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Diagnostic Value of microRNAs for Gastric Carcinoma: a Meta-Analysis

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Abstract: *Purpose: To systematically evaluate the potential diagnostic value of MicroRNA for gastric cancer (GC). Methods: The relevant literature was identified in databases such as PubMed, Embase and the Cochrane Library (up to December 25, 2020). Two researchers independently selected the literature based on the inclusion and exclusion criteria, extracted data, and evaluated the risk of bias. Review Manager 5.4, Meta-Disc 1.4 and STATA (version 15.1) software were performed the Meta-analysis. Results: A total of 5914 patients from 41 studies were ultimately included. The pooled sensitivity (SENS) was 0.79 (95% CI: 0.75–0.82), the pooled specificity (SPEC) was 0.87 (95% CI: 0.82–0.91), the pooled positive likelihood ratio (PLR) was 4.95 (95% CI: 3.81–6.43), the pooled negative likelihood ratio (NLR) was 0.28 (95% CI: 0.24–0.32), the pooled diagnostic odds ratio (DOR) was 20.53 (95% CI: 14.57–28.94), and the area under the curve (AUC) was 0.87 (95% CI: 0.84–0.90). A Deeks' funnel plot demonstrates no publication bias existed (P=0.40). Meta-regression analysis showed that sample size, sample source and sample type were potential sources of heterogeneity. Conclusions: MicroRNA might be the potential biomarke diagnosing gastric cancer.*

Keywords: *MicroRNA; gastric cancer; diagnosis; Meta-analysis*

1. Introduction

Malignant tumor is a worldwide public problem, among which gastric cancer (GC) is the sixth most common cancer and the fourth leading cause of cancer-related death in the world (1-3). Unfortunately, a majority of GC patients have been at a progressive stage when they were confirmed diagnosis, owing to lacking sensitive biomarkers for early-stage GC. A number of studies have revealed that the 5-year survival rate of patients with early GC can reach 90%, however, for patients with advanced GC, the median survival time was only 6-9 months (4). Therefore, it is crucial to obtain an efficient diagnosis to raising the 5-year survival rate. Currently, endoscopy has been widely used in the diagnosis of GC, but it still has limitations due to its invasive nature and relatively high costs (5). Therefore, bio-markers which can be stably detected in cell free body fluids, such as serum or plasma, are the key to reducing the mortality rate and improving the prognosis of people in early stage of GC.

To create a non-invasive and low-priced method, bio-marker detection have been widely used in the diagnosis of GC. However, methods for the detection of carcinoembry-onic antigen (CEA), carbohydrate antigen 199 (CA199), and carbohydrate antigen 724 (CA724) lack adequate

sensitivity and specificity to distinguish aggressive from indolent tumors which has precluded their widespread application in early diagnosis of GC (6).

MicroRNAs is a class of evolutionarily conserved and 22nt non-coding RNA molecules that plays roles in regulating gene transcription and expression via multiple pathways, and in physiological processes such as cell cycle and senescence. The expression profile of miRNAs in GC patients usually exhibits exceptionally high in contrast to that in normal specimens (7). It is reported that MicroRNAs can be stably detected in serum or plasma and remain stable after up to eight cycles of freeze-thawing or after incubation at room temperature for up to 24h. Compared with other biomarkers, their stability and easily testable length (about 22 bp) make MicroRNAs well suited to be effective, non-invasive, novel and operable GC biomarkers.

In 2008, Mitchell et al first reported that expression levels of microRNAs were significantly abnormal in the GC tissue, as compared to the unaffected controls (8). Recently, several studies have shown that microRNAs are highly specific in the diagnosis of GC (9, 10). In particular, it has a very high sensitivity

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for cases of GC, suggesting that microRNAs are helpful for the early diagnosis of GC (11, 12). Numerous studies demonstrated that microRNAs may be a potential non-invasive molecule for GC, but with varying diagnostic accuracy (13-19). In the present meta-analysis, we included 41 studies involving miRNA expression profiling to systematically and comprehensively evaluate the diagnostic efficacy of microRNAs for GC through quantitative Meta-analysis, and then provide a scientific basis for clinical guidance.

2. Methods

The PRISMA statement (S1 PRISMA Checklist) was followed in this meta-analysis. The study protocol was registered with the PROSPERO international prospective register of systematic reviews (registry number CRD42020214532).

2.1. Literature search

Two authors (HZ and ZYF) independently searched PubMed, Embase and the Cochrane Library to identify potentially eligible studies published before December 25, 2020. The keywords used for literature retrieval were ('microRNA' or 'miR' or 'miRNA') and ('gastric cancer' or 'gastric tumor' or 'gastric carcinoma' or 'gastric neoplasm') and ('diagnostic' or 'diagnosis' or 'sensitivity and specificity' or 'ROC curve') and ('circulating' or 'serum' or 'plasma' or 'blood'). Citations of review articles and identified articles are also studied. All publications identified by our search strategy were independently evaluated by two reviewers. Any disagreement on a controversial study was resolved by discussion to consensus.

2.2. Eligibility criteria

All studies included in the meta-analysis meet the following criteria:

①All cases were confirmed by pathological examination;

②The study explored the correlation between GC levels and MicroRNA expression diagnosis;

③Studies should contain the data of specificity, sensitivity (or the possibility of deriving such values from the data);

Publications were excluded if they got any of the following items:

①The subjects of the literature were animals, not humans;

②Letters, editorials, meeting abstracts, case reports and reviews;

③Studies lacking sufficient data to construct a diagnostic 2 × 2 table;

2.3. Data extraction and quality assessment

The following patients' characteristics were collected for each study: the first author's name, publication year, country, specimen, sample size, specificity, sensitivity and area under the curve (AUC), etc. Any disagreement among researchers was resolved through discussions with a third researcher (ZHX) until a consensus was reached.

Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) was appraising the risk of bias and applicability of the included studies using Review Manager 5.4 software. This scale was composed of four domains consisting of patient selection, index test, reference standard, and flow and timing domain. Each signaling question was judged as 'yes', 'no', or 'unclear' and each study's risk of bias and concern for applicability was estimated as 'high', 'low', or 'unclear' except for the flow and timing domain, for which the applicability concern did not apply. An answer of 'yes' meant the risk of bias could be judged as being low, whereas an answer of 'no' or 'unclear' meant that the risk of bias could be judged as being high.

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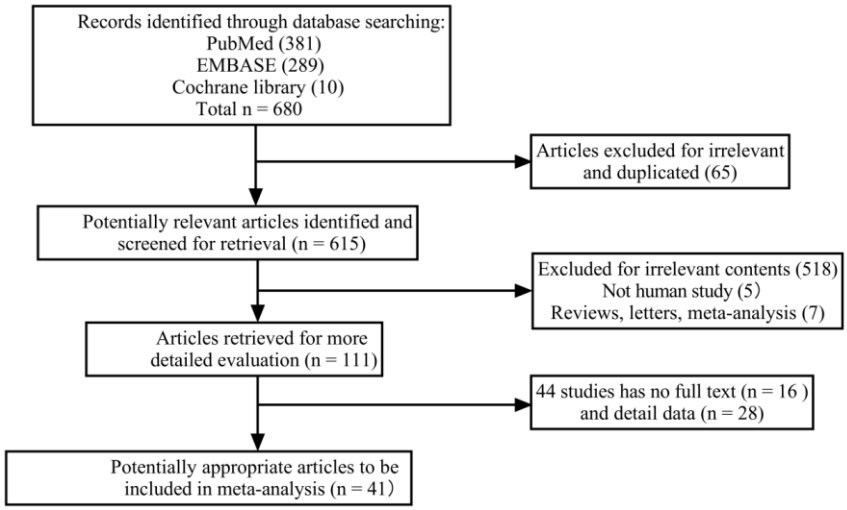

Figure 1: Literature screening process and results

2.4. Statistical analysis

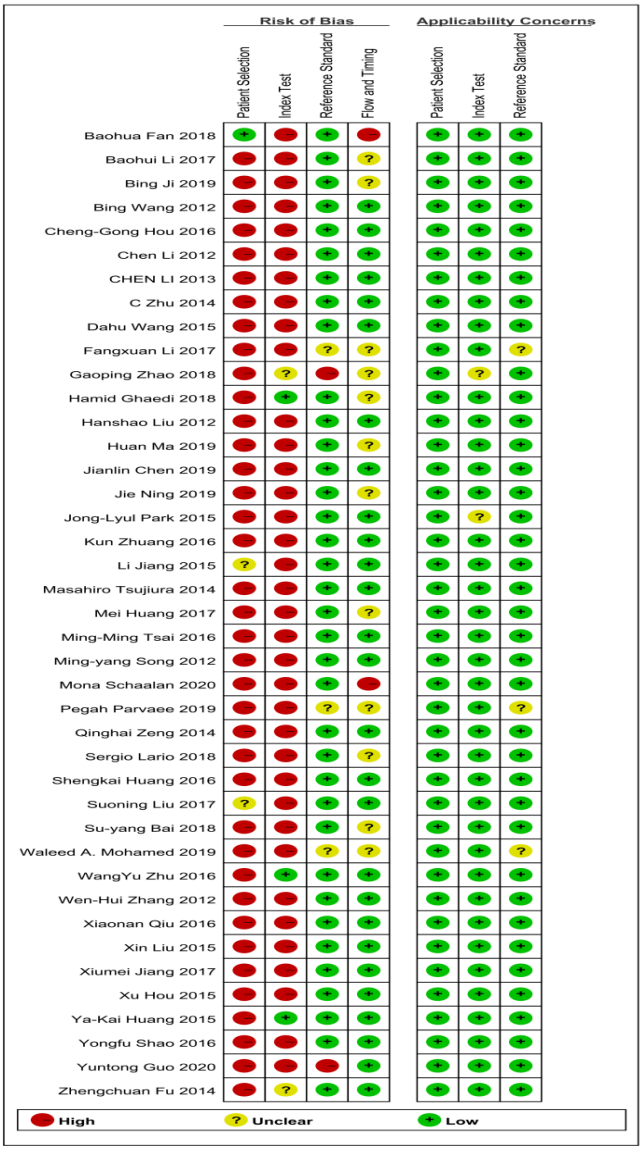

Figure 2: Risk of bias and applicability concern graph.

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Statistical analysis was performed using StataSE15.1, Meta-Disc1.4, and Review Manager5.4. Q tests and I^2 statistics were used to estimate the heterogeneity caused by a non-threshold effect among the included studies. Either P<0.1 or I^2 >50% suggested the existence of substantial heterogeneity; in this study, a random-effects model was applied to quantify the pooled sensitivity, specificity, PLR, NLR, DOR and AUC. Otherwise, a fixed-effects model was used. Spearman correlation analysis was conducted to verify the threshold effects. Moreover, sources of heterogeneity were explored by meta-regression analysis based on possible characteristics. Sensitivity analysis was performed to assess the stability of our analysis. A Deeks' funnel plot was performed for evaluating publication bias.

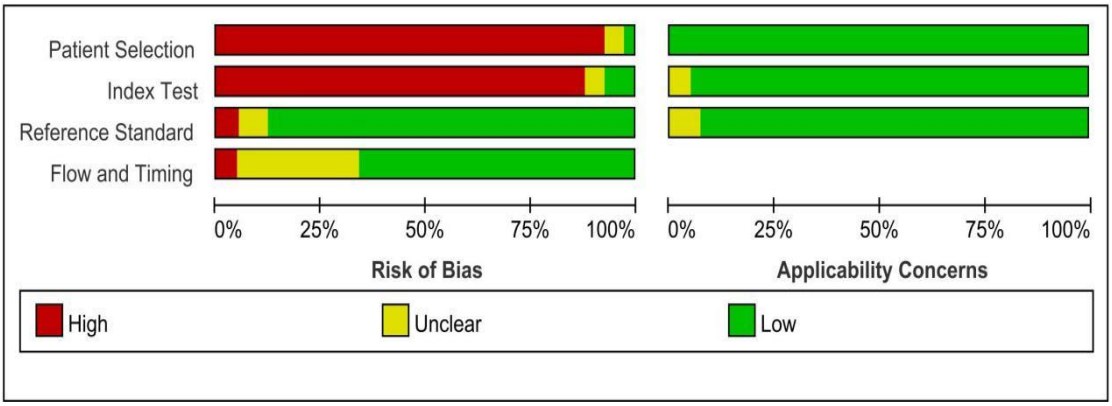

Figure 3: Quality assessments of included studies according to QUADAS-2

3. Results

3.1. Literature search and selection of studies

The detailed procedure of study selection was presented in Figure 1. A total of 680 articles were systematically retrieved from a primary literature search. First, we roughly screened the titles and abstracts and eliminated 65 publications that were irrelevant to the topic. The remaining 615 articles were further examined by careful review of the full text; as a result, 518 articles were excluded, 5 studies were not considered as they were not human study. Seven studies regarding literature reviews, abstracts and case reports were excluded. After a more detailed evaluation, 44 studies were removed as they did not contain full text or had insufficient data for extraction. Finally, the selection process revealed 41 studies that were eligible for diagnostic analysis.

3.2. Study characteristics

In this study, 41 articles were included, involving a total of 5914 subjects. Among these 41 studies, 21 used serum samples, whereas the rest used plasma. The included studies were performed in China, Iran, Spain, Egypt, Korea, and Japan. Table 1 presents the detailed characteristics of each subject.

Table 1: Information of the included studies.

First Author	Year	Country	Specimen	Bio-markers	Cancer	Control	Sensitivity	Specificity	AUC
Yuntong Guo (20)	2020	China	Serum	miR-296-5p	90	90	84.44%	92.22%	0.9190
Mona Schaalan (21)	2020	Egypt	Serum	miRNA 200c	50	80	81.20%	100.00%	0.9060
Huan Ma (22)	2019	China	Serum	miR-647	105	60	80.00%	78.30%	0.8290
Jie Ning (23)	2019	China	Plasma	miR-138-5p	51	20	79.41%	64.71%	0.7690
Pegah Parvaee (24)	2019	Iran	Plasma	Multiple (miR-107, 194, 210)	50	50	93.80%	78.80%	0.9470
Jianlin Chen (25)	2019	China	Plasma	miR-421	90	45	96.67%	95.56%	0.9810
Waleed A. Mohamed (26)	2019	Egypt	Plasma	miR-204	35	40	72.70%	60.00%	0.6880
Bing Ji (27)	2019	China	Plasma	miR-214	168	74	73.20%	91.90%	0.8800
Hamid Ghaedi (28)	2018	Iran	Plasma	miR-675-5p	62	42	77.42%	52.50%	0.6610
Su-yang Bai (29)	2018	China	Serum	miR-551b-3p	50	53	70.01%	96.20%	0.8600
Gaoping Zhao (30)	2018	China	Plasma	Multiple (miR-21, 93, 106a,	147	28	88.70%	79.20%	0.8870

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				106b)					
Baohua Fan (31)	2018	China	Serum	miR-17-5p	14	46	97.10%	100.00%	0.9890
Sergio Lario (32)	2018	Spain	Serum	miR-144-3p	92	31	62.50%	90.00%	0.7688
Mei Huang (33)	2017	China	Plasma	miR_0000745	60	60	85.50%	45.00%	0.6830
Baohui Li (34)	2017	China	Plasma	MicroRNA-320	116	85	82.40%	75.90%	0.8610
Fangxuan Li (35)	2017	China	Plasma	miR 106b	65	65	86.20%	92.30%	0.8980
Xiumei Jiang (36)	2017	China	Serum	miR-451a	10	10	63.33%	87.78%	0.8220
Suoning Liu (37)	2017	China	Serum	miR-144	96	40	71.50%	83.60%	0.8210
Cheng-Gong Hou (38)	2016	China	Serum	miRNA-206	150	150	78.00%	86.00%	0.8900
Shengkai Huang (39)	2016	China	Serum	miR-31	92	89	85.50%	98.30%	0.9190
Yongfu Shao (40)	2016	China	Serum	miR-116b	132	37	59.10%	67.80%	0.6390
Ming-Ming Tsai (41)	2016	China	Serum	miR-196a	98	126	62.20%	96.10%	0.8110
WangYu Zhu (42)	2016	China	Serum	Multiple (miR-18, 183, 210,126)	112	104	81.30%	100.00%	0.9650
Xiaonan Qiu (43)	2016	China	Plasma	miR-26a	285	285	83.60%	81.50%	0.8820
Kun Zhuang (44)	2016	China	Plasma	miR-23b	138	50	71.00%	74.00%	0.8000
Xu Hou (45)	2015	China	Plasma	miR-106a	80	80	77.50%	93.80%	0.8950
Dahu Wang (46)	2015	China	Serum	Hsa-miR-29	24	26	70.00%	78.00%	0.7500
Ya-Kai Huang (47)	2015	China	Serum	Multiple (miR-200c, 20a, 27a, 34a)	52	15	65.40%	100.00%	0.7150
Jong-Lyul Park (48)	2015	Korea	Plasma	miR-27a	15	15	75.00%	56.00%	0.7000
Xin Liu (49)	2015	China	Plasma	miR-940	115	105	60.00%	96.67%	0.8956
Li Jiang (50)	2015	China	Plasma	miR-106	25	36	74.00%	75.00%	0.8100
Qinghai Zeng (51)	2014	China	Serum	miR-17	40	36	80.60%	87.50%	0.8790
Zhengchuan Fu (52)	2014	China	Serum	miR-222	114	56	66.10%	88.30%	0.8500
Masahiro Tsujiura (53)	2014	Japan	Plasma	miR-18a	104	65	84.60%	69.20%	0.8059
C Zhu (54)	2014	China	Plasma	Multiple (miR-16, 25, 92a, 451, 486-5p)	48	102	90.00%	95.00%	0.9250
CHEN LI (55)	2013	China	Plasma	miRNA-199a-3p	30	70	76.00%	74.00%	0.8180
Hanshao Liu (56)	2012	China	Serum	miR-378	61	61	87.50%	70.73%	0.8610
Chen Li (57)	2012	China	Plasma	miRNA-199a-3p	20	20	80.00%	74.00%	0.8370
Bing Wang (58)	2012	China	Serum	miR-21	174	39	56.70%	94.90%	0.8100
Ming-yang Song (59)	2012	China	Serum	miR-221	82	46	82.40%	58.80%	0.7000
Wen-Hui Zhang (60)	2012	China	Serum	miR-375	20	20	85.00%	80.00%	0.8350

3.3. Quality of the Included Studies

QUADAS-2 quality assessment of the included studies and the results of critical appraisal are shown in Figure 2 and Figure 3. Two figures depict the relatively moderate quality of the 41 included studies. Almost all studies had either low or unclear risks of bias due to a lack of information on patient selection, index test, or reference standard.

3.4. Diagnostic accuracy

Heterogeneity might come from either threshold effect or non-threshold effect. The threshold effect was the main cause of heterogeneity, which occurred due to differences in sensitivity/specificity and cut-off value. Heterogeneity among studies was evaluated by examining the threshold and non-threshold effects. In this study, the Spearman correlation coefficient and P-value were 0.658 and 0.218, respectively, indicating that there was no threshold effect. The chart of the ROC curve did not show a “shoulder arm” point distribution also indicates that there was no threshold effect. Heterogeneity owing to non-threshold effects was then assessed with Q-tests and I^2 statistics.

There was significant heterogeneity in the pooled sensitivity (I^2 =81.2%, P<0.1) and specificity (I^2 =88.5%, P<0.1); thus, a random-effects model was applied to analyze the diagnostic parameters. Through meta-regression analysis, we found that sample size, sample source, and sample type were the major potential sources of heterogeneity in this study (Figure 7).

To further explain the heterogeneity of individual studies, we performed a sensitivity analysis by removing individual studies. As shown in Figure 8, 7 studies were identified, which may be the reason for heterogeneity.

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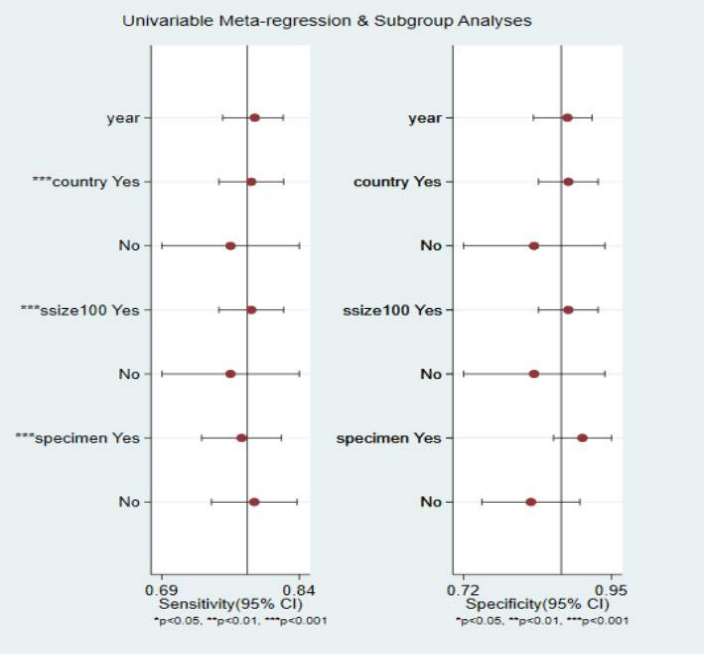

Figure 4: Meta-regression.

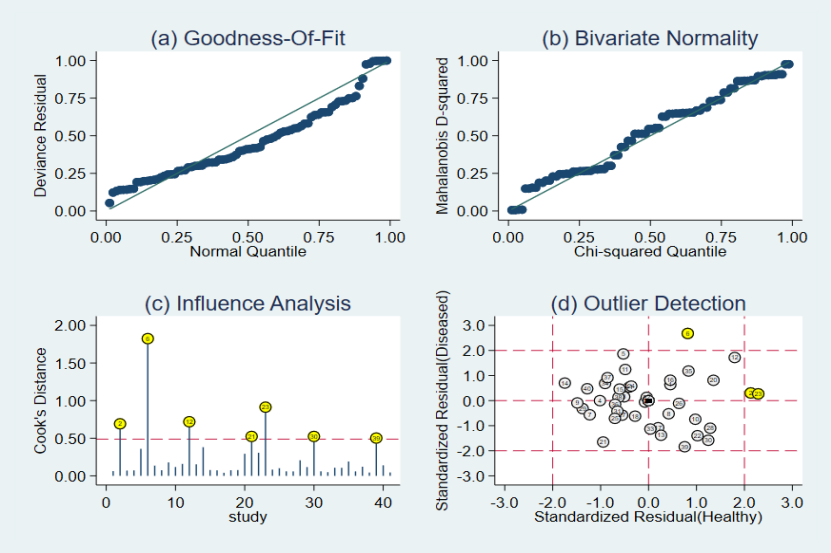

Figure 5: Sensitivity analysis

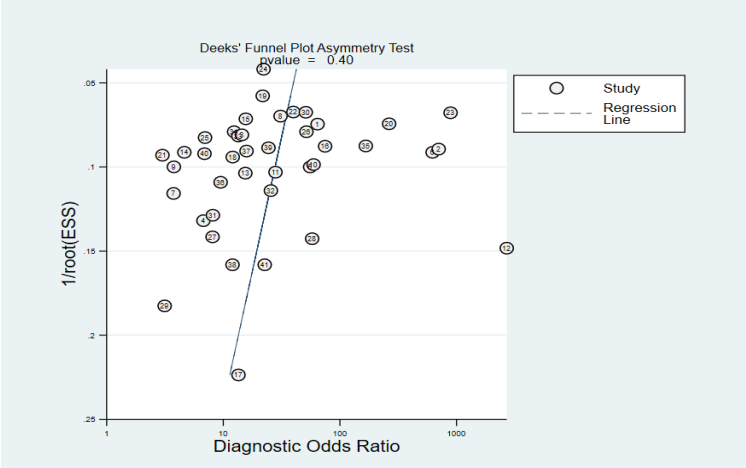

Figure 6: Deeks' funnel plot.

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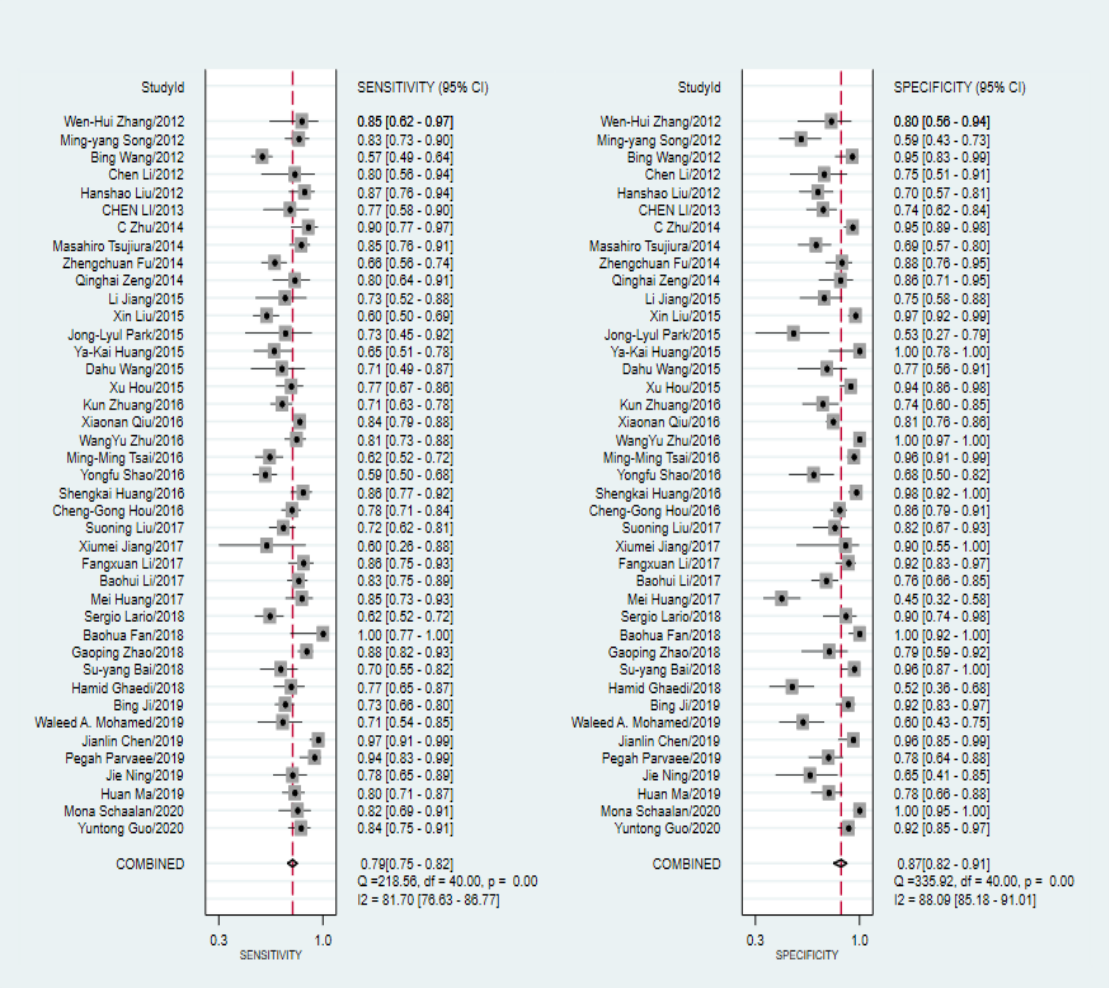

Figure 7: Forest plots of sensitivity and specificity of MicroRNAs for GC diagnosis

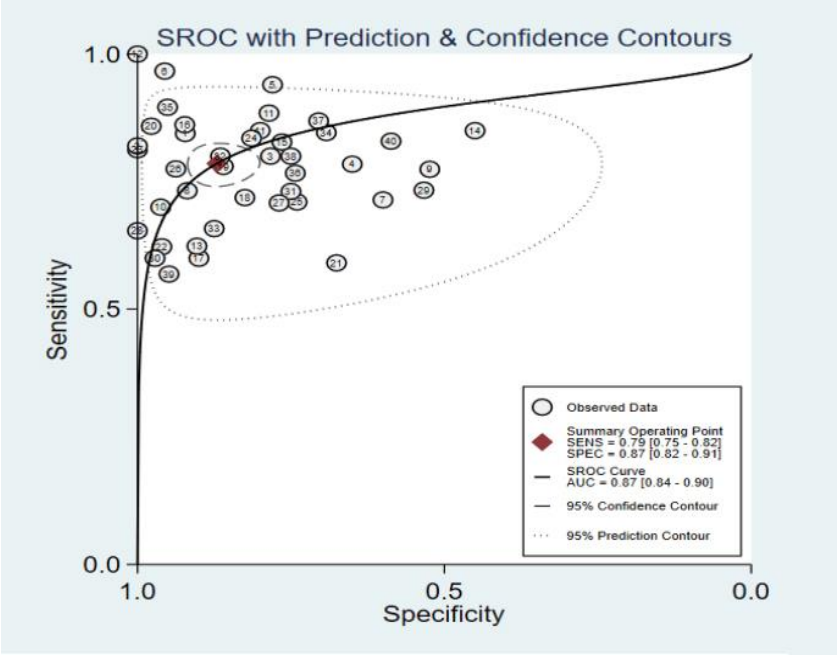

Figure 8: The summary receiver operator characteristic (SROC) curve of MicroRNAs for GC diagnosis

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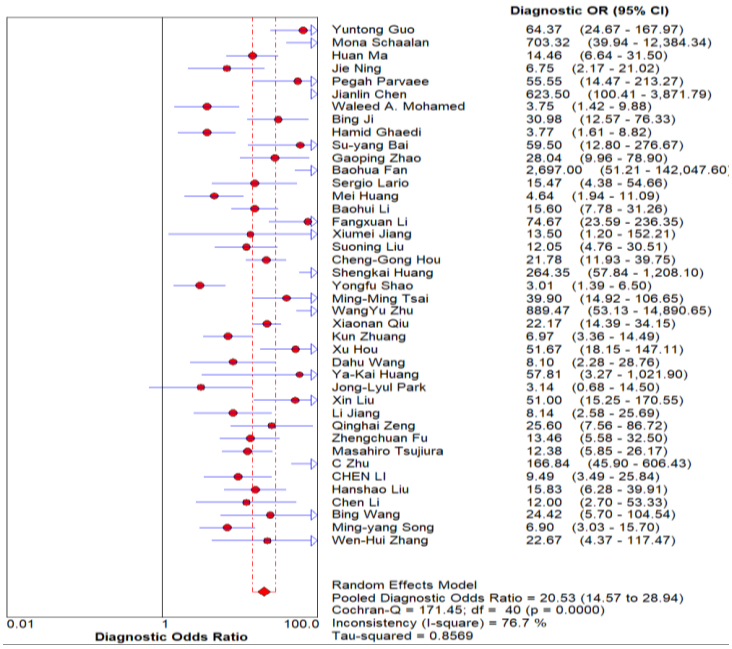

Figure 9: Forest plots of diagnostic odds ratio (DOR) of MicroRNAs for GC diagnosis

3.5. Publication bias

Deeks' funnel plot asymmetry tests were applied to estimate publication bias of included studies. The slope coefficient was associated with a P value of 0.40, suggesting a low likelihood of publication bias in our meta-analysis (shown in Figure 9).

4. Discussion

GC is responsible for the highest number of cancer-related mortalities, primarily since the majority of patients have a terminal disease at stage III or IV at the time of diagnosis (61). Methods for the detection of CEA, CA199, and CA724 lack adequate sensitivity and specificity to distinguish aggressive from indolent tumors. Compared with other biomarkers, their stability and easily testable length (about 22 bp) make MicroRNAs well suited to be effective, non-invasive, novel and operable GC biomarkers. Based on the present research situation, the present study undertook a meta-analysis to evaluate the diagnostic efficacy of microRNAs for GC.

The pooled outcomes of sensitivity, specificity, and AUC (0.79, 0.87, and 0.87, respectively) with the random effects model revealed that microRNAs have better diagnostic value than CEA and CAA199 (AUC of 0.55 and 0.60, respectively) (Figure 4,6) in distinguishing GC patients from control groups. The DOR is an index measuring of the effectiveness of a diagnostic test. In this study, the DOR of microRNAs for GC detection was 20.53 (95% CI: 14.57-28.94) (Figure 7). There is heterogeneity among the studies included in this meta-analysis. Meta-regression analysis showed that sample size, sample source, and sample type were potential sources of heterogeneity. A Deeks' funnel plot demonstrates no publication bias existed (P=0.40). The SROC curve is located near the lower left corner with an AUC of 0.87. All of the data shown above support that microRNAs can be a good indicator for the diagnosis of GC.

Despite our efforts, several limitations should be noted in the meta-analysis. One of the major drawbacks is unpublished and currently being studied data. This may cause publication bias in the study and have a slight impact on the final pooled results. The most obvious disadvantages is that the included studies in the present meta-analysis only distinguished the tumor patients from healthy controls, but other risk factors, such as chronic gastritis, infectious disease, ulcers, and reflux esophagitis, were not included. These factors may contribute to alter miRNA expression. In spite of the limitations mentioned above, this meta-analysis demonstrates a comprehensive assessment and robust evidence that microRNAs have high diagnostic accuracy for assessing GC.

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