

MicroRNA-195 as a diagnostic biomarker in human cancer detection: A meta-analysis

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Received February 2, 2018; Accepted September 13, 2018

DOI: 10.3892/ol.2018.9489

Abstract. MicroRNAs (miRNAs/miRs) show great promise as novel cancer biomarkers. Several studies have revealed an association between abnormal miRNA expression and the risk of various cancer types. However, the diagnostic accuracy and reliability of miRNAs remains unclear. The present meta-analysis was performed to summarize the overall diagnostic performance of miR-195 for cancer. The PubMed, Cochrane Library, Wanfang and China National Knowledge Infrastructure databases were searched for associated literature published until December 10, 2017. Eligible studies were selected using multiple search strategies based on study selection criteria. Measures, including sensitivity and specificity, of the performance of miR-195 as a cancer diagnostic tool were pooled using bivariate meta-analysis models. All analyses were performed using Stata 14.0. The pooled analysis included 8 studies comprising 735 cases and 547 controls. The pooled diagnostic results calculated from all studies were as follows: Sensitivity, 0.79 [95% confidence interval (CI), 0.69-0.87]; specificity, 0.84 (95% CI, 0.68-0.93); positive likelihood ratio, 4.9 (95% CI, 2.50-9.50); negative likelihood ratio, 0.25 (95% CI, 0.18-0.35); diagnostic odds ratio, 20 (95% CI, 10.00-38.00); and area under the curve, 0.87 (95% CI, 0.84-0.90). Deeks' funnel plot asymmetry test suggested no potential publication bias ($P=0.53$). The present meta-analysis indicated that miR-195 could be a reliable non-invasive biomarker for the diagnosis of cancer. Further large-scale prospective studies are necessary to confirm the present findings and the clinical value of miR-195 for future diagnostics.

Introduction

Cancer is a substantial health and economic burden to humans. Globally, there is an annual increase in the incidence of cancer and its associated mortality rate (1). In 2017, it was estimated that there would be ~1,688,780 new cancer cases and 600,920 cancer-related mortalities in the United States alone (2). Biomarkers that may assist with the clinical diagnosis of various tumors and the assessment of prognosis are being investigated. To date, microRNAs (miRNAs/miRs) have received considerable attention in research and are viewed as potential biomarkers for the early detection and diagnosis of cancer.

miRNAs are a class of small endogenous non-coding regulatory RNAs that are 18-25 nucleotides in length; they serve important roles in post-transcriptional gene regulation and are strongly linked to biological processes, including cell proliferation and metastasis (3-5). Accumulating studies have demonstrated that miRNAs can function as tumor suppressors or as oncogenes by targeting genes involved in tumor cell differentiation, proliferation, apoptosis and metastasis (6). Growing evidence also suggests that miRNAs may act as novel and non-invasive biomarkers for diagnosing a range of cancer types at an early stage (7-11).

miR-195 is located on chromosome 17p13.1, a region frequently deleted in human cancer (12). Studies have suggested that abnormal expression of miR-195 serves a critical role in tumorigenesis in bladder, stomach, thyroid, colorectal, prostate and cervical cancer types, as well as in hepatocellular carcinoma, glioblastoma, tongue squamous cell carcinoma, esophageal squamous cell carcinoma and osteosarcoma (13-23). More importantly, miR-195 has been consistently detected in bodily fluids, including blood and saliva, in cancer patients, suggesting that it may be valuable as a non-invasive biomarker for cancer diagnosis and detection (12,24-29). However, the diagnostic value of miR-195 remains uncertain. No meta-analyses of the association between miR-195 expression and cancer diagnosis and detection have been published. Therefore, a quantitative meta-analysis to clarify the diagnostic value of miR-195 expression in human cancer was performed in the present study.

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Key words: microRNA-195, cancer, diagnosis, meta-analysis

Materials and methods

Search strategy and study selection criteria. A meta-analysis was performed based on published guidelines for diagnostic meta-analyses (30). Searches were performed in the PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>), Cochrane Library (<https://www.cochranelibrary.com/>), Wanfang (<http://www.wanfangdata.com.cn/index.html>) and China National Knowledge Infrastructure databases (<http://cnki.net/>), for eligible articles published up to December 10, 2017. The following search terms were used: ‘Cancer’ or ‘tumor’ or ‘carcinoma’ or ‘neoplasm’ or ‘malignancy’, and ‘miR-195’, and ‘sensitivity’ or ‘specificity’ or ‘ROC curve’ (ROC, receiver operator characteristic). The titles and abstracts of the studies were checked, and the full texts were scanned for relevance by two investigators independently based on their titles and abstracts, following which full texts were perused for potential eligibility. The following article inclusion criteria were used: i) Test indices for diagnosis [sensitivity, specificity and area under the curve (AUC)] were provided or could be calculated from the available data; ii) population and control group(s) were explicitly defined; iii) the diagnostic value of miR-195 for detecting cancer was assessed; and iv) the study was published in English or Chinese.

Data extraction and quality assessment. The following information from the included studies was recorded by two researchers independently: Name of the first author, year of publication, country, ethnicity of cohort, sample size, specimen and cancer type, detection method, cut-off value, and true-positive, false-positive, true-negative and false-negative numbers. The quality of the diagnostic test studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (<http://www.bristol.ac.uk/population-health-sciences/projects/quadas/>). Specifically, 14 items from the QUADAS checklist were applied to each article, and an answer of ‘Yes’, ‘No’ or ‘Unclear’ was determined. Only ‘Yes’ resulted in a score.

Statistical analysis. Statistical analyses were performed using the Stata 14.0 software (StataCorp, College Station, TX, USA). The bivariate meta-analysis model was used to calculate the relevant measures, including pooled sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio (PLR) and negative likelihood ratio (NLR). Summary receiver operator characteristic (SROC) curve analysis was performed and the AUC was calculated to evaluate the overall diagnostic value of miR-195 in cancer detection and diagnosis. The data were confirmed using a hierarchical summary receiver operating characteristics (HSROC) model. Spearman's correlation [testing that $-1 \leq r \leq 1$, with a permutation test, which compares the sensitivity and (1-specificity)] and ROC plane analyses were conducted to assess the heterogeneity of threshold effects. The heterogeneity of non-threshold effects was assessed by the Cochran's Q and inconsistency index (I^2) tests (31). $P < 0.10$ for the Cochran's Q test or $I^2 > 50\%$ indicated obvious heterogeneity between the studies (32). Fagan's nomogram was used to certify associations between the pre-test probability, the likelihood ratio and the post-test probability. The publication bias was tested using Deeks' funnel plots (33).

Table I. Summary of information of the included studies.

First author	Publication year	Country	Ethnicity	Cancer type	Sample type	Test method	Cut-off	Cases/controls	TP	FP	FN	TN	QUADAS-2 score	(Refs.)
Heneghan <i>et al</i>	2010	Ireland	Caucasian	BRC	Serum	RT-qPCR	NA	83/63	73	6	10	57	6	(25)
Zhu <i>et al</i>	2013	China	Asian	BRC	Serum	RT-qPCR	NA	20/10	17	3	3	7	4	(24)
Zhao <i>et al</i>	2014	China	Asian	BRC	Serum	RT-qPCR	0.505	210/102	145	11	65	91	5	(29)
Motawi <i>et al</i>	2015	Egypt	Caucasian	HCC	Serum	RT-qPCR	0.77	112/42	75	10	37	32	6	(26)
Su <i>et al</i>	2016	China	Asian	NSCLC	Plasma	RT-qPCR	NA	100/100	78	14	22	86	5	(12)
Yang <i>et al</i>	2016	China	Asian	CRC	Tissue	RT-qPCR	0.93	50/54	48	40	2	14	4	(27)
Zhang <i>et al</i>	2016	China	Asian	BRC	Serum	RT-qPCR	NA	54/70	38	5	16	65	5	(28)
Hong <i>et al</i>	2018	China	Asian	AML	Serum	RT-qPCR	2.09	106/106	73	4	33	102	6	(34)

TP, true-positive; FP, false-positive; FN, false-negative; TN, true-negative; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies 2; BRC, breast cancer; HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; AML, acute myeloid leukemia; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; NA, not available.

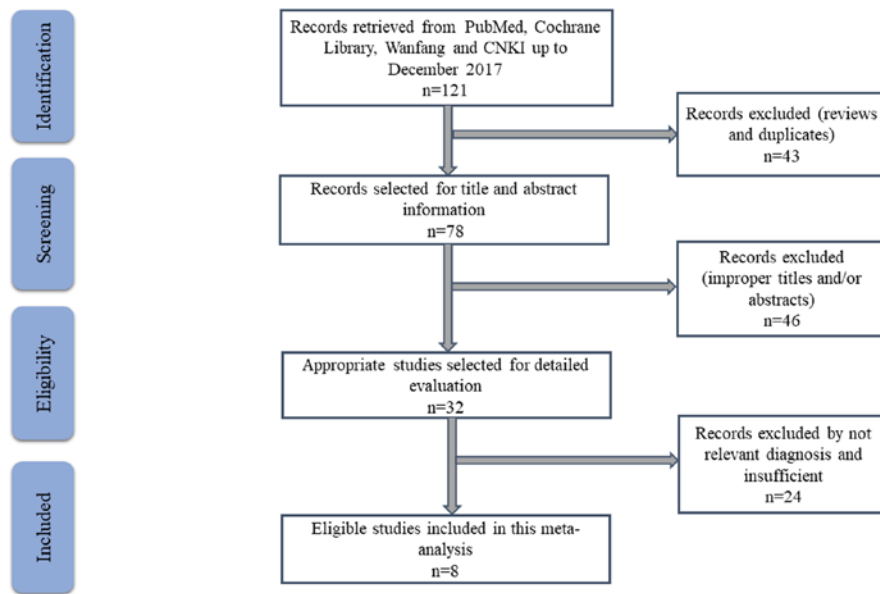


Figure 1. Flow diagram of the study selection and inclusion process. CNKI, China National Knowledge Infrastructure.

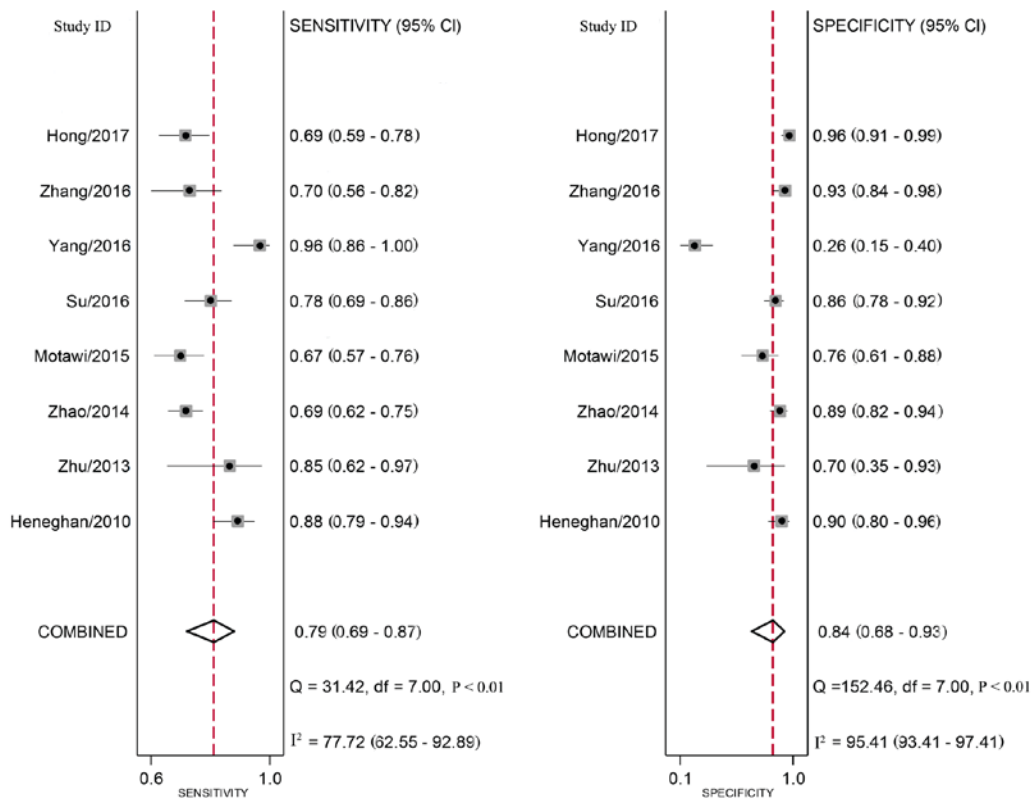


Figure 2. Forest plots of the pooled sensitivity and specificity results for the 8 included studies. CI, confidence interval; Q, Cochran's Q value; DF, degrees of freedom; I², inconsistency index.

Results

Study selection and characteristics of included studies. Of 121 published articles that were determined using the stated search terms in the aforementioned databases, 8 studies (12,24-29,34) met the inclusion criteria for meta-analysis (Fig. 1). Details about the included subjects (546 cases and 547 controls) are displayed in Table I. In total, 4 studies focused on breast

cancer, and 1 each on hepatic carcinoma, colorectal cancer, non-small cell lung cancer and acute myeloid leukemia. The miR-195 expression was assessed using reverse transcription-quantitative polymerase chain reaction methods in serum (n=6), plasma (n=1) or tissue (n=1).

Quality assessment. The methodological quality of diagnosis in the present study was assessed using the QUADAS-2

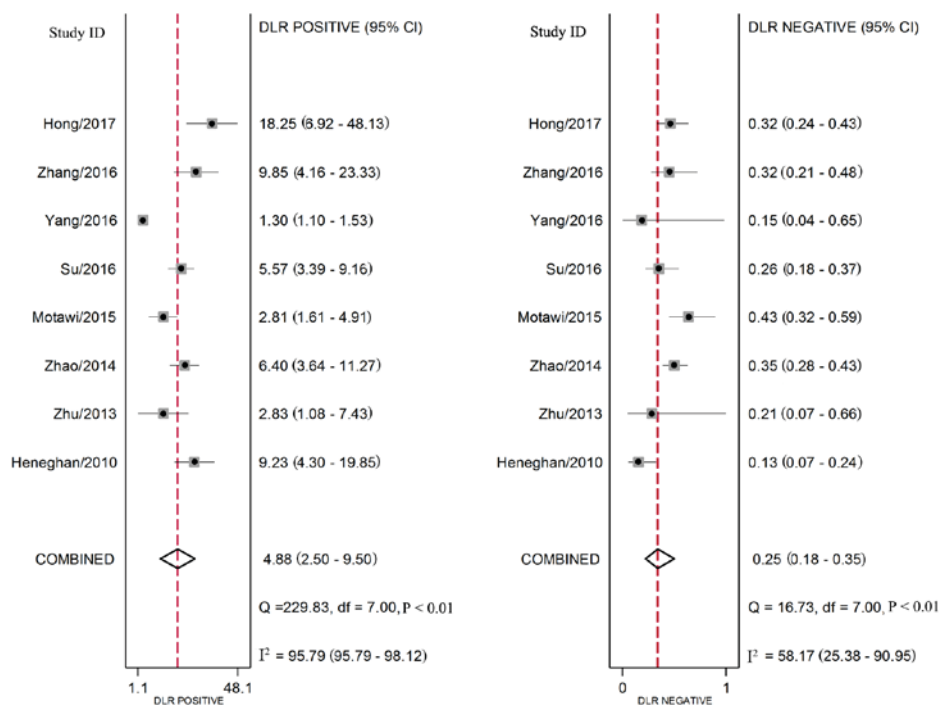


Figure 3. Forest plots of the positive and negative likelihood ratios for microRNA-195 in the diagnosis of cancer. CI, confidence interval; Q, Cochran's Q value; DF, degrees of freedom; I^2 , inconsistency index; DLR, diagnostic likelihood ratio.

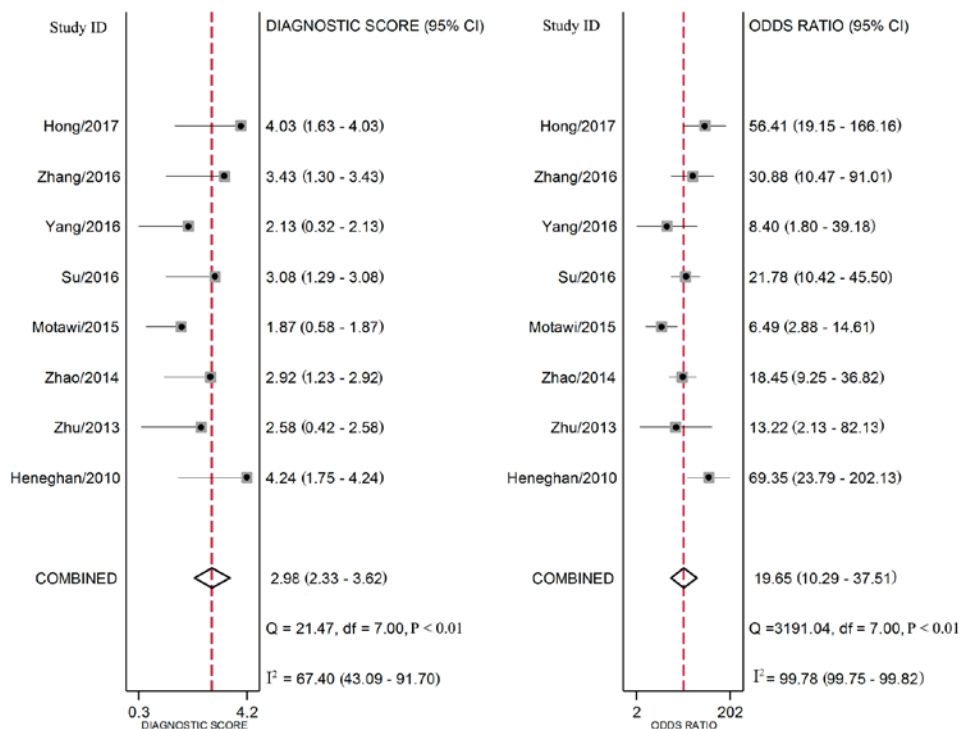


Figure 4. Forest plots of the pooled diagnostic odds ratio for microRNA-195 in the diagnosis of cancer. CI, confidence interval; Q, Cochran's Q value; DF, degrees of freedom; I^2 , inconsistency index.

tool. All the studies were of moderate to high quality, with QUADAS-2 scores between 4 and 7 (Table I), indicating a reliable foundation for the present meta-analysis.

Data analysis. Forest plots of data from the 8 studies on the sensitivity and specificity of miR-195 in diagnosing various

cancer types are shown in Fig. 2. The calculated metrics from all included studies are as follows: Sensitivity 0.79 [95% confidence interval (CI), 0.69-0.87], specificity 0.84 (95% CI, 0.68-0.93), PLR 4.9 (95% CI, 2.50-9.50), NLR 0.25 (95% CI, 0.18-0.35; Fig. 3) and DOR 20 (95% CI, 10.00-38.00; Fig. 4). The overall SROC curve for the 8 included studies is shown

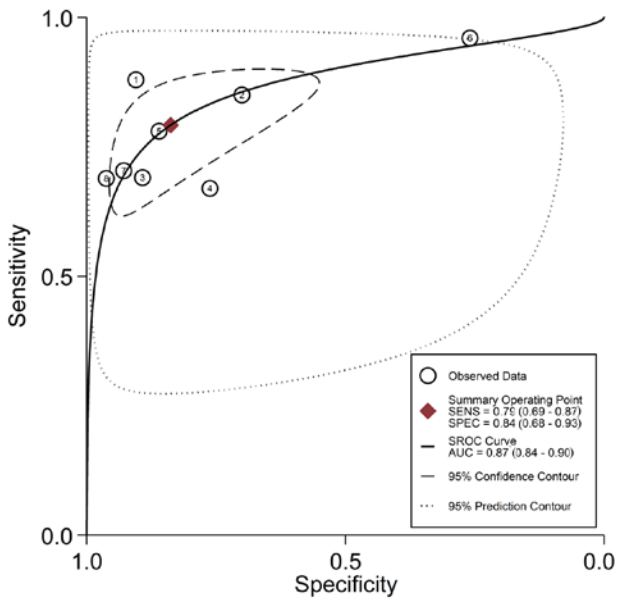


Figure 5. SROC curve with pooled estimates of sensitivity, specificity and area under the curve. SROC, summary receiver operating characteristic; AUC, area under the curve; SENS, sensitivity; SPEC, specificity.

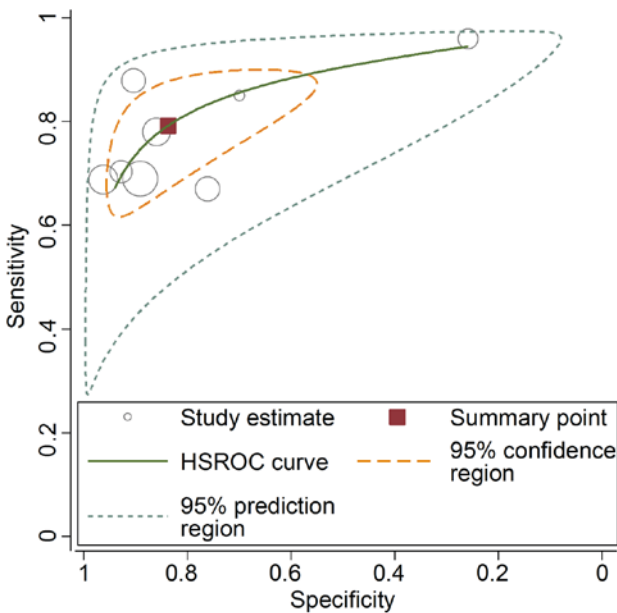


Figure 6. HSROC curve for microRNA-195 in the diagnosis of cancer. HSROC, hierarchical summary operating characteristic.

in Fig. 5. The AUC of miR-195 was 0.87 (95% CI, 0.84-0.90). These results indicate that miR-195 differentiates cancer patients from controls with high accuracy. The HSROC curve of the included studies was in line with the results from the bivariate model (Fig. 6). The value of β (a scale of parameter, which indicated the asymmetry of the curve) was 0.579 (95% CI, -0.128-1.286) and the P-value was 0.108, which indicated that the HSROC was symmetrical. The value of γ (the statistical value representing the accuracy of the diagnostic tests) was 3.015 (95% CI, 2.490-3.539), which indicated that miR-195 had high accuracy in differentiating patients with cancer from control patients. In order to assess the clinical

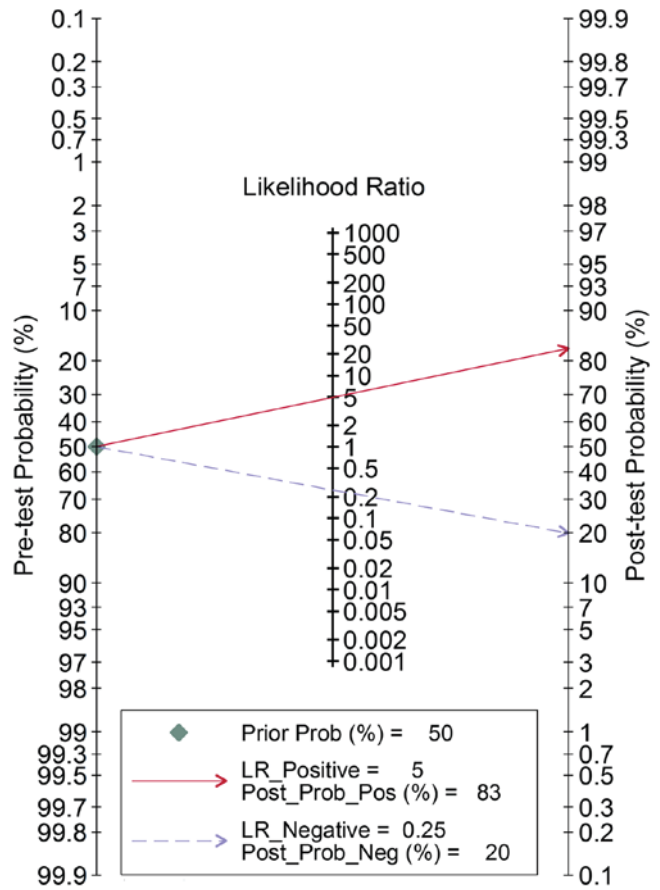


Figure 7. Fagan's nomogram for assessing the post-test probabilities. LR, likelihood ratio.

utility of the index test, Fagan's nomogram was used to predict the increasing inerrability of a positive diagnosis by estimating post-test probabilities. As shown in Fig. 7, when miR-195 was tested in all individuals with a pre-test probability of cancer of 50%, a positive result improved the post-test probability of having cancer to 83%, while a negative result dropped the post-test probability to 20%. Combined, the results indicated that miR-195 displays a moderate accuracy for distinguishing patients with cancer from all individuals.

Influence analysis and robustness tests. Goodness-of-fit (Fig. 8A) and bivariate normality (Fig. 8B) analyses demonstrated that the bivariate model was moderately robust. Influence analysis (Fig. 8C) and outlier detection (Fig. 8D) only identified 1 outlier. Exclusion of the outlier gave rise to small changes to the present analysis results, with the overall metrics varying as follows: Sensitivity decreased from 0.79 to 0.75, specificity increased from 0.84 to 0.89, PLR increased from 4.9 to 6.7, NLR increased from 0.25 to 0.29, DOR increased from 20 to 24 and AUC increased from 0.87 to 0.88. The Deeks' funnel plot asymmetry test suggested no significant publication bias (P=0.53; Fig. 9). The tests confirm the robustness of the present results in the pooled analysis.

Threshold effect and heterogeneity. In the present analysis, the ROC plane revealed a non-typical shoulder arm appearance

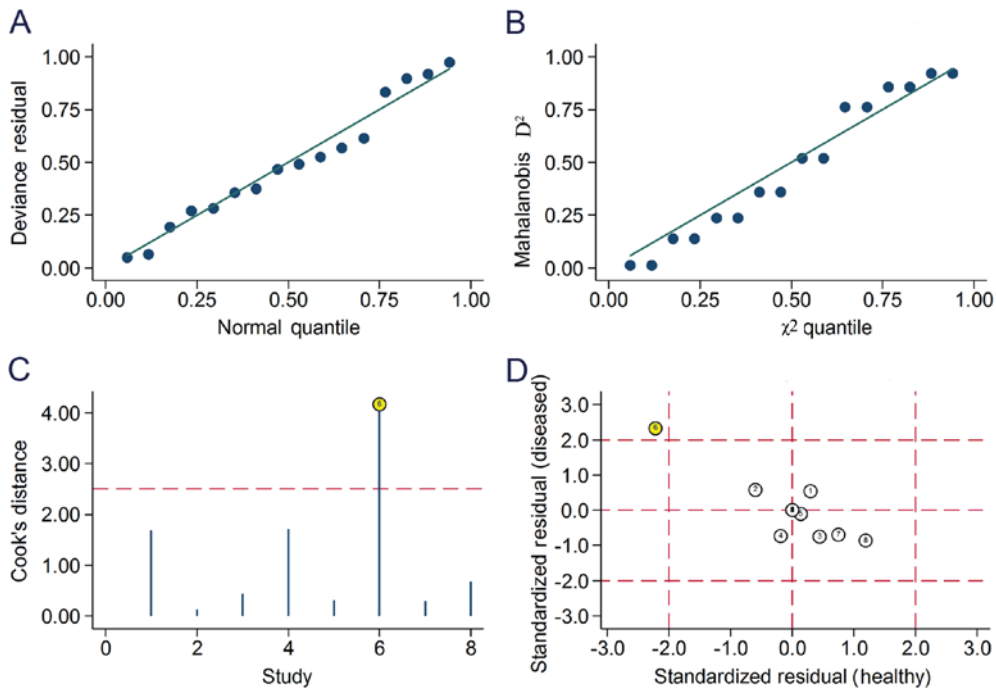


Figure 8. Graphs of sensitivity analyses: (A) goodness-of-fit, (B) bivariate normality, (C) influence analysis and (D) outlier detection. The yellow point represents the outlier, which was excluded.

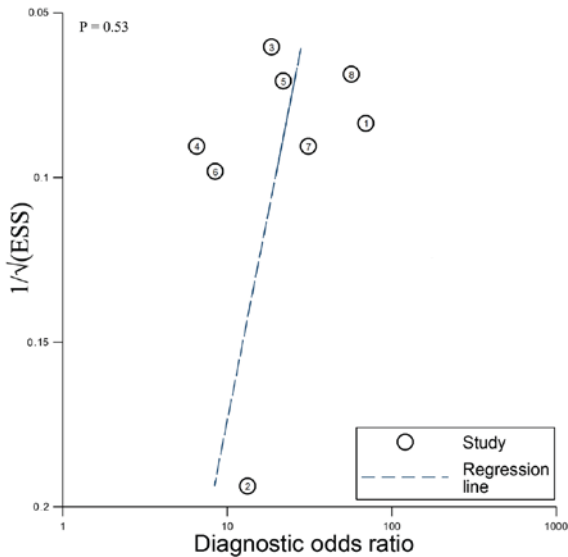


Figure 9. Graph of Deek's funnel plot asymmetry test. ESS, effective sample size.

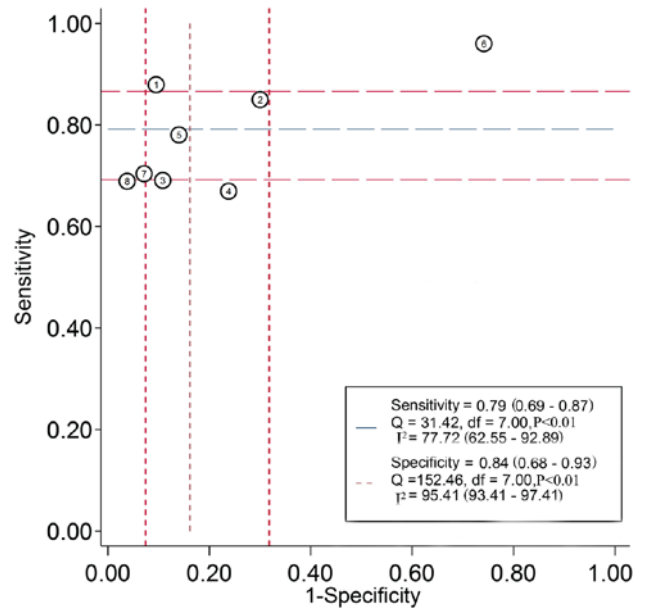


Figure 10. ROC space for the assessment of the threshold effect of microRNA-195. ROC, receiver operating characteristic; Q, Cochran's Q value; DF, degrees of freedom; I², inconsistency index.

suggesting that there was no threshold effect (Fig. 10). The calculated Spearman's correlation coefficient was -0.81 (P=0.66), also indicating no threshold effect. An I² value of 98% indicated high heterogeneity. Due to only 8 studies being included in the present meta-analysis, subgroup and meta-regression analyses could not be performed to investigate the sources of heterogeneity.

Discussion

The initial diagnosis of malignant tumors currently involves use of screening endoscopy, random tissue biopsies and exfoliative

cytological examination. The first two methods are invasive and uncomfortable, and exhibit a low sensitivity, which limits their application in the early diagnosis of cancer due to issues with inter-observer reproducibility (35). Therefore, there is an urgent requirement for reliable biomarkers that require minimally invasive sampling to detect the presence of malignant tumor tissues.

The present study describes the first meta-analysis to be performed for the evaluation of the diagnostic value of

miR-195 in cancer detection. An AUC of 0.87 (95% CI, 0.84-0.90), with a sensitivity of 0.79 (95% CI, 0.69-0.87) and a specificity of 0.84 (95% CI, 0.68-0.93), demonstrated that miR-195 could be used as a novel biomarker for the detection of cancer in patients. In the present analysis, the pooled DOR of 20 (95% CI, 10.00-38.00) suggested that use of miR-195 for cancer diagnosis is credible.

The PLRs and NLRs also reflected the diagnostic accuracy of miR-195. In the present analysis, the pooled PLR was 4.9 (95% CI, 2.50-9.50) and the NLR was 0.25 (95% CI, 0.18-0.35), reflecting the fact that patients with cancer had a 4.9-fold higher probability of being miR-195-positive compared with control patients, and 25% of all individuals were negative. Fagan's nomogram revealed that when a pre-test probability of 50% was specified, the positive post-test probability would increase to 83% with a PLR of 5, and the negative post-test probability would decrease to 20% with a NLR of 0.25. The results suggest that miR-195 is reliable in cancer detection and diagnosis.

There was heterogeneity among the studies included in the present meta-analysis due to the existence of other confounding factors. In the present analysis, the Spearman's rank correlation test was used to analyze the threshold effect and a correlation coefficient of -0.81 ($P=0.66$) indicated that the threshold effect was not a major source of heterogeneity. However, meta-regression analysis and subgroup analysis could not be performed due to the small number of eligible studies. Therefore, factors such as ethnicity and the test method were not investigated as potential sources of variance.

The role of long non-coding RNAs, including miRNA-210, plasmacytoma variant translocation 1 gene and metastasis-associated lung adenocarcinoma transcript-1, as molecular diagnostic and prognostic markers for cancer, has been investigated by previous meta-analyses (36-38). To search for a suitable diagnostic marker, the diagnostic value of miR-195 expression in human cancer was addressed. The present meta-analysis was the first to investigate miR-195 expression and cancer detection using published data.

The present study was restricted by several limitations: First, the numbers of studies available and participants included were small; second, a high proportion of data was from Chinese populations, which may cause ethnicity bias; third, the overall cut-off value for the miR-195 test could not be determined as different cut-off values were adopted in each study; fourth, the present analysis was retrospective, which may limit its possible conclusions due to selection bias; fifth, only studies published in English or Chinese were included, creating the possibility that studies published in other languages were neglected; and finally, it is difficult to detect cancer early using just a single marker, and as such, a combination of several markers may improve the accuracy.

In conclusion, the results of the present meta-analysis indicate that miR-195 has a moderate diagnostic value in distinguishing cancer patients from healthy controls. The data suggest that miR-195 may supplement and improve the accuracy of existing diagnostic methods. Future studies should concentrate on the combined use of miR-195 with other miRNAs to improve the diagnostic accuracy of human cancer detection.

Acknowledgements

Not applicable.

Funding

The present study was supported by the fund of 'San-ming' Project of Medicine in Shenzhen (grant no. SZSM201612010), the Shenzhen Foundation of Science and Technology International Cooperative Project (grant no. GJHZ20160301164637011), and the Shenzhen Health and Family Planning Commission Scientific Research Project (grant nos. 201601023 and 201601025).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

BL and YL conducted the conception and design, acquisition of data, analysis of data and drafting the manuscript. XL and YP performed the acquisition of data, and the drafting and revising of the manuscript. LY and FL assisted with acquisition of data. RG assisted with the statistical analysis. WC and JH participated in the design and coordination of the study and assisted to revise the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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