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REVIEW

Diagnostic significance of miR-210 as a potential tumor biomarker of human cancer detection: an updated pooled analysis of 30 articles

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Abstract: A large number of studies have explored the diagnostic value of miR-210 as a potential diagnostic cancer biomarker to detect various cancers in patients. However, the results of its diagnostic accuracy and reliability in individual studies are still inconsistent. Therefore, we conducted this updated pooled analysis to derive a more reliable conclusion of the overall accuracy of miR-210 in cancer detection and diagnosis. A comprehensive literature search was performed using the PubMed, Cochrane Library, Web of Science, China National Knowledge Infrastructure, and Wanfang databases. The quality of all eligible studies was scored according to Quality Assessment of Diagnostic Accuracy Studies-2 guidelines. The bivariate mixed model was applied to pooled sensitivity, specificity, likelihood ratios, and diagnostic ORs. The summary receiver operator characteristic (SROC) curve and the hierarchical SROC models were used to check overall diagnostic performance. Thirty articles with 2,304 patients and 1,673 controls were included in this study. The pooled parameters calculated from all studies are as follows: sensitivity –0.74 (95% CI: 0.68–0.79), specificity –0.79 (95% CI: 0.74–0.83), positive likelihood ratio –3.57 (95% CI: 2.85–4.47), negative likelihood ratio –0.32 (95% CI: 0.26–0.40), diagnostic OR –10.98 (95% CI: 7.55–15.98), SROC –0.84 (95% CI: 0.80–0.87). All of these results revealed that miR-210 had relatively moderate accuracy in distinguishing patients with various cancers from all other individuals. However, well-designed prospective studies with large sample sizes using different groups of the population are urgently warranted to confirm our findings.

Keywords: microRNA-210, cancer, biomarker, diagnosis, meta-analysis, ROC

Introduction

Cancer is a major public health problem all over the world because of its increasing incidence and mortality in recent years.[1] According to Cancer Statistics, it was estimated that in 2017, 1,688,780 new cases of cancer and 600,920 cancer deaths were projected to occur in the US.[1] In China, an estimated 4,292,000 new cases of cancer and 2,814,000 cancer deaths occurred in 2015.[2] Lung, stomach, liver, and esophageal cancers were the most commonly diagnosed and were recognized as the foremost reasons of cancer death.[3] Up to now, the gold standard for detecting and diagnosing cancers has been pathological biopsy, which has several limitations, including its invasive and unpleasant nature and the risk of cancer metastasis.[3] Several blood-based clinical biomarkers are useful in the early detection and diagnosis of cancer, including prostate specific antigen, carcinoembryonic antigen, carbohydrate antigen 15-3, and alpha-fetoprotein.[4–7] However, their low specificity and sensitivity limit their clinical usage. Therefore, finding an

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effective tumor-specific biomarker for early detection and diagnosis of cancer is becoming urgent and vital.

miRNAs, a class of small, non-coding, endogenous, single-stranded RNAs of a length of 22 nucleotides, function as potential oncogenes or tumor suppressor genes and play vital regulatory roles in tumorigenesis and tumor progression.[8,9] Accumulating evidence has demonstrated that blood-based miRNAs could serve as novel and noninvasive biomarkers for detecting and diagnosing patients with various cancers.[10,11] miR-210, located on chromosome 11p15.5, contributes to the development of several cancers, including bladder cancer (BLCA), renal cell carcinoma (RCC), lung cancer (LC), and pancreatic cancer (PAAD).[12] A number of studies have explored the possible clinical usage of miR-210 in detecting and diagnosing cancers. Due to limited sample sizes and variation in study design, the overall result is inconsistent and inconclusive. Although two previous meta-analyses about the diagnostic significance of miR-210 in cancer detection have already been published several years ago, there are some defects in these studies.[13,14] First, the results of both meta-analyses may lack statistical power due to the limited number of eligible studies enrolled. Recently, a large number of new studies have been conducted to explore the accuracy of miR-210 in the detection and diagnosis of cancer. Second, one of the two meta-analyses explored the accuracy of miRNA-210 only in LC detection.[14] To avoid the previously mentioned limitations, we conducted this pooled analysis to derive a more reliable conclusion of the overall accuracy of miR-210 in the detection and diagnosis of cancer.

Materials and methods

Identification of miR-210 associated with various cancers

For identification of miR-210 expression in various cancers, we used SPSS-23 and GraphPad Prism 6 based on transcriptome profiling of TCGA with information of clinicopathological characteristics downloaded from UCSC Xena (http://xena.ucsc.edu/). All data from UCSC Xena were analyzed using the Student's *t*-test and the non-parametric test. The results are expressed as mean ± SD and *P*-values of less than 0.05 are considered as statistically significant.

Search strategy

The electronic databases PubMed, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang were searched to identify relevant papers about miR-210 and cancer published by October 20, 2017. The search terms were as follows: ("diagnosis" OR "sensitivity" OR "specificity" OR "ROC") and ("microRNA-210" OR "miRNA-210" OR "miR-210" OR "miR-210" OR "hsa-mir-210") and ("cancers" OR "carcinomas" OR "neoplasms"). Two reviewers (Anbang He and Song Feng) independently checked the abstract after the articles were found and read the full text if necessary to evaluate the quality of the articles. Conflicts of opinion between the two reviewers regarding the articles were resolved by other reviewers.

Inclusion and exclusion criteria

The inclusion criteria included: 1) the diagnostic value of miR-210 in detecting cancer; 2) a case control group designed with benign tumors; and 3) sufficient data that could be extracted or calculated from the article to obtain diagnostic parameters. The exclusion criteria were as follows: 1) letters, reviews or meta-analyses; 2) not related to either miR-210 or cancer or diagnostic value; 3) insufficient data that could not be extracted or calculated from the article to obtain diagnostic parameters.

Data extraction and quality assessment

The necessary information from the eligible studies was extracted by two investigators independently. The data extracted from eligible studies were listed as follows: 1) first author, 2) year of publication, 3) country, 4) ethnicity, 5) cancer type, 6) normalizer, 7) sample type, 8) test method, 9) the value of the cutoff, 10) number of cases and controls, 11) the diagnostic parameters including true positive, false positive, false negative, and true negative. Moreover, information missing from the original articles was obtained by contacting the relevant corresponding author. Study quality was assessed according to Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) guidelines.[15] The QUADAS-2 list was used on each article, with each answer being either "yes(Y)," "no(N)" or "unclear(U)."

Statistical analysis

All the statistical analyses were performed by using Stata (StataCorp LP, College Station, TX, USA, version 13.0). The bivariate meta-analysis model was applied to our analysis to calculate pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic OR (DOR).[16] We also established a summary receiver operator characteristic (SROC) curve and calculated the AUCs and 95% CI. These data were confirmed by a hierarchical SROC (HSROC) model.[17] Spearman correlation coefficients and ROC plane analyses were conducted to evaluate the heterogeneity of the threshold effect.[18] Heterogeneity

of non-threshold effects was assessed using Cochran-Q and Inconsistency index (I^2) tests. A *P*-value less than 0.10 for the Q test or an I^2 value higher than 50% indicated obvious heterogeneity between the studies. Meta-regression and subgroup analyses were applied to find out potential sources of heterogeneity. Fagan's nomogram was used to certify relationships between prior-test probability, likelihood ratio, and post-test probability. Deeks' funnel plot asymmetry test was used to assess potential publication bias.[19]

Result

miR-210 expression and clinicopathological characteristics

The clinicopathological characteristics of various cancers, including the expression of miR-210 (3 p and 5 p), overall survival, and relapse-free survival (RFS) were analyzed by using data from the UCSC Xena website. All results are shown in Table 1. As shown in Figure 1, the expression of both miR-210-3p and miR-210-5p were up-regulated in BLCA, breast cancer (BRCA), kidney clear cell carcinoma (KIRC), kidney papillary cell carcinoma (KIRP), stomach cancer (STAD), and lung squamous cell carcinoma (LUSC) (Figure 1). Up-regulated miR-210-3p expression in KIRC was positively correlated with shorter RFS (Table 1).

Literature search

Three hundred and thirty-three potentially relevant articles were found using the PubMed, Cochrane Library, Web of Science, CNKI, and Wanfang databases. The abstracts of all of these studies and the full-text, if necessary, were checked by two reviewers; after duplicates, irrelevant articles, reviews or meta-analyses were excluded, 30 articles remained and were included in our meta-analysis as shown in Figure 2.

Data characteristics and quality assessment

The necessary information from the 30 articles that were included, as shown in Table 2, was extracted and included the following: 1) first author; 2) year of publication: ranged from 2009–2017; 3) country: one from Egypt, one from France, one from Germany, two from Japan, the rest of the studies from China; 4) ethnicity: 17 studies were Asian, eight studies were Caucasian/African, three studies were Caucasian, one study was African; 5) cancer type: included non-small-cell lung cancer: six studies, LC: four studies, BLCA: two studies, RCC: five studies, PAAD: six studies, colorectal carcinoma (CRC): two studies, BRCA: one study, gastric cancer (GC): one study, glioma: one study, leukemia: one study; 6) sample type: serum: 20 studies, sputum: five studies, urine: two studies, pancreatic juice: one study, fecal matter: one study; 7) test method: qRT-PCR: 28 studies, microarray: one study. We evaluated all of the included studies according to the QUADAS-2 tool. The results are summarized in Table 3. We found that the overall quality of the studies included was relatively moderate.

Table 1 Correlation between miR-210 expression and clinicopathological characteristics of patients with various cancers

Cancer type	miR-210	Sample type			OS		RFS	
		Primary tumor	Solid tissue normal	*P*-value	Log-rank	*P*-value	Log-rank	*P*-value
BLCA	miR-210-3p	9.0667	3.4918	1.05509E-11	0.0664	0.7967	0.09716	0.7553
	miR-210-5p	1.1792	0.3952	1.9562E-05	0.3517	0.5532	0.005649	0.9401
KIRC	miR-210-3p	11.4017	7.8702	0	0.003842	0.9506	4.093	0.0431
	miR-210-5p	1.5756	0.671	2.64233E-14	0.5693	0.4505	0.242	0.6228
KIRP	miR-210-3p	9.0781	7.1327	4.12448E-11	2.363	0.1242	0.1231	0.7257
	miR-210-5p	1.0426	0.5412	2.96369E-07	1.064	0.3022	0.008749	0.9255
PAAD	miR-210-3p	8.4673	7.5524	0.263	3.045	0.081	2.722	0.099
	miR-210-5p	0.9083	0.6031	0.399	0.7011	0.4024	0.3621	0.5473
BRCA	miR-210-3p	8.2153	5.7278	0	0.7134	0.3983	0.357	0.5502
	miR-210-5p	0.7765	0.33119	0.002	0.09328	0.7601	0.03927	0.8429
READ	miR-210-3p	8.947	9.2383	0.587	1.42	0.2335	0.4132	0.5204
	miR-210-5p	0.7184	2.6834	0.000207331	1.013	0.3141	0.000004748	0.9983
LUSC	miR-210-3p	10.8598	6.2018	0	0.5837	0.4449	1.147	0.2841
	miR-210-5p	1.4413	0.5197	4.44089E-16	0.1682	0.6817	0.7755	0.3785
STAD	miR-210-3p	7.8327	6.1979	0.000215803	1.782	0.1819	2.747	0.0974
	miR-210-5p	0.7643	0.5017	0.003617978	0.09764	0.7547	0.03605	0.8494

Abbreviations: BRCA, breast cancer; BLCA, bladder cancer; KIRC, kidney clear cell carcinoma; KIRP, kidney papillary cell carcinoma; LUSC, lung squamous cell carcinoma; OS, overall survival; PAAD, pancreatic cancer; READ, rectal cancer; RFS, relapse-free survival; STAD, stomach cancer.

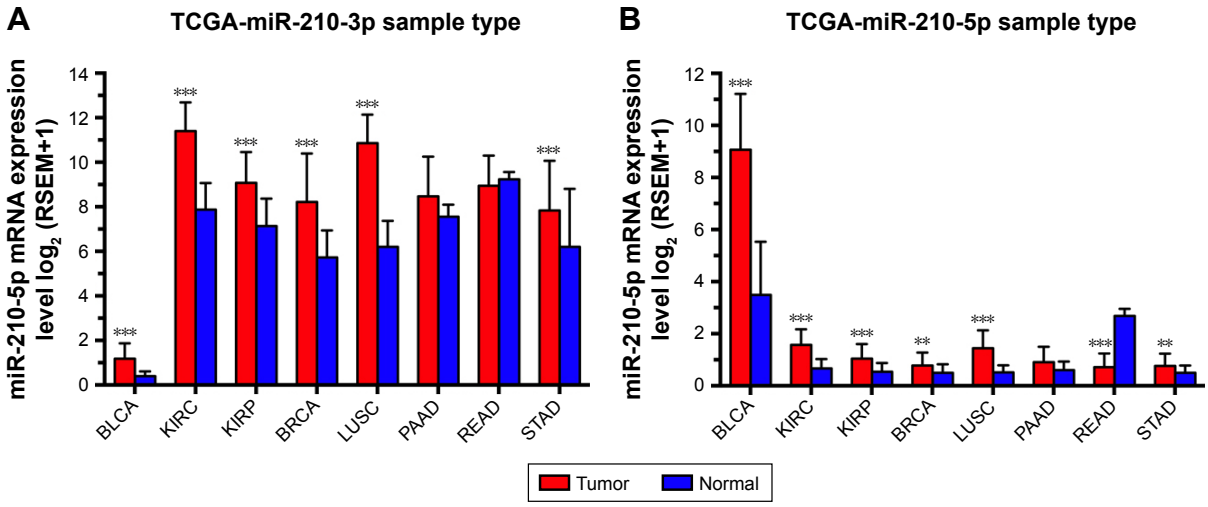

Figure 1 The expression of miR-210 was up-regulated in various cancers compared with adjacent normal tissues.
Note: The expression of both miR-210-3p (**A**) and miR-210-5p (**B**) were up-regulated in BLCA, KIRC, KIRP, BRCA, LUSC, and STAD (**$P<0.01$, ***$P<0.001$).
Abbreviations: BLCA, bladder cancer; BRCA, breast cancer; KIRC, kidney clear cell carcinoma; KIRP, kidney papillary cell carcinoma; LUSC, lung squamous cell carcinoma; PAAD, pancreatic cancer; READ, rectal cancer; STAD, stomach cancer.

Diagnostic accuracy of miR-210 for cancers

The pooled sensitivity and specificity of the studies overall were 0.74 (95% CI: 0.68–0.79) and 0.79 (95% CI: 0.74–0.83), respectively (Figure 3). Considering that the I^2 values for sensitivity and specificity were 88.07% (95% CI: 84.69–91.44) and 79.44% (95% CI: 72.67–86.22), respectively, this suggests significant heterogeneity in sensitivity and specificity.

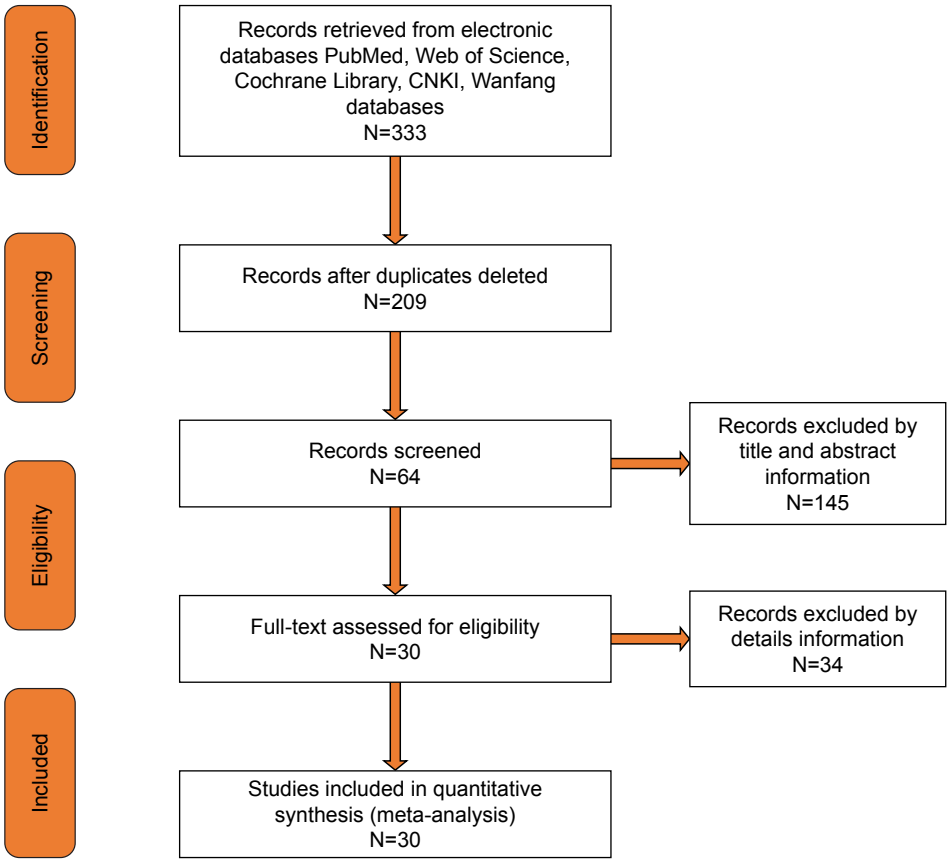

Figure 2 Flow diagram of the selection process of studies included.
Abbreviation: CNKI, China National Knowledge Infrastructure.

Table 2 Characteristics of the included studies

	First author	Year	Country	Ethnicity	Cancer type	Normalizer	Sample type	Test method	Cut-off	Cases/controls	TP	FP	FN	TN
1	Yang et al[27]	2015	China	Asian	BLCA	miR-16	Serum	qRT-PCR	22.37	168/104	164	32	4	72
2	Eissa et al[28]	2015	Egypt	African	BLCA	U6	Urinary	qRT-PCR	1.17	94/116	72	8	22	108
3	Eissa et al[29]	2015	Egypt	African	BLCA	U6	Urinary	qRT-PCR	NA	188/180	134	16	54	164
4	Li et al[30]	2017	China	Asian	RCC	miR-39	Urinary	qRT-PCR	0.0002	75/45	43	9	32	36
5	Zhang et al[31]	2016	China	Asian	RCC	U6	Serum	qRT-PCR	NA	82/80	57	30	25	50
6	Iwamoto et al[32]	2013	Japan	Asian	RCC	miR-16	Serum	qRT-PCR	NA	34/23	22	4	12	19
7	Zhao et al[33]	2013	France	Caucasian	RCC	5s rRNA	Serum	qRT-PCR	NA	68/42	55	9	13	33
8	Li et al[34]	2015	China	Asian	RCC	U6	Serum	qRT-PCR	NA	22/20	18	4	4	16
9	Zhu et al[35]	2016	China	Asian	NSCLC	U6	Serum	qRT-PCR	0.1069	112/40	38	0	74	40
10	Wang et al[36]	2016	China	Asian	NSCLC	miR-16	Serum	qRT-PCR	3.34	59/59	44	15	15	44
11	Li et al[37]	2013	China	Asian	NSCLC	miR-16	Serum	qRT-PCR	1.307	60/30	47	8	13	22
12	Shen et al[38]	2010	USA	Mixed	NSCLC	miR-16	Serum	qRT-PCR	NA	58/29	43	9	15	20
13	Shen et al[39]	2011	USA	Mixed	NSCLC	miR-16	Serum	qRT-PCR	NA	32/33	18	9	14	24
14	Anjuman et al[40]	2013	USA	Mixed	NSCLC	U6	Sputum	qRT-PCR	NA	39/42	27	10	12	32
15	Xing et al[41]	2015	USA	Mixed	LC	miR-16	Sputum	qRT-PCR	36.56	60/62	45	9	15	53
16	Shen et al[42]	2014	USA	Mixed	LC	U6	Sputum	qRT-PCR	NA	66/68	43	18	23	50
17	Xing et al[43]	2010	USA	Mixed	LC	U6	Sputum	qRT-PCR	1.64	48/48	28	10	20	38
18	Li et al[44]	2014	USA	Mixed	LC	U6	Sputum	qRT-PCR	NA	35/40	20	4	15	36
19	Wang et al[45]	2014	USA	Mixed	PAAD	U6	Pancreatic Juice	qRT-PCR	NA	50/19	38	1	12	18
20	Wang et al[46]	2009	USA	Caucasian	PAAD	miR-16	Serum	qRT-PCR	NA	28/19	12	5	16	14
21	Kojima et al[47]	2015	Japan	Asian	PAAD	NA	Serum	microarray	NA	100/21	59	15	41	6
22	Ren et al[48]	2012	China	Asian	PAAD	miR-16	Fecal	qRT-PCR	1.54	29/13	25	4	4	9
23	Chen et al[49]	2015	China	Asian	PAAD	miR-39	Serum	qRT-PCR	NA	37/40	30	3	7	37
24	Pan et al[50]	2014	China	Asian	PAAD	miR-39	Serum	qRT-PCR		30/26	21	4	9	22
25	Madhavan et al[51]	2012	Germany	Caucasian	BRCA	miR-39	Serum	qRT-PCR	NA	61/76	51	14	10	62
										72/76	45	37	27	39
26	Wang et al[52]	2016	China	Asian	CRC	miR-191-5p/U6	Serum	qRT-PCR	1.1476	268/102	200	27	68	75
27	Fang et al[53]	2015	China	Asian	CRC	U6	Serum	qRT-PCR	38.31	48/40	40	12	8	28
28	Qi et al[54]	2016	China	Asian	GC	U6	Serum	qRT-PCR	NA	100/100	86	18	14	82
29	Lai et al[55]	2015	China	Asian	Glioma	miR-16	Serum	qRT-PCR	2.259	136/50	124	14	12	36
30	Xie et al[56]	2015	China	Asian	Leukemia	miR-16	Serum	qRT-PCR	NA	45/30	41	6	4	24

Abbreviations: BLCA, bladder cancer; BRCA, breast cancer; CRC, colorectal carcinoma; FN, false negative; FP, false positive; GC, gastric cancer; LC, lung cancer; Mixed, Caucasian/African; NA, ; NSCLC, non-small-cell lung cancer; PAAD, pancreatic cancer; RCC, renal cell carcinoma; TN, true negative; TP, true positive.

Table 3 QUADAS-2 assessment for the eligible studies

Studies	Risk of bias										
	Patient selection			Index test		Reference standard		Flow and timing			
	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩	⑪
Yang 2015[21]	Y	U	U	N	N	Y	Y	Y	Y	Y	Y
Eissa 2015[28]	Y	N	N	N	N	Y	Y	Y	Y	Y	Y
Eissa 2015[29]	Y	N	N	N	N	Y	Y	Y	Y	Y	Y
Li et al 2017[30]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Zhang 2016[31]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Iwamoto 2013[32]	Y	N	U	N	N	Y	Y	Y	Y	Y	Y
Zhao 2013[33]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Li 2015[34]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Zhu 2016[35]	Y	N	U	N	N	Y	Y	Y	Y	Y	Y
Wang 2016[36]	Y	N	U	N	N	Y	Y	Y	Y	Y	Y
Li 2013[37]	Y	N	U	N	N	Y	Y	Y	Y	Y	Y
Shen 2010[38]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Shen 2011[39]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Anjuman 2013[40]	U	N	U	N	N	Y	Y	Y	Y	Y	Y

(*Continued*)

Table 3 (*Continued*)

Studies	Risk of bias										
	Patient selection			Index test		Reference standard		Flow and timing			
	①	②	③	④	⑤	⑥	⑦	⑧	⑨	⑩	⑪
Xing 2015[41]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Shen 2014[42]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Xing 2010[43]	Y	N	U	N	N	Y	Y	Y	Y	Y	Y
Li 2014[44]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Wang 2014[45]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Wang 2009[46]	Y	N	U	N	N	Y	Y	Y	Y	Y	Y
Kojima 2015[47]	Y	N	U	N	N	Y	Y	Y	Y	Y	Y
Ren 2012[48]	Y	N	U	N	N	Y	Y	Y	Y	Y	Y
Chen 2015[49]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Pan 2014[50]	Y	N	U	N	N	Y	Y	Y	Y	Y	Y
Madhavan 2012[51]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Wang 2016[52]	Y	N	U	N	N	Y	Y	Y	Y	Y	Y
Fang 2015[53]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Qi 2012[54]	U	N	U	N	N	Y	Y	Y	Y	Y	Y
Lai 2015[55]	Y	N	U	N	N	Y	Y	Y	Y	Y	Y
Xie 2012[56]	U	N	U	N	N	Y	Y	Y	Y	Y	Y

Notes: ① Was a consecutive or random sample of patients enrolled? ② Was a case control design avoided? ③ Did the study avoid inappropriate exclusions? ④ Were the index test results interpreted without knowledge of the results of the reference standard? ⑤ If a threshold was used, was it prespecified? ⑥ Is the reference standard likely to correctly classify the target condition? ⑦ Were the reference standard results interpreted without knowledge of the results of the index test? ⑧ Was there an appropriate interval between index tests and reference standard? ⑨ Did all patients receive a reference standard? ⑩ Did all patients receive the same reference standard? ⑪ Were all patients included in the analysis? N for "no," Y for "yes," U for "unclear."

Abbreviation: QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2.

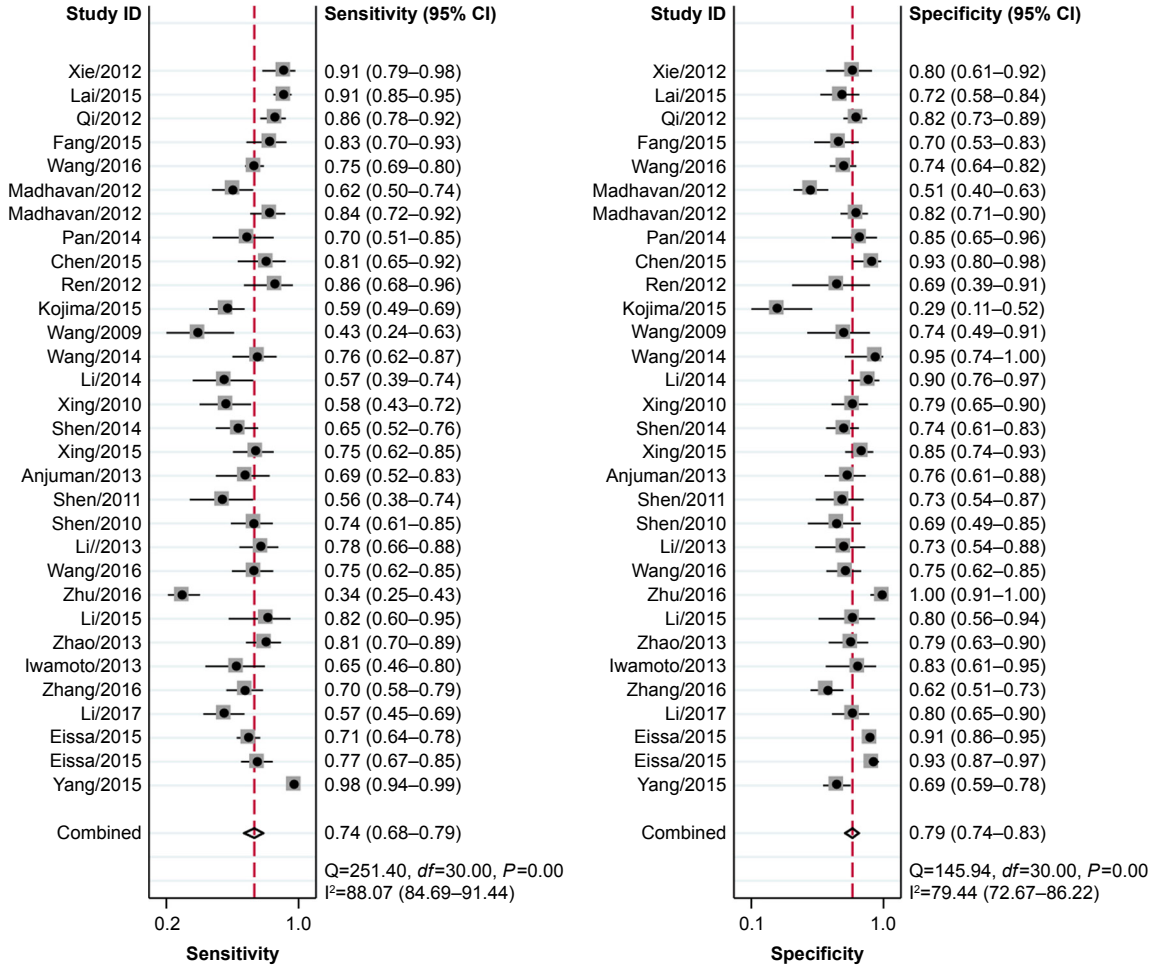

Figure 3 Forest plots of sensitivity and specificity of the overall results.

The pooled PLR and NLR were 3.57 (95% CI: 2.85–4.47) and 0.32 (95% CI: 0.26–0.40), respectively (Figure 4). The DOR was 10.98 (95% CI: 7.55–15.98) (Figure 5). The area under the SROC curve was 0.84 (95% CI: 0.80–0.87) (Figure 6). Figure 7 shows Fagan's nomogram of likelihood ratios, which was used to determine the post-test probabilities that resulted from different pre-test probabilities. As shown in Figure 7, when miR-210 assays were tested for all individuals with a 50% pre-test probability of having cancer, a positive result would increase the post-test probability of having cancer to 78%, while a negative result would decrease the post-test probability to 25%. Thus, miR-210 can be applied as a noninvasive biomarker to supplement existing diagnostic methods. As shown in Figure 8, an HSROC curve was constructed. The hierarchical summary operating point estimate of sensitivity and specificity was 0.74 (95% CI: 0.68–0.79) and 0.79 (95% CI: 0.74–0.83), respectively. The estimated value of β was −0.087 (95% CI: −0.55–0.38), the value of z was −0.37, and the *P*-value was 0.75, implying that the SROC curve was not symmetrical. The value of Lambda was 2.41 (95% CI: 2.03–2.79). All of these results revealed that miR-210 had relatively moderate accuracy in distinguishing cancer patients from all other individuals.

Meta-regression and robustness tests

In order to find potential sources of heterogeneity, we performed a meta-regression analysis based on variables including the number of cases (yes ≥60, no <60) and controls (yes ≥60, no <60), cancer type, sample type (blood-based: serum, non-blood-based: sputum, urine, pancreatic juice, fecal matter), normalizer, and ethnicity. As shown in Figure 9, several variables including normalizer (U6), ethnicity (mixed: Caucasian/African), the number of cases (yes ≥60, no <60), and cancer type (RCC, LC, PAAD) had a large effect on sensitivity. However, all variables had a great impact on specificity. Therefore, we then conducted subgroup analyses based on these factors. All results are presented in Table 4. Goodness-of-fit and bivariate normality analyses (Figure 10A and B) showed that the bivariate model was moderately robust. Influence analysis identified

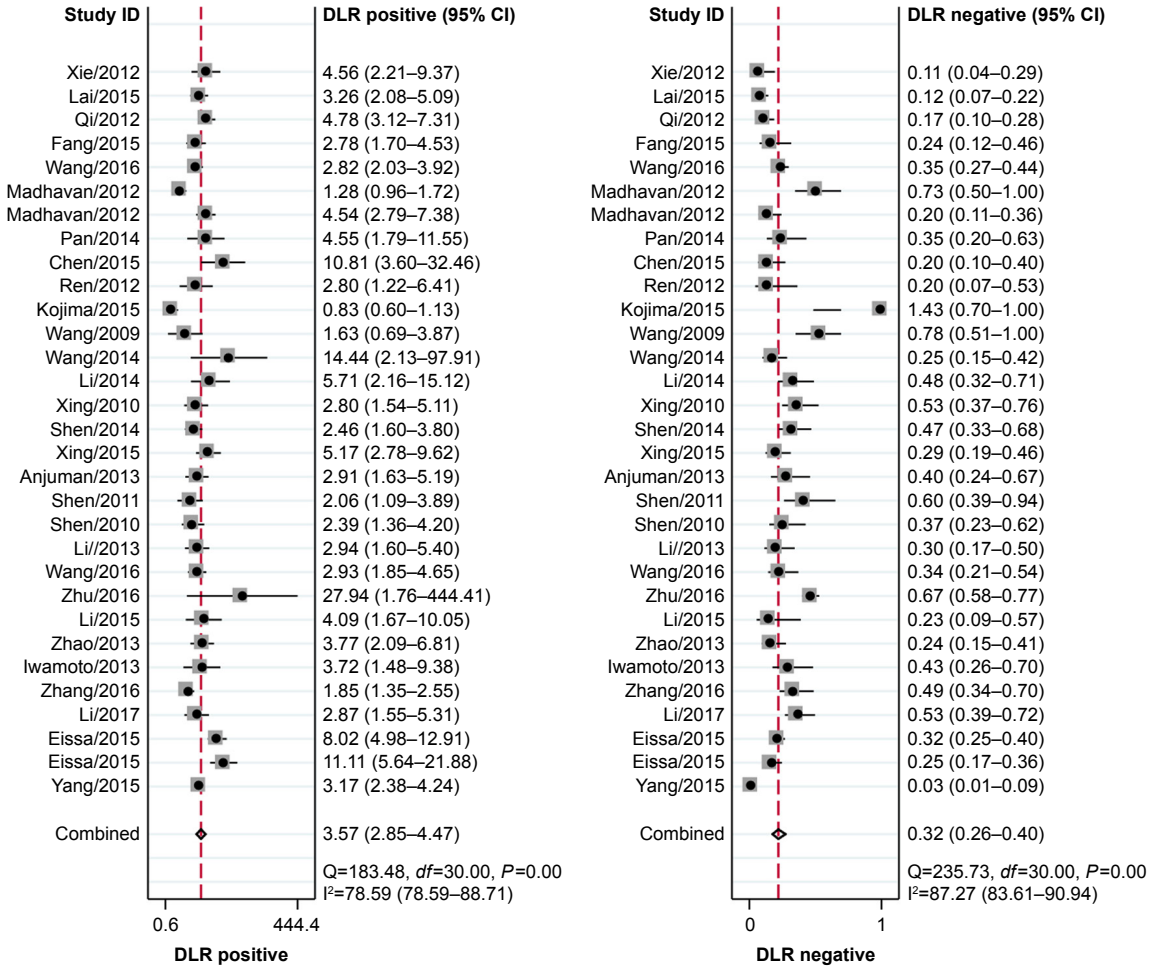

Figure 4 Forest plots of the positive likelihood ratio and the negative likelihood ratio of miR-210 in the diagnosis of cancers.
Abbreviation: DLR, diagnostic likelihood ratio.

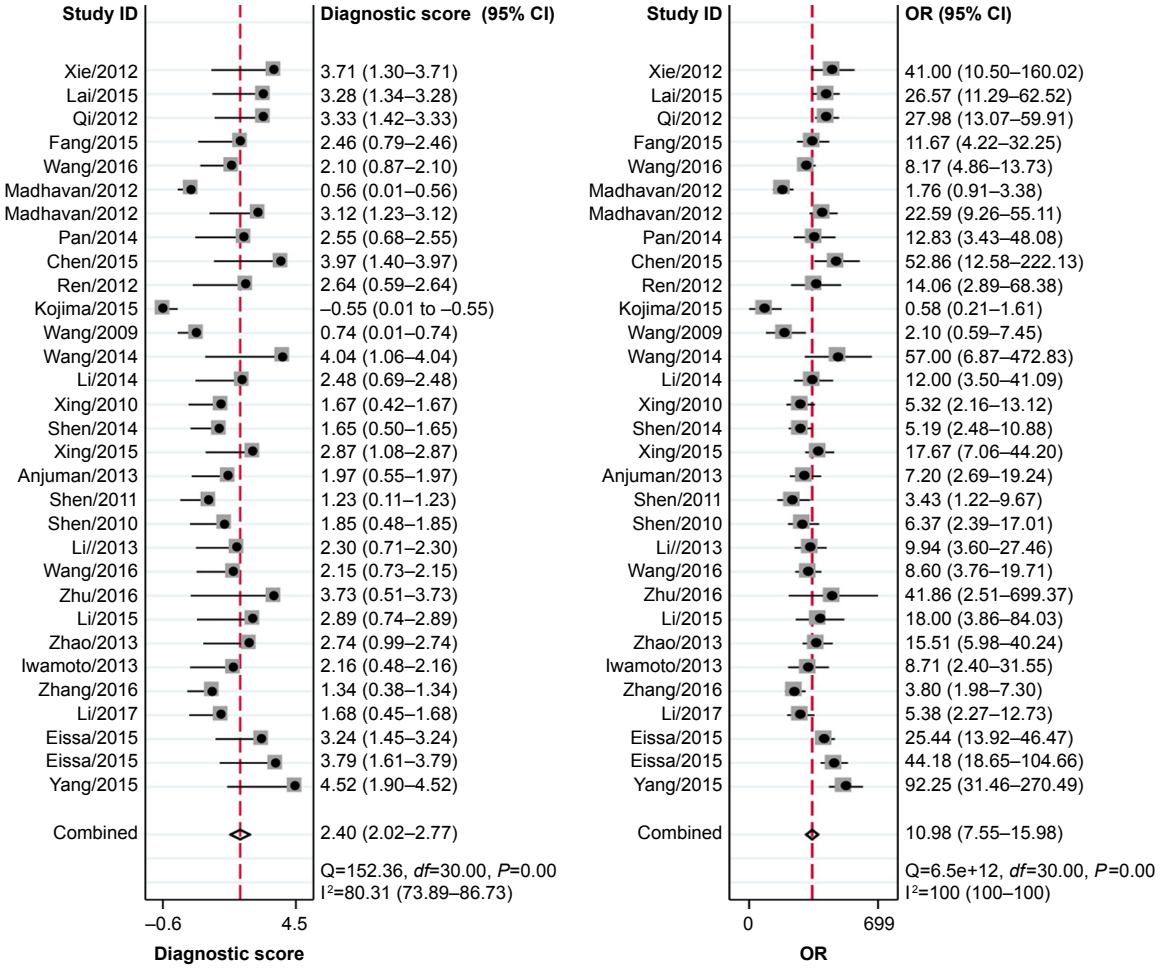

Figure 5 Forest plots of the diagnostic OR of miR-210 in the diagnosis of cancers.

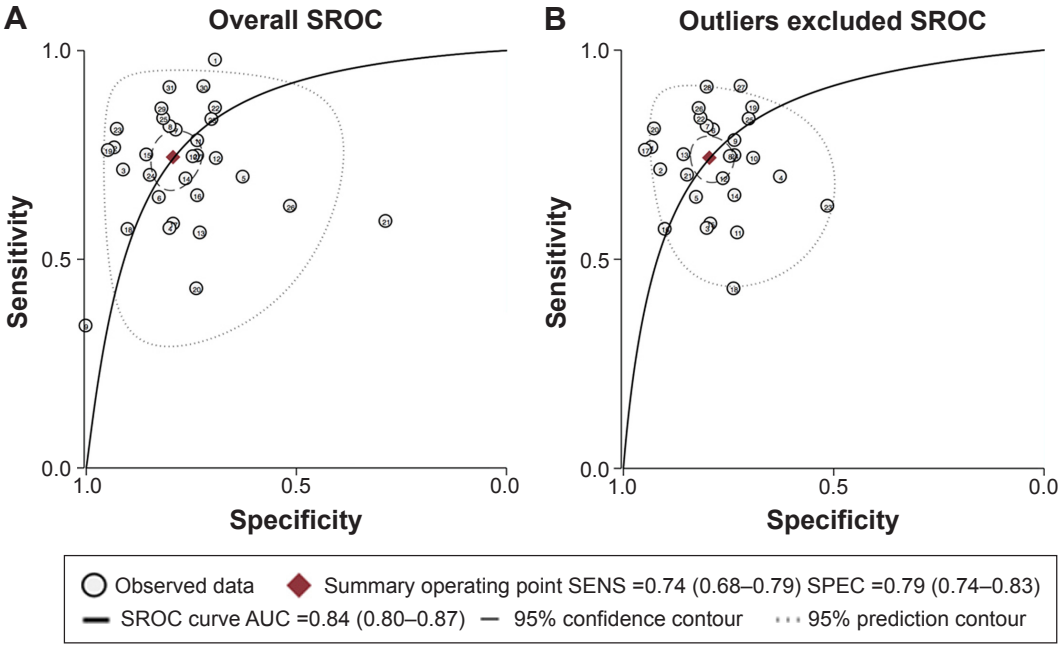

Figure 6 Summary receiver operator characteristic (SROC) curve of miR-210 in the diagnosis of cancers.
Notes: (**A**) Overall result including the outliers. (**B**) Outliers excluded. The numerals in the figure correspond with studies listed in Table 2.
Abbreviations: SENS, sensitivity; SPEC, specificity.

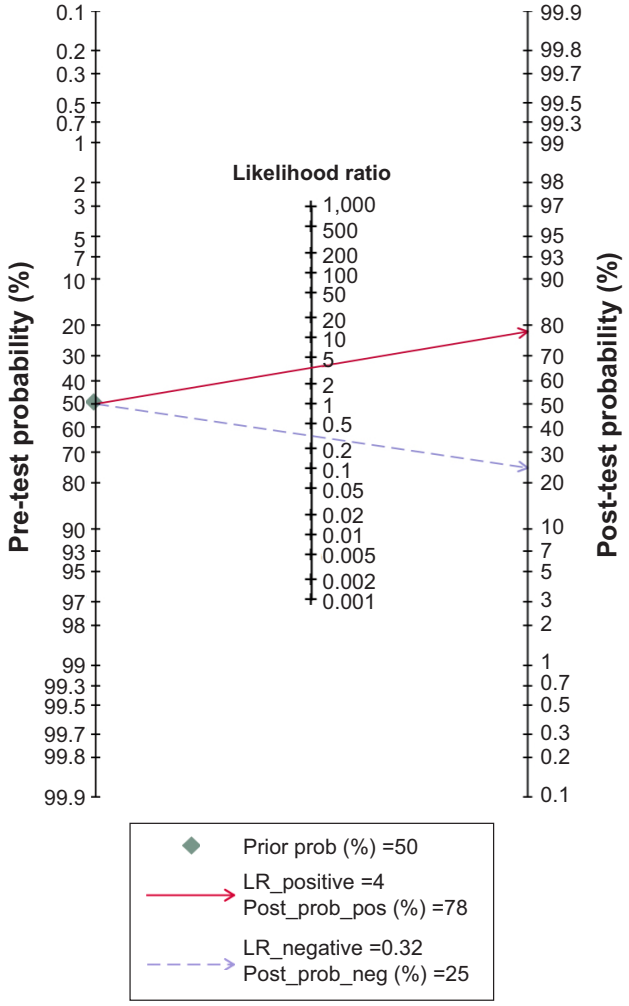

Figure 7 Fagan's nomogram for assessing post-test probabilities.
Abbreviations: Prob, probability; LR, likelihood ratio; pos, positive; neg, negative.

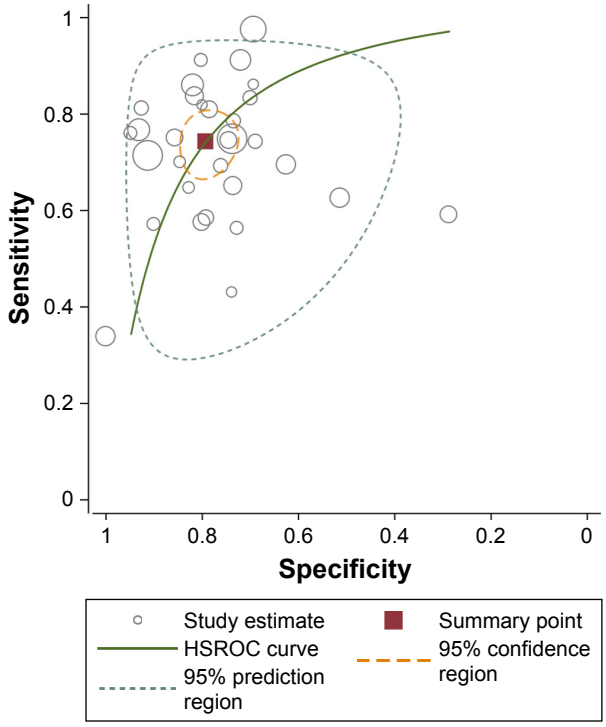

Figure 8 Hierarchical summary receiver operator characteristic (HSROC) curve of miR-210 in the diagnosis of cancers.

four outliers, while three outliers were found through outlier detection (Figure 10C and D). After comprehensive consideration, we decided to exclude these three outliers (①⑨㉑) and retain the fourth outlier (㉑). After exclusion, there was no significant change between these results and the overall results (Table 2).

Threshold effect and heterogeneity

Both the ROC plane and Spearman rank correlation coefficient were conducted to evaluate the threshold effect because of differences among cut-off values. The ROC plane was generated using Stata 13.0, and displayed a non-typical shoulder arm appearance, indicating that there was no threshold effect (Figure 11A). The Spearman correlation coefficient was −0.15 (P=0.02), suggesting that there was no threshold effect. The I^2 of the heterogeneity tests of sensitivity and specificity were 96.95% and 96.95%, respectively, indicating significant heterogeneity. Therefore, meta-regression analysis and subgroup analyses were used to explore potential sources of heterogeneity in sensitivity and specificity.

Publication bias

Deeks' funnel plot asymmetry test was used to explore potential publication bias. The P-value of the linear regression was 0.09, suggesting that there was no publication bias (Figure 11B).

Discussion

With the rapid development of next-generation sequencing technology, a large number of genes have been identified to be dysregulated during expression and involved in the occurrence and development of tumors. In recent years, miRNAs have been identified to function as regulators of gene expression that contribute to tumorigenesis and tumor progression.[20] Since miRNAs can be easily collected from body fluids such as plasma, serum, urine, and secretions using noninvasive procedures, accumulating evidence suggests that body fluid-based miRNAs could function as potential novel and noninvasive biomarkers for the detection and diagnosis of cancer.[21,22] miR-210 is an miRNA that has been found to be up-regulated in various cancers compared with adjacent normal tissues.[12,23,24] A large number of studies have revealed that miR-210 acts as an oncogene to promote tumor development and progression via different signaling

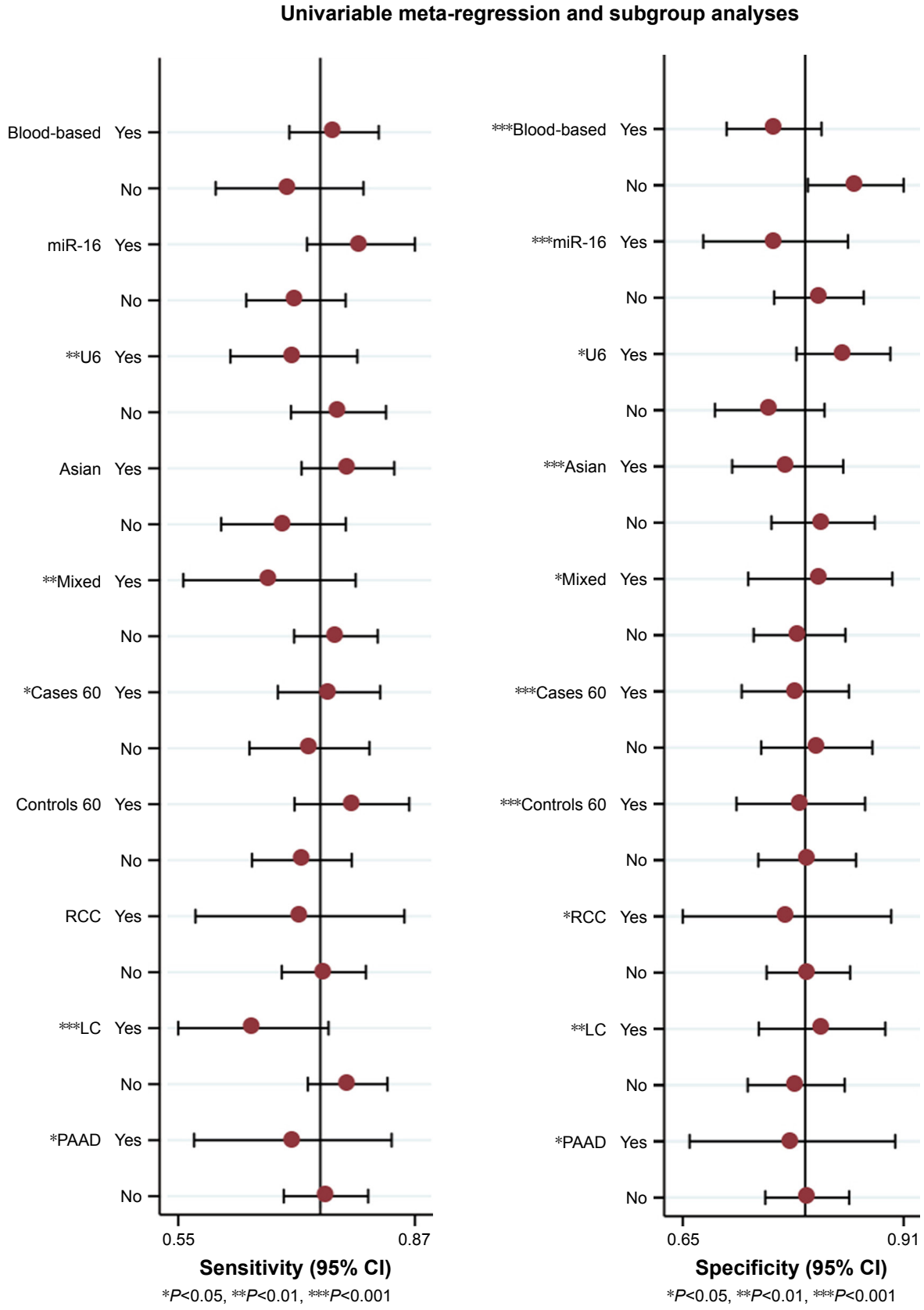

Figure 9 Univariable meta-regression analysis for sensitivity and specificity of miR-210 in the diagnosis of cancers.
Note: Factors marked with an asterisk are potential sources of heterogeneity.
Abbreviations: LC, lung cancer; PAAD, pancreatic cancer; RCC, renal cell carcinoma.

Table 4 Summary results of subgroup analysis for miR-210 in the diagnosis of cancer

Variable	Number of studies	SEN (95% CI)			SPE (95% CI)			PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
		Value	I^2 (%)	P_H	Value	I^2 (%)	P_H				
Ethnicity											
Asian	17	0.78 (0.70, 0.85)	93.05	0	0.77 (0.70, 0.83)	73.24	0	3.5 (2.6, 4.7)	0.28 (0.20, 0.40)	12 (7, 21)	0.85 (0.81, 0.87)
Mixed	8	0.68 (0.62, 0.72)	35.41	0.12	0.80 (0.74, 0.85)	73.05	0	3.4 (2.5, 4.4)	0.41 (0.34, 0.49)	8 (5, 13)	0.77 (0.73, 0.81)
Caucasian	4	0.71 (0.54, 0.83)	85.95	0	0.70 (0.55, 0.82)	84.09	0	2.4 (1.3, 4.4)	0.42 (0.22, 0.79)	6 (2, 19)	0.76 (0.72, 0.80)
Cancer type											
NSCLC	6	0.66 (0.52, 0.77)	90.64	0	0.81 (0.66, 0.90)	65.29	0.01	3.4 (2.1, 5.6)	0.42 (0.32, 0.55)	8 (5, 13)	0.79 (0.75, 0.82)
LC	4	0.65 (0.58, 0.72)	33.83	0.21	0.82 (0.74, 0.87)	45.88	0.14	3.5 (2.4, 5.1)	0.43 (0.34, 0.53)	8 (5, 14)	0.75 (0.71, 0.79)
RCC	5	0.70 (0.61, 0.78)	65.79	0.02	0.75 (0.66, 0.83)	51.99	0.08	2.9 (2.0, 4.1)	0.39 (0.29, 0.53)	7 (4, 13)	0.79 (0.76, 0.83)
PAAD	6	0.71 (0.59, 0.80)	80.31	0	0.79 (0.57, 0.92)	86.89	0	3.4 (1.4, 8.4)	0.37 (0.23, 0.61)	9 (2, 35)	0.79 (0.75, 0.82)
Normalizer											
miR-16	11	0.80 (0.68, 0.88)	89.17	0	0.75 (0.71, 0.80)	0	0.63	3.3 (2.7, 3.9)	0.26 (0.16, 0.43)	12 (7, 23)	0.78 (0.74, 0.82)
U6	10	0.70 (0.62, 0.77)	88.08	0	0.85 (0.77, 0.91)	82.63	0	4.8 (3.1, 7.3)	0.35 (0.37, 0.45)	14 (8, 23)	0.84 (0.81, 0.87)
miR-39	4	0.72 (0.61, 0.80)	77.34	0	0.80 (0.65, 0.89)	88.86	0	3.5 (1.8, 6.8)	0.36 (0.23, 0.56)	10 (3, 29)	0.81 (0.77, 0.84)
Sample type											
Blood-based	21	0.76 (0.68, 0.83)	91.6	0	0.76 (0.69, 0.81)	74.9	0	3.1 (2.4, 4.1)	0.31 (0.23, 0.43)	10 (6, 17)	0.83 (0.79, 0.86)
Non-blood-based	5	0.69 (0.64, 0.73)	53.26	0.02	0.85 (0.80, 0.90)	68.14	0	4.7 (3.3, 6.8)	0.31 (0.37, 0.44)	13 (8, 22)	0.80 (0.77, 0.84)
Case											
≥60	16	0.76 (0.67, 0.83)	92.81	0	0.78 (0.69, 0.85)	88.03	0	3.5 (2.4, 5.1)	0.31 (0.22, 0.43)	11 (6, 20)	0.84 (0.80, 0.87)
<60	15	0.72 (0.66, 0.78)	67.18	0	0.79 (0.75, 0.83)	21.69	0.21	3.5 (2.8, 4.4)	0.35 (0.27, 0.44)	10 (7, 15)	0.83 (0.79, 0.86)
Control											
≥60	12	0.77 (0.66, 0.86)	94.19	0	0.81 (0.71, 0.88)	89.04	0	4.1 (2.7, 6.2)	0.28 (0.18, 0.42)	15 (8, 27)	0.86 (0.83, 0.89)
<60	19	0.72 (0.66, 0.77)	71.04	0	0.78 (0.72, 0.83)	61.68	0	3.2 (2.5, 4.2)	0.36 (0.29, 0.45)	9 (6, 14)	0.81 (0.78, 0.85)
Overall	31	0.74 (0.68, 0.79)	88.07	0	0.79 (0.74, 0.83)	79.44	0	3.6 (2.8, 4.5)	0.32 (0.26, 0.40)	11 (8, 16)	0.84 (0.80, 0.87)
Outlier excluded	28	0.74 (0.70, 0.78)	73.05	0	0.79 (0.75, 0.83)	73.91	0	3.6 (2.9, 4.4)	0.32 (0.27, 0.39)	11 (8, 16)	0.84 (0.80, 0.87)

Abbreviations: DOR, diagnostic OR; LC, lung cancer; NLR, negative likelihood ratio; NSCLC, non-small-cell lung cancer; PAAD, pancreatic cancer; P_H, *P*-value of heterogeneity test; PLR, positive likelihood ratio; RCC, renal cell carcinoma; SEN, sensitivity; SPE, specificity.

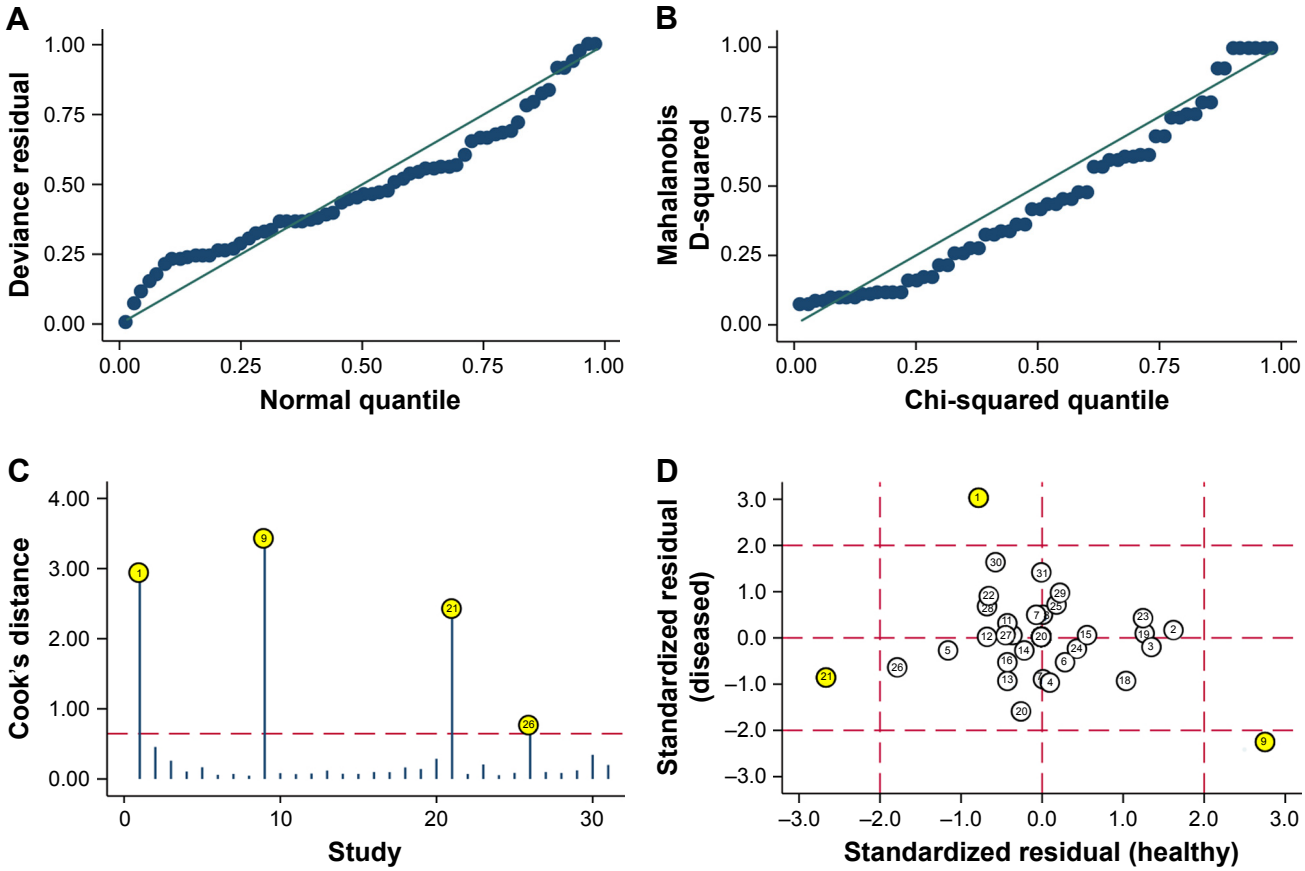

Figure 10 Influence analysis and outlier detection.
Notes: (**A**) Goodness-of-fit, (**B**) bivariate normality, (**C**) influence analysis, and (**D**) outlier detection. The numerals in the figure correspond with studies listed in Table 2.

pathways, including the NF-κB signaling pathway.[25,26] Many studies have explored the possible clinical usage of miR-210 in detecting and diagnosing cancers. However, the overall diagnostic accuracy of miR-210 is inconsistent in the literature due to the inescapable limitations of each study. Although two previous meta-analyses about the diagnostic significance of miR-210 in the detection of cancer have already been published several years ago, there are some

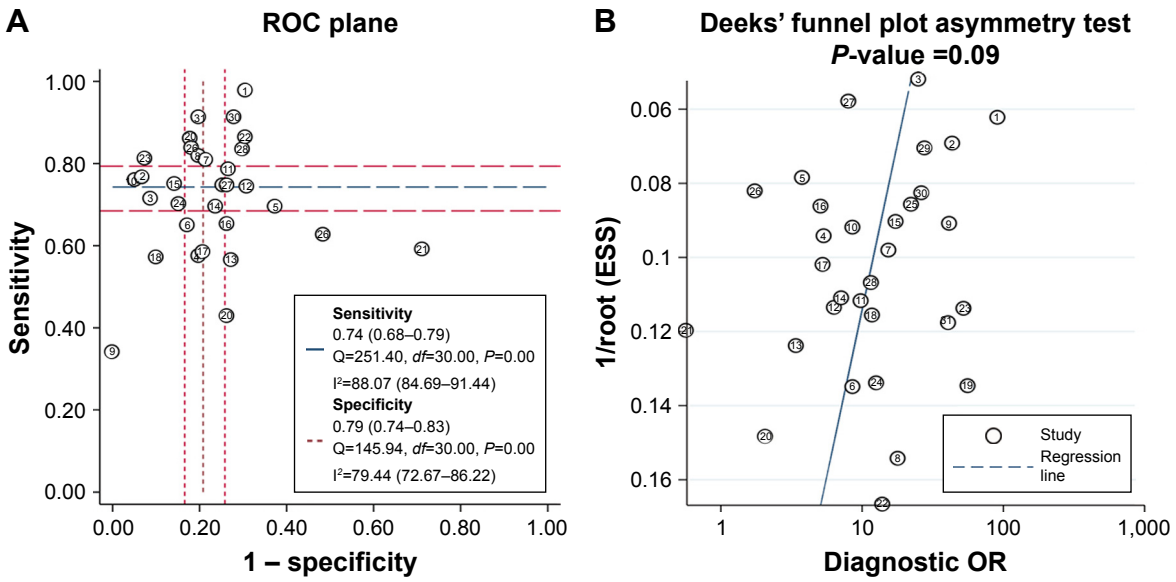

Figure 11 (**A**) Receiver operating characteristic (ROC) plane to assess threshold effects; (**B**) Deeks' funnel plot asymmetry test to assess publication bias.
Note: The numerals in the figure correspond with studies listed in Table 2.

defects in these studies. To avoid the limitations mentioned previously, we conducted this meta-analysis to derive a more reliable conclusion of the overall accuracy of miR-210 in the detection and diagnosis of cancer.

The pooled overall sensitivity and specificity of the studies were 0.74 (95% CI: 0.68–0.79) and 0.79 (95% CI: 0.74–0.83), respectively (Figure 3). The I^2 values for sensitivity and specificity were 88.07% (95% CI: 84.69–91.44) and 79.44% (95% CI: 72.67–86.22) respectively, suggesting significant heterogeneity in sensitivity and specificity. Therefore, meta-regression analysis and subgroup analysis were used to explore potential sources of heterogeneity in sensitivity and specificity. We found that ethnicity, cancer type, normalizer, sample type, and the number of cases and controls had great influence on inter-study heterogeneity, which can be seen in Figure 9. Therefore, we then conducted subgroup analyses of these factors. All results are presented in Table 4. The pooled PLR and NLR were 3.57 (95% CI: 2.85–4.47) and 0.32 (95% CI: 0.26–0.40), respectively. The DOR was 10.98 (95% CI: 7.55–15.98). The area under the SROC curve was 0.84 (95% CI: 0.80–0.87). The hierarchical summary operating point estimate of sensitivity and specificity were 0.74 (95% CI: 0.68–0.79) and 0.79 (95% CI: 0.74–0.83), respectively. The estimated value of β was −0.087 (95% CI: −0.55–0.38), the value of z was −0.37, and the *P*-value was 0.75, implying that the SROC curve was not symmetric. The value of lambda was 2.41 (95% CI: 2.03–2.79). Furthermore, Fagan's nomogram was used to determine post-test probabilities resulting from different pre-test probabilities to explore the clinical value of miR-210. As shown in Figure 7, when miR-210 assays were tested for all individuals with a pre-test probability of 50% to get cancer, a positive result would increase the post-test probability of having cancer to 78%, while a negative result would decrease the post-test probability to 25%. All of these results revealed that miR-210 had relatively moderate accuracy in distinguishing cancer patients from all other individuals.

Several limitations of this study should still be highlighted for a comprehensive and synthetic interpretation. First, a majority of eligible studies did not mention the stage of cancer. Therefore, the present study did not evaluate differences in the diagnostic accuracy of miR-210 in various cancers at different stages. Second, not all of the studies reported a cutoff value for miR-210, which largely contributed to potential sources of heterogeneity. Third, the sample types were inconsistent and included serum (19 studies), sputum (five studies), urine (three studies), pancreatic juice (one study), and fecal matter (one study). Due to the limited study size of each individual study, subgroup analysis by sample type could not be explored. Fourth, the studies included were not randomly compared tests, implying that subjective judgement may exist, possibly leading to a low study quality QUADAS-2 score. Despite these limitations, our study is the most comprehensive meta-analysis to evaluate the diagnostic value of miR-210 for patients with various cancers.

Conclusion

To summarize, the results of this meta-analysis revealed that miR-210 had relatively moderate accuracy in distinguishing patients with various cancers from all other individuals, and provided comprehensive and synthetic evidence of miR-210 as a potential noninvasive biomarker in the detection and diagnosis of cancer. However, well-designed prospective studies with large sample sizes of different groups of the population are urgently needed to confirm our findings.

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Disclosure

The authors report no conflicts of interest in this work.

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