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ORIGINAL RESEARCH

Serum pepsinogen assay is not recommended for the diagnosis of esophageal squamous cell carcinoma: a systematic review and meta-analysis

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Background: Serum pepsinogen I (PGI) concentration and PGI/PGII ratio (PGR) are often used as serological markers for gastric fundus atrophy (AGA) and gastric carcinoma. However, their diagnostic value in esophageal carcinoma (EC) is inaccurate.

Methods: This study evaluated the diagnostic value of PGI and PGR in EC by searching the PubMed, Web of Science, Embase, Cochrane Library and Cochrane Central Register of Controlled Trials databases for literature on the diagnosis of EC with PGI and PGR from January 1, 2000 to October 2, 2018. The included literature were systematically evaluated using QUSDAS-2 software. Meta-analysis was conducted using STATA 15.0 software. The summary receiver operating characteristic curve (SROC) accuracy was plotted, the area under the curve was calculated.

Results: A total of 84 papers were selected, and after screening, nine papers on esophageal squamous cell carcinoma (ESCC) were finally included. Results showed low an ESCC-specific diagnostic sensitivity (0.27), high specificity (0.85), and 0.63 AUC of SROC when PGI≤70 ng/mL. When PGR≤3, the ESCC-specific diagnostic sensitivity was low (0.29), the specificity was high (0.83), and the AUC of SROC was 0.63.

Conclusion: According to the current research results, PGI≤70 ng/mL or PGR≤3 diagnostic ESCC sensitivity is low, and specificity is high. These findings indicate that neither PGI≤70 ng/mL nor PGR≤3 can be used as an ESCC-screening index.

Keywords: esophageal squamous cell carcinoma, PGI, PGR, diagnosis, meta-analysis

Introduction

Esophageal carcinoma (EC) is the seventh most common cancer worldwide, and its mortality ranks sixth.[1] EC includes two main types: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC).[2] EC is dominated by EA in Western countries, whereas ESCC is predominant in Eastern countries.[3] China is a high-incidence country for EC, mainly ESCC. Moreover, the incidence rate of ESCC in China mainland ranks fifth in carcinomas, and its mortality rate ranks fourth.[4]

The knowledge of EC pathogenesis remains incomplete. Most patients are diagnosed in the middle or advanced stages, and the 5-year survival is approximately 20%.[5] Early diagnosis and treatment are key factors for EC prognosis. Therefore, finding an economical and noninvasive method for screening high-risk populations for EC and for monitoring patients with esophageal squamous dysplasia (ESD) is extremely urgent. The diagnostic rate of EC via endoscopy is gradually

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increasing, but the diagnostic approach is invasive and expensive. Moreover, certain patients fail in successful compliance, and operator skills vary. In China, the current diagnosis rate of early EC is low, and EC-specific markers are lacking. Furthermore, our previous study found that serum IL-6 and IL-8 may be an effective indicator for the early diagnosis of ESCC, but the clinical application needs further investigation.[6]

Serum pepsinogen (PG) mainly includes two types: pepsinogen I (PGI) and pepsinogen Ⅱ (PGⅡ).[7] PG is mainly produced by the stomach and basal cells in the gastric fundus and cervical mucus cells.[8] The gastric mucosa atrophy leads to a decrease in PGI, but PGⅡ shows no change nor increase, further leading to a decrease in PGI/PGII ratio (PGR). Therefore, PGI and PGR are serologically used as markers of gastric fundus atrophy (AGA), in a process "serological biopsy".[9,10] The present study aimed to evaluate the EC-specific diagnostic sensitivity and specificity of PGI and PGR via meta-analysis and to comprehensively assess their application values in EC diagnosis.

Materials and methods

Literature search strategy

The Preferred Reporting Items for Systematic reviews and Meta-Analyses statement was followed to conduct this systematic review (Table S1).[11] We searched for research literature on PGI and PGR diagnostic EC in PubMed, Web of Science, Embase, Cochrane Library, and Cochrane Central Register of Controlled Trials databases. The retrieval time covered January 1, 2000 to October 2, 2018, and we used the search terms:("PGI" or "PGⅡ" or "PGI/Ⅱ" or "PGR" or"PG",or "pepsinogen"), and ("esophageal carcinoma" or "esophageal cancer" or "esophageal tumor" or "esophageal squamous dysplasia" or "esophageal plasma") and ("diagnosis" or "sensitivity" or "specificity"). Search strategy is shown in Table S2. Reference lists of all selected articles were retrieved manually to identify any additional published studies. In the case of repeat reports from the same study, the one with the larger population or extended follow-up was selected. Only published clinical studies were included.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients with EC were diagnosed based on pathology. (2) The control group included adults without any history of malignant tumors, and patients with benign gastrointestinal diseases were included. (3) Peripheral blood samples were collected before patients received treatment. (4) Moreover, inclusion studies must have been followed up for more than 6 months after biomarker assessment to rule out the delayed diagnosis of malignancy. (5) The diagnostic performance evaluation indexes included sensitivity and specificity. Additionally, patient data included in the study were comprehensive and included original information. The data of true positive (TP) number, true negative (TN) number, false positive (FP) number, false negative (FN) number, or sensitivity and specificity were obtained directly or indirectly. (6) Lastly, the study should only be conducted once, and the sample size of each study should be more than 10.

Exclusion criteria: (1) Only those with esophageal and gastric junction cancer, high-grade intraepithelial neoplasia of esophagus or no difference between appeal and esophageal cancer were excluded. (2) We were unable to obtain complete data and cannot construct a diagnostic analysis in a 2×2 form. (3) Review, editorial non-experimental research literature such as case reports and conference abstracts. (4) Research specimens are basic research such as pathological tissues and animal experiments. (5) Repeated publication studies.

Data extraction

According to the above criteria, two researchers (Liu and Zhang) independently screened the literature and obtained data. In case of disagreements, a third researcher was consulted to intervene in the discussion to reach a final conclusion. The main information to be extracted in relevant literature included the following: author, year, pathological type, biomarker type and boundary point, number of cases and controls, specificity, sensitivity, negative likelihood ratio (NLR), positive likelihood ratio (PLR), relative-risk ratio and 95% confidence interval (95% CI). We converted the extracted data into a four-table data, that is, TP, FP, TN, and FN.

Data extraction and quality assessment

This study was conducted using QUADA-2 developed on the basis of (quality assessment of diagnostic accuracy studies, QUADAS).[12] Risk assessment criteria were used to evaluate the quality of the literature and included four elements: case selection, trials to be evaluated, gold criteria, case flow, and progress.[13] The results were divided into three types: "Yes", "No", and "Unknown". When "Yes"≥7, the literature quality is good, and vice versa.

Statistical analysis

Meta-analysis was performed using STATA software (Stata Corporation, version 15.0, College Station, TX, USA). First, the between-study threshold effect was analyzed. The Spearman correlation coefficients for the logarithms of sensitivity and of (1-specificity) were calculated. If $P<0.05$, a threshold effect existed. Heterogeneity test was performed using Cochran's Q test with a test value of I^2. If $P>0.05$ or $I^2<50\%$ indicated the absence of heterogeneity, and the fixed effect model was used. Otherwise, the random effects model was employed.[14] The summary receiver operating characteristic curve (SROC) was plotted, and the area under the curve (AUC) and Q indexes were calculated. AUC is another indicator of the overall accuracy of diagnostic tests. The AUC value ranges from 0 to 1, wherein a value close to 1, means good diagnostic effect;meanwhile, diagnostic odds ratio (DOR) ranges from 0 to ∞, wherein large value, means good diagnostic accuracy.[15] When DOR=1, diagnostic tests present difficulty in distinguishing patients from the healthy population. The present study adopted these commonly used criteria for screening gastric cancer in Japan as a cut-in point, that is, PGI≤70 ng/mL, PGR≤3 or PGI≤70 ng/mL and PGR≤3 allow merging of the effect amount without any heterogeneity.[16] If no heterogeneity was observed, the effect amount was combined. Publication bias was assessed by Egger's regression. Differences and analytical parameters were considered as statistically significant when $P<0.05$.

Results

Search results and characteristics of the included study

Finally, ten articles were included in the study.[6–14] Figure 1 shows the literature screening process. Table 1 list the basic features of the literature, including nine articles on ESCC. The sources of funds for each study has been listed in Table S3. Three articles mentioned EAC, including two studies according to the PGR≤3 standard.[17,18] At least four articles were used

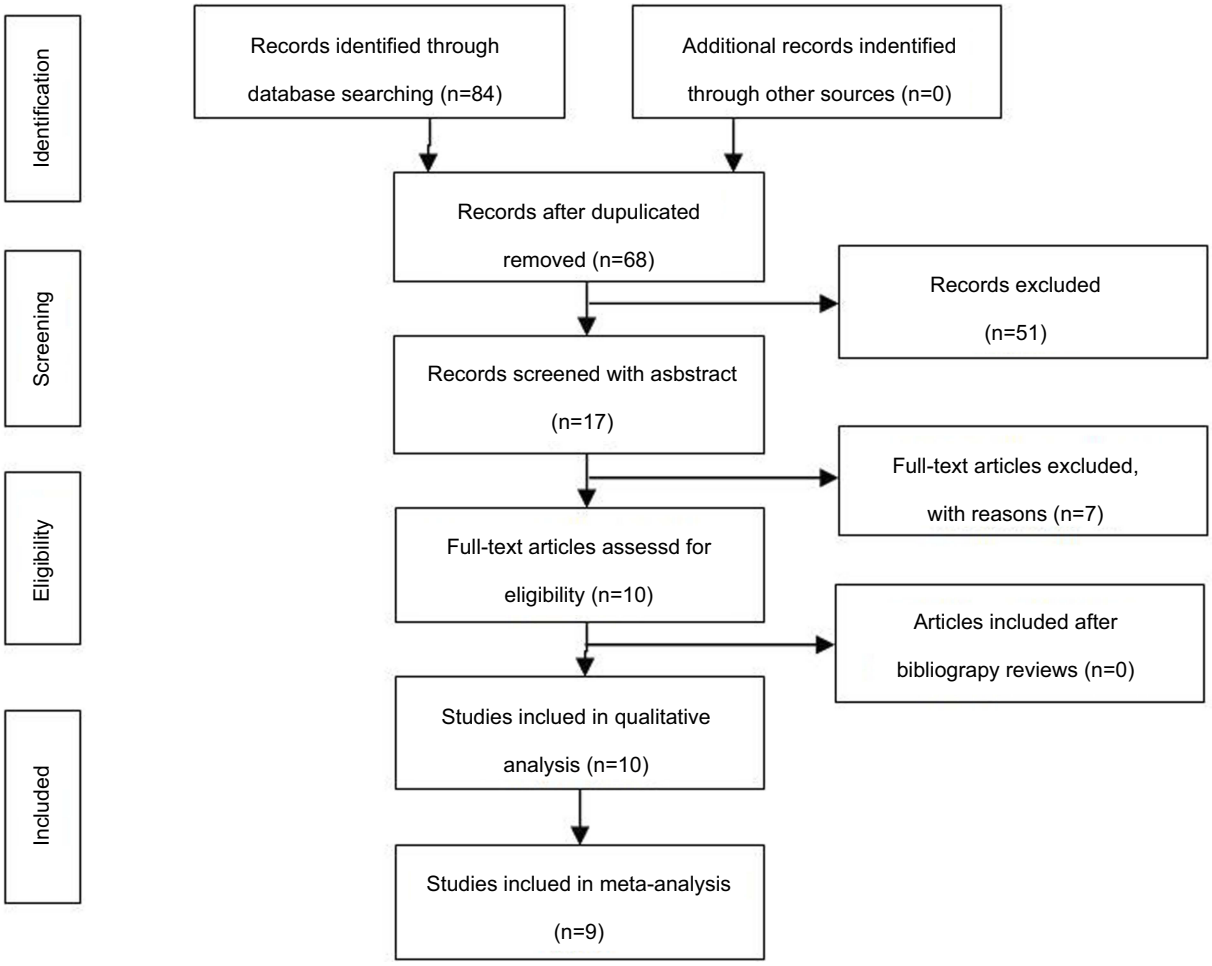

Figure 1 Flow diagram of study search and selection.

Table 1 Basic characteristics of the included literature

Author	Year	Country	Type of study	Pathological type	PG diagnostic threshold	Follow-up	Case/Control group number	TP	FP	FN	TN
Ye et al[18]	2004	Sweden	Prospective Case-Control	ESCC	PGI<28 ng/mL	NA	85/499	19	49	66	450
Iijima K et al[30]	2007	Japan	Prospective Case-Control	ESCC	PGI<25 ng/mL	24 months	73/73	31	11	38	56
Yokoyama A et al[38]	2009	Japan	Prospective Case-Control	ESCC	PGI<28 ng/mL & PGR<2	7–160 months	99/180	45	71	45	109
Iijima K et al[31]	2010	Japan	Prospective Case-Control	ESCC	PGI<25 ng/mL	48 months	100/100	48	26	42	63
					PGR<2		100/100	49	28	41	61
Cook MB et al[33]	2011	Finland	Prospective Nested Case-Control	ESCC	PGI≤70 ng/mL	NA	79/94	28	19	51	75
					PGR≤3		79/94	23	11	56	83
Venerito M et al[37]	2011	Germany	Prospective Case-Control	ESCC	PGI<70 ng/mL	NA	75/75	16	15	59	60
					PGR<3		75/75	6	5	69	70
Nasrollahzadeh D et al[32]	2012	Iran	Prospective Case-Control	ESCC	PG1/PG2<3	NA	293/524	27	34	266	490
					PGI<70 ng/mL & PGR<3		293/524	25	27	268	497
Murphy G et al[9]	2012	United States	Prospective Case-Control	ESCC	PGI≤25 ng/mL	10 Years	82/82	7	4	75	78
					PGR<5		82/82	42	23	40	59
Sadjadi A et al[28]	2013	Iran	Prospective Case-Control	ESCC	PGR<2.5	NA	59/59	29	14	30	45

Abbreviations: ESCC, esophageal squamous cell carcinoma; TP, true positive; FP, false positive; TN, true negative; FN, false negative; PGI, pepsinogen I; PGR, PGI/PGII ratio.

with the Midas instruction and were thus excluded in the study. Two reports stated that reduced PGR is associated with a high risk of ESD;[19,20] however, its data were incomprehensible, and thus the study was excluded in this work.

The quality of QUADAS-2 scale was evaluated for inclusion in the literature (Table 2), and a data extraction form (Figure 2) was developed for risk bias evaluation (Figure 3). Prospective studies showed low patient-selection bias, whereas retrospective studies displayed a high bias. Regarding the "evaluation test", that is, the bias assessment by using PGI and PGR, six articles presented a low risk and three were unclear. In the "case flow and progress" offset risk assessment, seven articles were at low risk, and two performances were unclear. We indicated that literature inclusion features a low risk of bias in case selection. Moreover, a relatively low risk in the "tests to be evaluated, gold standards, case processes, and progress" was detected and showed a low risk in terms of "clinical adaptability." In summary, the quality of included literature is considered high.

Meta-analysis results

Meta-analysis results when PGI≤70 ng/mL is used as a diagnostic index

Heterogeneity test

The SROC curve did not show a "shoulder–arm" distribution, and as revealed by the effect test results, the Spearman correlation coefficient r was −1.00 (P=0.98), suggesting that no significant between-study threshold effect existed. When P=0.00 in the sensitivity Q test, the between-study heterogeneity was statistically significant, and the I^2 statistic was 95.06%, indicating that heterogeneity was evident (Figure 4). When P=0.01 in the specificity Q test, the between-study heterogeneity was statistically significant, and the I^2 statistic

Table 2 Qualitative evaluation of the selected articles using the QUADAS-2 criteria

Ref Ye et al[18]			Iijima et al[30]	Yokoyama et al[38]	Iijima et al[31]	Cook MB et al[33]	Venerito M et al[37]	Nasrollahz-adeh D et al[32]	Murphy G et al[9]	Sadjadi A et al[28]
Patient selection										
Risk of bias	Question 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Question 2	No	No	No	No	No	No	No	No	No
	Question 3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Risk assessment	LR	LR	LR	LR	LR	LR	LR	LR	LR
Concerns regarding applicability		LC	LC	LC	LC	LC	LC	LC	LC	LC
Index test										
Risk of bias	Question 1	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes
	Question 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Risk assessment	LR	UR	UR	UR	LR	LR	LR	LR	LR
Concerns regarding applicability		LC	UC	UC	UC	LC	LC	LC	LC	LC
Reference standard										
Risk of bias	Question 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Question 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Risk assessment	LR	LR	LR	LR	LR	LR	LR	LR	LR
Concerns regarding applicability		LC	LC	LC	LC	LC	LC	LC	LC	LC
Flow and timing										
Risk of bias	Question 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Question 2–3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Question 4	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
	Risk assessment	LR	UR	LR	UR	LR	LR	LR	LR	LR

Abbreviations: LR, low risk; UR, unclear risk; LC, low concern; UC, unclear concern.

was 95.88%, indicating significant heterogeneity (Figure 4). Between-study DOR homogeneity was demonstrated (I^2=20.2%, P=0.270) (Figure 5). Therefore, the effect merger in the meta-analysis was performed using a random effect model.

Combined effect amount

Meta-analysis was performed using a random effects model; Table 3 presents the sensitivity, specificity, PLR, NLR, DOR, and other results.

Diagnostic value analysis

The AUC of SROC was 0.63 (95% CI: 0.59–0.67), suggesting that when PGI≤70 ng/mL, the ESCC diagnosis becomes less accurate (Figure 6). Fagan results showed that when PGI≤70 ng/mL, the probability of diagnosing ESCC reached 31%. When PGI>70 ng/mL, the probability totaled 18% (Figure S1). The matrix distribution map suggested that the included literature occupies the lower right quadrant and cannot be used for disease diagnosis and screening (Figure 7).

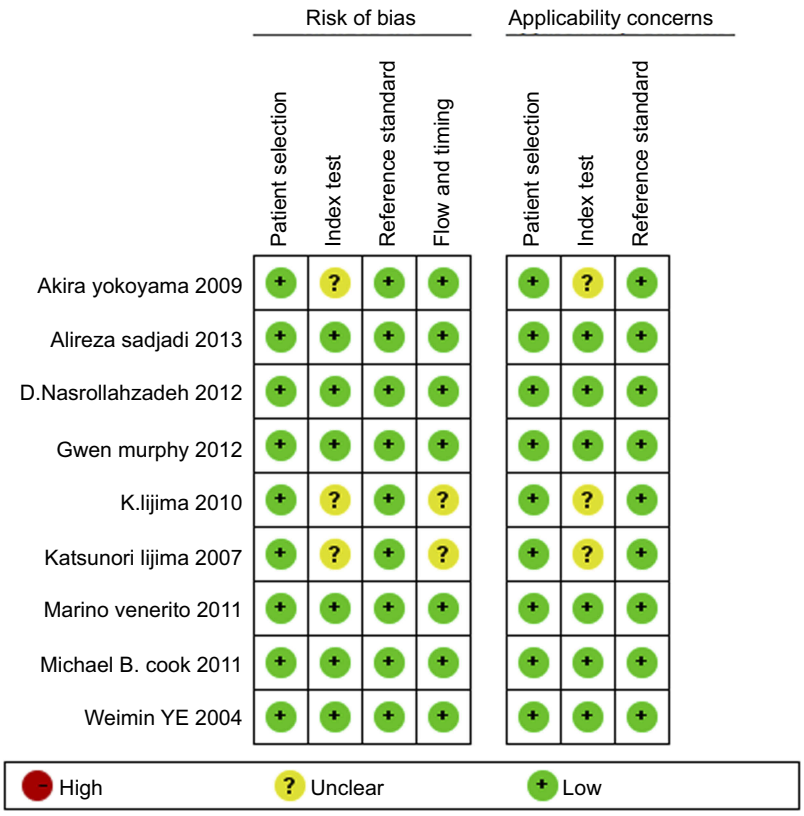

Figure 2 Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.

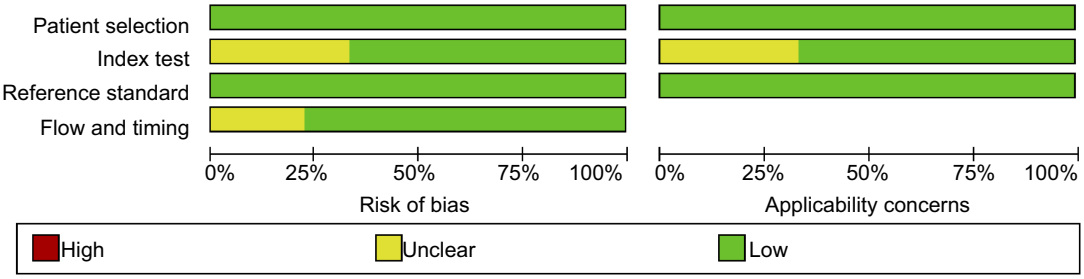

Figure 3 Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

Publication bias

Deek test results showed that the funnel plot was symmetrical without any significant bias (P=0.47) (Figure 8).

Meta-analysis results when PGR≤3 is used as a diagnostic index

Heterogeneity test

The SROC curve did not show a "shoulder–arm" distribution, and as revealed by the effect test results, the Spearman correlation coefficient r was −1.00 (P=1.00), suggesting that no significant between-study threshold effect existed. When P=0.00 in the sensitivity Q test, the between-study heterogeneity was statistically significant, and the I^2 statistic was 96.33%, indicating that heterogeneity was evident (Figure 9). When P=0.00 in the specificity Q test, the between-study heterogeneity was statistically significant, and the I^2 statistic was 96.49%, indicating significant heterogeneity (Figure 9). The DOR of each literature was homogenous (I^2=17.6%, P=0.300) (Figure 10). Therefore, the effect merger in the meta-analysis was performed using a random effect model.

Combined effect amount

Meta-analysis was performed using a random effects model. Table 3 presents the sensitivity, specificity, PLR, NLR, DOR, and other results.

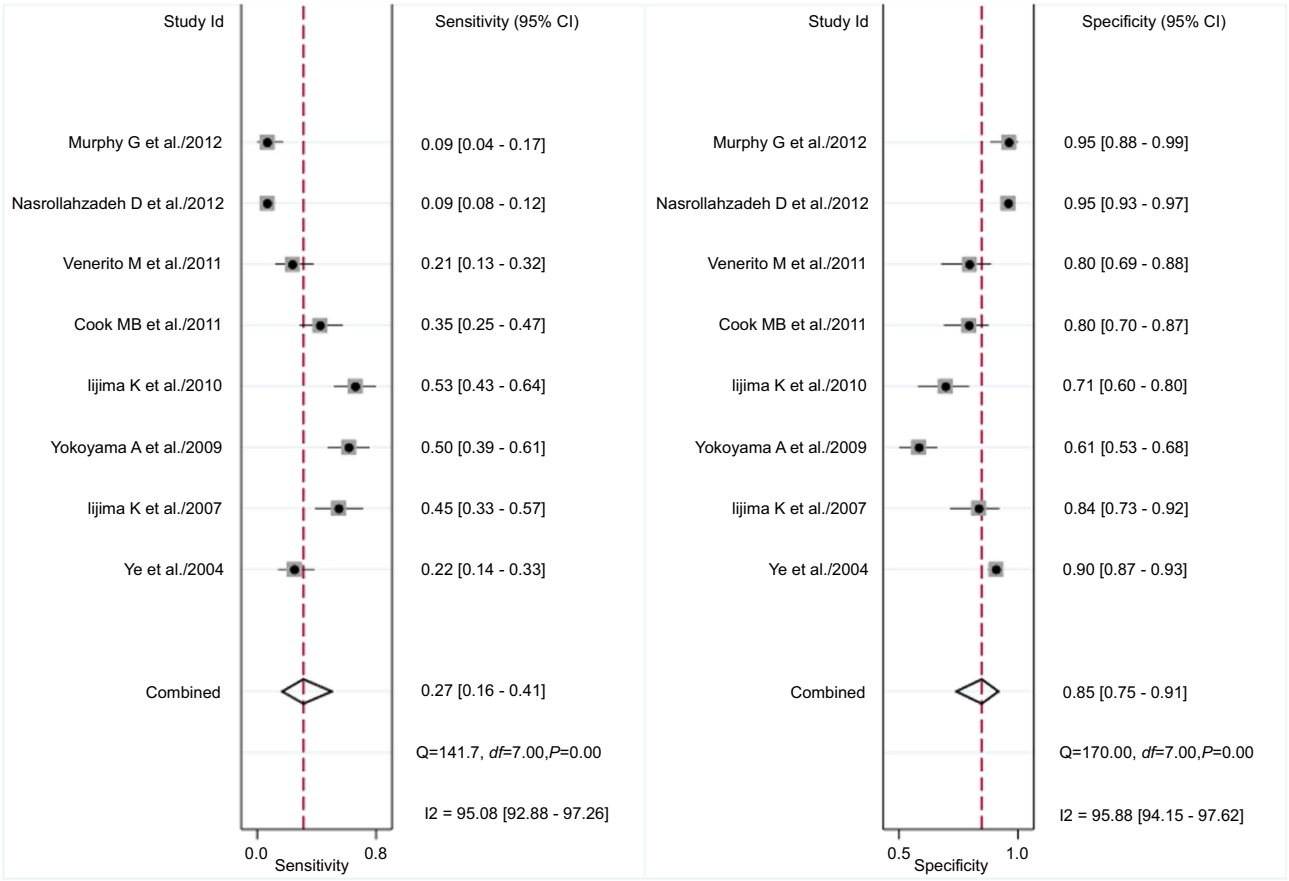

Figure 4 PGI≤70 ng/mL diagnosis ESCC forest plot for sensitivity and specificity.

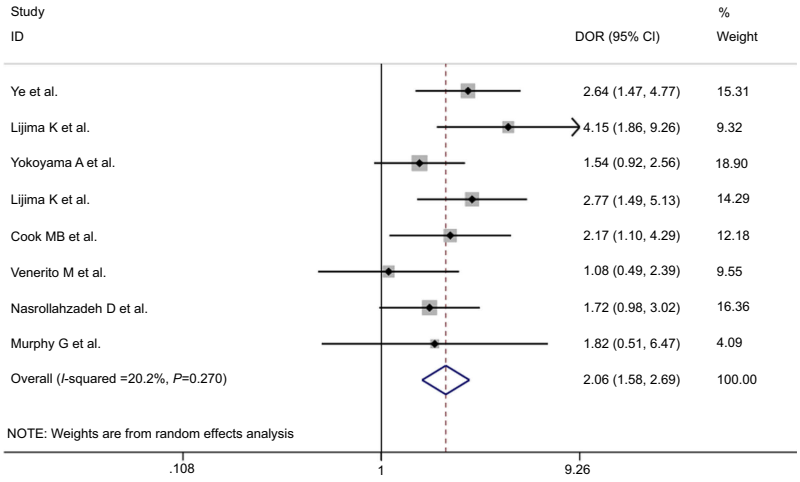

Figure 5 DGI forest map for diagnosis of ESCC with PGI≤70 ng/mL.

Diagnostic value analysis

The AUC of SROC was 0.63 (95% CI: 0.59–0.67), suggesting that when PGR≤3, the ESCC diagnosis becomes less accurate (Figure 11). Fagan results showed that when PGR≤3, the probability of diagnosing ESCC reached 29%. When PGR>3, the probability totaled 18% (Figure S2). The matrix distribution map suggested that the included literature occupy the lower right quadrant and cannot be used for disease diagnosis and screening (Figure 12).

Table 3 Meta-analysis of pepsinogen in the diagnosis of ESCC

Diagnostic threshold	Sensitivity (95%CI)	Specificity (95%CI)	Positive likelihood ratio (95%CI)	Negative likelihood ratio (95%CI)	AUC
PGI≤70 ng/mL	0.27(0.16–0.41)	0.85(0.75–0.91)	1.8(1.4–2.2)	0.86(0.78–0.85)	0.63
PGr≤3	0.29(0.15–0.48)	0.83(0.69–0.91)	1.7(1.3–2.0)	0.86(0.76–0.98)	0.63

Abbreviation: CI, confidence interval.

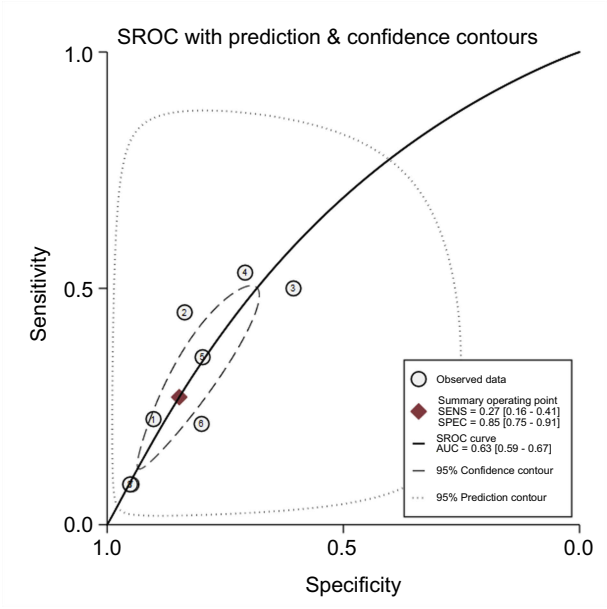

Figure 6 SROC curve for diagnosis of ESCC with PGI ≤ 70ng/mL.

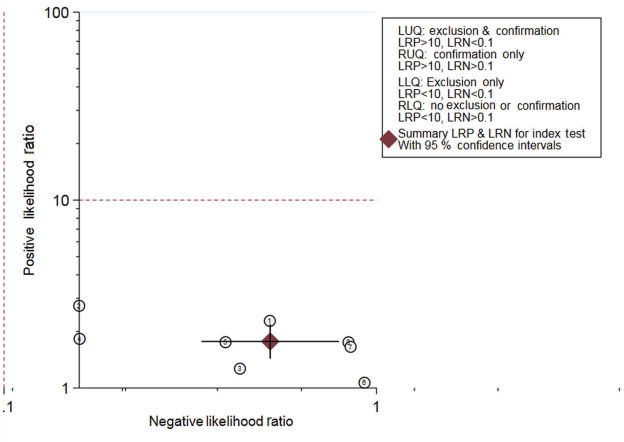

Figure 7 Matrix diagram of diagnostic ESCC with PG ≤ 70ng/mL.

Publication bias

Deek test results showed that the funnel plot was symmetrical without any significant bias (P=0.19) (Figure 13).

Discussion

PG is an inactive precursor for pepsin, and its main source is the stomach.[21] PG can be divided into two subgroups of PGI and PGII.[21] Most of the synthesized PG enters the gastric cavity and is activated by gastric juice to form pepsin, a small amount of PG can enter the blood circulation.[22] The PG levels in the gastric fluid and blood are consistent with biopsies.[23] Serum PGI reflects the gastric mucosal secretion at different sites,[24], and any PGR reduction is associated with gastric mucosal dysfunction.[25] Any PGI or PGR reduction is believed to be a byword, for atrophic gastritis (AG), especially for fundic gastric atrophy (FGA).

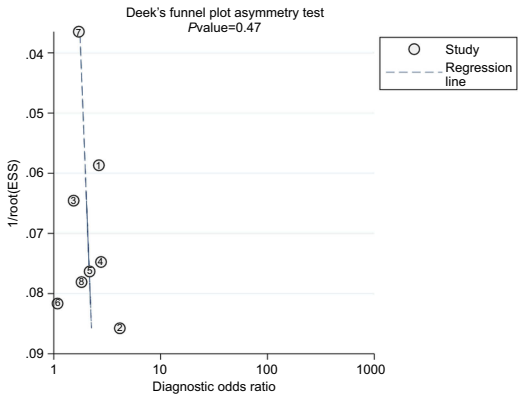

Figure 8 Funnel plot incorporating literature bias analysis.

In the 1990s, Rakic S et al, reported that gastric mucosal atrophy is common in patients with ESCC patients,[26] and endoscopic diagnosis of corpus trophic gastritis (open-type 2–3 gastric mucosal atrophy, Kimura and Takemoto Classification) may be a risk factor for ESCC.[27] To date, the mechanism of increasing risks for ESCC in patients with AG is still unclear, but it is possibly related to an increase innitrosamine compounds or the growth of other cancer-related products, caused by excessive growth of bacteria.[28] In 2004, Ye et al, observed that gastric atrophy may increase the risk for ESCC, but it showed no association with increased the risk for EAC.[18] A Northern Ireland population study reported that although FGA is rare, the risk for EAC or reflux esophagitis reduced after *Helicobacter pylori* infection and atrophy. Whether FGA is related to EAC risk requires further study.[17]

ESD is a precancerous lesion of ESCC.[29] Japanese scholar Iijima K and his colleagues noted that gastric

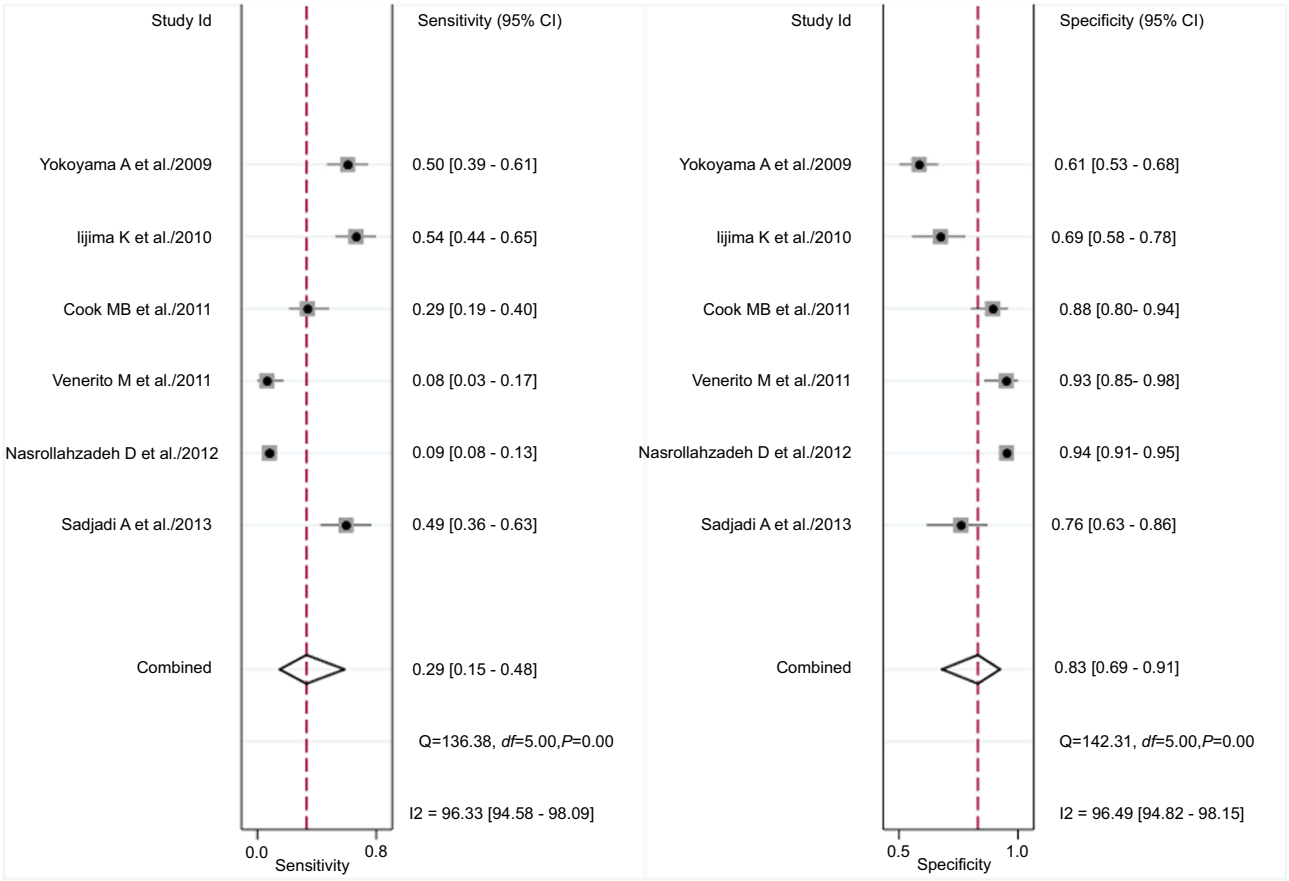

Figure 9 PGR≤3 forest map for diagnosis of sensitivity and specificity of ESCC.

atrophy is an independent risk factor for ESCC, and ESCC visibly increases with aggravated atrophy.[30] Using PGI<25 ng/mL or PGR<2.0 as the standard for diagnosing atrophy, their team revealed that although no atrophy is present, severe gastric acid deficiency remains an independent risk factor for ESCC.[31] Kamangar F et al, stated that ESD presents no significant association with serum PGI but is linearly associated with a decrease in PGR (P=0.03).[19]

The Iranian study discovered that controlling other potential confounding factors confound may increase the risk for ESCC in patients with atrophy (PGI<55 ng/mL) twice as those without atrophy (PGI<11.8 ng/mL), and gastric atrophy is a risk factor for ESCC.[32] Cook MB et al, observed that in the Finnish population, gastric atrophy (PGR<4)is associated with the risk for ESCC.[33] In the same period, a Chinese mainland study revealed that although the risks for ESCC in the subjects slightly increased when PGR≤4, evidence for diagnosing the risk for ESCC with PGR remains lacking.[34] In the Netherlands, scholars noted that despite their association, the risk for ESCC shows no increase with gastric atrophy severity (P=0.90).[35] Xue et al, observed in his prospective studies that in rural Chinese areas, no significant correlation exists between the PG level (PGI≤70 ng/mL alone, PGR≤3 or PGI≤70 ng/mL and PGR≤3) and ESCC onset.[36] Venerito M et al, defined PGI≤70 ng/mL and PGR≤3 as FGA, and he reckoned that serological and histological diagnosis of atrophy exhibits no association with the risk for ESCC(OR=1.17, 95% CI: 0.54–2.56 vs OR=1.91, 95% CI: 0.6–5.99).[37]

The DOR of this study was 2 (95% CI: 2–3), indicating that the two diagnostic methods restrict ESCC diagnosis. When AUC >0.9, a high accuracy was observed, and an AUC of 0.5, indicates that the diagnostic test is meaningless. In this study, the AUC of SROC reached 0.63 (95% CI: 0.59–0.67), and the appeal method diagnosed ESCC with low accuracy.

When the diagnostic method was PGI≤70 ng/mL, the PLR equaled 1.8 (95% CI: 1.4–2.2), indicating that the positive rate of the diagnostic index in patients with ESCC was 1.8 times higher than that of the non-ESCC population. The NLR amounted to 0.86 (95%

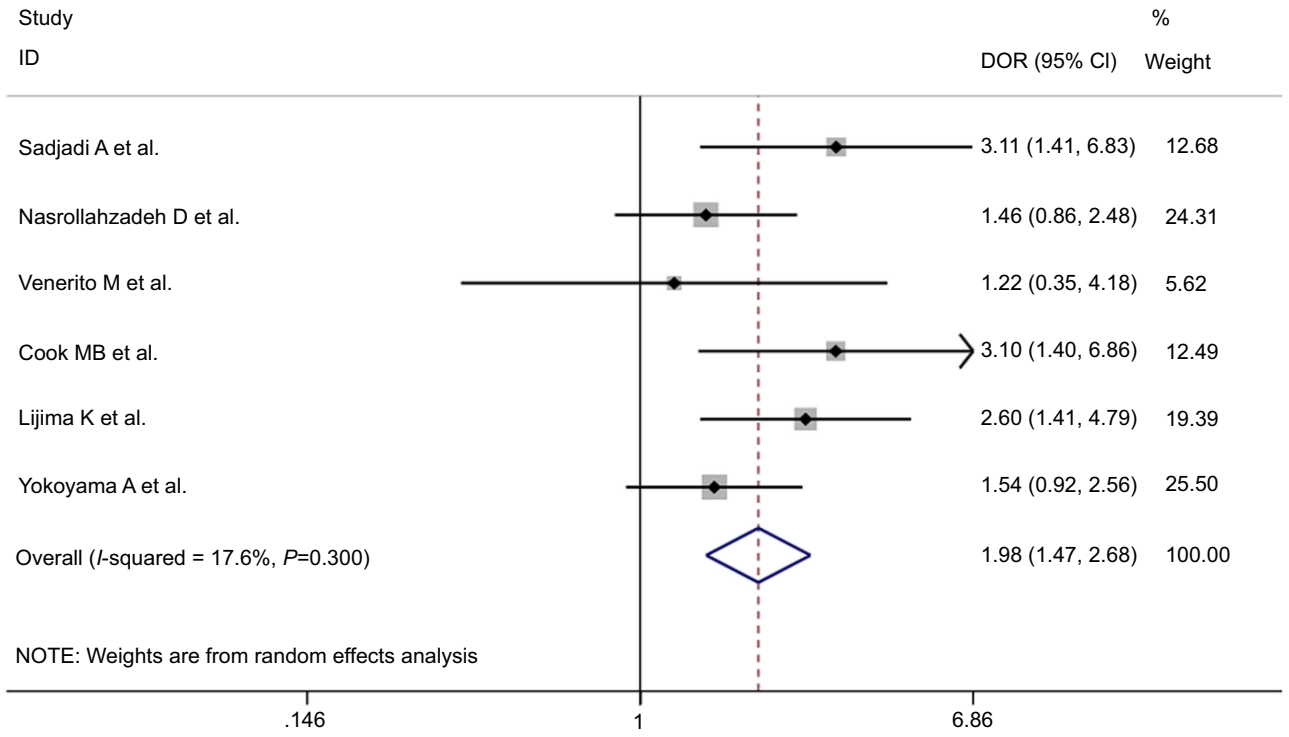

Figure 10 DOR forest map of PGR≤3 diagnostic ESCC.

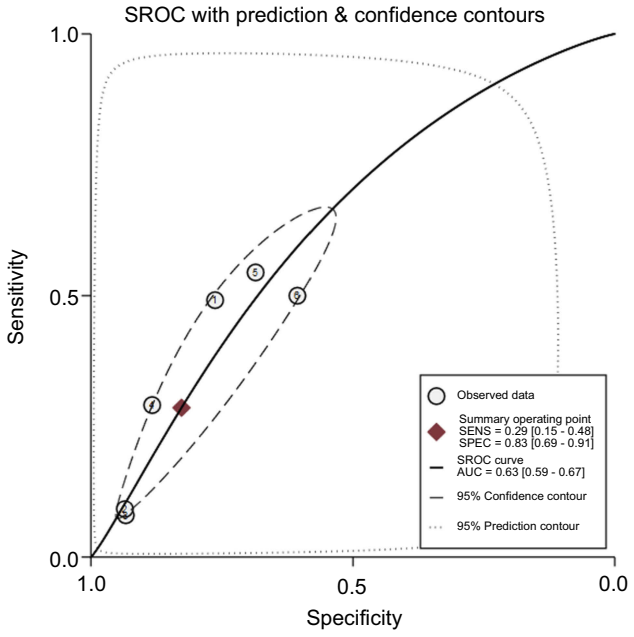

Figure 11 PGR≤3 diagnostic SROC curve.

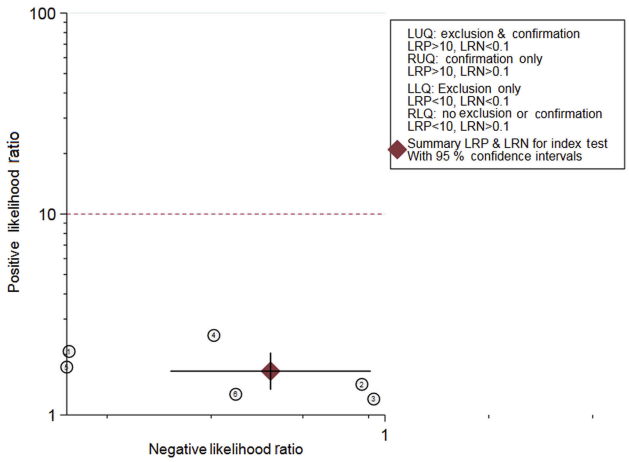

Figure 12 Matrix diagram of diagnostic ESCC with PGR≤3.

CI: 0.78–0.85), suggesting that 86% of the non-ESCC people feature PGI≤70 ng/mL. Therefore, the above method possesses a limited diagnostic value for ESCC. When the diagnostic method was PGR≤3, the PLR reached 1.7 (95% CI: 1.4–2.2), suggesting that the positive rate of this diagnostic index in patients with ESCC was 1.7 times higher than that of patients in the non-ESCC population. The NLR was 0.86 (95% CI: 0.75–0.97), suggesting that 86% of the people without ESCC exhibit PGR≤3. In view of this result, the two diagnostic methods manifest limited diagnostic value for ESCC.

The present study features certain limitations, such as the definite literature that were included and which failed to analyze, the effects of tumor staging and pathological type on the diagnostic sensitivity and specificity. In this research,

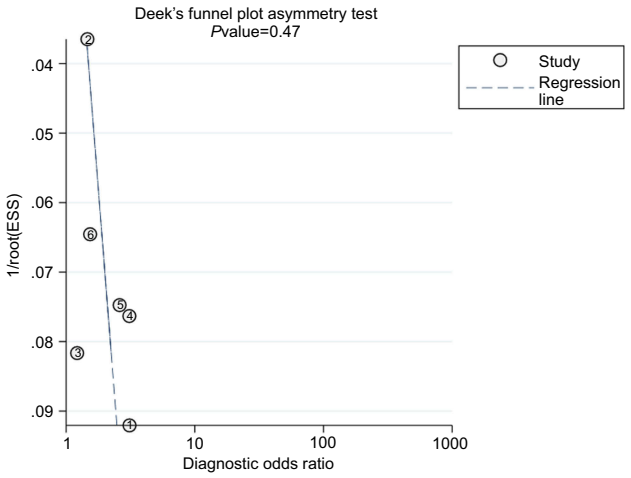

Figure 13 Graph of Deeks' funnel plot asymmetry test. ESS, effective sample size.

small number of publications available were included, part of which were used to analyze the diagnostic PGI value, however, some of which were used to research PGR, and the thresholds were different, it was possible to produce heterogeneity. Moreover, several retrospective studies used in this work may feature blind loopholes.

In summary, when PGI≤70 ng/mL or PGR≤3, the diagnostic specificity of ESCC is high, but the sensitivity is low. Thus, the results cannot be used for ESCC diagnosis. Therefore, high-quality studies are necessary to explore their clinical diagnostic value, to obtain accurate results with less heterogeneity.

Abbreviation list

PGI, pepsinogen I; PGR, PGI/PGII ratio; AGA, gastric fundus atrophy; EC, esophageal carcinoma; SROC, summary receiver operating characteristic curve; AUC, area under the curve; ESCC, esophageal squamous cell carcinoma; ESD, esophageal squamous dysplasia; TP, true positive; FP, false positive; TN, true negative; FN, false negative; DOR, diagnostic odds ratio; PLR, positive likelihood ratio; NLR, negative likelihood ratio; AG, atrophic gastritis; FGA, fundic gastric atrophy.

Ethical approval

This article does not contain examinations performed on human participants therefore, ethical approval was not necessary.

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Disclosure

The authors report no conflicts of interest in this work.

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