

# Diagnostic value of exosome derived long noncoding RNA in gastric cancer in Chinese population

## A PRISMA-compliant systematic review and meta-analysis

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### Abstract

**Background:** Objective to systematically evaluate the diagnostic value of long noncoding RNA (lncRNA) in gastric cancer (GC) in the Chinese population.

**Methods:** PubMed, Web of Science, EMBASE, Cochrane Library, CNKI, and Wanfang Database were searched. According to the search strategy and inclusion and exclusion criteria, 2 staff members screened the relevant kinds of literature from January 2010 to December 2020 and extracted the relevant data. Revman5.3, Meta-Disc1.4, and Stata15.1 software were used to analyze the relationship between lncRNA from exosomes and the diagnosis of GC. The combined values of sensitivity (SEN), specificity (SPE), positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR) and their corresponding 95% confidence intervals (CIs) were calculated. The summary receiver operating characteristic curve was drawn and the area under the ROC curve (AUC) value was calculated.

**Results:** In 9 studies, 1314 samples were included, including 792 cases in the case group and 522 cases in the control group. The combined SEN was 0.82 (95% CI: 0.77–0.86), the combined SPE was 0.78 (95% CI: 0.72–0.83), the combined positive likelihood ratio was 3.7 (95% CI: 2.9–4.6), the negative likelihood ratio was 0.23 (95% CI: 0.18–0.29), and the DOR was 16 (95% CI: 12–23), AUC was 0.87 (95% CI: 0.84–0.90). Subgroup analysis showed that the SEN, SPE, likelihood ratio, DOR, and AUC of plasma-derived lncRNA in the diagnosis of GC were better than those of serum.

**Conclusions:** Exosome-derived lncRNA may be a new potential biomarker for the clinical diagnosis of GC.

**Abbreviations:** AUC = area under the ROC curve, CI = confidence interval, DOR = diagnostic odds ratio, GC = gastric cancer, lncRNA = long noncoding RNA, NLR = negative likelihood ratio, PLR = positive likelihood ratio, SEN = sensitivity, SPE = specificity.

**Keywords:** diagnosis, exosome, gastric cancer, long noncoding RNA, meta-analysis

### 1. Introduction

Gastric cancer (GC) is the most common malignant tumor worldwide and also the most common malignant tumor of the digestive tract in China. In China, GC ranks second only to lung cancer in morbidity and mortality.<sup>[1–2]</sup> In recent years, the

prevention, diagnosis, and treatment of GC have been improved. However, most patients are in the advanced stage when the diagnosis is confirmed, and there is no significant advantage of surgery and chemotherapy as the main treatments for patients with advanced GC, resulting in a poor prognosis. Through

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Ethics approval and consent to participate is not applicable.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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continuous research on molecular and cellular mechanisms, monoclonal antibodies have been used for the treatment of GC, but they induce new complications and are currently mainly used as an adjuvant and second-line treatment for patients with advanced GC.<sup>[3]</sup> Early detection, diagnosis, and treatment are important principles to improve the survival and prognosis of GC. Early diagnosis is the prerequisite for early treatment, therefore, early diagnosis of GC is particularly important.<sup>[4]</sup> Endoscopic and pathological examination are the gold standards for the diagnosis of GC, but this examination has such problems as a large population, causing pain and discomfort to patients due to operation, and relying on the level of examiners.<sup>[5]</sup> In addition, although serum tumor markers such as carcinoembryonic antigen (CEA), CA199, and CA724 commonly seen in clinical play a role in the auxiliary diagnosis, their sensitivity (SEN) and specificity (SPE) are not ideal.<sup>[6]</sup> Therefore, there is a need for a novel and effective biological marker for a better diagnosis of GC.

Exosomes are membranous extracellular vesicles released by living cells and exist in blood, urine, saliva, and other body fluids, with a diameter of 30 to 100 nm. They contain DNA, mRNA, microRNA, long noncoding RNA (lncRNA), and other nucleic acid molecules, as well as a variety of proteins.<sup>[7]</sup> In addition, exosomes are considered to be ideal biomarkers for early diagnosis of cancer due to their increased number when tumors invade the body, stable existence in body fluids, availability, and difficulty in enzyme decomposition.<sup>[8]</sup> lncRNA is a kind of RNA molecule with a length of more than 200 nucleotides, a lack of a specific open reading frame, and no protein-coding function. Studies have demonstrated that exosome-derived lncRNA plays a key role in the regulation of GC biology and is closely related to the occurrence, development, invasion, metastasis, and prognosis of GC.<sup>[9]</sup> At present, many studies have found that the expression level of exosome-derived lncRNA in GC patients is significantly different from that without disease, which may become a biomarker for GC diagnosis and prognosis evaluation.<sup>[10]</sup>

Therefore, in this study, we intended to evaluate the clinical value of exosome-derived lncRNA in the diagnosis of GC in the Chinese population by systematic meta-analysis, to provide an evidence-based reference for the diagnosis of GC.

## 2. Materials and methods

### 2.1. Ethics statement

All analyses were based on previously published studies, this article does not contain any studies with human participants or animals performed by any of the authors; thus, ethical approval and patient consent are not applicable.

### 2.2. Search strategy

**2.2.1. Database.** Foreign databases include PubMed, Web of Science, EMBASE, Cochrane Library, and Chinese databases include China National Knowledge Infrastructure, Wanfang Database.

**2.2.2. Search keywords.** The English search terms were “exosomes”, “exosome”, “lncRNA”, “long noncoding RNA”, “stomach neoplasm”, “stomach carcinoma”, “stomach cancer”, “Gastric cancer”, “gastric carcinoma”, and “gastric neoplasm”.

**2.2.3. Years retrieved.** Chinese and English kinds of literature from January 2010 to December 2020.

## 2.3. Inclusion and exclusion criteria

### 2.3.1. Inclusion criteria.

- (1) Cancer patients were diagnosed by the gold standard.
- (2) To evaluate the diagnostic value of exosome derived lncRNAs for GC in a Chinese population.
- (3) To extract the SEN, SPE, and area under the ROC curve (AUC) values of exosomal lncRNAs for cancer diagnostic accuracy from raw data.
- (4) The number of cases was clear and could be used to construct a  $2 \times 2$  Quad surface for diagnostic analysis.

### 2.3.2. Exclusion criteria.

- (1) Study subjects were not patients.
- (2) Type of literature: reviews, conference reports, case reports, etc.
- (3) Complete data could not be obtained and a  $2 \times 2$  table for diagnostic analysis could not be constructed
- (4) Duplicate literature.

## 2.4. Data extraction and quality assessment

Two staff members screened the relevant literature and extracted relevant data according to the search strategy and inclusion–exclusion criteria. We mainly included the study population, first author, publication year, type of lncRNA, expression level, tumor type of sample source, number of samples, SEN, SPE, AUC, etc, and applied statistical software to calculate the true positives, false positives, false negatives, and true negatives if disagreement was resolved by discussion. The QUADAS-2 quantity was used to evaluate the quality of pieces of literature finally included in the meta-analysis.

## 2.5. Statistical analysis

Rvman5.3, Meta-disc1.4, and Stata15.1 software were used to analyze the relationship between exosomal lncRNAs and tumor diagnosis, and the pooled values of SEN, SPE, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) and their corresponding 95% confidence intervals (CIs) were calculated. The summary receiver operating characteristic curve was drawn and AUC value was calculated. The closer the AUC value to 1, the higher the diagnostic efficacy. The presence or absence of a threshold effect between studies was assessed using the Spearman correlation coefficient test; heterogeneity from nonthreshold sources of effect was assessed using the  $I^2$  test, and significant heterogeneity was considered when  $I^2$  was  $> 50\%$ . Subgroup analysis and multiple regression analysis were performed to explore the causes of between-study heterogeneity, the stability of meta-analysis was verified by SEN analysis, and a Deek funnel plot was used to assess publication bias, with  $P < .1$  indicating publication bias.

## 3. Results

### 3.1. Literature screening results

A total of relevant articles were retrieved through the search strategy: EMBASE 24, PubMed 102, Web of Science 25, Cochrane Library 0, CNKI 22, and Wanfang Database 5. After excluding 79 duplicates and initially screening the titles, 81 remained. 31 articles were excluded after abstract reading, leaving

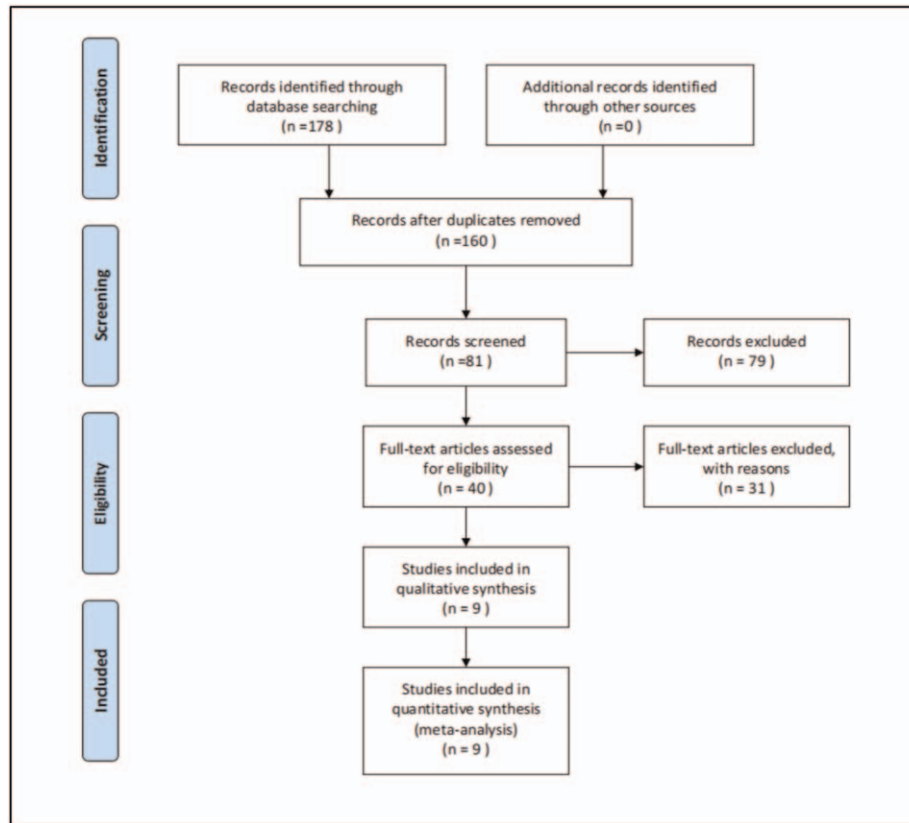


Figure 1. Literature screening and results.

40 articles. After reading the full text, 9 articles were included, and the process of literature screening and the results are shown in Figure 1.

**3.2. Basic information and bias assessment of included literatures**

Of the 9 studies finally included, a total of 1314 samples were included, 792 cases and 522 controls, the basic characteristics of the included studies are shown in Table 1.<sup>[11-19]</sup> Evaluation of article quality using the QUADAS-2 rating scale for diagnostic trials results in Figure 2 shows that the quality of the included literature was found to be high.

**3.3. Heterogeneity analysis and diagnostic accuracy evaluation of exosomal lncRNA**

Meta-disc1.4 software was used for threshold effect analysis, and the Spearman correlation coefficient was 0.126, the *P*-value was .748, which indicated that no threshold effect existed in this study and the data could be pooled. In this study, there was heterogeneity in pooled SEN and SPE are shown in Figure 3 ( $I^2=68.37\%$ ,  $I^2=63.89\%$ ), so the random-effects model was chosen. The pooled SEN was 0.82 (95% CI: 0.77-0.86), the pooled SPE was 0.78 (95% CI: 0.72-0.83), the pooled PLR was 3.7 (95% CI: 2.9-4.6), the pooled NLR was 0.23 (95% CI: 0.18-0.29), and the DOR was 16 (95% CI: 12-23) and the AUC was 0.87 (95% CI: 0.84-0.90). Forest plots of exosomal lncRNA

**Table 1**  
Basic characteristics of included studies.

Studys	Countrys	lncRNAs	Expression	Tumors	Origin	Case/control	TP	FP	FN	TN	Sen	Spe	AUC
Pan et al (2017) <sup>[11]</sup>	China	ZFAS1	Up	Gastric	Serum	40/37	32	9	8	28	0.800	0.757	0.837
Lin et al (2018) <sup>[12]</sup>	China	UEGC1	Up	Gastric	Plasma	51/60	45	10	6	50	0.882	0.833	0.876
Zhao et al (2018) <sup>[13]</sup>	China	HOTTIP	Up	Gastric	Serum	126/120	88	18	38	102	0.698	0.850	0.827
Zhang et al (2019) <sup>[14]</sup>	China	RPN2-4	Down	Gastric	Serum	47/32	41	13	6	19	0.872	0.594	0.772
Cai et al (2019) <sup>[15]</sup>	China	PCSK2-2:1	Down	Gastric	Serum	63/29	53	4	10	25	0.840	0.865	0.896
Li et al (2019) <sup>[16]</sup>	China	lnc-GNAQ-6:1	Down	Gastric	Serum	43/27	36	12	7	15	0.837	0.556	0.732
Piao et al (2020) <sup>[17]</sup>	China	CEBPA-ASI	Up	Gastric	Plasma	281/80	247	17	34	63	0.879	0.788	0.824
Zhou et al (2020) <sup>[18]</sup>	China	HI9	Up	Gastric	Serum	81/78	60	13	21	65	0.743	0.839	0.849
Zheng et al (2020) <sup>[19]</sup>	China	lnc-SLC2A12-10: 1	Up	Gastric	Plasma	60/60	47	15	13	45	0.783	0.75	0.776

AUC=area under the ROC curve, FN=false negativity, FP=false positivity, SEN=sensitivity, SPE=specificity, TN=true negativity, TP=true positivity.



Figure 2. Quality assessment of included studies using QUADAS-2.

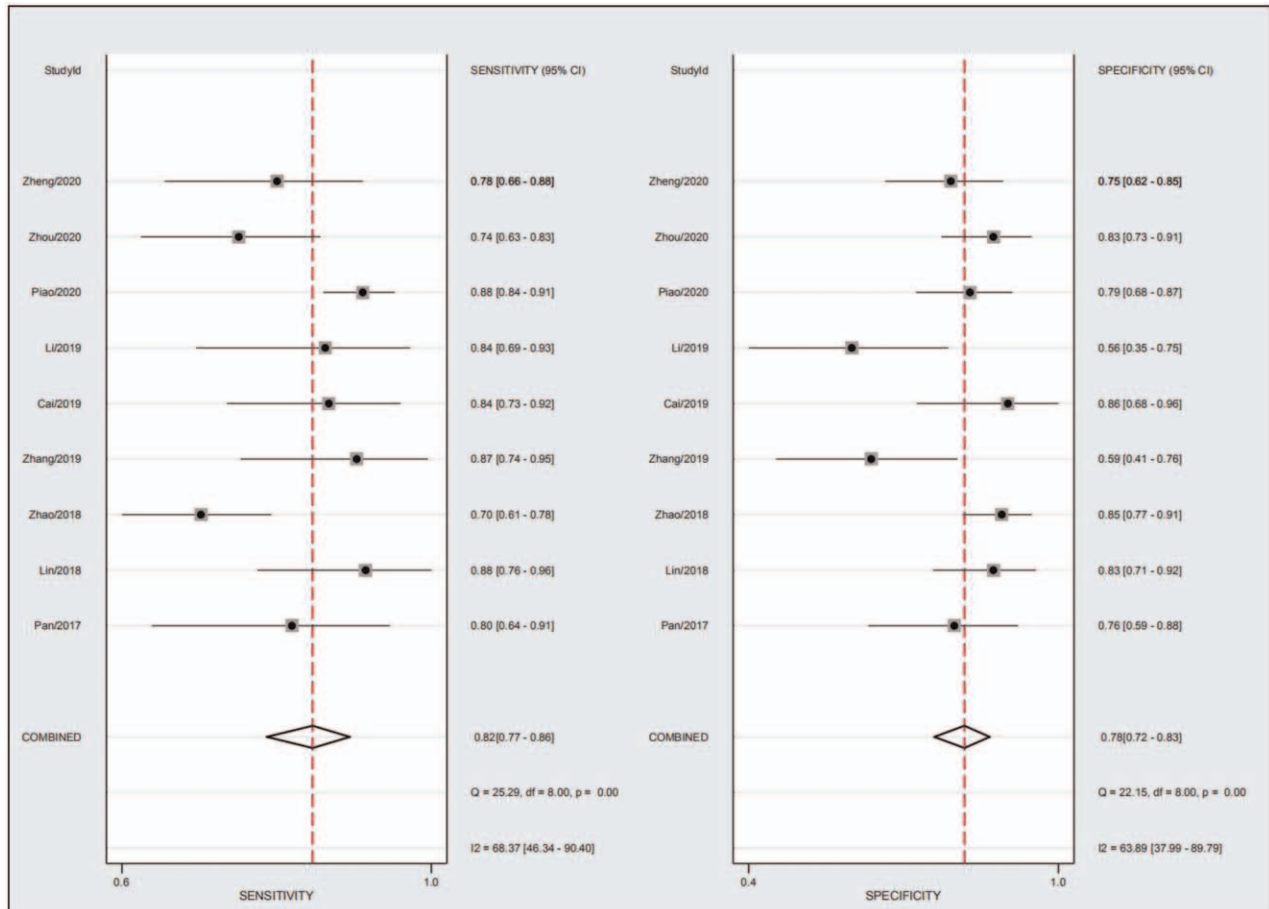


Figure 3. Forest plot of sensitivity and specificity of exosomal lncRNAs for GC.

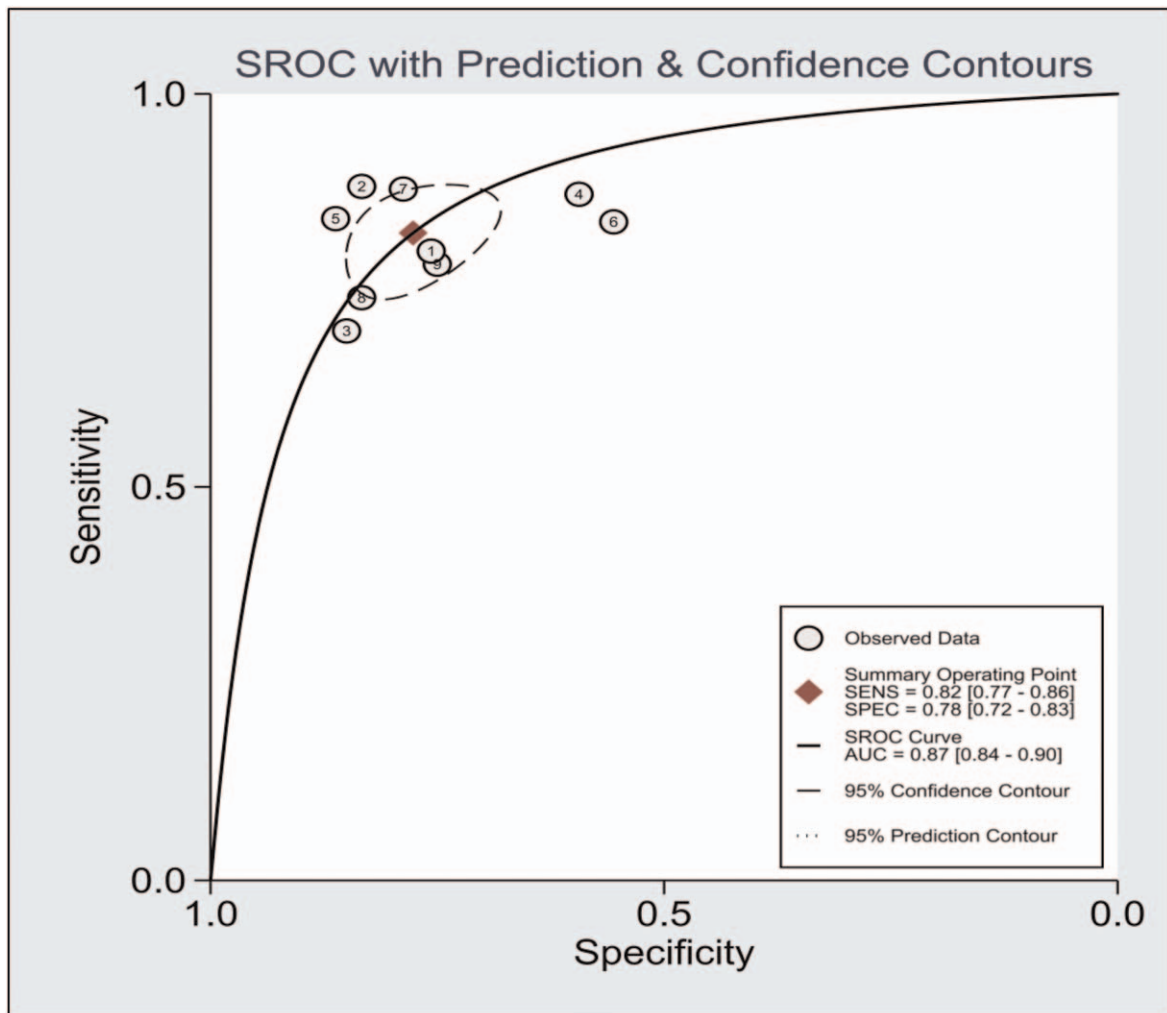


Figure 4. Exosomal lncRNAs diagnose SROC of GC. SROC = summary receiver operating characteristic.

diagnostic accuracy for GC and summary receiver operating characteristic are shown in Figure 4. Meanwhile, the Fagan nomogram was used to describe the possibility that exosome-derived lncRNA detection identified or excluded patients with GC, as shown in Figure 5. For those with a 20% risk of GC before testing, the probability of GC after testing would reach 48% if the exosome-derived lncRNA test was positive, however, if the test was negative, it would mean that the probability of GC after testing would drop to 4%. Therefore, lncRNA detection from exosome sources plays an important role in GC diagnosis.

#### 3.4. Meta regression analysis and subgroup analysis

Because there was heterogeneity between studies due to nonthreshold effects, lncRNA expression, exosome source, and sample number were included in the meta-regression analysis model to explore the source of heterogeneity. The results showed that  $P > .05$ , and no source of heterogeneity was found in Table 2. lncRNA expression, source of exosomes, the number of samples were subjected to subgroup analysis. The results showed that the SEN, SPE, likelihood ratio, DOR, and AUC of plasma-derived exosomal lncRNA for the diagnosis of GC were superior to those

of serum. The SPE, likelihood ratio, DOR, and AUC of exosome derived lncRNAs detected with a sample size  $> 100$  for the diagnosis of GC were superior to those of the subgroups with a sample size  $< 100$ , and the SPE, likelihood ratio, and AUC of exosome derived lncRNAs detected with an upregulated expression for the diagnosis of GC were superior to those detected with a downregulated expression are shown in Table 3.

#### 3.5. Sensitivity analysis

The results of SEN analysis are shown in Figure 6 that the study is stable, and the goodness of fit and bivariate normality show that the bivariate model of random effects is suitable for analysis (Fig. 6A, B). The impact analysis found that Zhao et al,<sup>[13]</sup> Zhang et al,<sup>[14]</sup> Cai et al,<sup>[15]</sup> Piao et al<sup>[17]</sup> had a large weight (Fig. 6C). The detection of outliers suggests that the above studies may be responsible for the heterogeneity (Fig. 6D).

#### 3.6. Publication bias

Another factor affecting the accuracy of diagnosis is publication bias. Deek test was used to evaluate the publication bias of the



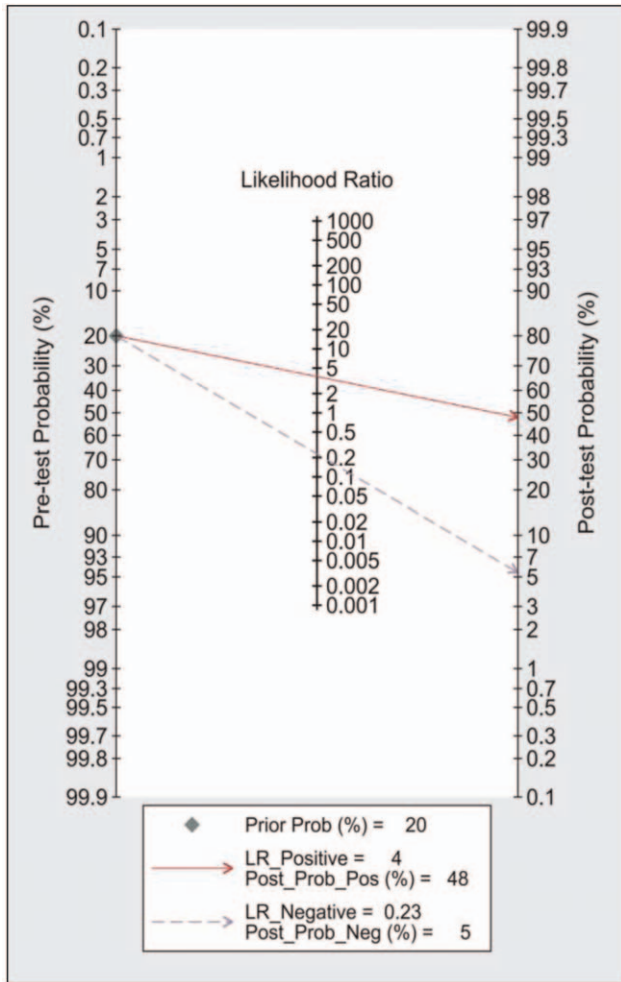


Figure 5. Fagan nomogram for exosomal lncRNA diagnosis of GC.

included articles. Deek method was used to measure publication bias are found in Figure 7. No significant publication bias was found.

#### 4. Discussion

GC is the fifth most common cancer worldwide, and its mortality rate is high.<sup>[20]</sup> The incidence and mortality of GC in the Chinese

Table 2

Meta regression analysis results.

Var	Regression coefficient	Estimating standard errors	P value	DOR	95%CI
lncRNA expression	0.587	0.7989	.5033	1.80	0.20–16.53
Origin of exosomes	0.789	0.5981	.2576	2.20	0.42–11.58
Number of samples	0.001	0.0022	.6226	1.00	1.00–1.01

CI = confidence interval, DOR = diagnostic odds ratio.

population is the second-highest among malignant tumors, which poses a serious threat to human life and health.<sup>[21]</sup> Some patients with GC are in the advanced stage of cancer when they see a doctor and lose the chance of surgical cure. The prognosis is very poor. With the promotion and application of standardized treatment for tumors, the five-year survival rate of patients with early diagnosis and therapeutic effects has been significantly improved.<sup>[22]</sup> Therefore, early diagnosis is particularly important. Endoscopy combined with pathological biopsy is the gold standard for the diagnosis of early GC at present, but this method is invasive and not easy to be used as a long-term method for diagnosis and monitoring of tumor progression.<sup>[23]</sup> At present, indicators commonly used in clinical practices such as CEA and carbohydrate antigen (CA-199) have low SEN and SPE for early GC. Therefore, molecular markers that can predict, screen, and diagnose GC at an early stage have been further explored. In recent years, studies have found that molecular markers such as noncoding RNA, exosomes, and circulating tumor cells are important signals for the occurrence and development of the tumor microenvironment. These markers can be detected in the blood, and have good clinical application prospects in the early diagnosis of GC.<sup>[24]</sup>

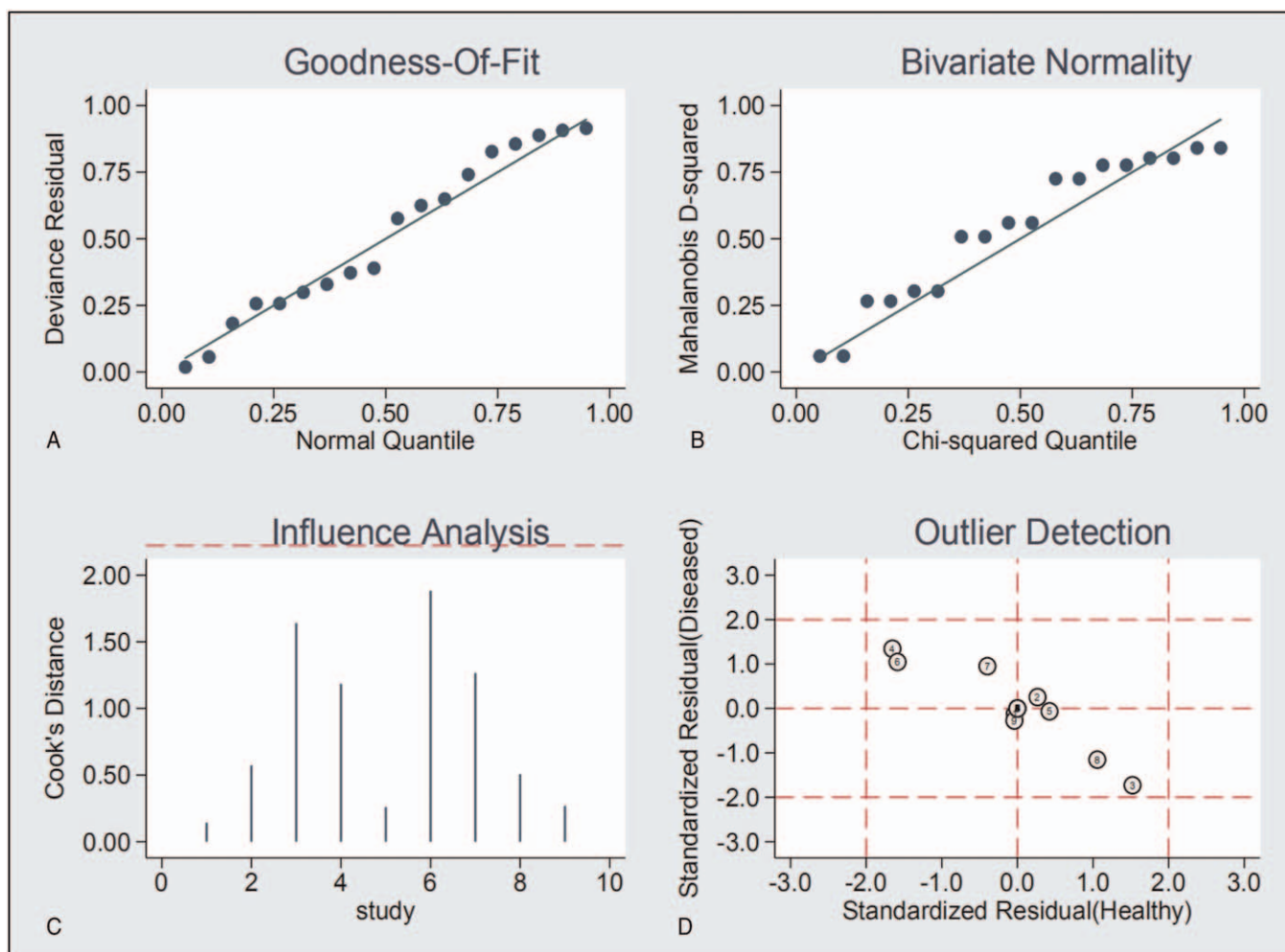
Exosomes are membranous extracellular vesicles released by living cells and present in various body fluids, with a diameter of 30 to 100 nm, and contain nucleic acid molecules such as DNA, mRNA, microRNA, lncRNA, as well as various protein. Compared with conventional biomarkers, exosome biomarkers have the following advantages: higher SEN and SPE; It widely exists in body fluid and is easy to be obtained, including blood, tears, urine, saliva, milk, ascites, etc., making exosome detection have a great prospect in tumor diagnosis and treatment, and can become an ideal “liquid biopsy” method.<sup>[25]</sup> Tumor cells have a precise targeted regulation mechanism for exosomes, suggesting that exosomes play an important role in the formation and development of tumors.<sup>[26]</sup> lncRNA is a noncoding RNA with a

Table 3

Results of subgroup analysis of exosomal lncRNA diagnosis of GC.

Subgroup	Number	SEN (95%CI)	SPE (95%CI)	PLR (95%CI)	NLR (95%CI)	DOR (95%CI)	AUC
lncRNA							
Up	6	0.81 (0.74~0.86)	0.81 (0.77~0.85)	4.2 (3.5~5.2)	0.20 (0.18~0.32)	18 (12~26)	0.85
Down	3	0.85 (0.78~0.90)	0.67 (0.56~0.77)	2.6 (1.4~4.5)	0.21 (0.25~0.32)	12 (5~31)	0.91
Origin							
Serum	6	0.80 (0.73~0.85)	0.76 (0.66~0.84)	3.3 (2.4~4.6)	0.27 (0.21~0.34)	12 (8~19)	0.85
Plasma	3	0.86 (0.83~0.90)	0.79 (0.73~0.84)	4.0 (3.0~5.2)	0.19 (0.12~0.29)	22 (11~43)	0.84
Number							
>100	5	0.81 (0.73~0.86)	0.81 (0.77~0.85)	4.3 (3.5~5.4)	0.24 (0.17~0.33)	18 (12~28)	0.86
≤100	4	0.84 (0.78~0.89)	0.70 (0.57~0.81)	2.8 (1.9~4.2)	0.23 (0.16~0.33)	12 (6~24)	0.85

AUC = area under the ROC curve, DOR = diagnostic odds ratio, NLR = negative likelihood ratio, PLR = positive likelihood ratio, SEN = sensitivity, SPE = specificity.



**Figure 6.** Sensitivity analysis of exosome lncRNA in the diagnosis of GC. A: Goodness-of-fit; B: bivariate normality; C: influence analysis; D: outlier detection.

length of more than 200 bp and is abundant in exosomes. Studies have shown that the exosome lncRNA is related to the occurrence and development of GC.<sup>[15]</sup> In recent years, Lin et al<sup>[12]</sup> found that lncRNA UEGC1 is highly expressed in plasma exosome of GC patients and GC cell exosome, and this study also found that almost all of the lncRNA UEGC1 isolated from plasma is present in the exosome, which indicated that the plasma exosome lncRNA UEGC1 has a development prospect as a noninvasive biomarker in the early diagnosis of GC. In addition, Yang et al<sup>[27]</sup> found a high expression level of anti-differentiation antagonistic nonprotein-encoded RNA (DANCR) targeting lncRNA-LET in serum exosomes of patients with GC. The results of ROC curve analysis showed that DANCR could indirectly reflect the level of lncRNA-LET and was superior to traditional serological markers CEA and carbohydrate antigen 19-9 (CA19-9) in the diagnosis of GC. More and more studies have reported that exosome lncRNA has potential application value in the clinical diagnosis of GC.<sup>[11-19]</sup>

Nine studies with a sample of 1314 patients, 792 in the case group and 522 in the control group, were included in this study. Meta-analysis showed that pooled SEN was 0.82 (95% CI: 0.77-0.86), pooled SPE was 0.78 (95% CI: 0.72-0.83), pooled

PLR was 3.7 (95% CI: 2.9-4.6), pooled NLR was 0.23 (95% CI: 0.18-0.29), and DOR (PLR) was 0.7) was 16 (95% CI: 12-23) and the AUC was 0.87 (95% CI: 0.84-0.90). The closer the AUC value was to 1, indicating the higher value of this study, and the AUC of this study reflects that exosomal lncRNAs have a high value in tumor diagnosis. The DOR value can reflect the correlation between the diagnostic results and the disease, and a larger value indicates a higher diagnostic value for the disease.<sup>[28]</sup> With a DOR > 1, the larger the value, the better the discriminative effect of the diagnostic test. The DOR of this study was 16, further illustrating that exosomal lncRNAs have a high value in tumor diagnosis. By threshold effect analysis of Meta-disc1.4 software, the Spearman correlation coefficient was 0.126, and the *P*-value was .748 > .05, indicating that the heterogeneity of this study was not caused by the threshold effect. In addition, lncRNA expression, source of exosomes, and several samples were included in the meta-regression analysis model to explore the source of heterogeneity, and the source of heterogeneity was not found. It was found by a SEN analysis that the studies of Zhao et al,<sup>[13]</sup> Zhang et al,<sup>[14]</sup> Cai et al,<sup>[15]</sup> Piao et al<sup>[17]</sup> may be the cause of heterogeneity.

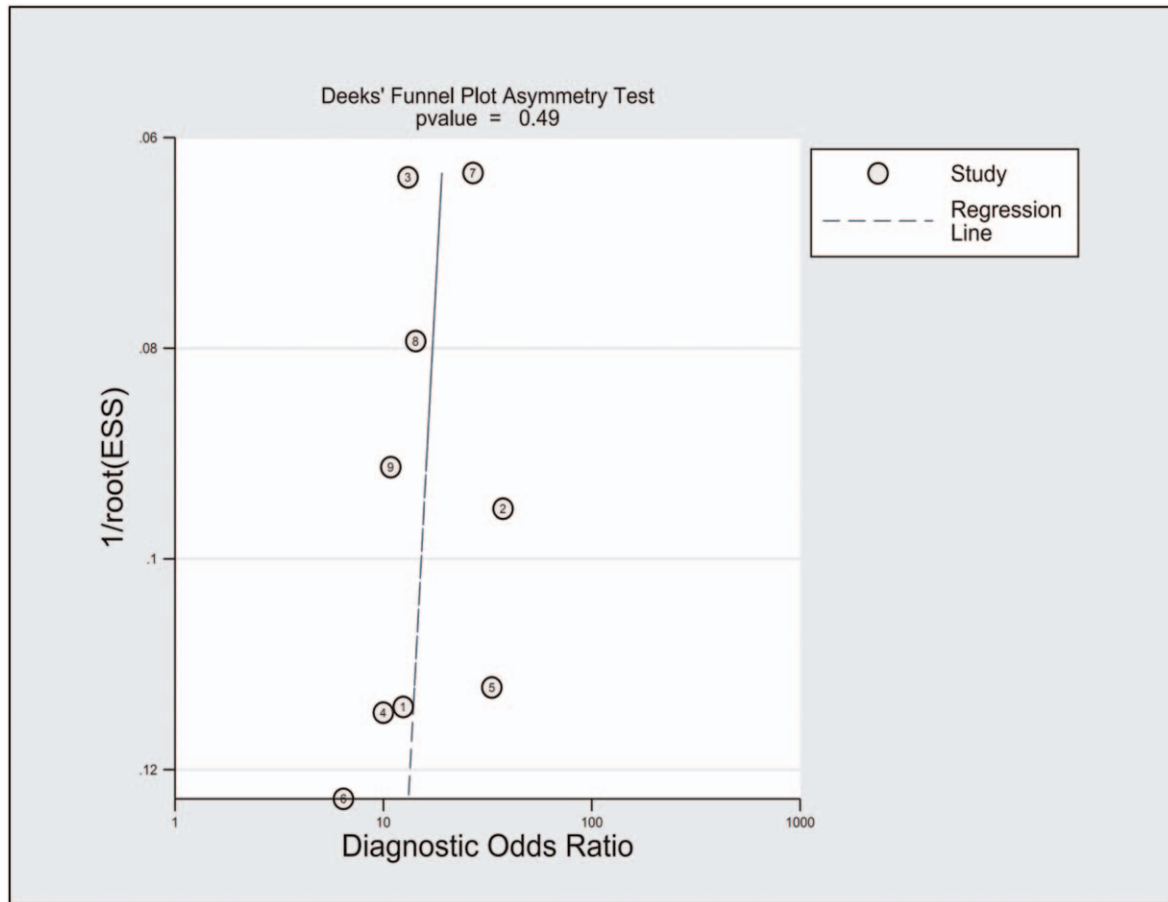


Figure 7. Publication bias of diagnosis of GC from Deek test.

## 5. Conclusions

Exosomal lncRNAs have a high diagnostic value for tumors and can be used as one of the auxiliary indicators for tumor diagnosis. There are still many limitations in this study, including the overabundance of tumor types, regional limitations, and the existence of heterogeneity among studies. Therefore, exosomal lncRNAs have a promising prospect in the diagnosis of tumors, but the conclusions of this study need caution in clinical promotion, and high-quality studies still need to be carried out for validation.

## Author contributions

**Data curation:** Kangle Zhu.

**Formal analysis:** Kangle Zhu.

**Funding acquisition:** Jinxian Yang.

**Investigation:** Kangle Zhu.

**Methodology:** Kangle Zhu.

**Software:** Kangle Zhu.

**Supervision:** Qingqing Wang, Huixia Zhu

**Writing – original draft:** Kangle Zhu.

**Writing – review & editing:** Kangle Zhu, Huixia Zhu, Qingqing Wang.

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