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Diagnostic value of circulating microRNAs for esophageal cancer: a meta-analysis based on Asian data

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ABSTRACT

Background and objective: esophageal cancer (EC) is one of the most common gastrointestinal malignant diseases. We conducted a comprehensive meta-analysis to explore the clinical applicability of circulating microRNA for the diagnosis of EC.

Methods: as of September 10, 2021, a comprehensive literature search was conducted on PubMed, Embase, Web of Science, Cochrane Library, Wanfang Database, and China National Knowledge Infrastructure (CNKI) to identify eligible studies. The sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood

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ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) were pooled to evaluate the test performance. The potential sources of heterogeneity were analyzed by subgroup analysis. Deeks' funnel plot was used to assess publication bias.

Results: 85 studies from 50 articles were included in the current meta-analysis. The overall pooled sensitivity was 0.82 (95 % CI, 0.79-0.84), specificity was 0.84 (95 % CI, 0.81-0.86), PLR was 4.9 (95 % CI, 4.2-5.9), NLR was 0.22 (95 % CI, 0.19-0.25), DOR was 22 (95 % CI, 17-29) and AUC was 0.89 (95 % CI, 0.86-0.92), respectively. Subgroup analysis suggested that miRNA clusters with a large sample size showed better diagnostic accuracy. Publication bias was not found.

Conclusions: circulating miRNAs can be used as a potential non-invasive biomarker for the diagnosis of EC in Asian populations.

Keywords: Esophageal cancer. Esophageal squamous cell carcinoma. MicroRNA. Biomarkers. Meta-analysis.

INTRODUCTION

Esophageal cancer (EC) is one of the most common gastrointestinal malignant diseases, and the sixth leading cause of cancer-related deaths worldwide (1). The incidence rate of EC varies considerably with location, mainly occurring in Asia, China accounting for over 70 % (2). Due to absence of typical clinical symptoms in the early stages of EC and lack of early diagnostic strategy, most patients have progressed into an advanced stage when they are diagnosed so the prognosis is extremely poor, and the 5-year survival rate is < 20 % (3). At present, endoscopy combined with histopathological examination is the gold standard for diagnosing EC. However, due to its invasiveness, high cost, and missed diagnoses in early patients, it cannot be used as a common physical examination screening method (3). The commonly used non-invasive blood biomarkers in EC are carcinoembryonic antigen (CEA), squamous cell carcinoma-associated antigen (SCC), and cytokeratin 19 fragment (CYFRA21-1). However, due to its poor sensitivity and insufficient prognostic value, it is difficult that it becomes the main auxiliary diagnostic indicators for EC (4). Therefore, there is

an urgent need for finding a non-invasive biomarker with high sensitivity and specificity for the diagnosis of EC.

MicroRNA (miRNA) is a group of small endogenous non-coding RNAs (5) that participate in the regulation of various cancer-associated biological processes (6). At present, more and more studies have evaluated the feasibility of circulating miRNAs as biomarkers for the diagnosis of EC. Results are exciting, but there are still some inconsistent conclusions. Therefore, we conducted a comprehensive meta-analysis to explore the clinical applicability of circulating miRNA for the diagnosis of EC.

MATERIALS AND METHODS

Search strategy and literature selection

This meta-analysis was performed according to the PRISMA statement (7). Two investigators independently conducted a comprehensive search of PubMed, Embase, Web of Science, Cochrane Library, Wanfang Database, and China National Knowledge Infrastructure (CNKI). Medical subject headlines (MeSH) terms, and keywords were used as follows: ("esophageal cancer" OR "esophageal neoplasm" OR "esophageal carcinoma" OR "esophageal squamous cell carcinoma" OR "ESCC" OR "esophageal adenocarcinoma") AND ("microRNA" OR "microRNAs" OR "miRNA" OR "miRNAs" OR "miR" OR "miRs"). Searches were limited to publications with human subjects as of September 10, 2021, and without language restrictions. The references listed in the original articles and the retrieved review article were also manually examined to find additional eligible studies.

Inclusion and exclusion criteria

Eligible studies had to meet the following inclusion criteria: a) studies aimed at evaluating the diagnostic capacity of microRNA for EC detection; b) all patients with EC should have definitely been diagnosed through histopathology or biopsy; c) all patients with EC should not have a past medical history of malignancy; d) all patients with EC should not have received any treatment (chemotherapy, radiotherapy or surgery); e) healthy people were used as controls; f) the miRNAs obtained were restricted to serum or plasma specimens; and g) sufficient data were available to

construct a diagnostic two-by-two table. The exclusion criteria were: a) publications without complete information or duplicate reports; b) patients who had received radiotherapy or chemotherapy or surgical treatment; c) studies focused on survival or prognosis of EC; d) microRNAs obtained from cell lines, animals, tissues or saliva; and e) case reports, comments, letters to the editors, and systematic reviews or meta-analysis.

Data extraction and quality assessment

Two investigators independently selected the most relevant studies, guided by the title, abstract, and full text. If the study had been collected by any investigator, it should be reviewed for further evaluation. Subsequently, from each of the studies selected, the most revealing data, previously determined, were extracted like the author's first name, year of publication, miRNA profile, regulation mode (up- or down-regulated), sample size (number of patients with EC and healthy controls), source of specimen (serum or plasma), as well as relevant statistical data required and methodological quality information. The quality of the studies included was assessed using the Quality Assessment for Diagnostic Accuracy Studies-2 (QUADAS-2) tool (8). Any disagreement was resolved by consulting a third author and finally reaching consensus.

Statistical analysis

All statistical analyses were performed using Review Manager 5.2 and STATA version 13.0. In this meta-analysis, it was important to extract the number of true positives, false positives, false negatives, and true negatives from the patients of each study. The percentage of Higgins I-squared statistic (I^2) was used to assess heterogeneity. If the I^2 value is > 50 %, it indicated significant heterogeneity, and then a random-effects model was performed. Thus, the possible sources of heterogeneity were explored by regression and subgroup analysis. We also estimated sensitivity (SEN), specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR). Besides, we generated the summary receiver operating characteristics (SROC) curve and estimated the area under the SROC curve (AUC) for

the overall and subgroup analysis. The diagnostic efficacy evaluation criteria were AUC = 1.00 (perfect), AUC > 0.90 (excellent), AUC > 0.80 (good), and AUC < 0.80 (medium). Finally, the potential publication bias was evaluated by using the Deeks' funnel plot asymmetry test. *p* values < .05 were considered statistically significant.

RESULTS

Study selection and literature characteristics

A total of 5880 articles were initially identified from the primary literature search strategy, of which 1358 were from PubMed; 2245 from Embase; 1488 from Web of Science; 7 from Cochrane Library; 402 from Wan-fang Databases, and 380 from the Chinese National Knowledge Infrastructure (CKNI). Out of all of them, we selected 4671 after eliminating 1209 duplicates. After reviewing titles and abstracts, 4573 articles were excluded of which 3364 were irrelevant studies; 825 investigations were conducted on animals or cell lines, and 384 were reviews and letters. Subsequently, the full texts of the remaining 98 articles were read of which 48 were excluded. Finally, 85 studies from 50 articles were included in the current meta-analysis (9-58). The flow chart of the article selection process is shown on figure 1.

The main characteristics of the 85 articles included are shown on table 1, which are presented by year of publication from 2010 to 2021. In total, 7567 patients with EC (including 6409 patients with ESCC) and 6005 healthy controls were included. In total, 39 articles focused on a single miRNA, and 11 articles refer to miRNA clusters. Real-time quantitative reverse transcription PCR (qRT-PCR) was used to detect miRNA expression levels in 32 serum and 18 plasma specimens. All articles were conducted on Asian populations including 41 studies in China, 8 studies in Japan, and 1 study in India.

Quality assessment

The QUADAS-2 tool was used to assess the quality of the 50 articles included. Overall, the records included displayed moderate and high quality according to the QUADAS-2 criteria as shown on figure 2.

Diagnostic accuracy of circulating miRNAs in EC

The sensitivities and specificities of miRNAs in the 85 studies that included 7567 patients of EC and 6005 healthy controls were analyzed using a forest plot. There was significant heterogeneity in all the studies (I^2 = 84.06 % for sensitivity and I^2 = 84.52 % for specificity). Therefore, a random-effects model was used to calculate the pooled estimates. Overall, the pooled sensitivity was 0.82 (95 % CI, 0.79-0.84), specificity was 0.84 (95 % CI, 0.81-0.86), PLR was 4.9 (95 % CI, 4.2-5.9), NLR was 0.22 (95 % CI, 0.19-0.25) and DOR was 22 (95 % CI, 17-29) (Fig. 3 A and B). The AUC was 0.89 (95 % CI, 0.86-0.92), indicative that circulating miRNAs had an outstanding diagnostic accuracy for patients with EC (Fig. 3C).

It has been widely known that ESCC is the most common subtype of EC. In addition, we performed an independent meta-analysis to access the diagnostic accuracy of circulating miRNA to discriminate patients with ESCC from healthy controls. A total of 70 studies that included 6409 patients with ESCC and 4866 healthy controls evaluated the diagnostic power of miRNAs in patients with ESCC were included in the pooled analysis. The pooled results were: sensitivity, 0.80 (95 % CI, 0.78-0.82); specificity, 0.82 (95 % CI, 0.79-0.85); PLR, 4.6 (95 % CI, 3.8-5.4); NLR, 0.24 (95 % CI, 0.21-0.27); DOR, 19 (95 % CI, 15-25); and AUC was 0.88 (95 % CI, 0.85-0.90). The miRNA diagnostic accuracy of ESCC was similar to that of EC.

Subgroup analysis

We conducted a subgroup analysis, and the results of all subgroup analyses are shown on table 2. We found that the studies of the Japanese population showed better diagnostic accuracy compared to the Chinese population: sensitivity (0.89 vs 0.80), specificity (0.85 vs 0.83), PLR (6.0 vs 4.7), NLR (0.13 vs 0.24), DOR (45 vs 20), and AUC (0.93 vs 0.88). Moreover, the miRNA clusters exhibited higher diagnostic value than single miRNA: sensitivity (0.91 vs 0.80), specificity (0.89 vs 0.83), PLR (8.0 vs 4.6), NLR (0.10 vs 0.25), DOR (84 vs 19), and AUC (0.95 vs 0.87). Furthermore, studies with a sample size > 100 showed better performance: sensitivity (0.81 vs 0.79), specificity (0.86 vs 0.83), PLR (4.7 vs 2.8), NLR (0.23 vs 0.51), DOR (21 vs 17), and AUC (0.88 vs 0.85). The regulation mode of miRNA and the specimen type did

not have an impact on diagnosis.

Publication bias

To assessed potential publication bias, the Deeks' funnel plot asymmetry test was used. The pooled Deeks' test result of all studies was $p = 0.23$ (Fig. 3D) indicative that this meta-analysis did not have significant publication bias.

DISCUSSION

Esophageal cancer has become one of the deadliest tumors in Asian countries due to its high mortality and low survival rate. Despite the complete resection of the primary tumor and multimodal treatment more than two-thirds of patients with EC experienced local recurrence or distant metastases, and even death (59). This is because EC lacks typical symptoms and specific biomarkers, and is usually diagnosed at an advanced stage. Since Guo (60) first discovered the differential expression profile of miRNA in EC tissues back in 2008, successive studies have confirmed that miRNA is involved in the post-transcriptional regulation of EC target genes. By negatively regulating the target gene to degrade its transcription product or inhibit its translation, it then affects the biological functions of EC such as proliferation, migration, invasion, and apoptosis (61,62). Subsequently, many studies have confirmed the diagnostic value of miRNA in digestive tract cancers (63), especially in EC, but findings are different. In addition, the advantage of blood over other bodily fluids depends on its easy access in a relatively non-invasive way and long-term storage. Therefore, we performed this meta-analysis to systematically evaluate the diagnostic value of circulating miRNAs for EC diagnosis.

In our meta-analysis, a total of 85 studies from 50 articles were included including 7567 patients with EC and 6005 healthy controls. We find that circulating miRNAs could distinguish patients with EC from healthy controls, the overall pooled sensitivity was 0.82, specificity was 0.84, and the AUC was 0.89. We also calculated PLR, NLR, and DOR to further test the distinguishing ability of miRNA, which can provide a more meaningful reference for clinical use. The combined PLR was 4.9, NLR was 0.22 and DOR was 22. This shows that the probability of a correct diagnosis of

patients with EC is 22 times higher compared to that of a false negative diagnosis in healthy controls. However, the PLR is < 10 and the NLR is < 0.1, which does not meet the general criteria to accept or exclude the decision (64). ESCC is the predominant type of EC worldwide, a total of 70 included studies evaluated the diagnostic value of miRNAs in patients with ESCC in this meta-analysis. The results showed that pooled sensitivity was 0.80, specificity was 0.82, and AUC was 0.88. The miRNA diagnostic accuracy obtained for ESCC was similar compared to EC.

Due to the high heterogeneity found, we conducted subgroup analysis based on the country, miRNA profile, regulation mode, sample size, and type of specimen to find possible sources of heterogeneity. It showed that circulating miRNAs could be used as EC diagnostic biomarkers in both Japanese and Chinese populations. However, trials with a Japanese population had better diagnostic accuracy compared to a Chinese population. This is inconsistent with previous results. Liu and Li et al. showed that there was no difference between Chinese and Japanese populations (65, 66). Moreover, subgroup analyses suggested that the miRNA clusters assay showed better diagnostic value compared to single miRNA, which is inconsistent with previous meta-analyses (65). A single miRNA is not only expressed in GI tumors, but also is differentially expressed in other diseases so the specificity of a single miRNA is poor. Besides, miRNA clusters have complex molecular mechanisms, which can form a more reliable and stable network diagnostic structure through a variety of pathways (67). In addition, studies with a sample size > 100 are better compared to studies with a smaller sample size in the diagnosis of EC, which provides support for larger research samples in the future. Furthermore, the type of specimen did not have an impact on diagnosis, both plasma and serum specimen could be recommended as clinical specimens, which is consistent with previous meta-analyses (65). However, some studies believe that plasma-based specimens showed a better accuracy than serum-based specimens, which may be due to the fact that more proteins are retained in plasma for co-separation of miRNA (68), so further verification tests are required. At the same time, both up- and down-regulated miRNAs showed high diagnostic accuracy for EC. Therefore, a large sample, multi-country, multi-center study is needed to verify our findings.

This comprehensive meta-analysis has several advantages. Compared to the previous meta-analysis (65,66), it contains the latest published research. In addition, all included studies were independently selected by two investigators based on strict inclusion and exclusion criteria. Although we have done our best to avoid publication bias, we acknowledge that there are still some limitations. First, although we have carried out a comprehensive search strategy on multiple databases during the literature search process and tried to include all relevant studies, some useful publications may still be missing. Secondly, all studies come from Asia, mainly from China. The diagnostic value of circulating miRNAs for esophageal cancer still needs further evaluation in other countries. Therefore, the results may be affected by population selection bias. Thirdly, due to the different standards of the included studies, we did not extract cut-off values, which may lead to inconsistent results. Finally, it is important to determine the diagnostic value of miRNA in EC based on tumor TNM classification characteristics.

CONCLUSION

In conclusion, circulating miRNAs can be used as a potential non-invasive biomarker for the diagnosis of EC in Asian populations. In addition, the use of miRNA clusters and increasing sample size can improve the diagnostic value. In the future, large-scale, multi-country, multi-center clinical studies are warranted to confirm our analysis.

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Table 1. Characteristics of the studies included

Autor/Year	Country	microRNAs	Regul-ation mode	EC group		Control group		Speci-men	Referen-ce RNA	Diagnostic power		
				Sample size	Gender (M/F)	Sample size	Gender (M/F)			Sen	Spe	AUC
Zhang, C./2010	China	miR-10a	Down	149[a]	116/33	100	74/26	Serum	U6	0.812	0.800	0.886
Zhang, C./2010	China	miR-22	Down	149[a]	116/33	100	74/26	Serum	U6	0.886	0.860	0.949
Zhang, C./2010	China	miR-100	Down	149[a]	116/33	100	74/26	Serum	U6	0.638	0.810	0.817
Zhang, C./2010	China	miR-148b	Down	149[a]	116/33	100	74/26	Serum	U6	0.664	0.870	0.855
Zhang, C./2010	China	miR-223	Down	149[a]	116/33	100	74/26	Serum	U6	0.832	0.830	0.911
Zhang, C./2010	China	miR-133a	Down	149[a]	116/33	100	74/26	Serum	U6	0.651	0.830	0.830
Zhang, C./2010	China	miR-127-3p	Down	149[a]	116/33	100	74/26	Serum	U6	0.785	0.870	0.899
Zhang, T./2011	China	miR-31	Up	201[a]	128/73	202	119/83	Serum	miR-16	0.867	0.843	0.902
Zhang, Y./2012	China	miR-223	Up	199[a]	148/51	107	78/28	Serum	miR-16	0.700	0.800	0.840
Wang, B./2012	China	miR-21	Up	31[c]	23/8	39	9/30	Serum	miR-16	0.710	0.692	0.740
Xie, Z./2013	China	miR-10b	Down	29[b]	24/5	16	13/3	Plasma	miR-16	0.813	1.000	0.929
Hirajima, S./2013	Japan	miR-18a	Up	106[a]	87/19	54	NR	Plasma	U6	0.868	1.000	0.945
Takeshita, N./2013	Japan	miR-1246	Up	101[a]	89/12	46	NR	Serum	miR-16	0.713	0.739	0.754
Zhang, T./2013	China	miR-1322	Up	201[a]	NR	202	NR	Serum	miR-16	0.817	0.825	0.847
Komatsu, S./2014	Japan	miR-25	Up	50[a]	NR	20	NR	Plasma	U6	0.850	0.860	0.856
Ye, M./2014	China	miR-21	Up	100[a]	80/20	50	NR	Plasma	miR-16	0.970	0.560	0.837
Yu, Q./2014	China	miR-375	Up	24[a]	18/6	19	NR	Plasma	miR-16	0.917	0.778	0.924

Wu, C./2014	China	miR-25	Up	63[a]	55/8	63	55/8	Serum	U6	0.793	0.682	0.780
Wu, C./2014	China	miR-100	Up	63[a]	55/8	63	55/8	Serum	U6	0.762	0.650	0.750
Wu, C./2014	China	miR-193a-3p	Up	63[a]	55/8	63	55/8	Serum	U6	0.904	0.619	0.850
Wu, C./2014	China	miR-194	Up	63[a]	55/8	63	55/8	Serum	U6	0.873	0.556	0.810
Wu, C./2014	China	miR-223	Up	63[a]	55/8	63	55/8	Serum	U6	0.746	0.682	0.770
Wu, C./2014	China	miR-337-5p	Up	63[a]	55/8	63	55/8	Serum	U6	0.873	0.778	0.850
Wu, C./2014	China	miR-483-5	Up	63[a]	55/8	63	55/8	Serum	U6	0.793	0.603	0.740
Dong, W./2015	China	miR-24	Down	105[a]	69/36	30	NR	Serum	cel-miR-39	0.819	0.833	0.866
Li, W./2015	China	miR-21	Up	112[c]	65/47	100	52/48	Plasma	miR-16	0.902	0.707	0.882
He, FC./2015	China	miR-20a	Up	70[a]	46/24	40	NR	Plasma	SV40	0.643	0.750	0.767
He, FC./2015	China	let-7	Down	70[a]	46/24	40	NR	Plasma	SV40	0.743	0.850	0.829
Hui, B./2015	China	miR-129	Up	78[a]	57/21	23	NR	Serum	miR-1228	0.788	0.733	0.792
Hui, B./2015	China	miR-451	Up	78[a]	57/21	23	NR	Serum	miR-1228	0.825	0.790	0.882
Hui, B./2015	China	miR-365	Up	78[a]	57/21	23	NR	Serum	miR-1228	0.806	0.867	0.831
Jiang, Z./2015	China	miR-218	Down	106[b]	69/37	60	NR	Serum	miR-16	0.717	0.767	0.833
Li, BX./2015	China	miR-21	Up	24[b]	18/6	19	NR	Plasma	miR-1228	0.917	0.737	0.895
Xu, H./2015	China	miR-10b	Up	50[a]	27/23	50	30/20	Serum	U6	0.760	0.840	0.850
Xu, H./2015	China	miR-29c	Down	50[a]	27/23	50	30/20	Serum	U6	0.780	0.860	0.890
Xu, H./2015	China	miR-205	Down	50[a]	27/23	50	30/20	Serum	U6	0.760	0.860	0.880
Shi, XY./2016	China	miR-100	Up	40[c]	24/16	50	28/22	Serum	U6	0.650	0.950	0.832
Sun, L./ 2016	China	miR-781	Down	120[a]	79/41	51	NR	Plasma	miR-16	0.692	0.667	0.715
Dong, S./2016	China	miR-216a	Down	120[a]	79/41	51	NR	Plasma	miR-16	0.800	0.902	0.877
Dong, S./2016	China	miR-216b	Down	120[a]	79/41	51	NR	Plasma	miR-16	0.558	0.902	0.756
Guan, S./2016	China	miR-613	Down	75[a]	43/32	75	NR	Serum	U6	0.813	0.627	0.767

Wang, C./2016	China	miR-146a	Down	84[a]	46/38	154	NR	Serum	miR-16	0.821	0.833	0.891
Li, SP./2016	China	miR-506	Up	100[a]	55/45	40	NR	Plasma	U6	0.812	0.873	0.835
Wang, C./2016	China	miR-1297	Down	81[a]	38/43	156	NR	Serum	miR-16	0.907	0.743	0.819
Zheng, S./2017	China	miR-138	Down	128[a]	76/52	40	NR	Serum	U6	0.695	0.875	0.871
Li, J./2017	China	miR-15a	Down	106[a]	70/36	106	68/38	Serum	U6	0.864	1.000	0.951
Bai, Y./2017	China	miR-19a	Up	89[c]	69/20	80	NR	Plasma	miR-39	0.893	0.525	0.767
Cui, Y./2017	China	miR-9	Up	131[a]	86/45	131	86/45	Plasma	U6	0.855	0.985	0.913
Xiao, X./2017	China	miR-21	Up	27[c]	19/8	24	13/11	Plasma	U6	0.814	0.979	0.943
Xiao, X./2017	China	miR-143	Down	27[c]	19/8	24	13/11	Plasma	U6	0.851	0.979	0.958
Qin, J./2017	China	miR-25-3p	Up	23[a]	NR	11	NR	Serum	miR-16	0.667	0.810	0.794
Qin, J./2017	China	miR-223-3p	Up	23[a]	NR	11	NR	Serum	miR-16	0.619	1.000	0.839
Qin, J./2017	China	miR-373-3p	Up	23[a]	NR	11	NR	Serum	miR-16	0.905	0.810	0.873
Yang, Y./2017	China	miR-451	Up	50[b]	30/20	20	NR	Serum	miR-2911	0.880	0.850	0.911
Chen, J./2018	China	miR-183	Up	51[a]	41/10	55	42/13	Serum	U6	0.789	0.762	0.762
Wang, K./2018	China	miR-21	Up	31[a]	23/8	32	19/13	Serum	U6	0.710	0.960	0.880
Wang, K./2018	China	miR-25	Up	31[a]	23/8	32	19/13	Serum	U6	0.710	0.680	0.720
Wang, K./2018	China	miR-145	Up	31[a]	23/8	32	19/13	Serum	U6	0.903	0.688	0.830
Wang, K./2018	China	miR-203	Up	31[a]	23/8	32	19/13	Serum	U6	0.548	0.625	0.510
Zhang, L./2018	China	miR-21	Up	125[a]	76/49	125	76/49	Plasma	U6	0.740	0.780	0.800
Zhang, L./2018	China	miR-223	Up	125[a]	76/49	125	76/49	Plasma	U6	0.680	0.680	0.730
Zhang, L./2018	China	miR-375	Down	125[a]	76/49	125	76/49	Plasma	U6	0.780	0.590	0.690
Xu, LJ./2019	China	miR-143	Down	150[a]	92/58	80	NR	Serum	U6	0.712	0.825	0.801
Sun, H./2019	China	miR-1290	Up	118[a]	17/101	120	NR	Serum	U6	0.653	0.983	0.822
Bai, Y./2019	China	miR-1	Down	128[b]	73/55	134	69/65	Serum	U6	0.843	0.922	0.940

Hoshino, I./2020	Japan	miR-1246	Up	101[a]	85/16	34	NR	Serum	cel-miR-39	0.713	0.706	0.779
Hoshino, I./2020	Japan	miR-106b	Down	101[a]	85/16	34	NR	Serum	cel-miR-39	0.743	0.735	0.815
Wang, XJ./2020	China	miR-19a	Up	80[a]	49/31	80	45/35	Serum	U6	0.870	0.970	0.880
Wang, XJ./2020	China	miR-9	Up	80[a]	49/31	80	45/35	Serum	U6	0.910	0.900	0.860
Wang, XJ./2020	China	miR-218	Down	80[a]	49/31	80	45/35	Serum	U6	0.920	0.920	0.910
Wu, YB./2020	China	miR-15b	Down	113[b]	64/49	113	66/47	Serum	U6	0.895	0.727	0.836
Wu, YB./2020	China	miR-34c	Down	113[b]	64/49	113	66/47	Serum	U6	0.632	0.836	0.804
Hoshino, I./2021	Japan	miR-1246	Up	72[a]	65/7	50	42/8	Serum	cel-miR-39	0.917	0.760	0.912
Liu, X./2021	China	miR-630	Down	58[c]	34/24	60	32/28	Serum	U6	0.733	0.767	0.778
Zhang, C./2010	China	miRNA clusters (miR-10a+22+ 100+148b+223 + 133a+127-3p)	Down	149[a]	116/33	100	74/26	149[a]	116/33	0.960	0.785	0.929
Komatsu, S./2011	Japan	miRNA clusters (miR-21/375)	Up	50[a]	NR	20	NR	Plasma	U6	0.880	0.700	0.816
Yu, Q./2014	China	miRNA clusters (miR-375+148b)	Up	24[a]	18/6	19	NR	Plasma	miR-16	0.917	0.944	0.965
Wu, C./2014	China	miRNA clusters (miR-25+100+ 193a-3p+194+ 223+337-5p+ 483-5p)	Up	63[a]	55/8	63	55/8	Serum	U6	0.810	0.810	0.830
Sharma, P./2016	India	miRNA clusters (miR-21+144+93	Down	24[c]	18/6	21	16/5	Serum	5S rRNA	0.875	0.905	0.968

		+342+107+152)										
Zhou, X./2017	China	miRNA clusters (miR-106a+18a+ 20b+223-3p+ 486-5p+584)	Up	137[a]	75/62	155	NR	Plasma	U6	0.857	0.958	0.950
Sudo, K./2019	Japan	miRNA clusters (miR-8073+3196 +6820-5p+744-5p 6794-5p+6799-5p)	Up	283[b]	236/47	283	235/48	Serum	U6	1.000	0.980	1.000
Hoshino, I./2020	Japan	miRNA clusters (miR-1246/106b)	Up	101[a]	85/16	34	NR	Serum	cel-miR-39	0.821	0.823	0.903
Ibuki, Y./2020	Japan	miRNA clusters (miR-574-3p+ 205-5p+30a-5p)	Up	18[a]	13/5	12	9/3	Serum	U6	0.938	0.810	0.950
Sun, G./2020	China	miRNA clusters (miR-21+100+ 375)	Up	125[a]	76/49	125	76/49	Plasma	U6	0.610	0.900	0.860
Wu, YB./2020	China	miRNA clusters (miR-15b+34c)	Down	113[b]	64/49	113	66/47	Serum	U6	0.930	0.818	0.949

[a]The histological type of patients with esophageal carcinoma was esophageal squamous cell carcinoma. [b]These studies included esophageal squamous cell carcinoma and esophageal adenocarcinoma histological types; [c]The histological type of patients with esophageal carcinoma was not identified in this study; AUC: area under the curve; Down: down-regulated; EC: esophageal cancer; M/F: male/female; NR: no reference; Sen: sensitivity; Spe: specificity; Up: up-regulated.

Table 2. Summary estimates of diagnostic power and their 95 % confidence intervals

Subgroup	Sen (95 % CI)	Spe (95 % CI)	PLR (95 % CI)	NLR (95 % CI)	DOR (95 % CI)	AUC (95 % CI)
Country						
China	0.80 (0.78-0.83)	0.83 (0.80-0.86)	4.7 (4.0-5.6)	0.24 (0.21-0.27)	20 (15-25)	0.88 (0.85-0.91)
Japan	0.89 (0.77-0.95)	0.85 (0.75-0.92)	6.0 (3.3-11.2)	0.13 (0.06-0.30)	45 (12-176)	0.93 (0.91-0.95)
miRNAs profile						
Single miRNA	0.80 (0.77-0.82)	0.83 (0.79-0.85)	4.6 (3.9-5.5)	0.25 (0.22-0.27)	19 (15-24)	0.87 (0.84-0.90)
miRNA cluster	0.91 (0.82-0.96)	0.89 (0.82-0.93)	8.0 (4.8-13.4)	0.10(0.04-0.21)	84 (26-267)	0.95 (0.93-0.97)
Regulation mode						
Up-regulated	0.83 (0.79-0.86)	0.83 (0.79-0.87)	4.9 (3.8-6.3)	0.21 (0.17-0.25)	24 (16-35)	0.90 (0.87-0.92)
Down-regulated	0.80 (0.76-0.83)	0.84 (0.80-0.87)	4.9 (3.9-6.0)	0.24 (0.20-0.29)	20 (14-28)	0.89 (0.85-0.91)
Sample size						
< 100	0.79 (0.76-0.83)	0.83 (0.79-0.86)	2.8 (1.9-5.6)	0.51 (0.26-0.78)	17 (12-19)	0.85 (0.81-0.87)
≥ 100	0.81 (0.78-0.84)	0.86 (0.80-0.90)	4.7 (3.9-5.7)	0.23 (0.19-0.26)	21 (15-28)	0.88 (0.86-0.91)
Specimen types						
Serum	0.81 (0.78-0.84)	0.83 (0.80-0.85)	4.7 (3.9-5.6)	0.23 (0.19-0.27)	21 (15-28)	0.89 (0.86-0.91)

Plasma	0.81 (0.77-0.85)	0.85 (0.78-0.90)	5.5 (3.6-8.3)	0.22 (0.17-0.28)	25 (14-44)	0.89 (0.86-0.92)

AUC: area under the curve; CI: confidence interval; DOR: diagnostic odds ratio; EC: esophageal cancer; ESCC: esophageal squamous cell carcinoma; NLR: negative likelihood ratios; PLR: positive likelihood ratios; Sen: sensitivity; Spe: specificity.

Figure 1. Flow chart of meta-analysis to identify inclusion studies.

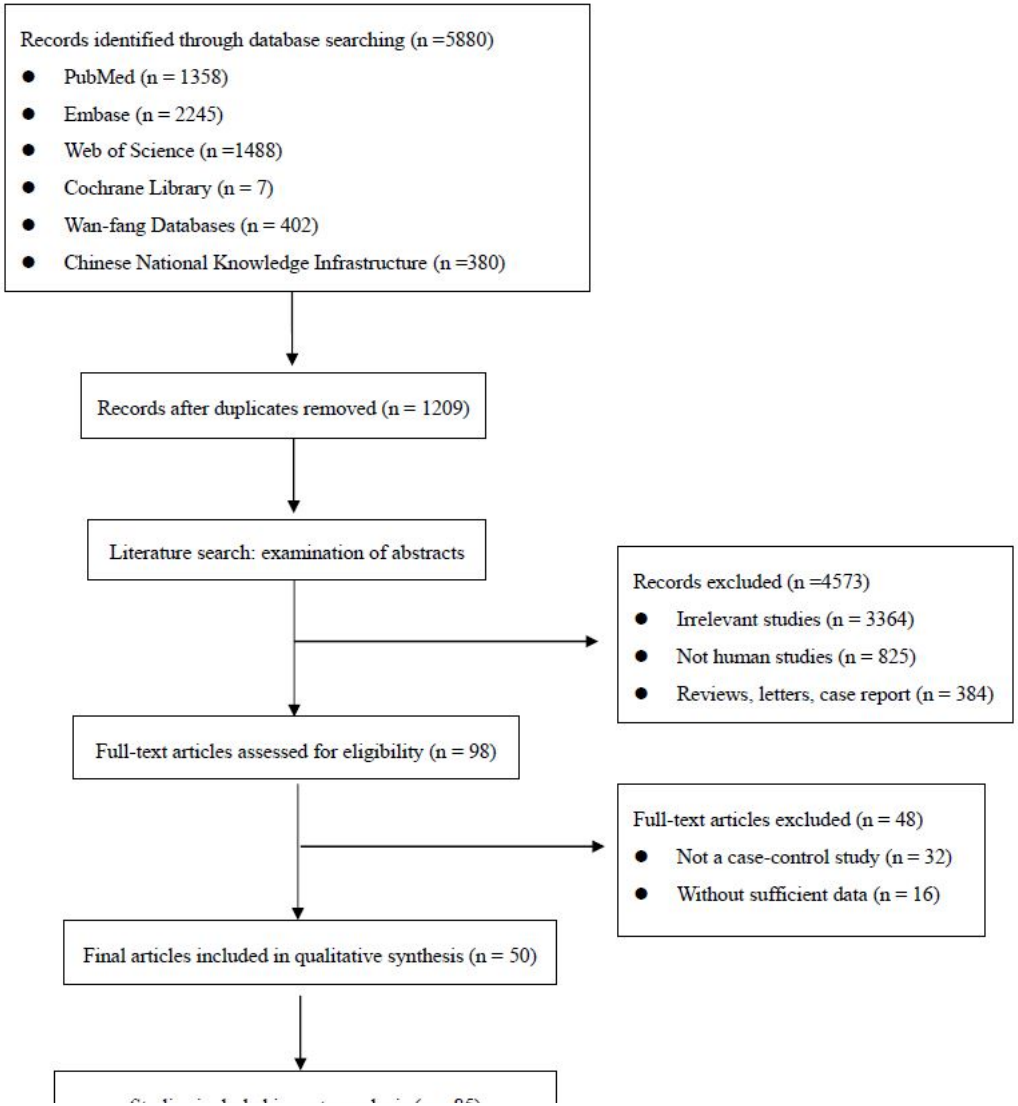
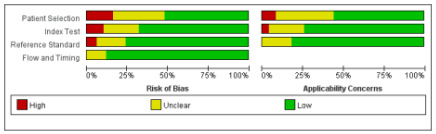

Records identified through database searching (n =5880)
PubMed (n = 1358)
Embase (n = 2245)
Web of Science (n =1488)
Cochrane Library (n = 7)
Wan-fang Databases (n = 402)
Chinese National Knowledge Infrastructure (n =380)
Records after duplicates removed (n = 1209)
Literature search: examination of abstracts
Records excluded (n =4573)
Irrelevant studies (n = 3364)
Not human studies (n = 825)
Reviews, letters, case report (n = 384)
Full-text articles assessed for eligibility (n = 98)
Full-text articles excluded (n = 48)
Not a case-control study (n = 32)
Without sufficient data (n = 16)
Final articles included in qualitative synthesis (n = 50)

Figure 2. Quality evaluation according to the QUADAS-2 criteria


Patient Selection
Index Test
Reference Standard
Flow and Timing
0%
25%
50%
75%
100%
Risk of Bias
Applicability Concerns
High
Unclear
Low

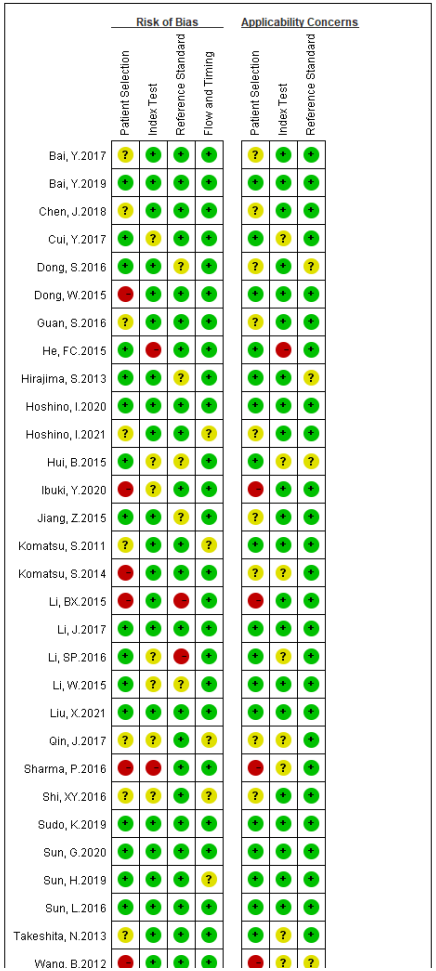
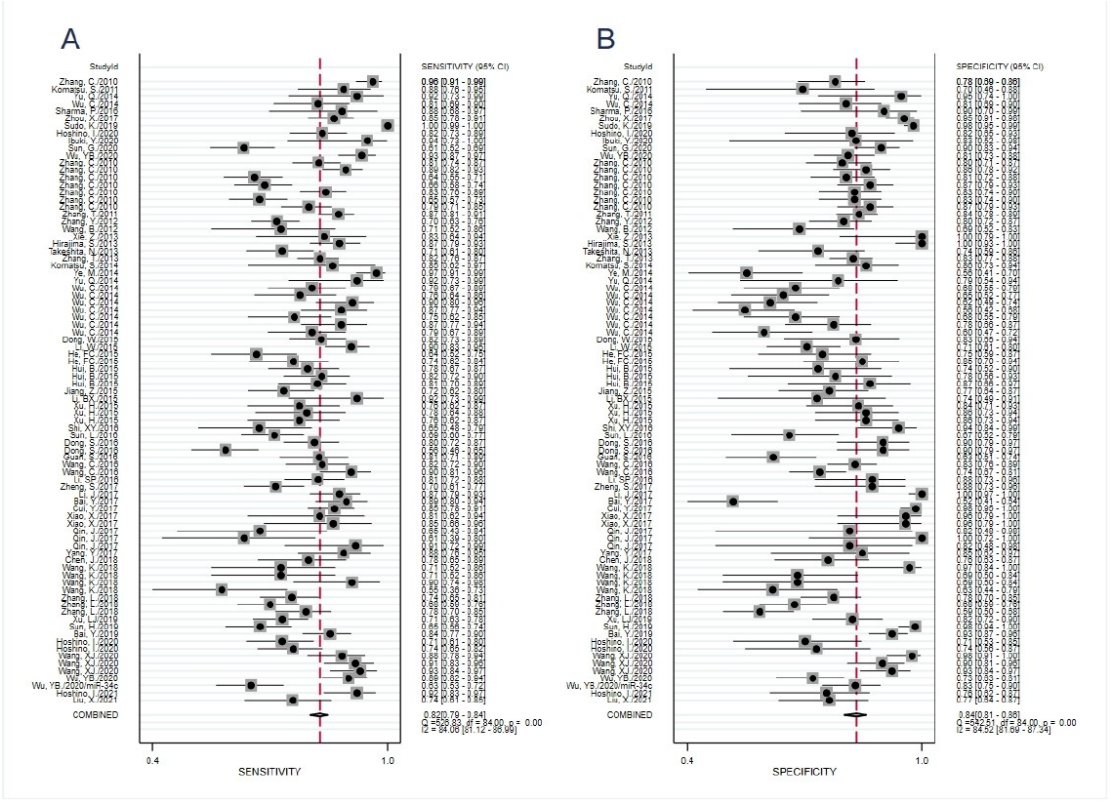
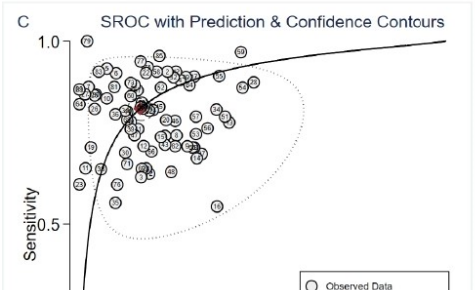
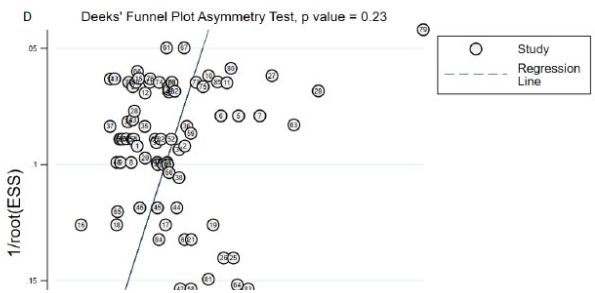

Risk of Bias
Applicability Concerns
Patient Selection
Index Test
Reference Standard
Flow and Timing
Patient Selection
Index Test
Reference Standard
Bai, Y.2017
Bai, Y.2019
Chen, J.2018
Cui, Y.2017
Dong, S.2016
Dong, W.2015
Guan, S.2016
He, FC.2015
Hirajima, S.2013
Hoshino, I.2020
Hoshino, I.2021
Hui, B.2015
Ibuki, Y.2020
Jiang, Z.2015
Komatsu, S.2011
Komatsu, S.2014
Li, BX.2015
Li, J.2017
Li, SP.2016
Li, W.2015
Liu, X.2021
Qin, J.2017
Sharma, P.2016
Shi, XY.2016
Sudo, K.2019
Sun, G.2020
Sun, H.2019
Sun, L.2016
Takeshita, N.2013
Wang, B.2012

Figure 3. Forest plot of (A) sensitivity, (B) specificity, (C) area under the curve (AUC), and (D) Deeks' funnel plot of circulating miRNAs for the diagnosis of patients with EC compared to healthy controls among overall studies.


A
Studyid
SENSITIVITY (95% CI)
COMBINED
SENSITIVITY
0.4
1.0
B
Studyid
SPECIFICITY (95% CI)
COMBINED
SPECIFICITY
0.4
1.0


C
SROC with Prediction & Confidence Contours
1.0
0.5
Sensitivity
Observed Data


D
Deeks' Funnel Plot Asymmetry Test, p value = 0.23
1/root(ESS)
Study
Regression Line