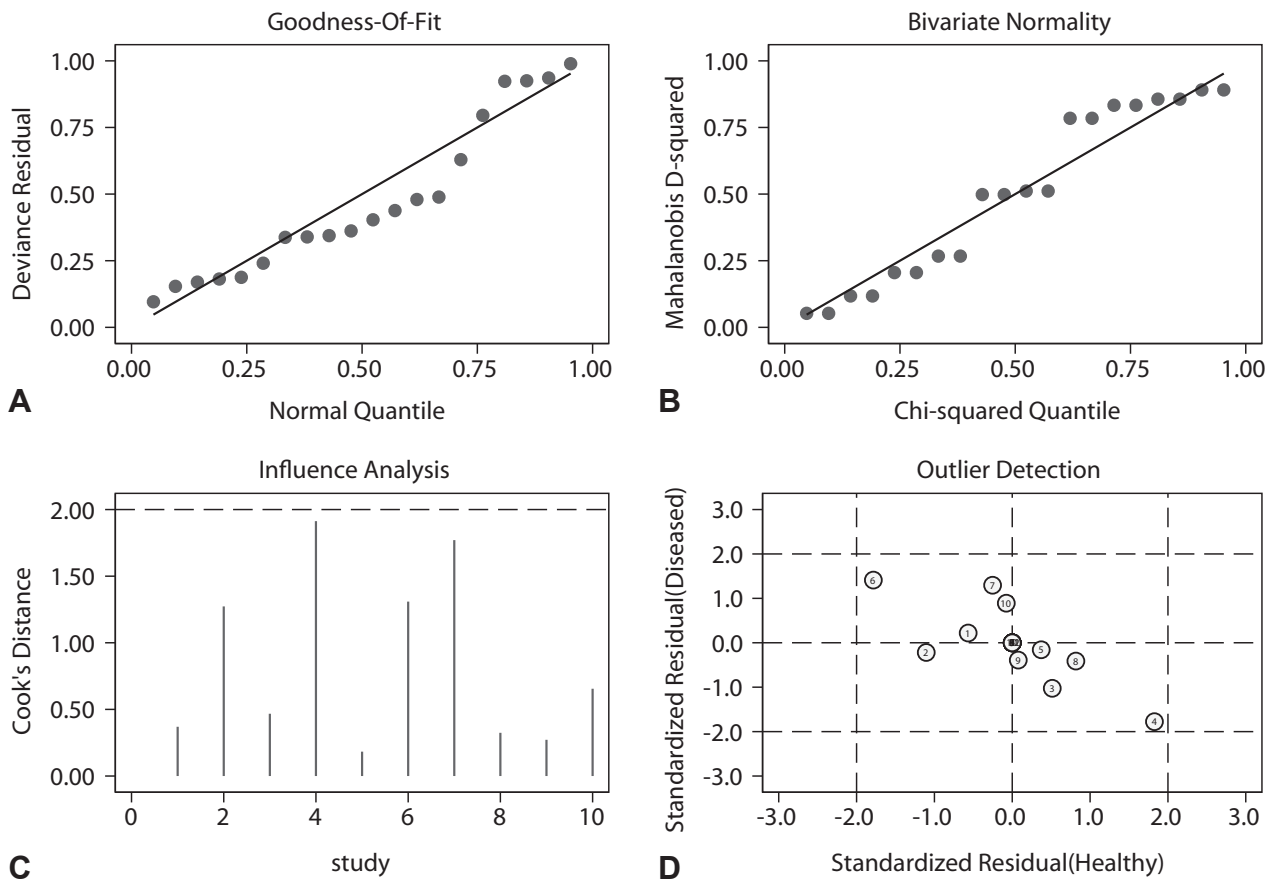
Supplementary Figure 22. Sensitivity analyses of cytology.

SUPPLEMENTARY TABLE 1. Search strategies for literature search of this study

Embase (from 1910 to October 31, 2020)	Medline (from 1946 to October 31, 2020)
1. ((Esophageal adj5 Squamous adj3 Cell adj5 Carcinoma) OR (Esophageal adj5 Squamous adj3 Cell adj5 Neoplasms) OR (Esophageal adj5 Squamous adj3 Cell adj5 Cancer) OR (Esophagus adj5 Squamous adj3 Cell adj5 Carcinoma) OR (Esophagus adj5 Squamous adj3 Cell adj5 Neoplasms) OR (Esophagus adj5 Squamous adj3 Cell adj5 Cancer)).mp (n = 19464)	1. ((Esophageal adj5 Squamous adj3 Cell adj5 Carcinoma) OR (Esophageal adj5 Squamous adj3 Cell adj5 Neoplasms) OR (Esophageal adj5 Squamous adj3 Cell adj5 Cancer) OR (Esophagus adj5 Squamous adj3 Cell adj5 Carcinoma) OR (Esophagus adj5 Squamous adj3 Cell adj5 Neoplasms) OR (Esophagus adj5 Squamous adj3 Cell adj5 Cancer)).mp (n = 8994)
2. (narrow band imaging OR optical imaging OR nbi OR chromoendoscopy OR lugol OR iodine OR virtual imaging OR flexible spectral imaging color enhancement OR i-scan OR bli OR blue laser imaging OR endoscopy OR endoscopic OR Fuji intelligent chromoendoscopy OR FICE OR transnasal endoscopy OR TNE OR Endocytoscopy OR High-resolution microendoscopy OR HRME OR capsule endoscopy).tw (n = 388381)	2. (narrow band imaging OR optical imaging OR nbi OR chromoendoscopy OR lugol OR iodine OR virtual imaging OR flexible spectral imaging color enhancement OR i-scan OR bli OR blue laser imaging OR endoscopy OR endoscopic OR Fuji intelligent chromoendoscopy OR FICE OR transnasal endoscopy OR TNE OR Endocytoscopy OR High-resolution microendoscopy OR HRME OR capsule endoscopy).tw (n = 215092)
3. (Esophageal cytology samples OR brush OR balloon OR sponge OR Volatile organic compounds OR Autoantibodies OR Methylated DNA OR MDM OR circulating tumor cell* OR circulating tumour cell* OR CTC OR CTCs).tw (n = 252434)	3. (Esophageal cytology samples OR brush OR balloon OR sponge OR Volatile organic compounds OR Autoantibodies OR Methylated DNA OR MDM OR circulating tumor cell* OR circulating tumour cell* OR CTC OR CTCs).tw (n = 152878)
4. ((miRNAs OR microRNAs OR miR*) AND (circulating OR blood OR serum OR plasma)).tw (n = 44601)	4. ((miRNAs OR microRNAs OR miR*) AND (circulating OR blood OR serum OR plasma)).tw (n = 19882)
5. 2 OR 3 OR 4 (n = 668988)	5. 2 OR 3 OR 4d (n = 381222)
6. (screening OR diagnosis OR validity OR sensitivity OR true positive rate OR false negative rate OR specificity OR true negative rate OR false positive rate OR Youden index OR likelihood ratio OR LR OR positive predictive value OR negative predictive value OR consistency rate OR Kappa OR receiver operator curve OR ROC OR Area Under Curve OR AUC).tw (n = 4315533)	6. (screening OR diagnosis OR validity OR sensitivity OR true positive rate OR false negative rate OR specificity OR true negative rate OR false positive rate OR Youden index OR likelihood ratio OR LR OR positive predictive value OR negative predictive value OR consistency rate OR Kappa OR receiver operator curve OR ROC OR Area Under Curve OR AUC).tw (n = 2734858)
7. 1 AND 5 AND 6 (n = 1206)	7. 1 AND 5 AND 6 (n = 428)
8. Limit 7 to (embase AND (editorial OR letter OR "review")) (n = 127)	8. Limit 7 to (comment OR editorial OR letter OR "review") (n = 56)
9. Limit 7 to (meta analysis OR "systematic review") (n = 35)	9. Limit 7 to (meta analysis OR "systematic review") (n = 8)
10. 7 not (8 OR 9) (n = 1057)	10. 7 not (8 OR 9) (n = 367)

SUPPLEMENTARY TABLE 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist

Section/topic	No.	Checklist item	Reported on page no.
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	N/A
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	8-9

SUPPLEMENTARY TABLE 2. Continued

Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policymakers).	9
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias) and at review level (eg, incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	No funding

SUPPLEMENTARY TABLE 3. Main characteristics of included studies

First author and reference	Publication year	Study design	Country	Age: mean, median or range (y)	Screening methods	Screening category	No. of participants	Sensitivity	Specificity
Kumagai[1]	2012	Case-control study			Endocytoscope (peroral)	Endoscopic	53	1.000	.800
Heresbach[2]	2009	Cross-sectional study	Israel	59	Esophageal capsule endoscopy (peroral)	Endoscopic	47	.581	.813
Safatle-Ribeiro[3]	2017	Cross-sectional study		59	Probe-based confocal laser endomicroscopy (peroral)	Endoscopic	37	.941	.900
Arantes[4]	2013	Cross-sectional study	Brazil	60.7	White-light imaging endoscopy (transnasal)	Endoscopic	106	.923	.989
Arantes[4]	2013	Cross-sectional study	Brazil	60.7	Flexible spectral imaging color enhancement (transnasal)	Endoscopic	106	1.000	.989
Ide[5]	2013	Cross-sectional study		59	White-light imaging endoscopy (peroral)	Endoscopic	43	1.000	1.000
Ide[5]	2013	Cross-sectional study		59	Narrow-band imaging endoscopy (peroral)	Endoscopic	43	1.000	.857
Ide[5]	2013	Cross-sectional study		59	Lugol's iodine chromoendoscopy (peroral)	Endoscopic	43	1.000	.810
Uedo[6]	2010	Cross-sectional study		65	Autofluorescence imaging video endoscopy system (peroral)	Endoscopic	47	1.000	.830
Uedo[6]	2010	Cross-sectional study		65	White-light imaging endoscopy (peroral)	Endoscopic	47	0.600	.930
Dawsey[7]	1998	Cross-sectional study	China		Lugol's iodine chromoendoscopy (peroral)	Endoscopic	253	.960	.630
Peng[8]	2011	Cross-sectional study			Lugol's iodine chromoendoscopy (peroral)	Endoscopic	356	.894	.973
Peng[8]	2011	Cross-sectional study			Lugol's iodine+methylene blue chromoendoscopy (peroral)	Endoscopic	356	.979	.958
Furuhashi[9]	2018	Cross-sectional study	Japan		Narrow-band imaging endoscopy (peroral)	Endoscopic	339	.886	.959
Boller[10]	2009	Cross-sectional study	Switzerland	56.6	Lugol's iodine chromoendoscopy (peroral)	Endoscopic	61	1.000	.965
Ide[11]	2011	Cross-sectional study	Brazil	59	White-light imaging endoscopy (peroral)	Endoscopic	129	.667	1.000
Ide[11]	2011	Cross-sectional study	Brazil	59	Narrow-band imaging endoscopy (peroral)	Endoscopic	129	1.000	.867
Ide[11]	2011	Cross-sectional study	Brazil	59	Lugol's iodine chromoendoscopy (peroral)	Endoscopic	129	1.000	.725
Shin[12]	2015	Cross-sectional study	China		High-resolution microendoscopy (peroral)	Endoscopic	375	.877	.947
Wang[13]	2014	Cross-sectional study	China	58.9	White-light imaging endoscopy (transnasal)	Endoscopic	338	.473	.974

SUPPLEMENTARY TABLE 3. Continued

First author and reference	Publication year	Study design	Country	Age: mean, median or range (y)	Screening methods	Screening category	No. of participants	Sensitivity	Specificity
Wang[13]	2014	Cross-sectional study	China	58.9	Narrow-band imaging endoscopy (transnasal)	Endoscopic	338	.842	.956
Wang[13]	2014	Cross-sectional study	China	58.9	Lugol's iodine chromoendoscopy (transnasal)	Endoscopic	338	.930	.907
Lee[14]	2009	Cross-sectional study	China	60.5	White-light imaging endoscopy (transnasal)	Endoscopic	54	.556	.972
Lee[14]	2009	Cross-sectional study	China	60.5	Narrow-band imaging endoscopy (transnasal)	Endoscopic	54	.889	.972
Lee[14]	2009	Cross-sectional study	China	60.5	Lugol's iodine chromoendoscopy (transnasal)	Endoscopic	54	.889	.694
Takenaka[15]	2009	Cross-sectional study	Japan	64	Narrow-band imaging endoscopy (peroral)	Endoscopic	142	.909	.954
Takenaka[15]	2009	Cross-sectional study	Japan	64	Lugol's iodine chromoendoscopy (peroral)	Endoscopic	142	1.000	.847
Dong[16]	2015	Case-control study	China	65	microRNA-24	microRNA	135	.819	.833
Sun[17]	2019	Case-control study	China	63	microRNA-21, microRNA-223, microRNA-375	microRNA	250	.610	.900
Ibuki[18]	2020	Case-control study	Japan	66	microRNA/isomicroRNAs	microRNA	30	.938	.810
Ibuki[18]	2020	Case-control study	Japan	68	microRNA/isomicroRNAs	microRNA	60	.938	.810
Ibuki[18]	2020	Case-control study	Japan	65	microRNA/isomicroRNAs	microRNA	36	.889	.723
Xu[19]	2015	Case-control study	China		microRNA-10b	microRNA	100	.760	.840
Xu[19]	2015	Case-control study	China		microRNA-29c	microRNA	100	.780	.860
Xu[19]	2015	Case-control study	China		microRNA-205	microRNA	100	.760	.860
Wang[20]	2017	Case-control study	China	52	microRNA-21	microRNA	67	.710	.969
Wang[20]	2017	Case-control study	China	52	microRNA-25	microRNA	67	.710	.688
Wang[20]	2017	Case-control study	China	52	microRNA-145	microRNA	67	.903	.688
Wang[20]	2017	Case-control study	China	52	microRNA-203	microRNA	67	.548	.625
Wang[21]	2019	Case-control study	China	65	microRNA-93	microRNA	173	.595	.912
Dong[22]	2015	Case-control study	China		microRNA-7	microRNA	135	.781	.833
Wu[23]	2014	Case-control study	China	61	Combined microRNA	microRNA	126	.810	.810
Sun[24]	2018	Case-control study	China	66	microRNA-31	microRNA	92	.774	.642
He[25]	2015	Case-control study	China	60.48	microRNA-20a	microRNA	117	.643	.750

(continued on the next page)

SUPPLEMENTARY TABLE 3. Continued

First author and reference	Publication year	Study design	Country	Age: mean, median or range (y)	Screening methods	Screening category	No. of participants	Sensitivity	Specificity
He[25]	2015	Case-control study	China	61.72	microRNA-let-7a	microRNA	117	.743	.850
Yang[26]	2008	Case-control study	China	40-70	Squamous cell carcinoma antigen 2 messenger RNA	microRNA	100	.820	.640
Zhang[27]	2010	Case-control study	China	61	microRNA-10a	microRNA	249	.812	.800
Zhang[27]	2010	Case-control study	China	61	microRNA-22	microRNA	249	.886	.860
Zhang[27]	2010	Case-control study	China	61	microRNA-100	microRNA	249	.638	.810
Zhang[27]	2010	Case-control study	China	61	microRNA-148b	microRNA	249	.664	.870
Zhang[27]	2010	Case-control study	China	61	microRNA-223	microRNA	249	.832	.830
Zhang[27]	2010	Case-control study	China	61	microRNA-133a	microRNA	249	.651	.830
Zhang[27]	2010	Case-control study	China	61	microRNA-127-3p	microRNA	249	.785	.870
Shen[28]	2019	Case-control study	China	60	Combined microRNA	microRNA	174	.896	.763
Zheng[29]	2019	Case-control study	China	59	Combined microRNA	microRNA	104	.807	.791
Zhang[30]	2013	Case-control study	China		microRNA-1322	microRNA	240	.817	.825
Zhang[30]	2013	Case-control study	China		microRNA-1322	microRNA	162	.837	.805
Guan[31]	2016	Case-control study	China	65	microRNA-613	microRNA	150	.813	.627
Zhang[32]	2011	Case-control study	China		microRNA-31	microRNA	241	.867	.843
Zhang[32]	2011	Case-control study	China		microRNA-31	microRNA	162	.861	.791
Yu[33]	2014	Case-control study			microRNA-375	microRNA	43	.917	.778
Chen[34]	2009	Case-control study	China		Cytokeratin-6	microRNA	100	.784	.632
Chen[34]	2009	Case-control study	China		Hypoxia-inducible factor-1α	microRNA	100	.608	.684
Chen[34]	2009	Case-control study	China		Interferon-stimulated gene 15	microRNA	100	.647	.632
Chen[34]	2009	Case-control study	China		Topoisomerase I	microRNA	100	.745	.658
Chen[34]	2009	Case-control study	China		Ubiquitin carrier protein	microRNA	100	.706	.763
Chen[34]	2009	Case-control study	China		Vascular endothelial growth factor	microRNA	100	.706	.711
Dong[35]	2016	Case-control study	China		microRNA-216a	microRNA	171	.800	.902

SUPPLEMENTARY TABLE 3. Continued

First author and reference	Publication year	Study design	Country	Age: mean, median or range (y)	Screening methods	Screening category	No. of participants	Sensitivity	Specificity
Sun[36]	2016	Case-control study	China		microRNA-718	microRNA	171	.692	.667
Wang[37]	2016	Case-control study	China	65	microRNA-146a	microRNA	140	.857	.686
Wang[37]	2016	Case-control study	China	65	microRNA-146a	microRNA	168	.821	.833
Chen[38]	2018	Case-control study	China	60	microRNA-183	microRNA	106	.789	.762
Takeshita[39]	2013	Case-control study	Japan		microRNA-1246	microRNA	147	.713	.739
Huang[40]	2019	Case-control study	China	65.04	microRNA-16	microRNA	1665	.802	.640
Wang[41]	2016	Case-control study	China		microRNA-1297	microRNA	150	.813	.853
Wang[41]	2016	Case-control study	China		microRNA-1297	microRNA	162	.840	.827
Hui[42]	2015	Case-control study	China	58.55	microRNA-129	microRNA	101	.788	.733
Hui[42]	2015	Case-control study	China	58.55	microRNA-451	microRNA	101	.825	.790
Hui[42]	2015	Case-control study	China	58.55	microRNA-365	microRNA	101	.806	.867
Zhou[43]	2017	Case-control study	China		Combined microRNA	microRNA	78	.853	.935
Zhou[43]	2017	Case-control study	China		Combined microRNA	microRNA	214	.925	.906
Zhou[43]	2017	Case-control study	China		Combined microRNA	microRNA	91	.935	.951
Hoshino[44]	2020	Case-control study	Japan		microRNA-1246	microRNA	94	.727	.692
Hoshino[44]	2020	Case-control study	Japan		microRNA-1246	microRNA	135	.713	.706
Hoshino[44]	2020	Case-control study	Japan		microRNA-106b	microRNA	94	.655	.616
Hoshino[44]	2020	Case-control study	Japan		microRNA-106b	microRNA	135	.743	.733
Hoshino[44]	2020	Case-control study	Japan		microRNA-1246/ microRNA-106b	microRNA	94	.800	.800
Hoshino[44]	2020	Case-control study	Japan		microRNA-1246/ microRNA-106b	microRNA	135	.821	.823
Bai[45]	2017	Case-control study	China	58	microRNA-19a	microRNA	169	.663	.664
Zhang[46]	2018	Case-control study	China	63	microRNA-21	microRNA	250	.740	.780
Zhang[46]	2018	Case-control study	China	63	microRNA-223	microRNA	250	.680	.680
Zhang[46]	2018	Case-control study	China	63	microRNA-100	microRNA	250	.580	.580
Zhang[46]	2018	Case-control study	China	63	microRNA-25	microRNA	250	.540	.570

SUPPLEMENTARY TABLE 3. Continued

First author and reference	Publication year	Study design	Country	Age: mean, median or range (y)	Screening methods	Screening category	No. of participants	Sensitivity	Specificity
Zhang[46]	2018	Case-control study	China	63	microRNA-375	microRNA	250	.780	.590
Komatsu[47]	2014	Case-control study	Japan	65	microRNA-25	microRNA	70	.850	.860
Li[48]	2017	Case-control study	China	62	microRNA-15a	microRNA	150	.864	1.000
Dong[49]	2010	Case-control study	China	60	Anti-cell division cycle 25B autoantibodies	Autoantibody	268	.567	.433
Dong[49]	2010	Case-control study	China	60	Squamous cell carcinoma antigen	Autoantibody	268	.172	.828
Kobayashi[50]	2019	Case-control study	Japan	67	Anti-far upstream element-binding protein-interacting repressorΔexon2 autoantibodies	Autoantibody	189	.179	.989
Kobayashi[50]	2019	Case-control study	Japan	67	Lysyl-tRNA synthetase	Autoantibody	189	.147	.968
Kobayashi[50]	2019	Case-control study	Japan	67	Sorting nexin 15	Autoantibody	189	.179	.947
Kobayashi[50]	2019	Case-control study	Japan	67	Spermatogenesis and oogenesis specific basic helix-loop-helix 1	Autoantibody	189	.126	.979
Kobayashi[50]	2019	Case-control study	Japan	67	Cilia and flagella-associated protein 70	Autoantibody	189	.126	.947
Zhou[51]	2011	Case-control study	China		Matrix metalloproteinase-7	Autoantibody	108	.780	.810
Sun[17]	2019	Case-control study	China	63	p62	Autoantibody	250	.270	.900
Sun[17]	2019	Case-control study	China	63	p53	Autoantibody	250	.310	.900
Sun[17]	2019	Case-control study	China	63	LETM1 domain-containing protein 1	Autoantibody	250	.300	.900
Sun[17]	2019	Case-control study	China	63	Murine double minute 2	Autoantibody	250	.440	.900
Sun[17]	2019	Case-control study	China	63	Heterogeneous nuclear ribonucleoproteins A2/B1	Autoantibody	250	.130	.900
Sun[17]	2019	Case-control study	China	63	Cellular-myelocytomatosis viral oncogene	Autoantibody	250	.220	.900
Sun[17]	2019	Case-control study	China	63	Notch intracellular domain	Autoantibody	250	.110	.900
Xu[52]	2014	Case-control study	China	57	Combined autoantibody	Autoantibody	513	.570	.950
Xu[52]	2014	Case-control study	China	56	Combined autoantibody	Autoantibody	371	.510	.960
Zhou[53]	2014	Case-control study	China	51	Combined autoantibody	Autoantibody	288	.640	.940
Cheng[54]	2012	Case-control study	China	58	Adenosine triphosphate-binding cassette C3_IgG	Autoantibody	340	.079	.951

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SUPPLEMENTARY TABLE 3. Continued

First author and reference	Publication year	Study design	Country	Age: mean, median or range (y)	Screening methods	Screening category	No. of participants	Sensitivity	Specificity
Cheng[54]	2012	Case-control study	China	58	Adenosine triphosphate-binding cassette C3_IgA	Autoantibody	340	.132	.951
Guan[55]	2013	Case-control study	China	58	Interleukin-2 receptor alpha chain_IgG	Autoantibody	323	.720	.900
Guan[55]	2013	Case-control study	China	58	Interleukin-2 receptor alpha chain_IgA	Autoantibody	323	.082	.903
Ye[56]	2013	Case-control study	China	58	Forkhead/winged helix transcription factor 3_IgG	Autoantibody	324	.227	.952
Xu[57]	2017	Case-control study	China	58	L1-cell adhesion molecule	Autoantibody	285	.262	.904
Xu[57]	2017	Case-control study	China	58	L1-cell adhesion molecule	Autoantibody	94	.277	.904
Tokita[58]	2013	Case-control study	Japan		Clathrin heavy chain	Autoantibody	88	.750	.950
Tokita[58]	2013	Case-control study	Japan		p53	Autoantibody	88	.430	.980
Tokita[58]	2013	Case-control study	Japan		Ki67	Autoantibody	88	.680	1.000
Peng[59]	2016	Case-control study	China	56	Dickkopf-1	Autoantibody	282	.373	.907
Peng[59]	2016	Case-control study	China	56	Dickkopf-1 autoantibodies	Autoantibody	282	.335	.918
Peng[59]	2016	Case-control study	China	56	Dickkopf-1	Autoantibody	157	.413	.849
Peng[59]	2016	Case-control study	China	56	Dickkopf-1 autoantibodies	Autoantibody	157	.337	.925
Li[60]	2017	Case-control study	China	57	Autoantibodies against Ezrin	Autoantibody	247	.275	.959
Sun[61]	2020	Case-control study	China	66	Combined autoantibody	Autoantibody	260	.715	.938
Sun[61]	2020	Case-control study	China	63	Combined autoantibody	Autoantibody	250	.776	.816
Gao[62]	2014	Case-control study	China		Heat shock protein 105	Autoantibody	86	.391	.950
Gao[62]	2014	Case-control study	China		Triosephosphate isomerase	Autoantibody	86	.348	.950
Zhang[63]	2016	Case-control study	China	62	Combined autoantibody	Autoantibody	648	.679	.867
Zhang[63]	2016	Case-control study	China	63	Combined autoantibody	Autoantibody	372	.677	.855
Huang[64]	2011	Case-control study	China		Minichromosome maintenance protein 2	Autoantibody	239	.913	.618
Huang[64]	2011	Case-control study	China		Proliferating cell nuclear antigen	Autoantibody	239	.884	.471
Huang[64]	2011	Case-control study	China		Ki67	Autoantibody	239	.783	.578
Zhang[65]	2016	Case-control study	China	>40	p53	Autoantibody	214	.530	.800

SUPPLEMENTARY TABLE 3. Continued

First author and reference	Publication year	Study design	Country	Age: mean, median or range (y)	Screening methods	Screening category	No. of participants	Sensitivity	Specificity
Zhang[65]	2016	Case-control study	China	>40	Carbohydrate antigen 19-9	Autoantibody	214	.440	.938
Fujita[66]	2006	Case-control study	Japan	53.2	Peroxiredoxin6 autoantibody	Autoantibody	60	.500	.934
Liu[67]	2008	Case-control study	China	62	Anti-cell division cycle 25B autoantibodies	Autoantibody	226	.363	1.000
Fujita[68]	2008	Case-control study	Japan	53.2	Heat shock protein 70	Autoantibody	29	.937	1.000
Onoyama[69]	2016	Case-control study	Japan		γ-glutamyl hydroxymethylrho-damine green	Autoantibody	74	.969	.857
Zhang[70]	2012	Case-control study	China		Stress Induced Phosphoprotein 1 autoantibodies	Autoantibody	120	.806	.787
Xu[71]	2017	Case-control study	China	58	Stress Induced Phosphoprotein 1 autoantibodies	Autoantibody	258	.419	.901
Xu[71]	2017	Case-control study	China	58	Stress Induced Phosphoprotein 1 autoantibodies	Autoantibody	100	.400	.925
Takeshita[39]	2013	Case-control study	Japan		Squamous cell carcinoma antigen	Autoantibody	147	.574	.674
Chen[72]	2016	Case-control study	China	57	Fascin autoantibodies	Autoantibody	247	.248	.990
Roshandel[73]	2014	Cohort study	Iran	54.9	p53	Autoantibody	301	1.000	.890
Sharma[74]	2004	Case-control study	India		Teratocarcinoma oncogene 21 protein	Autoantibody	112	.723	1.000
Choi[75]	2018	Case-control study	Korea	57	Circulating tumor cells	Cytology	104	.863	.903
Zhang[76]	2019	Case-control study	China	65	Circulating tumor cells	Cytology	113	.746	.740
Roth[77]	1997	Cross-sectional study	China	50-69	Balloon	Cytology	432	.440	.990
Roth[77]	1997	Cross-sectional study	China	50-69	Sponge	Cytology	376	.180	1.000
Yamaguchi[78]	2016	Case-control study		62.3	Circulating tumor cells	Cytology	33	.783	1.000
Wang[79]	2016	Cross-sectional study	China	40-69	Deoxyribonucleic acid image cytometry	Cytology	2420	.960	.408
Mariano[80]	2018	Cross-sectional study	Brazil	50	Brush	Cytology	123	.986	.962
Boller[10]	2009	Cross-sectional study	Switzerland	56.6	Brush	Cytology	61	.750	1.000
Lopes[81]	2009	Cross-sectional study		52.6	Balloon	Cytology	171	.667	.975
Roshandel[73]	2014	Cohort study	Iran	54.9	Sponge	Cytology	301	1.000	.970

References provided here can be found in Supplementary Table 4.

SUPPLEMENTARY TABLE 4. References for studies included in the systematic review

1. Kumagai Y, Kawada K, Yamazaki S, et al. Current status and limitations of the newly developed endocytoscope GIF-Y0002 with reference to its diagnostic performance for common esophageal lesions. J Dig Dis 2012;13:393-400.
2. Heresbach D, Leray E, Dhalluin PN, et al. Diagnostic accuracy of esophageal capsule endoscopy versus conventional upper digestive endoscopy for suspected esophageal squamous cell carcinoma. Endoscopy 2010;42:93-7.
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SUPPLEMENTARY TABLE 5. Univariable and multivariable meta-regression of endoscopy (POE)

			Univariable meta-regression					Multivariable meta-regression		
Parameter	Category	No. of studies	Sensitivity	P1*	Specificity	P2†	Likelihood-ratio tests χ^2	I^2 (95% confidence interval)	P‡
Screening methods									
White-light imaging endoscopy (POE)	Yes	3	.70 (.34-1.00)	.04	.99 (.97-1.00)	.06	9.48	79 (54-100)	.01
	No	16	.95 (.91-.99)		.90 (.85-.94)				
Narrow-band imaging (POE)	Yes	4	.95 (.87-1.00)	.69	.93 (.85-1.00)	.18	.19	0 (0-100)	.91
	No	15	.93 (.88-.99)		.92 (.87-.96)				
Lugol's iodine chromoendoscopy (POE)	Yes	7	.97 (.93-1.00)	.60	.89 (.81-.97)	<.01	3.53	43 (.0-100)	.17
	No	12	.89 (.81-.97)		.94 (.90-.98)				
Others§	Yes	5	.92 (.82-1.00)	.31	.89 (.78-.99)	.04	1.53	0 (0-100)	.47
	No	14	.94 (.89-.99)		.93 (.89-.97)				
Study design				.01		.16	3.70	46 (0-100)	.16
Cross-sectional study	Yes	18	.92 (.87-.98)		.92 (.89-.96)				
Case-control study	Yes	1	1.00 (1.00-1.00)		.80 (.42-1.00)				
Country									
Israel	Yes	1	.58 (.22-.95)	<.01	.82 (.46-1.00)	.71	10.02	80 (57-100)	.01
	No	18	.94 (.91-.97)		.92 (.88-.96)				
China	Yes	2	.93 (.81-1.00)	.96	.85 (.66-1.00)	.11	1.79	0 (0-100)	.41
	No	17	.94 (.89-1.00)		.93 (.89-.96)				
Japan	Yes	3	.95 (.85-1.00)	.76	.93 (.86-1.00)	.42	.29	0 (0-100)	.86
	No	16	.93 (.88-.99)		.92 (.87-.96)				
Brazil	Yes	3	.95 (.84-1.00)	.40	.92 (.83-1.00)	.42	.09	0 (0-100)	.96
	No	16	.93 (.88-.99)		.92 (.88-.96)				
Study period									
2005-2009	Yes	6	.98 (.93-1.00)	.04	.93 (.87-.99)	.12	1.62	0 (0-100)	.44
2010-2015	Yes	5	.92 (.82-1.00)	0.46	.94 (.88-1.00)	.22	.46	0 (0-100)	.80
Age		19	.94 (.74-.99)	.99	.91 (.85-.95)	.91	78.20	97 (96-99)	<.01

POE, Peroral endoscopy.
*P1: *P* value of sensitivity in univariable meta-regression.
†P2: *P* value of specificity in univariable meta-regression.
‡P: *P* value in multivariable meta-regression.
§Others include endocytoscope, esophageal capsule endoscopy, probe-based confocal laser endomicroscopy, high-resolution microendoscopy, and autofluorescence imaging video-endoscopy system.

SUPPLEMENTARY TABLE 6. Univariable and multivariable meta-regression of endoscopy (TNE)

Parameter	Category	No. of studies	Sensitivity	P1*	Specificity	P2†	Likelihood-ratio tests χ^2	I^2 (95% confidence interval)	P‡
Screening methods									
White-light imaging endoscopy (TNE)	Yes	3	.63 (.44-.81)	<.01	.98 (.96-1.00)	.35	9.21	78 (53-100)	.01
	No	5	.91 (.85-.98)		.94 (.89-.99)				
Narrow-band imaging (TNE)	Yes	2	.88 (.70-1.00)	.76	.97 (.91-1.00)	.89	.20	0 (0-100)	.91
	No	6	.84 (.70-.98)		.96 (.92-1.00)				
Lugol's iodine chromoendoscopy (TNE)	Yes	2	.93 (.81-1.00)	.29	.85 (.76-.95)	<.01	11.15	82 (62-100)	<.01
	No	6	.82 (.67-.96)		.98 (.96-.99)				
Country							9.86	80 (56-100)	.01
China	Yes	2	.97 (.90-1.00)	.02	.99 (.97-1.00)	.06			
Brazil	Yes	6	.81 (.68-.95)	.27	.94 (.90-.98)	.05			
Study period									
2005-2009	Yes	3	.80 (.60-1.00)	.40	.95 (.90-1.00)	.41	.72	0 (0-100)	.70
2010-2015	Yes	2	.97 (.90-1.00)	.02	.99 (.97-1.00)	.06	9.86	80 (56-100)	.01
Age		8	.90 (.68-.97)	.64	.97 (.88-.99)	.77	1.10	0 (0-100)	.58

TNE, Transnasal endoscopy.
*P1: P value of sensitivity in univariable meta-regression.
†P2: P value of specificity in univariable meta-regression.
‡P: P value in multivariable meta-regression.

SUPPLEMENTARY TABLE 7. Univariable and multivariable meta-regression of microRNA

Parameter	Category	No. of studies	Sensitivity	P1*	Specificity	P2†	Likelihood-ratio tests χ^2	I^2 (95% confidence interval)	P‡
Specimen origin							4.30	54 (0-100)	.12
Serum	Yes	51	.79 (.76-.81)	<.01	.78 (.75-.81)	<.01			
Plasma	Yes	18	.75 (.68-.80)		.80 (.73-.85)				
Country							9.48	79 (54-100)	.01
China	Yes	57	.77 (.75-.80)	<.01	.78 (.75-.81)	<.01			
Japan	Yes	11	.79 (.73-.85)		.77 (.70-.83)				
Study period									
2005-2009	Yes	12	.78 (.72-.83)	<.01	.75 (.68-.81)	<.01	34.44	94 (89-99)	<.01
	No	54	.77 (.75-.80)		.79 (.77-.82)				
2010-2014	Yes	53	.78 (.75-.80)	<.01	.79 (.76-.82)	<.01	33.31	94 (89-99)	<.01
	No	13	.76 (.71-.82)		.76 (.70-.82)				
2015-2019	Yes	1	.59 (.37-.82)	.03	.91 (.80-1.00)	.51	40.94	95 (91-99)	<.01
	No	65	.78 (.75-.80)		.78 (.76-.81)				
Age		69	.77 (.74-.80)	.84	.77 (.73-.80)	.93	362.75	99 (99-100)	<.01

*P1: P value of sensitivity in univariable meta-regression.
†P2: P value of specificity in univariable meta-regression.
‡P: P value in multivariable meta-regression.

SUPPLEMENTARY TABLE 8. Univariable and multivariable meta-regression of autoantibody

			Univariable meta-regression				Multivariable meta-regression		
Parameter	Category	No. of studies	Sensitivity	P1*	Specificity	P2†	Likelihood-ratio tests χ²	I² (95% confidence interval)	P‡
Specimen origin							13.89	86 (70-100)	<.01
Serum	Yes	43	.52 (.43-.61)	<.01	.92 (.88-.94)	<.01			
Plasma	Yes	12	.22 (.14-.33)		.92 (.90-.93)				
Country							11.02	82 (61-100)	<.01
China	Yes	41	.42 (.33-.52)	.62	.90 (.87-.92)	<.01			
Japan	Yes	14	.52 (.35-.69)		.95 (.93-.98)				
Study period									
2000-2004	Yes	2	.34 (.02-.67)	.59	.66 (.38-.93)	.01	286.57	99 (99-100)	<.01
	No	33	.48 (.39-.57)		.90 (.87-.93)				
2005-2009	Yes	11	.61 (.47-.75)	.14	.88 (.81-.94)	<.01	282.10	99 (99-100)	<.01
	No	24	.41 (.31-.50)		.90 (.86-.93)				
2010-2014	Yes	19	.36 (.27-.46)	.06	.91 (.87-.95)	<.01	285.62	99 (99-100)	<.01
	No	16	.60 (.49-.71)		.87 (.81-.92)				
2015-2019	Yes	2	.75 (.49,1.00)	.17	.89 (.76-1.00)	.46	280.88	99 (99-100)	<.01
	No	33	.45 (.37-.53)		.89 (.86-.92)				
Age		55	.33 (.26-.41)	.69	.92 (.90-.94)	.94	241.07	99 (99-100)	<.01

*P1: P value of sensitivity in univariable meta-regression.
†P2: P value of specificity in univariable meta-regression.
‡P: P value in multivariable meta-regression.

SUPPLEMENTARY TABLE 9. Univariable and multivariable meta-regression of cytology

			Univariable meta-regression					Multivariable meta-regression		
Parameter	Category	No. of studies	Sensitivity	P1*	Specificity	P2†	Likelihood-ratio tests χ^2	I^2 (95% confidence interval)	P‡
Study design									
Case-control study	Yes	3	.80 (.51-1.00)	.94	.86 (.62-1.00)	.27	3.83	48 (0-100)	.15
	No	7	.83 (.63-1.00)		.97 (.93-1.00)				
Cohort study	Yes	1	.94 (.75-1.00)	.03	.97 (.87-1.00)	.06	1.49	0 (0-100)	.47
	No	9	.79 (.61-.96)		.95 (.90-1.00)				
Cross-sectional study	Yes	6	.79 (.57-1.00)	.89	.97 (.93-1.00)	.13	1.24	0 (0-100)	.54
	No	4	.83 (.61-1.00)		.91 (.77-1.00)				
Country									
Brazil	Yes	1	.99 (.95-1.00)	<.01	.97 (.85-1.00)	.04	24.54	92 (84-99)	<.01
	No	7	.74 (.53-.95)		.95 (.89-1.00)				
China	Yes	4	.64 (.32-.97)	.09	.94 (.83-1.00)	.82	25.00	92 (85-99)	<.01
	No	4	.91 (.80-1.00)		.97 (.91-1.00)				
Korea	Yes	1	.87 (.48-1.00)	.28	.91 (.60-1.00)	.36	18.02	89 (78-100)	<.01
	No	7	.82 (.61-1.00)		.96 (.90-1.00)				
Switzerland	Yes	1	.79 (.09-1.00)	.54	.99 (.94-1.00)	<.01	18.39	89 (78-100)	<.01
	No	7	.83 (.64-1.00)		.95 (.87-1.00)				
Study period									
1995-1999	Yes	2	.30 (.01-.60)	<.01	1.00 (.99-1.00)	<.01	18.91	89 (79-100)	<.01
	No	7	.90 (.82-.97)		.91 (.81-1.00)				
2005-2009	Yes	3	.94 (.81-1.00)	.07	.91 (.74-1.00)	.86	10.95	82 (61-100)	<.01
	No	6	.74 (.51-.97)		.97 (.91-1.00)				
2010-2014	Yes	2	.93 (.80-1.00)	.08	.97 (.88-1.00)	.10	12.08	83 (65-100)	<.01
	No	7	.75 (.53-.96)		.95 (.89-1.00)				
2015-2019	Yes	2	.81 (.46-1.00)	.76	.83 (.49-1.00)	.45	12.48	84 (66-100)	<.01
	No	7	.83 (.64-1.00)		.97 (.93-1.00)				
Age		10	.79 (.71-.85)	.74	.82 (.72-.89)	.71	100.61	98 (97-99)	<.01

*P1: P value of sensitivity in univariable meta-regression.
†P2: P value of specificity in univariable meta-regression.
‡P: P value in multivariable meta-regression.

SUPPLEMENTARY TABLE 10. Summary estimates of diagnostic values excluding outlier studies in sensitivity analyses

Screening methods*	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Diagnostic odds ratio	Area under the curve†	P‡	I²§
Endoscopy (24/3730)								
POE (16/2342)	.97 (.90-.99)	.92 (.88-.95)	12.1 (8.1-18.0)	.04 (.01-.11)	332 (113,972)	.98 (.97-.99)	.09	27.6/88.3
Lugol's iodine chromoendoscopy (POE) (6/1087)	.94 (.90-.97)	.91 (.89-.93)	10.3 (3.2-33.1)	.08 (.04-.17)	218 (71,663)	.98 (.97-.99)	.10	46.1/93.1
White-light imaging endoscopy (POE) (2/90)	.67 (.22-.96)	.96 (.90-.99)	15.3 (2.5-95.0)	.39 (.15-1.05)	36 (4-312)	NA	NA	.00/76.6
Esophageal capsule endoscopy (POE) (0/0)								
TNE (7/1334)	.85 (.66-.94)	.97 (.94-.98)	25.5 (13.7-47.5)	.16 (.07-.38)	160 (52-491)	.98 (.96-.99)	.17	85.2/82.3
Lugol's iodine chromoendoscopy (TNE) (1/338)	.94 (.78-.99)	.91 (.87-.94)	10.2 (7.1-14.7)	.07 (.02-.26)	130 (128-131)	NA	NA	NA
MicroRNA (62/9976)	.78 (.76-.80)	.77 (.75-.79)	3.4 (3.0-3.8)	.28 (.26-.31)	12 (10-15)	.84 (.81-.87)	.32	64.2/77.6
Serum (50/8195)	.79 (.77-.81)	.77 (.75-.80)	3.5 (3.1-3.9)	.28 (.25-.31)	13 (10-15)	.85 (.81-.88)	.95	64.5/78.3
Plasma (12/1781)	.75 (.71-.79)	.77 (.69-.83)	3.2 (2.3-4.5)	.33 (.26-.41)	10 (6-16)	.81 (.77-.84)	.06	56.2/77.1
Autoantibody (51/11,544)	.46 (.37-.55)	.92 (.89-.94)	5.5 (4.4-6.9)	.59 (.51-.69)	9 (7-13)	.86 (.83-.89)	.06	94.3/93.2
Serum (39/8135)	.54 (.45-.63)	.92 (.89-.94)	6.9 (5.2-9.1)	.50 (.41-.60)	14 (10-19)	.86 (.83-.89)	.23	94.7/95.0
Plasma (12/3409)	.22 (.14-.33)	.92 (.90-.93)	2.6 (1.8-3.9)	.85 (.76-.95)	3 (2-5)	.89 (.86-.91)	.94	94.8/42.1

Values in parentheses are confidence intervals and n/N values are number of studies/number of participants.

POE, Peroral endoscopy; *TNE*, transnasal endoscopy; *NA*, not applicable.

*Only screening methods with outliers were presented. No outliers were identified for narrow-band imaging (POE and TNE), endocytoscope (POE), probe-based confocal laser endomicroscopy (POE), high-resolution microendoscopy (POE), autofluorescence imaging video-endoscopy system (POE), white-light imaging endoscopy (TNE), flexible spectral imaging color enhancement (TNE), and cytology.

†Several screening methods had insufficient studies so the area under the curve could not be calculated.

‡P value of Deeks' funnel plot asymmetry test. Several screening methods had insufficient studies so this index could not be calculated.

§I^2 of sensitivity/I^2 of specificity. Several screening methods had insufficient studies so this index could not be calculated.

SUPPLEMENTARY TABLE 11. Neoplasia detection rates based on individual studies

First author and reference	Study design	Country	Screening methods*	Screening category	High-grade dysplasia/ esophageal squamous cell carcinoma cases	Total sample size	Neoplasia detection rate (%)
Heresbach[2]	Cross-sectional study	Israel	Esophageal capsule endoscopy (peroral)	Endoscopic	21	47	44.7
Safatle-Ribeiro[3]	Cross-sectional study		Probe-based confocal laser endomicroscopy (peroral)	Endoscopic	18	37	48.6
Arantes[4]	Cross-sectional study	Brazil	White-light imaging endoscopy (transnasal)	Endoscopic	13	106	12.3
Arantes[4]	Cross-sectional study	Brazil	Flexible spectral imaging color enhancement (transnasal)	Endoscopic	14	106	13.2
Ide[5]	Cross-sectional study		White-light imaging endoscopy (peroral)	Endoscopic	1	43	2.3
Ide[5]	Cross-sectional study		Narrow-band imaging endoscopy (peroral)	Endoscopic	7	43	16.3
Ide[5]	Cross-sectional study		Lugol's iodine chromoendoscopy (peroral)	Endoscopic	9	43	20.9
Uedo[6]	Cross-sectional study		Autofluorescence imaging video-endoscopy system (peroral)	Endoscopic	12	47	25.8
Uedo[6]	Cross-sectional study		White-light imaging endoscopy (peroral)	Endoscopic	6	47	12.6
Dawsey[7]	Cross-sectional study	China	Lugol's iodine chromoendoscopy (peroral)	Endoscopic	161	253	63.6
Peng[8]	Cross-sectional study		Lugol's iodine chromoendoscopy (peroral)	Endoscopic	91	356	25.6
Peng[8]	Cross-sectional study		Lugol's iodine+methylene blue chromoendoscopy (peroral)	Endoscopic	103	356	28.9
Furuhashi[9]	Cross-sectional study	Japan	Narrow-band imaging endoscopy (peroral)	Endoscopic	51	339	15.1
Boller[10]	Cross-sectional study	Switzerland	Lugol's iodine chromoendoscopy (peroral)	Endoscopic	6	61	9.8
Ide[11]	Cross-sectional study	Brazil	White-light imaging endoscopy (peroral)	Endoscopic	6	129	4.7
Ide[11]	Cross-sectional study	Brazil	Narrow-band imaging endoscopy (peroral)	Endoscopic	25	129	19.3
Ide[11]	Cross-sectional study	Brazil	Lugol's iodine chromoendoscopy (peroral)	Endoscopic	42	129	32.6
Shin[12]	Cross-sectional study	China	High-resolution microendoscopy (peroral)	Endoscopic	60	375	16.0
Wang[13]	Cross-sectional study	China	White-light imaging endoscopy (transnasal)	Endoscopic	24	338	7.0
Wang[13]	Cross-sectional study	China	Narrow-band imaging endoscopy (transnasal)	Endoscopic	41	338	12.2
Wang[13]	Cross-sectional study	China	Lugol's iodine chromoendoscopy (transnasal)	Endoscopic	59	338	17.5
Lee[14]	Cross-sectional study	China	White-light imaging endoscopy (transnasal)	Endoscopic	11	54	19.9
Lee[14]	Cross-sectional study	China	Narrow-band imaging endoscopy (transnasal)	Endoscopic	17	54	31.0
Lee[14]	Cross-sectional study	China	Lugol's iodine chromoendoscopy (transnasal)	Endoscopic	26	54	48.1

SUPPLEMENTARY TABLE 11. Continued

First author and reference	Study design	Country	Screening methods*	Screening category	High-grade dysplasia/ esophageal squamous cell carcinoma cases	Total sample size	Neoplasia detection rate (%)
Takenaka[15]	Cross-sectional study	Japan	Narrow-band imaging endoscopy (peroral)	Endoscopic	16	142	11.3
Takenaka[15]	Cross-sectional study	Japan	Lugol's iodine chromoendoscopy (peroral)	Endoscopic	31	142	21.8
Roth[77]	Cross-sectional study	China	Balloon	Cytology	11	432	2.6
Roth[77]	Cross-sectional study	China	Sponge	Cytology	2	376	.5
Wang[79]	Cross-sectional study	China	DNA image cytometry	Cytology	1446	2420	59.8
Mariano[80]	Cross-sectional study	Brazil	Brush	Cytology	71	123	57.7
Boller[10]	Cross-sectional study	Switzerland	Brush	Cytology	3	61	4.9
Lopes[81]	Cross-sectional study		Balloon	Cytology	8	171	4.8
Roshandel[73]	Cohort study	Iran	Sponge	Cytology	22	301	7.2

References given here can be found in Supplementary Table 4.

*The neoplasia detection rates of endocytoscope, microRNA, autoantibody, and cytology (a part of studies) could not be calculated because their study design was case-control.

SUPPLEMENTARY TABLE 12. Neoplasia detection rates based on screening methods

Screening methods*	No. of studies	High-grade dysplasia/esophageal squamous cell carcinoma cases	Total sample size	Neoplasia detection rate (%)
Endoscopy	26			
POE	18	666	2718	24.5
Lugol's iodine chromoendoscopy (POE)	7	443	1340	33.0
White-light imaging endoscopy (POE)	3	13	219	5.9
Narrow-band imaging (POE)	4	99	653	15.2
Esophageal capsule endoscopy (POE)	1	21	47	44.7
Probe-based confocal laser endomicroscopy (POE)	1	18	37	48.6
High-resolution microendoscopy (POE)	1	60	375	16.0
Autofluorescence imaging video-endoscopy system (POE)	1	12	47	25.8
TNE	8	204	1388	14.7
Lugol's iodine chromoendoscopy (TNE)	2	85	392	21.7
White-light imaging endoscopy (TNE)	3	47	498	9.5
Narrow-band imaging (TNE)	2	58	392	14.8
Flexible spectral imaging color enhancement (TNE)	1	14	106	13.2
Cytology	7	1563	3884	40.2

POE, Peroral endoscopy; *TNE*, transnasal endoscopy.

*The neoplasia detection rates of endocytoscope, microRNA, autoantibody, and cytology (a part of studies) could not be calculated because their study design was case-control.

SUPPLEMENTARY TABLE 13. Neoplasia detection rates based on countries/regions

Countries*	No. of studies	High-grade dysplasia/esophageal squamous cell carcinoma cases	Total sample size	Neoplasia detection rate (%)
China	11	1858	5032	36.9
Brazil	6	171	722	23.7
Switzerland	2	9	122	7.4
Japan	3	98	623	15.7
Iran	1	22	301	7.2
Israel	1	21	47	44.7

*The neoplasia detection rates of endocytoscope, microRNA, autoantibody, and cytology (a part of studies) could not be calculated because their study design was case-control.