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Long noncoding RNAs as diagnostic biomarkers for the early detection of digestive tract cancers: a systematic review and meta-analysis

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ABSTRACT

Background: long noncoding RNAs (lncRNAs) have attracted attention recently. However, many inconsistencies frequently appeared for the early diagnosis of digestive tract cancers (DTCs). We performed this meta-analysis to describe the diagnostic performance of lncRNAs in the discrimination of DTCs.

Methods: data were extracted from PubMed, Web of Science, Embase, and Cochrane Library. Their quality was evaluated using the revised Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2). Such parameters as sensitivity and specificity were included for pooled analyses. The STATA 12.0 and Meta-Disc 1.4

software packages were used to perform the statistical analysis.

Results: sixty-nine papers were included in this meta-analysis. The pooled analysis of DTCs showed that lncRNAs had a sensitivity of 0.78 and a specificity of 0.80. The area under the summary ROC curve (AUC) was 0.86. For gastric cancer (GC), the pooled sensitivity and specificity were 0.77 (95 % CI: 0.72-0.81) and 0.75 (95 % CI: 0.71-0.79), respectively, and the AUC was 0.83. For colorectal cancer (CRC), these three parameters were 0.82 (95 % CI: 0.76-0.86), 0.84 (95 % CI: 0.79-0.88), and 0.90, respectively. For esophageal cancer (EC) sensitivity was 0.74 (95 % CI: 0.67-0.80) and specificity reached 0.86 (95 % CI: 0.72-0.93), with an AUC of 0.82.

Conclusions: LncRNAs show potential diagnostic value for discrimination between DTCs.

Keywords: Digestive tract cancer. lncRNAs. Diagnosis. Meta-analysis.

INTRODUCTION

Digestive tract cancers (DTCs) such as gastric cancer (GC), colorectal cancer (CRC), and esophageal cancer (EC) have attracted increasingly more attention because of their higher morbidity and mortality (1). It has been reported that a total of 18,240 new cases of, and 77,030 deaths from esophageal, gastric, and colorectal cancer occurred in the U.S. in 2013 (2). Similar figures were also reported in other countries. In Korea, the number of cases newly diagnosed with gastric, colorectal, and esophageal cancer was 30,184, 27,618, and 2,382, respectively, and the number of deaths from gastric, colorectal, and esophageal cancer was 9,180, 8,199, and 1,448, respectively, during 2010 (3). GC is the second most common fatal disease with an overall survival rate at 5 years inferior to 25 % (4). CRC is the third main cause of global cancer-related mortality (5), and its 5-year survival rate is below 10 % for advanced cases. Esophageal cancer (EC) is one of the leading causes of cancer-related deaths worldwide, causing more than 400 thousand deaths each year (6). Surgery is the most successful therapy for DTCs in the initial stage, but many patients are diagnosed with advanced cancer. There is a shortage of markers with

high sensitivity and specificity for the detection of early DTCs, which is detrimental to the treatment of patients. The extremely low survival rate and lack of typical early symptoms highlight the importance of early-stage tumor markers (7).

At present endoscopy, biopsies, double-contrast barium enema, and computed tomographic colonography are the most dependable diagnostic tests. They are useful for DTC surveillance. Nonetheless, many methods like gastroscopy and colonoscopy are widely accepted as effective tools, but being invasive procedures they have numerous disadvantages in clinical practice (8,9). The fecal occult blood test is a non-invasive technique that is widely used for the diagnosis of CRC (10). However, the diagnostic accuracy of this method for DTC identification is controversial.

With the development of science and technology, studies searching for small-molecule biomarkers for DTC are increasingly common. It is widely believed that some tumor markers in the blood are fairly favorable for early-stage cancer monitoring. There are a few accessible biomarkers, like matrix carcinoembryonic antigen (CEA) and carbohydrate antigen 242 (CA242), that represent non-invasive early-detection tools without recourse to endoscopy or surgery. Their low sensitivities have been an obstacle in discriminating DTCs from matched controls (10).

Long noncoding RNAs (lncRNAs) are a kind of newly-discovered RNAs whose length is longer than 200 nucleotides (4). It has been reported that lncRNAs are widely located in the serum, plasma, and tissues, and participate in gene expression regulation at different levels, exerting a key role in various biological processes (4,5). In addition, newly-presented evidence has demonstrated that lncRNAs may play a vital role in tumor metastasis, progression, and recurrence (11). A number of lncRNAs have been associated with clinical diagnosis and survival outcomes in cancer patients, and can be used as predictors for tumor prognosis (9-12). Recently, lncRNAs have been considered novel markers for cancer diagnosis, but with varying diagnostic accuracy (13).

Therefore, we carried out this meta-analysis to perform an overall assessment of lncRNAs for the screening of DTCs. The purpose of this research was to determine

the diagnostic significance of lncRNAs in DTC, and to explore the potential of lncRNAs as biomarkers for DTC diagnosis. Furthermore, the results of this study may provide some theoretical grounds for the clinical application of lncRNAs.

MATERIALS AND METHODS

Search strategy

We strictly adhered to the "preferred reporting items for systematic reviews and meta-analyses" (PRISMA) guidelines for diagnostic meta-analyses to carry out this study (14). Qualified reports from January 2011 to June 2019 were selected by searching electronic databases including PubMed, Web of Science, Embase, and Cochrane Library. The following search strategies were put into use: ('gastric cancer' OR 'gastric tumor' OR 'colorectal cancer' OR 'colorectal tumor' OR 'esophageal cancer' OR 'esophageal tumor') AND ('long noncoding RNAs' OR 'lncRNAs') AND ('diagnosis' OR 'sensitivity OR specificity' OR 'ROC curve'). In addition, we performed a manual search to obtain additional sources in order not to miss useful information.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) original research; (2) concerning the use of lncRNAs for the diagnosis of DTCs; (3) meeting the diagnostic criteria for DTCs; (4) with sufficient data (true positive, false positive, true negative, false negative) to construct a 2×2 table; (5) English-language papers.

Exclusion criteria were: (1) duplicated data; (2) irrelevant to the diagnostic yield of lncRNAs for DTC identification; (3) studies with serious design defects; (4) conference abstracts, letters, editorials, meta-analyses or reviews.

Data extraction

Two investigators independently extracted data from each included study by using the pre-stipulated inclusion and exclusion criteria. The basic characteristics of the studies, including first author, year of publication, country, case numbers, control numbers, control source, cancer type, detection method, sample, sensitivity, and

specificity were obtained. If a sharp disagreement appeared, advice could be sought from a third reviewer and conflict would be resolved through consultation.

Quality assessment

We used the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool to assess the qualities of each incorporated study (15). These criteria included 4 main parts, which were patient selection, index test, reference criterion, flow, and timing. Every item could be answered with ‘‘yes’’, ‘‘no’’, or ‘‘unclear’’. A ‘‘yes’’ answer implied low odds for bias; the other answers corresponded to high odds.

Statistical analysis

We used the STATA 12.0 and Meta-Disc 1.4 packages for data analysis. Indexes covered pooled sensitivity (SEN), pooled specificity (SPE), diagnostic odds ratio (DOR), positive likelihood ratio (PLR), and negative likelihood ratio (NLR). We depicted the summary receiver operating characteristic (SROC) curve and figured up the area under the SROC curve (AUC) by using sensitivity and specificity. We used the AUC value to estimate the accuracy with which early cases were discerned. An AUC approaching 1.0 showed that the experiment had a perfect discrimination. Using Cochran’s Q-test and the I^2 statistic we confirmed whether study heterogeneity was present. When $p < 0.05$ (Cochran’s Q-test) or $I^2 > 50$ % indicated significant heterogeneity among studies, a random-effect model was chosen (1). To find out the underlying origins of heterogeneity a meta-regression based on the features of the articles selected was applied. Fearing some publication bias, we applied Deeks’ funnel plot asymmetry test to check it out in this meta-analysis (1). Non-pre-specified subgroup analyses were carried out based on the number of cases and controls, as well as sample source. Furthermore, Fagan’s Nomogram was used to estimate post-test probabilities.

RESULTS

Search results and study characteristics

Through the above-mentioned search strategy we found 749 related papers. According to their inclusion and exclusion criteria, 84 studies were included. Finally, 69 eligible articles were incorporated into this meta-analysis due to lack of sufficient data to construct a 2×2 table. These articles were published ranging from January 2011 to June 2019. The flow chart is shown in figure 1. Forty of 69 articles dealt with GC detection (4,7,12,16,19-23,25-27,29-36,39-42,48-63), 24 of 69 with CRC (5,10,11,13,17,18,24,28,37,38,64-77), and only 5 with the diagnosis of EC (43-47). Sample sources included tissue (4,11,18,27-36,45,46,48-52,54,56,58,62,66,68,71-75), blood (5,7,10,12,13,16,17,19-26,37,38,43,44,47,53,55,57,59-61,63-65,67,69,70,76,77), and gastric juice (20,39-42). The primary characteristics of the included studies are shown in table 1.

Study quality assessment

The quality assessment of all studies was performed based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, as in figures 2 and 3. There was a high proportion of “low” and a low ratio of “high” values. So we concluded that each of the incorporated studies had a good quality regarding this meta-analysis.

Diagnostic accuracy

The overall SEN, SPE, PLR, NLR and DOR scores for DTC were 0.78 (95 % CI: 0.75-0.81), 0.80 (95 % CI: 0.76-0.82), 3.8 (95 % CI: 3.3-4.4), 0.27 (95 % CI: 0.24-0.31), and 14 (95 % CI: 11-18), respectively. There were 41 studies from 40 articles related to GC. The I^2 for SEN and SPE values for GC were 89.64 % and 86.17 %, respectively, illustrating a high heterogeneity amongst all 40 articles. Hence, a random-effects model was applied for this meta-analysis. For GC, the combined estimates were: SEN 0.77 (95 % CI: 0.72-0.81), SPE 0.75 (95 % CI: 0.71-0.79), PLR 3.1 (95 % CI: 2.6-3.6), NLR 0.31 (95 % CI: 0.26-0.36), and DOR 10 (95 % CI: 8-13). The forest plots of SEN and SPE are displayed in figure 4A. The SROC curve of all 40 articles about GC is shown in figure

5A. The AUC for lncRNAs was 0.83 (95 % CI: 0.79-0.86), demonstrating a relatively high diagnostic value.

With regard to CRC, since heterogeneity was high for SEN and SPE data (I^2 = 84.71 % and I^2 = 88.09 %, respectively), a random-effects model was used. The combined parameters were: SEN 0.82 (95 % CI: 0.76-0.86), SPE 0.84 (95 % CI: 0.79-0.88), PLR 5.1 (95 % CI: 4.0-6.6), NLR 0.22 (95 % CI: 0.17-0.28), and DOR 23 (95 % CI: 16-34). The forest plots for SEN and SPE are shown in figure 4B. The SROC curve for the 24 manuscripts about CRC is shown in figure 5B. The AUC for lncRNAs was 0.90 (95 % CI: 0.87-0.92), indicating that diagnostic accuracy for CRC detection is a little bit better than the overall diagnostic accuracy of lncRNAs in DTCs screening. SEN, SPE, PLR, NLR, and DOR for EC reached 0.74 (95 % CI: 0.67-0.80), 0.86 (95 % CI: 0.72-0.93), 5.3 (95 % CI: 2.6-10.7), 0.30 (95 % CI: 0.23-0.40) and 17 (95 % CI: 7-40), respectively, with an AUC of 0.82. The forest plots for SEN and SPE are shown in figure 4C. The SROC curve of the 5 papers about EC is shown in figure 5C.

Meta-regression and public bias

The results of the meta-regression revealed that the p-value was greater than 0.05 in all the analyses, implying that the numbers of cases and controls, as well as the sample sources were unlikely to be sources of heterogeneity (Table 2). To evaluate the publication bias of all the studies included Deeks' funnel plot asymmetry test was used. The p-values for GC, CRC and EC were 0.59, 0.86 and 0.15, suggesting an extremely low probability of publication biases in our study.

Subgroup analyses

To find out the source of heterogeneity we carried out subgroup analyses in our study. For GC, the subgroup analyses by sample (gastric juice, blood, or tissue) on 40 articles demonstrated that blood-based lncRNAs had a better diagnostic performance than those in gastric juice or tissue: SEN 0.79 (95 % CI: 0.77-0.81), SPE 0.71 (95 % CI: 0.68-0.73), PLR 2.64 (95 % CI: 2.14-3.27), NLR 0.29 (95 % CI: 0.23-0.37), and DOR 10.79 (95 % CI: 7.23-16.10) with an AUC of 0.84. Studies with a sample size

larger than 150 showed a better diagnostic value when compared to studies with a sample size smaller than 150: SEN 0.78 (95 % CI: 0.77-0.79), SPE 0.72 (95 % CI: 0.70-0.73), PLR 2.69 (95 % CI: 2.33-3.10), NLR 0.32 (95 % CI: 0.26-0.39), and DOR 9.35 (95 % CI: 6.93-12.63) with an AUC of 0.82. As for CRC, the subgroup analyses on 24 articles suggested that tissue-based lncRNAs had a better diagnostic yield than those found in the blood: SEN 0.80 (95 % CI: 0.78-0.83) *versus* 0.78 (95 % CI: 0.76-0.81), NLR 0.23 (95 % CI: 0.16-0.34) *versus* 0.26 (95 % CI: 0.22-0.32), and DOR 25.47 (95 % CI: 11.90-54.51) *versus* 21.95 (95 % CI: 14.76-32.64), with an AUC of 0.90 *versus* 0.89. In short, tissue-based assays are better for CRC screening. A number of cases and controls above 150 seemed better suited for the diagnosis of CRC than a number below 150: SEN 0.81 (95 % CI: 0.79-0.83), SPE 0.79 (95 % CI: 0.77-0.81), PLR 4.68 (95 % CI: 3.13-6.99), NLR 0.21 (95 % CI: 0.15-0.30), and DOR 26.34 (95 % CI: 13.49-51.42) with an AUC of 0.91 (Table 3).

Clinical application of diagnostic tests

In this meta-analysis we used Fagan's nomogram to estimate post-test probabilities. With Fagan's nomogram for GC, with a pre-test probability of 20 % the post-test probability was 44 % with a positive possibility rate of 3; likelihood was reduced to 7 %, and the negative possibility rate was 0.31. For CRC, with a pre-test probability of 20 % in Fagan's nomogram, the post-test possibility rate would raise to 56 % with a LR+ of 5, and likelihood would decline to 5 % with a LR- of 0.22. For EC, with a pre-test probability of 20 % in Fagan's nomogram, the post-test possibility rate would raise to 57 % with a LR+ of 5, and likelihood would decline to 7 %, with a LR- of 0.30.

DISCUSSION

DTCs are a class of diseases that seriously jeopardize human beings (1). Despite improved diagnosis technologies and effective treatment methods in the last few years, the 5-year survival rate for advanced cases of DTC remains quite low. Along with research advancements, lncRNAs have become promising biomarkers for the diagnosis of DTCs. In this meta-analysis lncRNAs generated an AUC of 0.86 with a

sensitivity of 0.78 and a specificity of 0.80 for the identification of DTC patients *versus* cancer-free controls, suggesting a good diagnostic efficiency. As an important parameter, the DOR of lncRNAs was calculated to be 14 (> 1), showing a low diagnostic accuracy. Moreover, the pooled PLR was 3.8, suggesting that patients with DTCs had over 3 times more possibilities of being positive than non-cancer patients. NLR can predict the chances to be diagnosed with a DTC when the test is negative. The pooled NLR was 0.27 in our analysis. The above parameters all showed that lncRNAs may be fairly good markers for the diagnosis of DTCs.

GC, CRC and EC are quite common types of DTCs. The AUCs of GC, CRC and EC were 0.83, 0.90 and 0.82, respectively. The I^2 for SEN and SPE in GC, CRC and EC both exceeded 50 %, indicating there was high heterogeneity. Therefore, we needed to figure out heterogeneity sources. We performed a meta-regression and subgroup analyses based on case and control numbers, and the sample sources for this meta-analysis. It turned out that these factors were not the cause of heterogeneity. Maybe some factors such as patient sex, age, occupation, etc., have influenced our results. So further research is needed.

A previous study had indicated that the sensitivity of AFP, CEA, CA125 and CA19-9 for gastric cancer ranged from 4.7 % to 20.8 %, and the specificity was above 99 % (78). Yang et al. reported that the sensitivity of CA19-9 and CA242 for colorectal cancer were 19.5 % and 20.0 %, respectively, with a specificity of 100 % in both cases (79). Bagaria et al. discovered that for CEA sensitivity was 28 %, and negative predictive value (NPV) was 61.72 %; and for CA19-9, sensitivity was 18 %, and NPV was 54.94 % for esophageal cancer (80). The above studies showed that these biomarkers did not qualify as a novel approach with high diagnostic efficiency. Compared with the above biomarkers, lncRNAs showed a superior performance in terms of both sensitivity and specificity. Research suggested that lncRNAs may be an ideal diagnostic biomarker for the detection of DTCs (11).

According to studies, lncRNAs were related to DTC progression, such as migration (81) and invasion (82). Furthermore, the aberrant expression of lncRNAs showed different levels of proliferation inhibition (83) and apoptosis induction effects (84) both in *in*

vivo and *in vitro* studies. All of these indicated an enormous potential of lncRNAs for tumor targeted therapy in the future. However, there are still some problems in the clinical application of lncRNAs. Primarily, the number of lncRNAs that can be effectively utilized remains to be determined since research about lncRNAs are ongoing. In addition, whether the functioning lncRNAs confirmed by experiments can be finally used in the clinical setting remains to be verified. Another problem was how to target inhibition or induce endogenous lncRNAs for tumor therapy effectively and safely. But, anyway, it was worth confirming that lncRNAs are superior markers for DTC detection.

The limitations of our study cannot be overlooked. First, we restricted our search to English-language publications. Articles in other languages were not considered. Secondly, the source of heterogeneity was not found. Thirdly, most of the included studies were from China. This may also lead to some bias in terms of race. Finally, we are still far from detecting specific lncRNAs able to screen DTCs from other cancers.

In this study we conducted a meta-analysis to clarify the diagnostic performance of lncRNAs for the discrimination of DTCs. The pooled analysis of DTCs showed that lncRNAs had a sensitivity of 0.78, and a specificity of 0.80. Although the results indicated a good diagnostic value, further studies are needed to confirm the usefulness of these markers for cancer discrimination.

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Table 1. Basic characteristics of the diagnostic tests included in this meta-analysis

First author	Year	Country	Case numbers	Control numbers	Control source	Cancer type	Detection method	Sample	Sensitivity	Specificity	Long noncoding RNA
Weiliang Sun	2013	China	78	78	Benign diseases	GC	qRT-PCR	Tissue	51.30 %	87.20 %	AC096655.1-002
Tomohiro Arita	2013	Japan	43	34	Healthy	GC	qRT-PCR	Plasma	74.00 %	58.00 %	H19
Dang Mei	2013	China	96	96	Benign diseases	GC	qRT-PCR	Tissue	65.90 %	63.60 %	SUMO1P3
Yongfu Shao	2014	China	83	120	Healthy	GC	qRT-PCR	Gastric juice	46.00 %	93.00 %	AA174084
Yan Zhao	2014	China	58	58	Normal	GC	qRT-PCR	Tissue	70.70 %	72.40 %	HULC
Qianqian Pang	2014	China	17	16	Benign diseases	GC	qRT-PCR	Gastric juice	62.50 %	68.10 %	LINC00152
Zhong Liu	2014	China	83	80	Healthy	GC	qRT-PCR	Plasma	67.20 %	80.30 %	FERIL-4
Long Liu	2014	China	138	138	Benign diseases	GC	qRT-PCR	Tissue	88.41 %	73.91 %	ncRuPAR
Xinxiu Lin	2014	China	75	75	Normal	GC	qRT-RCR	Tissue	67.00 %	64.00 %	ABHD11-AS1
Qier Li	2015	China	79	81	Healthy	GC	qRT-PCR	Plasma	48.10 %	85.20 %	LINC00152
Lei Dong	2015	China	30	34	Healthy	GC	qRT-PCR	Serum	74.10 %	100.00 %	CUDR LSINGT-5 PTENP1
Xiaoying Zhou	2015	China	70	70	Healthy	GC	qRT-PCR	Plasma	82.90 %	72.90 %	H19
Q,Zheng	2015	China	112	112	Healthy	GC	qRT-PCR	Gastric juice	67.20 %	80.30 %	UCA1
Jingxu Sun	2015	China	96	96	Benign diseases	GC	qRT-PCR	Tissue	44.80 %	82.30 %	RP11-119F7.4
Wenming Chen	2015	China	83	83	Normal	GC	qRT-PCR	Tissue	72.29 %	60.24 %	HIF1A-AS2
Hu Zhou	2016	China	77	60	Healthy	GC	RT-PCR	Plasma	76.60 %	63.90 %	ZFAS1
Bin Ma	2016	China	97	97	Normal	GC	qRT-PCR	Tissue	69.10 %	66.00 %	KRT18P55
Suxiu Chen	2016	China	106	106	Normal	GC	qRT-PCR	Tissue	64.20 %	74.50 %	SNHG15
Wenming Chen	2016	China	97	97	Normal	GC	qRT-PCR	Tissue	76.29 %	56.70 %	LINC00152
Yuben Yang	2016	China	39	45	Healthy	GC	qRT-PCR	Gastric juice	41.00 %	93.40 %	ABHD11-AS1
Yongfu Shao	2016	China	83	90	Healthy	GC	qRT-PCR	Plasma	59.10 %	67.80 %	RMRP
			39	45	Healthy	GC	qRT-PCR	Gastric juice	56.40 %	75.40 %	RMRP
Doaa Hashad	2016	Egypt	32	30	Healthy	GC	qRT-PCR	Plasma	68.75 %	56.67 %	H19
Xiaobo Guo	2016	China	130	130	Healthy	GC	qRT-PCR	Plasma	86.94 %	91.27 %	OR3A4
Chunjing Jin	2016	China	100	110	Healthy	GC	qRT-PCR	Serum	82.00 %	83.60 %	HULC
Jianbin Gu	2017	China	285	33	Normal	GC	qRT-PCR	Tissue	93.90 %	77.90 %	FEZF1-AS1
									87.90 %	87.70 %	HOTAIR
									93.90 %	76.80 %	LINC01234
Qin Lu	2017	China	76	76	Normal	GC	qRT-PCR	Tissue	84.60 %	59.00 %	XIST
									67.90 %	85.90 %	BCYRN1
									85.90 %	56.40 %	RRP1
									73.10 %	60.30 %	TDRG1

WenMing Chen	2017	China	65	65	Normal	GC	qPCR	Tissue	64.62 %	75.38 %	HOTAIR
Lei Pan	2017	China	94	94	Normal	GC	qRT-PCR	Tissue	80.00 %	75.70 %	ZFAS1
Kecheng Zhang	2017	China	30	30	Healthy	GC	qRT-PCR	Plasma	82.00 %	87.00 %	TINCR，CCAT2，AOC4P，BANCR，LINC00857
Min Fu	2018	China	72	72	Healthy	GC	qRT-PCR	Serum	80.00 %	70.00 %	LINC00978
Haipeng Xian	2018	China	10	10	Healthy	GC	qRT-PCR	Plasma	58.00 %	80.00 %	HULC
									84.00 %	68.00 %	ZNFX1-AS1
Xiaoqin Zhu	2018	China	18	13	Normal	GC	qRT-PCR	Tissue	69.20 %	75.60 %	LINC01006
Ebur esin Youuker	2018	Germany	40	42	Healthy	GC	qRT-PCR	Plasma	87.20 %	38.10 %	H19
Rui Zhao	2018	China	126	120	Healthy	GC	qRT-PCR	Serum	69.80 %	85.00 %	HOTTIP
Jingjing Liu	2018	China	100	100	Healthy	GC	qRT-PCR	Plasma	90.00 %	51.00 %	CTC-501010.1
									84.00 %	58.00 %	AC100830.4
									89.00 %	55.00 %	RP11-210K20.5
									99.00 %	49.00 %	CTC-501010.1、AC100830.4、RP11-210K20.5
Waleed A. Mohamed	2019	Egypt	35	40	Benign diseases	GC	qRT-PCR	Serum	95.50 %	100.00 %	H19
Xiaoyan Mo	2019	China	104	104	Normal	GC	qRT-PCR	Tissue	81.00 %	62.00 %	RP11-555H23.1
Farbod Esfandi	2019	Iran	30	30	Normal	GC	qPCR	Tissue	66.70 %	86.70 %	GHET1, TUG1, UCA1, PANDA
Yun Liu	2019	China	25	25	Normal	GC	qRT-PCR	Tissue	78.70 %	97.80 %	HOXA11-AS
Hamid Ghaedi	2019	Iran	62	40	Healthy	GC	qRT-PCR	Plasma	74.19 %	90.00 %	H19,
									95.16 %	42.50 %	MEG3
Lloyd.D Graham	2011	USA	20	28	Healthy	CRC	qRT-PCR	Tissue	85.00 %	96.00 %	CRNDE-b
Miroslav Svoboda	2014	Czech	84	40	Healthy	CRC	qRT-PCR	Plasma	67.00 %	92.50 %	HOTAIR
Bing Yan	2014	China	105	105	Benign diseases	CRC	qRT-PCR	Tissue	97.14 %	65.87 %	ncRuPAR
Wemin Zhao	2015	China	32	32	Healthy	CRC	qRT-PCR	Plasma	75.70 %	85.30 %	CCAT1
									84.30 %	80.20 %	CCAT1 HOTAIR
									67.50 %	89.90 %	HOTAIR
Yuchen Wu	2015	China	100	100	Healthy	CRC	qRT-PCR	Blood	69.00 %	79.00 %	NEAT1-V1
									70.00 %	96.00 %	NEAT2-V2
Rui Wang	2016	China	120	120	Healthy	CRC	qRT-PCR	Serum	81.67 %	80.00 %	BANCR NR_026817 NR_029373 NR_034119
Ledong Wan	2016	China	50	34	Healthy	CRC	qRT-PCR	Plasma	64.00 %	76.50 %	HOTAIRM1
Tong Liu	2016	China	142	142	Normal or benign diseases	CRC	qRT-PCR	Tissue	70.40 %	70.80 %	CRNDE-h
Tong Liu	2016	China	148	80	Benign diseases and healthy	CRC	qRT-PCR	Serum	70.30 %	94.40 %	CRNDE-h
Chuanxi Wang	2016	China	61	60	Healthy	CRC	qRT-PCR	Serum	68.33 %	86.89 %	LOC285194, RP11-462C24.1,Nbla12061

Chunxiang Ye	2016	China	62	37	Healthy	CRC	qRT-PCR	Plasma	88.71 %	94.59 %	lnc-GNAT1-1
Changyi Fang	2017	China	105	95	Healthy	CRC	qRT-PCR	Plasma	92.38 %	76.84 %	ZFAS1
Meiyu Dai	2017	China	30	30	Healthy	CRC	qRT-PCR	Serum	83.30 %	76.70 %	BLACAT1
Jining Fu	2017	China	108	108	Normal	CRC	qRT-PCR	Tissue	60.30 %	90.70 %	ZEB1-AS1
Wanjun Gong	2017		150	161	Healthy	CRC	qRT-PCR	Serum	86.80 %	92.50 %	HIF1A-AS1
Lin Liu	2018	China	158	173		CRC	qRT-PCR	Tissue	95.40 %	89.90 %	GAS5
Linbo Chen	2018	China	130	130	Normal	CRC	qRT-PCR	Tissue	82.30 %	43.90 %	LINC00472
Cristina Barbagallo	2018		20	20	Normal	CRC	qRT-PCR	Serum	100.00 %	43.00 %	UCA1
									93.00 %	64.00 %	TUG1, UCA1
Yeshuo Ma	2018	China	34	34	Normal	CRC	qRT-PCR	Tissue	55.90 %	76.50 %	RP1-85F18.6
Lili Wang	2018	China	142	207	Benign diseases and healthy	CRC	qRT-PCR	Serum	81.70 %	70.70 %	NORAD
Jixi Liu	2018	China	26	26	Normal	CRC	qRT-PCR	Tissue	86.70 %	100.00 %	ELFN1-AS1
									96.20 %	77.10 %	LINC01234
									59.60 %	96.20 %	SNHG17
Ehsan Gharib	2019	Iran	40	40	Healthy	CRC	qRT-PCR	Tissue	82.24 %	92.12 %	HOTTIP, PVT1, and UCA1
									68.29 %	78.05 %	HOTTIP
									72.50	87.50	PVT1
									63.41	85.37	UCA1
Shaojun Yu	2019	China	80	80	Normal	CRC	qRT-PCR	Tissue	97.50 %	80.00 %	TINCR
Paria Abedini	2019	Iran	74	74	Healthy	CRC	qRT-PCR	Plasma	82.00 %	75.00 %	ATB
Xilei Zhou	2015	China	40	40	normal Esophageal mucosa	EC	qRT-PCR	Tissue	79.40 %	73.30 %	AFAP1-AS1
Tong YS	2015	China	147	123	Healthy	EC	qPCR	Plasma	72.80 %	89.40 %	POU3F3
Wenjian Wang	2017	China	50	20	Healthy	EC	qRT-PCR	Serum	56.00 %	90.00 %	HOTAIR
Kaiyan Sun	2018	China	53	39	Healthy	EC	qRT-PCR	Plasma	77.36 %	64.15 %	MIR31HG
G.-D. Gao	2018	China	128	128	Normal	EC	qRT-PCR	Tissue	78.11 %	95.34 %	CASC9

GC: gastric cancer; CRC: colorectal cancer; EC: esophageal cancer; qRT-PCR: quantitative real-time polymerase chain reaction; qPCR: quantitative polymerase chain reaction.

Table 2. Meta-regression for the potential source of heterogeneity

Study characteristics	p-value	RDOR	95 %CI
GC			
sample (gastric juice, blood, tissue)	0.94	0.98	0.65-1.49
Case/control numbers (GC ＜ 150, GC ≥ 150）	0.97	1.01	0.57-1.79
CRC			
sample (tissue, blood)	0.96	1.02	0.43-2.42
Case/control numbers (CRC ＜ 150, CRC ≥ 150）	0.66	1.21	0.50-2.91

CI: confidence interval; RDOR: relative diagnostic odds ratio; GC: gastric cancer; CRC: colorectal cancer；
QUADAS-2: the revised Quality Assessment of Diagnostic Accuracy Studies-2.

Table 3. Summary of the diagnostic performance of lncRNAs for DTCs

Analysis	SEN (95 % CI)	SPE (95 % CI)	PLR (95 % CI)	NLR (95 % CI)	DOR (95 %)	AUC
GC						
sample						
gastric juice	0.56 (0.50,0.62)	0.86 (0.81,0.89)	3.49 (2.27,5.35)	0.54 (0.46,0.64)	7.55 (5.07,11.24)	0.75
blood	0.79 (0.77,0.81)	0.71 (0.68,0.73)	2.64 (2.14,3.27)	0.29 (0.23,0.37)	10.79 (7.23,16.10)	0.84
tissue	0.79 (0.77,0.80)	0.71 (0.69,0.73)	2.57 (2.22,2.98)	0.32 (0.25,0.41)	8.73 (6.23,12.23)	0.78
Case/control						
numbers						
＜ 150	0.75 (0.72,0.78)	0.74 (0.71,0.77)	2.75 (2.13,3.55)	0.36 (0.29,0.44)	8.91 (6.10,13.02)	0.82
≥ 150	0.78 (0.77,0.79)	0.72 (0.70,0.73)	2.69 (2.33,3.10)	0.32 (0.26,0.39)	9.35 (6.93,12.63)	0.80
CRC						
sample						
blood	0.78 (0.76,0.81)	0.82 (0.80,0.84)	4.60 (3.46,6.13)	0.26 (0.22,0.32)	21.95 (14.76,32.64)	0.89
tissue	0.80 (0.78,0.83)	0.78 (0.75,0.80)	4.61 (2.98,7.12)	0.23 (0.16,0.34)	25.47 (11.90,54.51)	0.90
Case/control						
numbers						
＜ 150	0.76 (0.72,0.79)	0.83 (0.81,0.86)	4.37 (3.27,5.83)	0.30 (0.24,0.37)	18.80 (12.35,28.63)	0.88
≥ 150	0.81 (0.79,0.83)	0.79 (0.77,0.81)	4.68 (3.13,6.99)	0.21 (0.15,0.30)	26.34 (13.49,51.42)	0.91
All studies						

AUC: area under the SROC curve; lncRNAs: long noncoding RNAs; DTCs: digestive tract cancers; SEN: sensitivity; SPE: specificity; PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio.

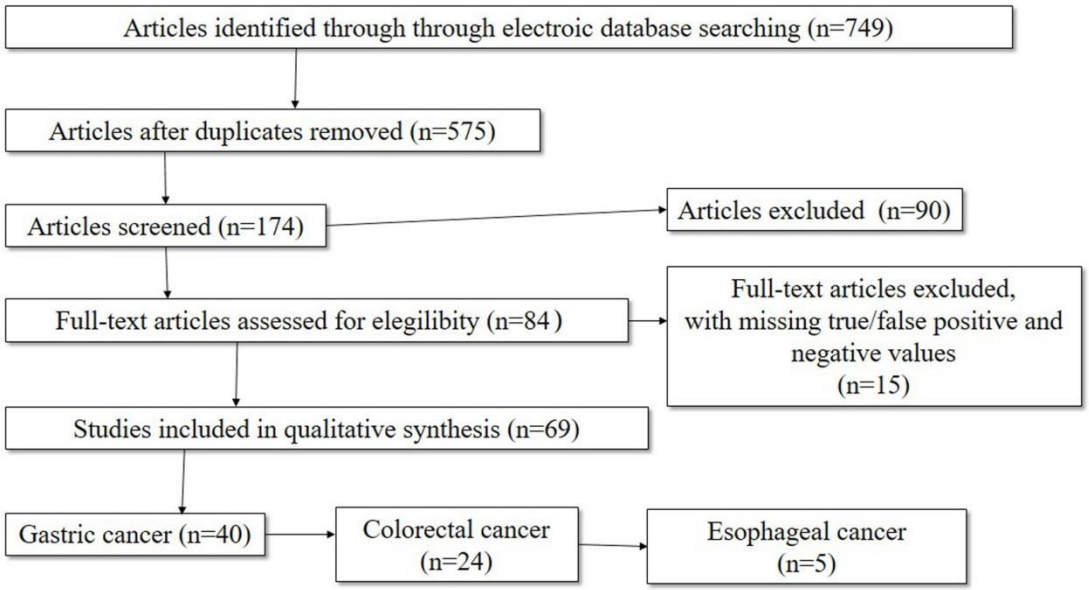

Fig. 1. The flow chart of this meta-analysis.

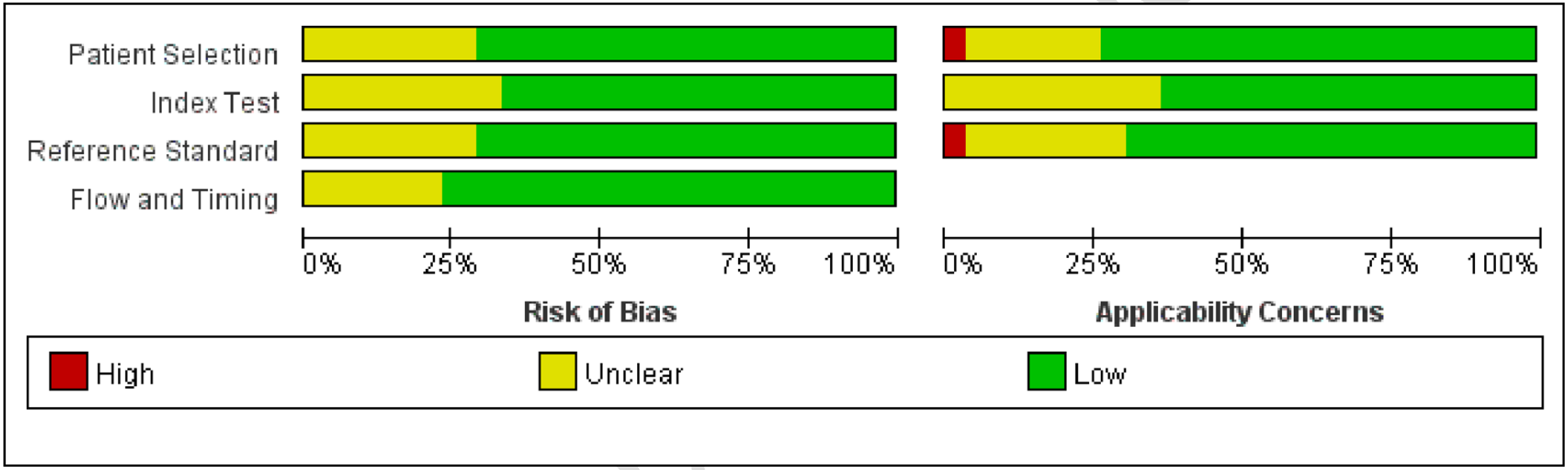

Fig. 2. Methodological quality summary.

Fig.3. Methodological quality graph.

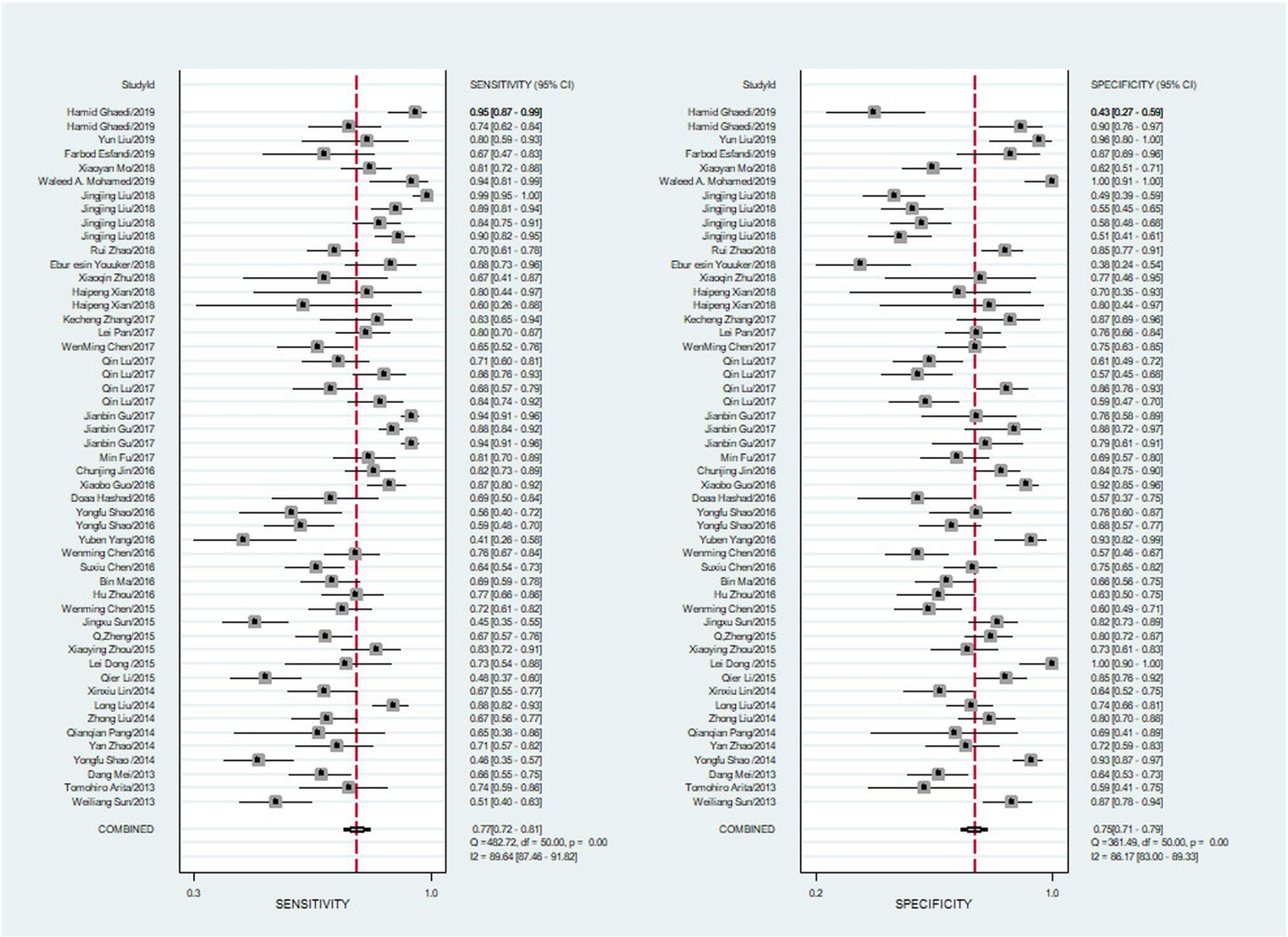
Studyld
SENSITIVITY (95% CI)
Hamid Ghaedi/2019 0.95 [0.87 - 0.99]
Hamid Ghaedi/2019 0.74 [0.62 - 0.84]
Yun Liu/2019 0.80 [0.59 - 0.93]
Farbod Esfandi/2019 0.67 [0.47 - 0.83]
Xiaoyan Mo/2018 0.81 [0.72 - 0.88]
Waleed A. Mohamed/2019 0.94 [0.81 - 0.99]
Jingjing Liu/2018 0.99 [0.95 - 1.00]
Jingjing Liu/2018 0.89 [0.81 - 0.94]
Jingjing Liu/2018 0.84 [0.75 - 0.91]
Jingjing Liu/2018 0.90 [0.82 - 0.95]
Rui Zhao/2018 0.70 [0.61 - 0.78]
Ebur esin Youuker/2018 0.88 [0.73 - 0.96]
Xiaoqin Zhu/2018 0.67 [0.41 - 0.87]
Haipeng Xian/2018 0.80 [0.44 - 0.97]
Haipeng Xian/2018 0.60 [0.26 - 0.88]
Kecheng Zhang/2017 0.83 [0.65 - 0.94]
Lei Pan/2017 0.80 [0.70 - 0.87]
WenMing Chen/2017 0.65 [0.52 - 0.76]
Qin Lu/2017 0.71 [0.60 - 0.81]
Qin Lu/2017 0.86 [0.76 - 0.93]
Qin Lu/2017 0.68 [0.57 - 0.79]
Qin Lu/2017 0.84 [0.74 - 0.92]
Jianbin Gu/2017 0.94 [0.91 - 0.96]
Jianbin Gu/2017 0.88 [0.84 - 0.92]
Jianbin Gu/2017 0.94 [0.91 - 0.96]
Min Fu/2017 0.81 [0.70 - 0.89]
Chunjing Jin/2016 0.82 [0.73 - 0.89]
Xiaobo Guo/2016 0.87 [0.80 - 0.92]
Dosa Hashad/2016 0.69 [0.50 - 0.84]
Yongfu Shao/2016 0.56 [0.40 - 0.72]
Yongfu Shao/2016 0.59 [0.48 - 0.70]
Yuben Yang/2016 0.41 [0.26 - 0.58]
Wenming Chen/2016 0.76 [0.67 - 0.84]
Suxiu Chen/2016 0.64 [0.54 - 0.73]
Bin Ma/2016 0.69 [0.59 - 0.78]
Hu Zhou/2016 0.77 [0.66 - 0.86]
Wenming Chen/2015 0.72 [0.61 - 0.82]
Jingxu Sun/2015 0.45 [0.35 - 0.55]
Q.Zheng/2015 0.67 [0.57 - 0.76]
Xiaoying Zhou/2015 0.83 [0.72 - 0.91]
Lei Dong /2015 0.73 [0.54 - 0.88]
Qier Li/2015 0.48 [0.37 - 0.60]
Xinxiu Lin/2014 0.67 [0.55 - 0.77]
Long Liu/2014 0.88 [0.82 - 0.93]
Zhong Liu/2014 0.67 [0.56 - 0.77]
Qianqian Pang/2014 0.65 [0.38 - 0.86]
Yan Zhao/2014 0.71 [0.57 - 0.82]
Yongfu Shao /2014 0.46 [0.35 - 0.57]
Dang Mei/2013 0.66 [0.55 - 0.75]
Tamohiro Arita/2013 0.74 [0.59 - 0.86]
Weiliang Sun/2013 0.51 [0.40 - 0.63]
COMBINED 0.77[0.72 - 0.81]
Q =482.72, df = 50.00, p = 0.00
I2 = 89.64 [87.46 - 91.82]
0.3
1.0
SENSITIVITY
Studyld
SPECIFICITY (95% CI)
Hamid Ghaedi/2019 0.43 [0.27 - 0.59]
Hamid Ghaedi/2019 0.90 [0.76 - 0.97]
Yun Liu/2019 0.96 [0.80 - 1.00]
Farbod Esfandi/2019 0.87 [0.69 - 0.96]
Xiaoyan Mo/2018 0.62 [0.51 - 0.71]
Waleed A. Mohamed/2019 1.00 [0.91 - 1.00]
Jingjing Liu/2018 0.49 [0.39 - 0.59]
Jingjing Liu/2018 0.55 [0.45 - 0.65]
Jingjing Liu/2018 0.58 [0.48 - 0.68]
Jingjing Liu/2018 0.51 [0.41 - 0.61]
Rui Zhao/2018 0.85 [0.77 - 0.91]
Ebur esin Youuker/2018 0.38 [0.24 - 0.54]
Xiaoqin Zhu/2018 0.77 [0.46 - 0.95]
Haipeng Xian/2018 0.70 [0.35 - 0.93]
Haipeng Xian/2018 0.80 [0.44 - 0.97]
Kecheng Zhang/2017 0.87 [0.69 - 0.96]
Lei Pan/2017 0.76 [0.68 - 0.84]
WenMing Chen/2017 0.75 [0.63 - 0.85]
Qin Lu/2017 0.61 [0.49 - 0.72]
Qin Lu/2017 0.57 [0.45 - 0.68]
Qin Lu/2017 0.86 [0.76 - 0.93]
Qin Lu/2017 0.59 [0.47 - 0.70]
Jianbin Gu/2017 0.76 [0.58 - 0.89]
Jianbin Gu/2017 0.88 [0.72 - 0.97]
Jianbin Gu/2017 0.79 [0.61 - 0.91]
Min Fu/2017 0.69 [0.57 - 0.80]
Chunjing Jin/2016 0.84 [0.75 - 0.90]
Xiaobo Guo/2016 0.92 [0.85 - 0.96]
Dosa Hashad/2016 0.57 [0.37 - 0.75]
Yongfu Shao/2016 0.76 [0.60 - 0.87]
Yongfu Shao/2016 0.68 [0.57 - 0.77]
Yuben Yang/2016 0.93 [0.82 - 0.99]
Wenming Chen/2016 0.57 [0.46 - 0.67]
Suxiu Chen/2016 0.75 [0.65 - 0.82]
Bin Ma/2016 0.66 [0.56 - 0.75]
Hu Zhou/2016 0.63 [0.50 - 0.75]
Wenming Chen/2015 0.60 [0.49 - 0.71]
Jingxu Sun/2015 0.82 [0.73 - 0.89]
Q.Zheng/2015 0.80 [0.72 - 0.87]
Xiaoying Zhou/2015 0.73 [0.61 - 0.83]
Lei Dong /2015 1.00 [0.90 - 1.00]
Qier Li/2015 0.85 [0.76 - 0.92]
Xinxiu Lin/2014 0.64 [0.52 - 0.75]
Long Liu/2014 0.74 [0.66 - 0.81]
Zhong Liu/2014 0.80 [0.70 - 0.88]
Qianqian Pang/2014 0.69 [0.41 - 0.89]
Yan Zhao/2014 0.72 [0.59 - 0.83]
Yongfu Shao /2014 0.93 [0.87 - 0.97]
Dang Mei/2013 0.64 [0.53 - 0.73]
Tamohiro Arita/2013 0.59 [0.41 - 0.75]
Weiliang Sun/2013 0.87 [0.78 - 0.94]
COMBINED 0.75[0.71 - 0.79]
Q =361.49, df = 50.00, p = 0.00
I2 = 86.17 [83.00 - 89.33]
0.2
1.0
SPECIFICITY

Fig.4A. Pooled sensitivity and specificity for gastric cancer.

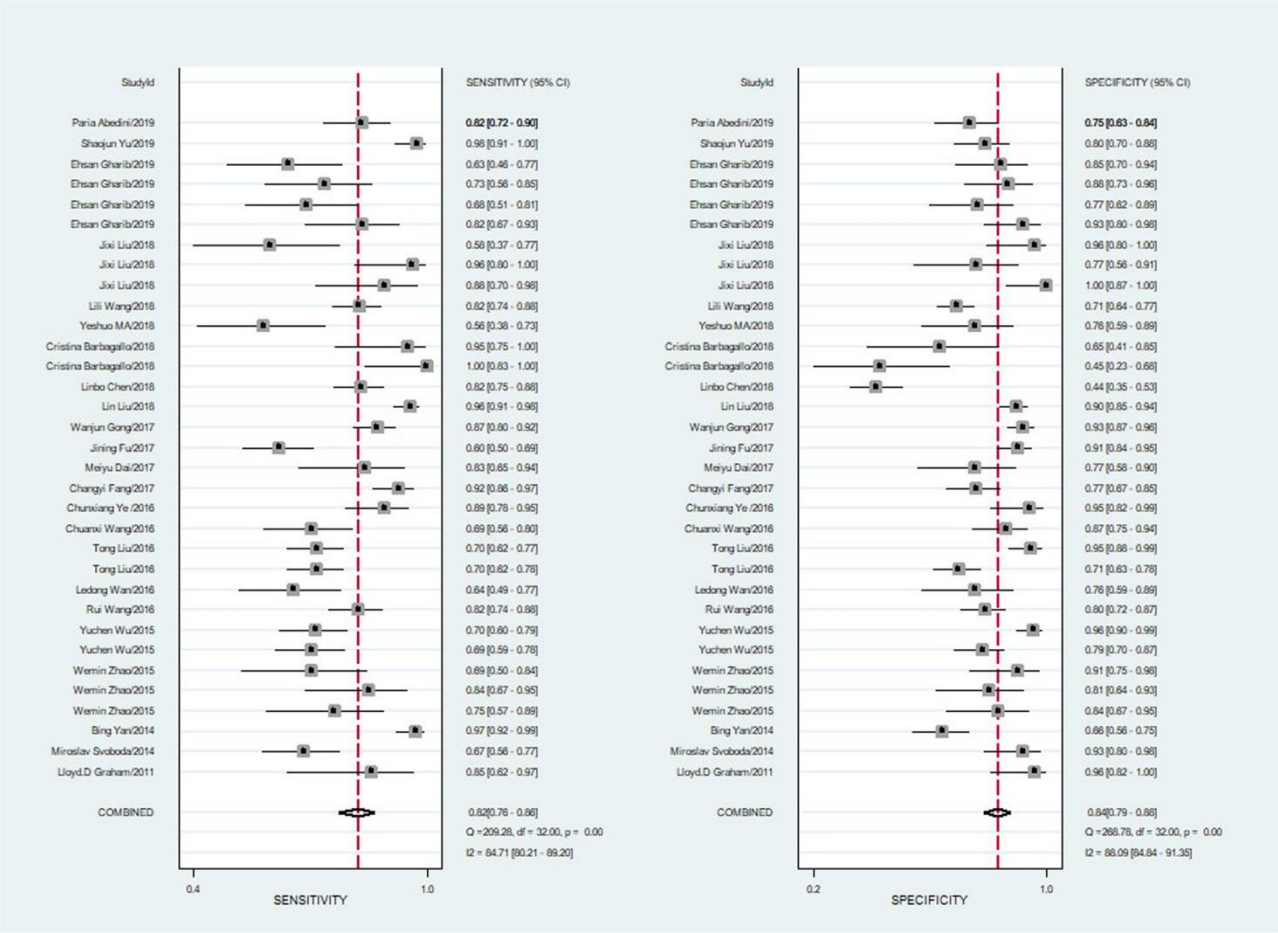

Fig. 4B. Pooled sensitivity and specificity for colorectal cancer.

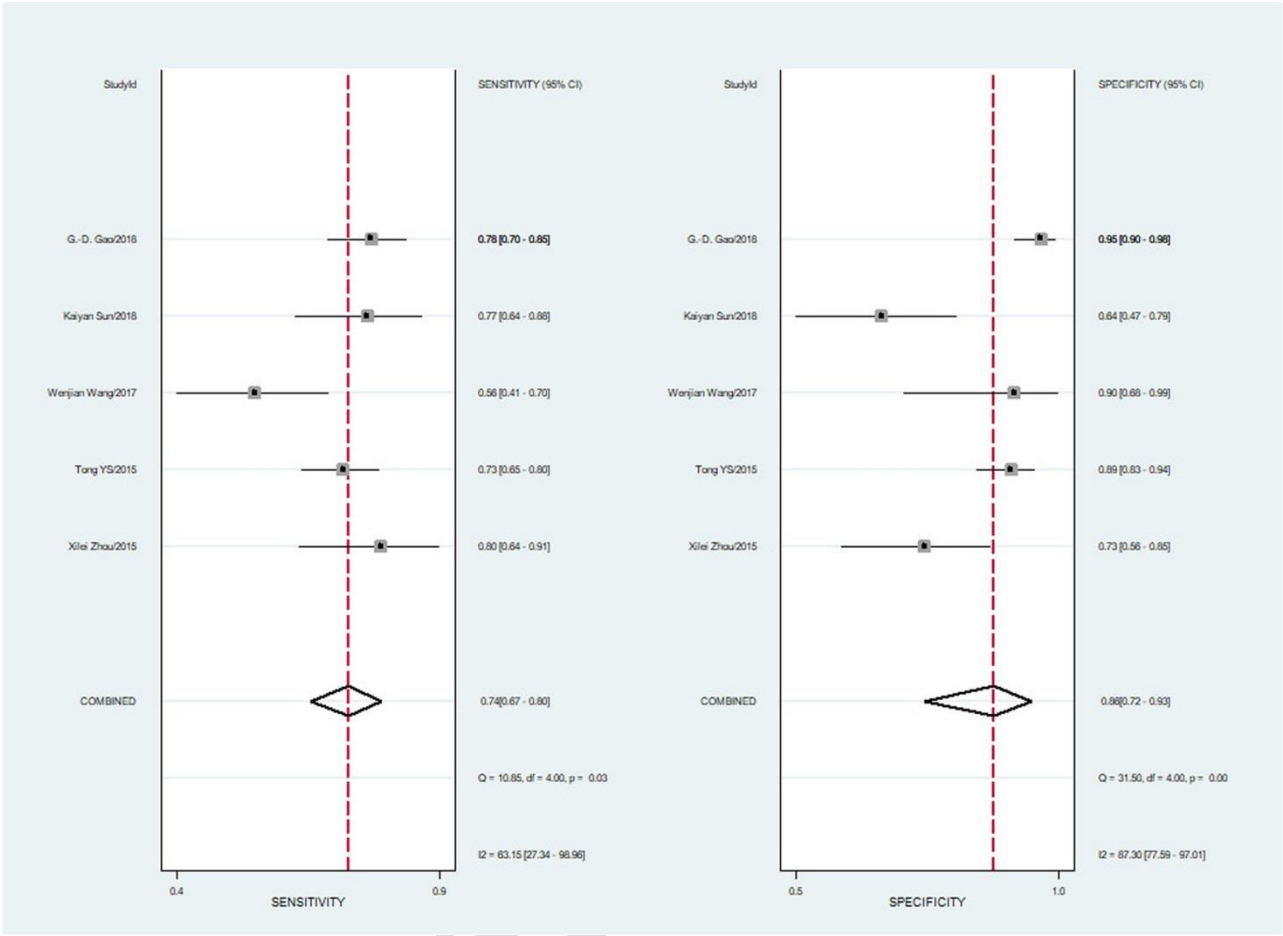

Fig. 4C. Pooled sensitivity and specificity for esophageal cancer.

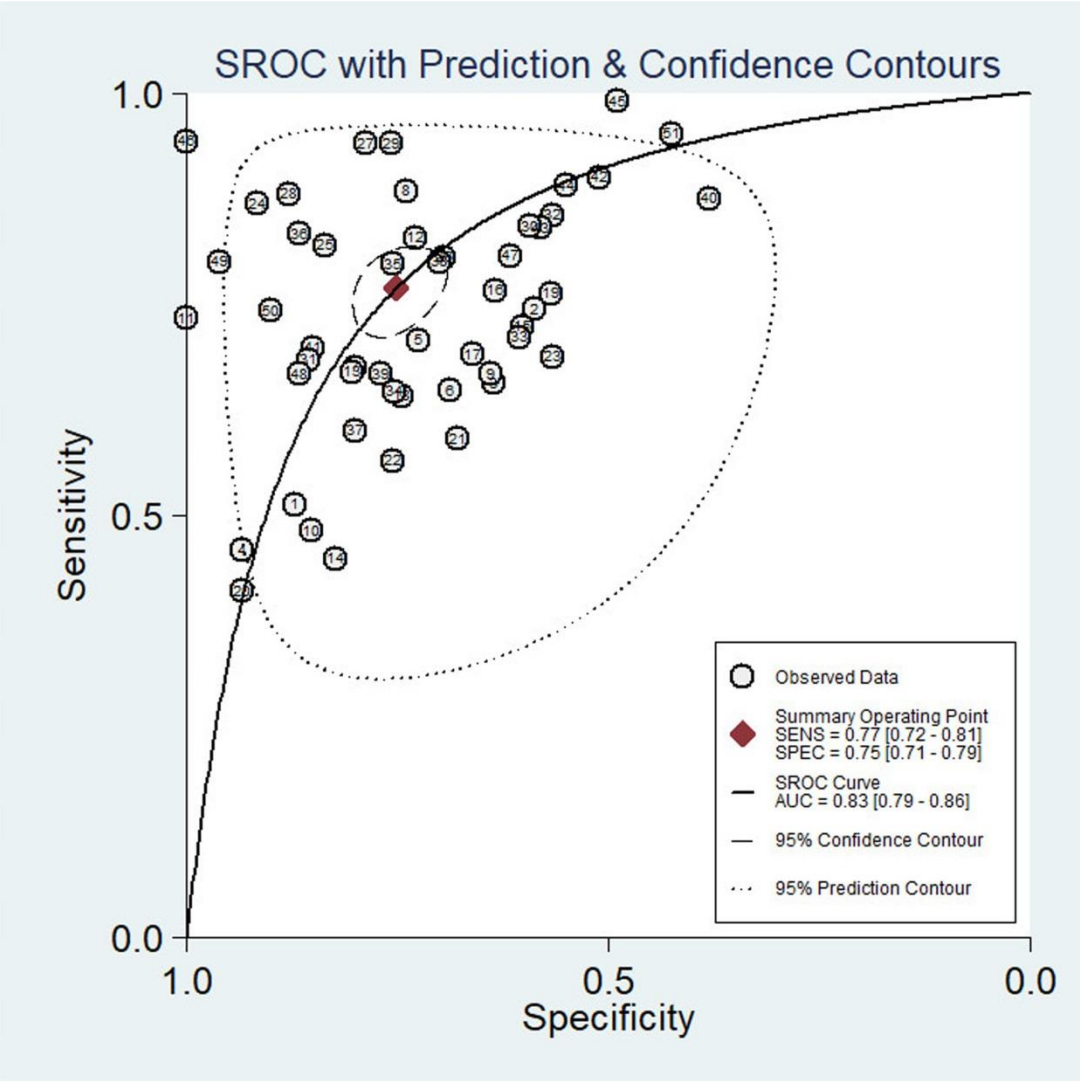
SROC with Prediction & Confidence Contours
Sensitivity
1.0
0.5
0.0
1.0
0.5
0.0
Specificity
Observed Data
Summary Operating Point
SENS = 0.77 [0.72 - 0.81]
SPEC = 0.75 [0.71 - 0.79]
SROC Curve
AUC = 0.83 [0.79 - 0.86]
95% Confidence Contour
95% Prediction Contour

Fig. 5A. Summary receiver operating characteristic curve for lncRNA expression profile in the diagnosis of gastric cancer.

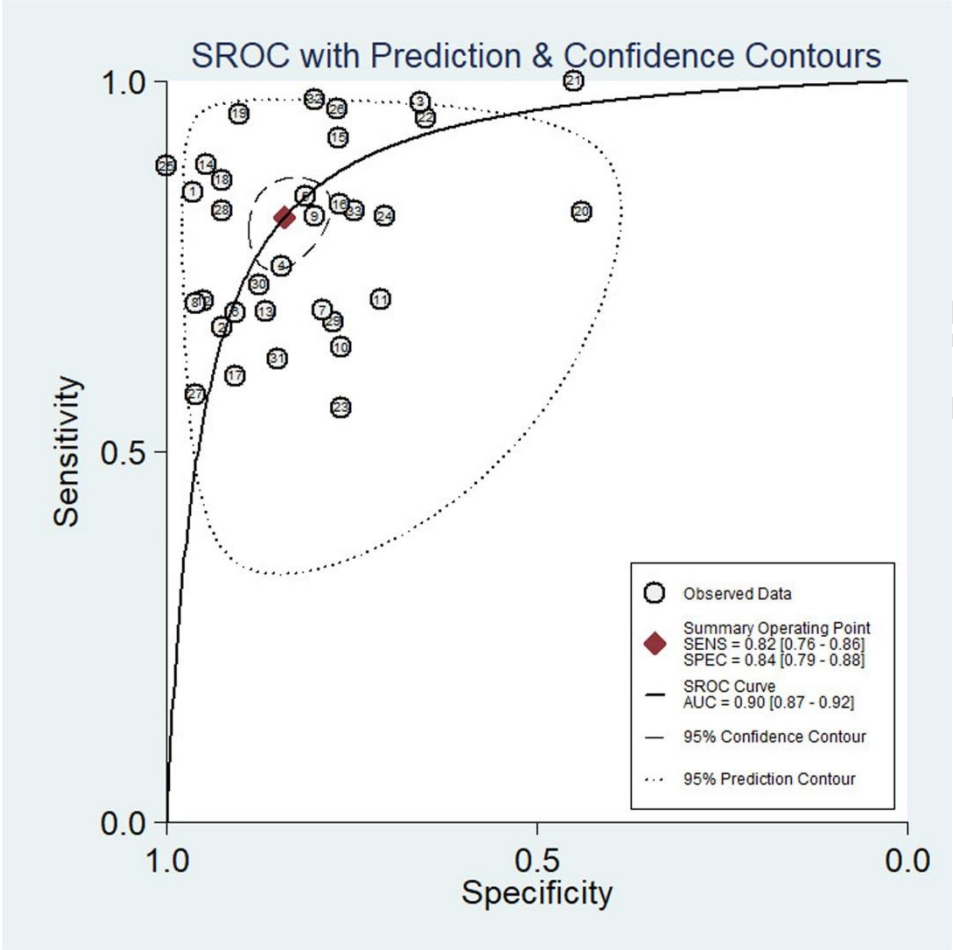

Fig. 5B. Summary receiver operating characteristic curve for lncRNA expression profile in the diagnosis of colorectal cancer.

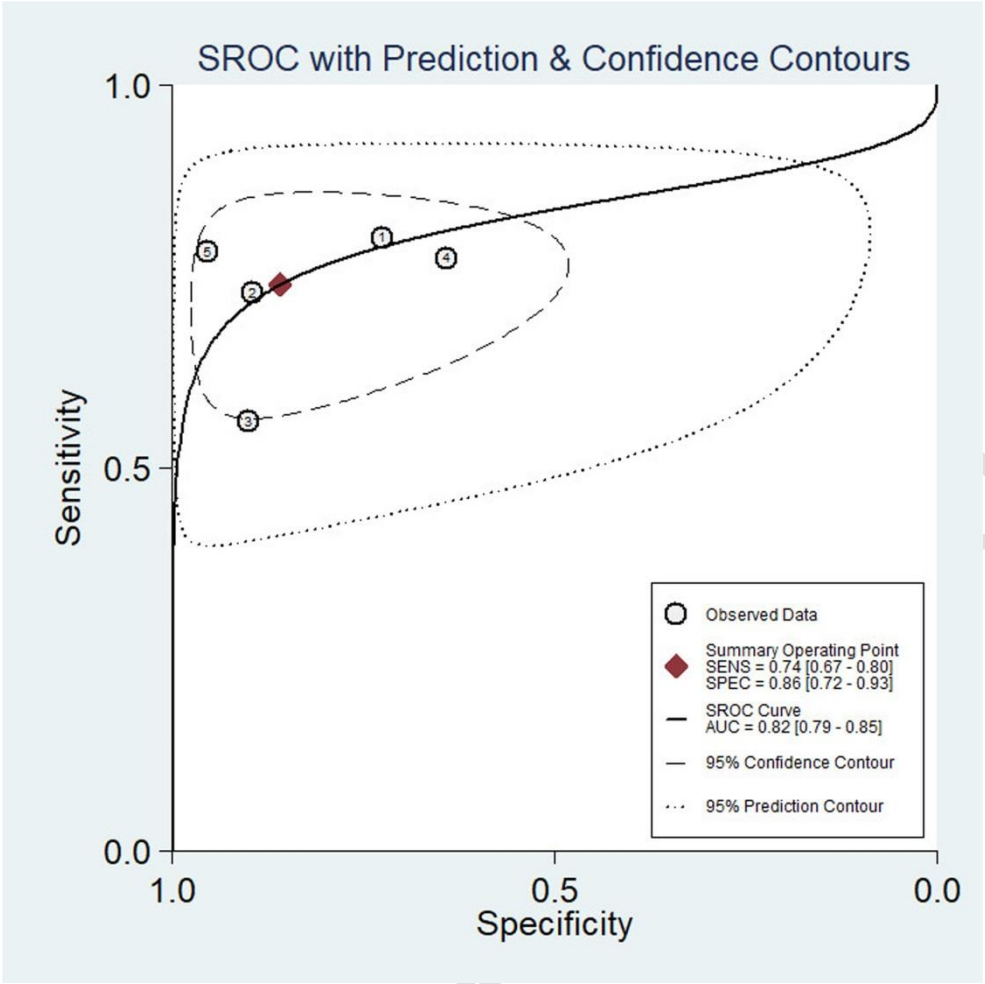

Fig. 5C. Summary receiver operating characteristic curve for lncRNA expression profile in the diagnosis of esophageal cancer.