

Review Article

Clinical value of microRNA-143 in the diagnosis of human cancers: a meta-analysis

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Abstract: Previous studies have found that microRNA-143 (miRNA-143 or miR-143) is abnormally expressed in various cancers, indicating that miR-143 may serve as a novel biomarker for cancer diagnosis. However, the diagnostic value of miR-143 in different cancers remains inconsistent. Based on evidence-based medicine, for the first time, the present meta-analysis aimed to explore the accuracy of miR-143 in cancer diagnosis. A total of seven relevant studies were selected, according to inclusion exclusion criteria, from online databases. Overall results of pooled analysis were: sensitivity 0.78 (95% CI = 0.74-0.82), specificity 0.85 (95% CI = 0.81-0.88), positive likelihood ratio (PLR) 5.17 (95% CI = 4.02-6.64), negative likelihood (NLR) 0.26 (95% CI = 0.21-0.30), diagnostic odds ratio (DOR) 20.25 (95% CI = 14.21-28.87), and area under the curve (AUC) 0.88 (95% CI = 0.85-0.91). No potential publication bias was detected based on results of Deeks' funnel plot asymmetry test ($P = 0.46$). The present study revealed that miRNA-143 had moderate accuracy in the diagnosis of different cancers. Nevertheless, further studies with large sample sizes and comprehensive experiments are required to confirm present conclusions.

Keywords: microRNA-143, cancer, diagnosis, meta-analysis

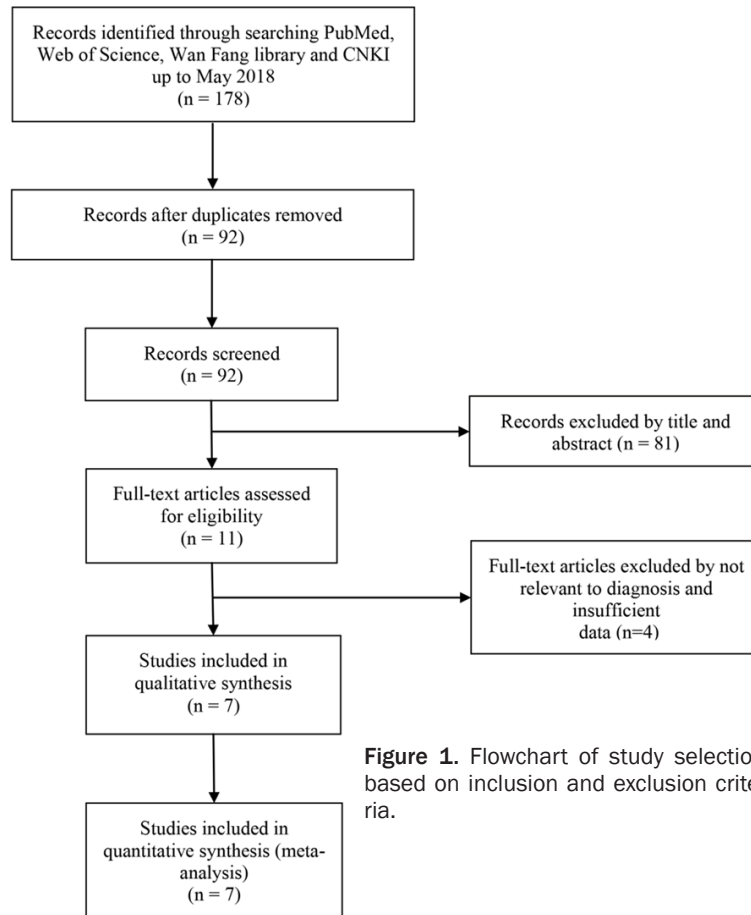
Introduction

Cancer has become one of the most serious threats to public health around the world. About 14.1 million people were expected to develop cancer annually, worldwide, according to a 2014 investigation [1]. Cancer has brought considerable economic burden to patients and to society. Many cancer patients have complained about experiencing some form of financial hardship, failing to continue using recommended prescription drugs due to high costs [2]. Apparently, this is a great obstacle for public health. Although plenty of effective options for cancer treatment have been provided, such as surgery, radiotherapy, chemotherapy, and immunotherapeutic and molecularly targeted agents [3], the prognosis of cancer patients is not ideal, especially for those with advanced stages. Early diagnosis of cancer is essential in improving patient outcome and life quality. Therefore, patients with cancer can benefit

greatly from the search for an effective early detection tool. The discovery of novel tumor markers for early diagnosis is urgently needed.

MicroRNAs (miRNAs), as endogenous ncRNAs with 19 to 25 nucleotides, are involved in many important biological functions. They participate in many cellular processes, from the genetic level, by inhibiting the stability and translation of messenger RNAs (mRNAs) [4, 5]. Mounting studies have revealed that almost all types of cancer present a specific profile of upregulated or downregulated miRNAs [6]. Moreover, dysregulation of miRNA expression could occur in the early stages of tumorigenesis [7], indicating that the measurement of circulating miRNA expression levels can be applied in early cancer detection [8].

MiR-143, located at chromosome 5q32, has been found to be frequently downregulated in primary tumor samples deriving from pancreatic adenocarcinoma [9], breast carcinoma [10],



non-small cell lung cancer [11, 12], bladder cancer [13-15], prostate cancer [16, 17], and many other cancers. Accumulating studies have demonstrated that miR-143 can inhibit proliferation, invasion, and migration of cancer cells while promoting apoptosis of cancer cells by directly targeting several mRNAs, including HK2, MMPs, Bcl-2, and P53 [18-21]. Additionally, some researchers have suggested that miR-143 could be used as a new biomarker for cancer screening. Therefore, research in this field has generated great interest and enthusiasm.

The present meta-analysis was performed to summarize the potential diagnostic value of miR-143 in different cancer patients, further exploring whether it could be used in clinical practice.

Materials and methods

Search strategy and study selection criteria

PubMed, Web of Science, and two Chinese databases, Wan Fang library and CNKI (updat-

ed to May 2018), were searched using the following keywords: “cancer or tumor or carcinoma or neoplasm or malignancy” and “miRNA-143 or miR-143 or microRNA-143” and “sensitivity or specificity or ROC curve or accuracy or AUC or diagnosis”. Three independent investigators (HAB, LYH, and HK) reviewed the titles and abstracts of these studies and browsed full texts. Corresponding qualified studies were selected according to the following criteria: (1) Studies utilized the “gold standard” to diagnose cancer; (2) Recruited enough healthy volunteers or patients with benign diseases to serve as the control group; (3) Sufficiently relevant data were provided to calculate the sensitivity and specificity of miR-143; and (4) Published in English or Chinese. Studies with the following characteristics were excluded: (1) Not enough reliable information concerning the diagnostic effects of miR-

143; (2) Similar repeated studies; and (3) Review articles, letters, and commentaries.

Data extraction and quality assessment

Extraction of relevant data for this meta-analysis was performed by three independent investigators. After comparison, the data was unified. Data was extracted into a table including the following characteristics of the original study: first author, year of publication, country, ethnicity, sample size, specimen and cancer type, detection method, cut-off value, true positive (TP), false positive (FP), true negative (TN), and false negative (FN). QUADAS-2 was used to systematically evaluate the quality of this diagnostic meta-analysis.

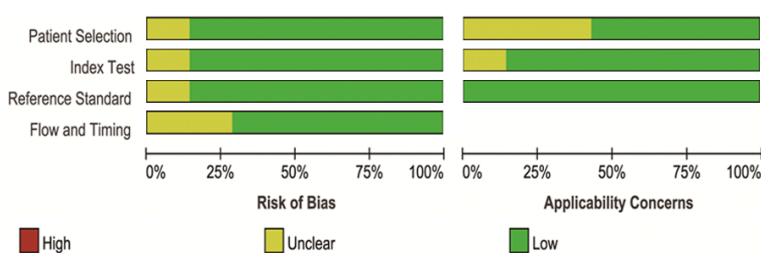
Statistical analysis

After data extraction, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were obtained through integration and calculation of key data, presented as a forest plot in combination with the

Table 1. Characteristics of included studies that reported using miR-143 as diagnostic biomarkers of various cancers

First author	Year	Country	Ethnicity	Cancer type	Sample type	Test method	Cutoff	Cases/controls	TP	FP	FN	TN
Mamdouh et al.	2017	Egypt	Caucasian	HCC	serum	qRT-PCR	3.177	50/20	38	4	12	16
Elhamamsy et al.	2017	Egypt	Caucasian	AML	plasma	qRT-PCR	0.65	65/50	57	10	8	40
Zhang et al.	2017	China	Asian	HCC	serum	qRT-PCR	NA	131/122	105	21	26	101
Motawi et al.	2016	Egypt	Caucasian	BC	plasma	qRT-PCR	0.164	70/62	55	4	15	58
Debernardi et al.	2015	UK	Caucasian	PDAC	urine	qRT-PCR	NA	6/26	5	3	1	23
Zhang et al.	2014	China	Asian	HCC	serum	qRT-PCR	2.21	95/127	69	22	26	105
Zeng et al.	2013	China	Asian	NSCLC	PBMC	qRT-PCR	0.628	64/26	48	2	16	24

HCC: hepatocellular carcinoma; PDAC: pancreatic ductal adenocarcinoma; AML: acute myeloid leukemia; BC: bladder cancer; NSCLC: non-small cell lung cancer; PBMC: peripheral blood mononuclear cell; qRT-PCR: quantitative reverse transcription polymerase chain reaction; NA: not available; TP: true positive; FP: false positive; FN: false negative; TN: true negative.

**Figure 2.** Quality of selected studies according to QUADAS-2 guidelines.

95% confidence interval. A random effects model was used on Stata 14.0 (Stata, College Station, TX, USA) to pool extracted data. Next, the receiver operator characteristic (SROC) curve concerning the diagnostic accuracy of miR-143 was obtained. Points on the curve corresponded to the sensitivity and specificity of extracted data, while the area under the ROC curve (AUC) was positively correlated with diagnostic accuracy [22]. Cochran-Q and Inconsistency index (I^2) tests were conducted as key indicators for evaluation of heterogeneity. When I^2 values were higher than 50%, significant heterogeneity was suspected in included studies [23]. Fagan's Nomogram was executed to more intuitively understand the diagnostic utility of miR-143, while Deeks' funnel plots were used to estimate publication bias.

Results

Study characteristics

After searching several large databases (PubMed, Web of Science, Wan Fang library, and CNKI) and further exclusion, a total of 7

studies were included [24-30] (481 patients, 433 controls) for pooled analysis. The process literature selection is shown in **Figure 1**. Main features of the seven studies are shown in **Table 1**. Reverse transcription polymerase chain reaction (RT-PCR) was used to detect expression of miR-143 from serum, urine, plasma, and peripheral blood mononuclear cells.

Quality assessment

Details of QUADAS-2 study quality assessment are shown in **Figure 2**. Most articles included in the current meta-analysis met most of the items in QUADAS-2 [31], indicating that the overall quality of included studies was moderately high.

Data analysis

Figure 3 shows forest plots for the sensitivity and specificity of the seven included studies regarding miR-143 in cancer diagnosis. Pooled sensitivity was 0.78 (95% CI = 0.74-0.82) and pooled specificity was 0.85 (95% CI = 0.81-0.88). Heterogeneity among the seven studies for sensitivity and specificity was (I^2 = 1.78%, 95% CI = 0.00%-100.00%) and (I^2 = 16.09%, 95% CI = 0.00%-78.13%), respectively. No significant heterogeneity was found. In addition, pooled forest plots for PLR, NLR, and DOR were obtained. Corresponding consolidation results were: 5.17 (95% CI = 4.02-6.64), 0.26 (95% CI

MicroRNA-143 in cancer diagnosis

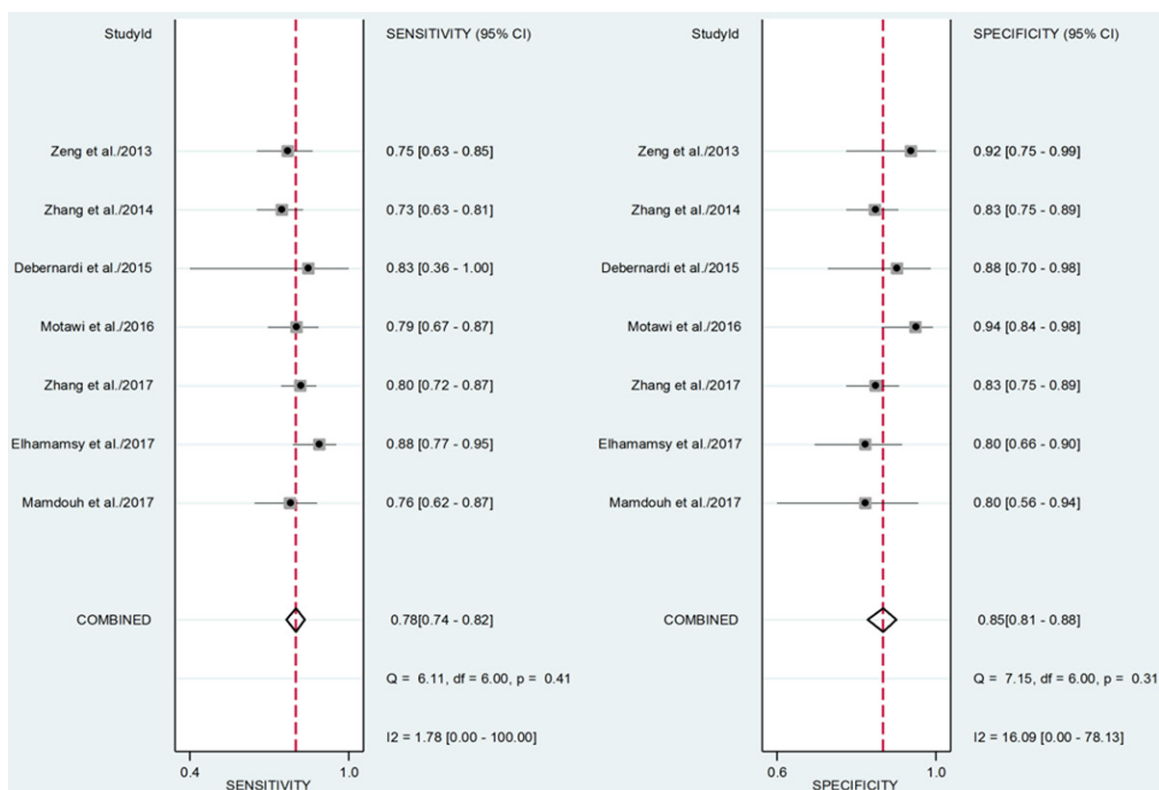


Figure 3. Forest plots of sensitivity and specificity for miR-143 in the diagnosis of cancer.

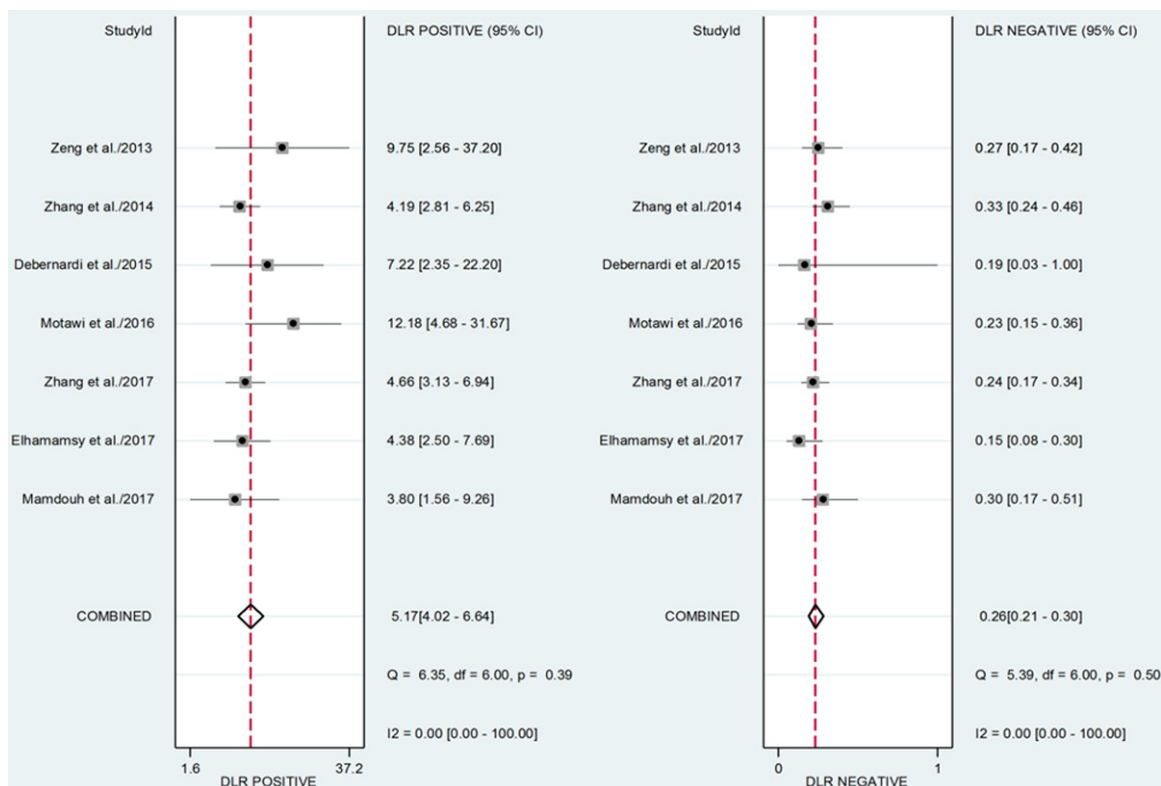


Figure 4. Forest plots of positive likelihood ratio and negative likelihood ratio for miR-143 in the diagnosis of cancer.

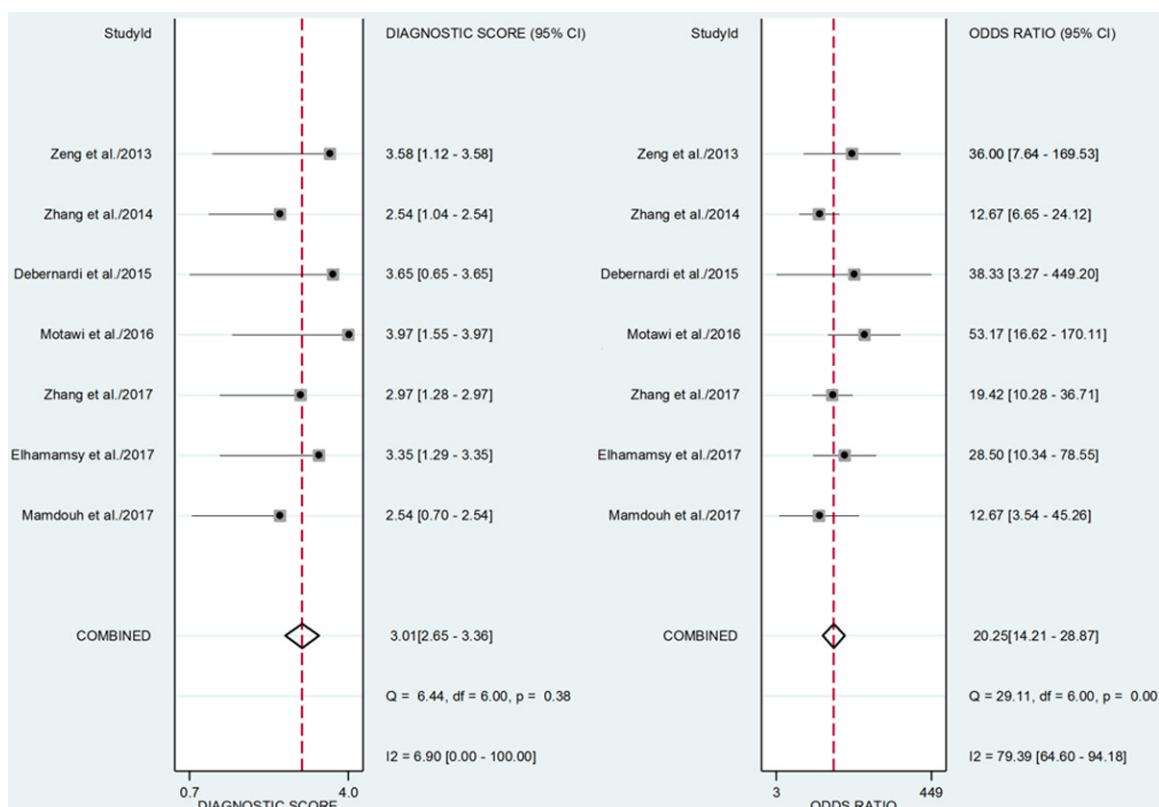


Figure 5. Forest plots of diagnostic odds ratio for miR-143 in the diagnosis of cancer.

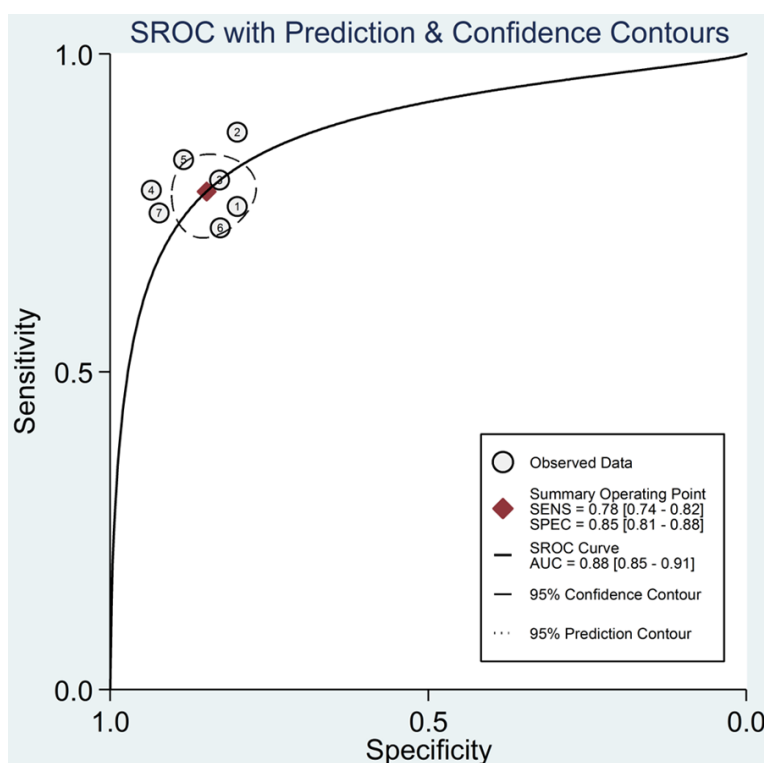


Figure 6. Summary receiver operating characteristic curve for miR-143 in the diagnosis of cancer.

= 0.21-0.30), and 20.25 (95% CI = 14.21-28.87) (**Figures 4 and 5**). The SROC curve is shown in **Figure 6**. Judging from the final AUC (0.88 [95% CI = 0.85-0.91]), a relatively high diagnostic value of miR-143 could be seen. As shown in Fagan's Nomogram, when given the pre-test probability of 50%, with a positive likelihood ratio of 5 and a negative likelihood ratio of 0.26, the two corresponding post-test probabilities of 84% and 20% were obtained (**Figure 7**). Deeks' funnel plot asymmetry is shown in **Figure 8**, indicating that no significant publication bias was found among studies in this meta-analysis, with P = 0.46.

Heterogeneity

As shown in the forest plots for sensitivity, specificity, PLR,

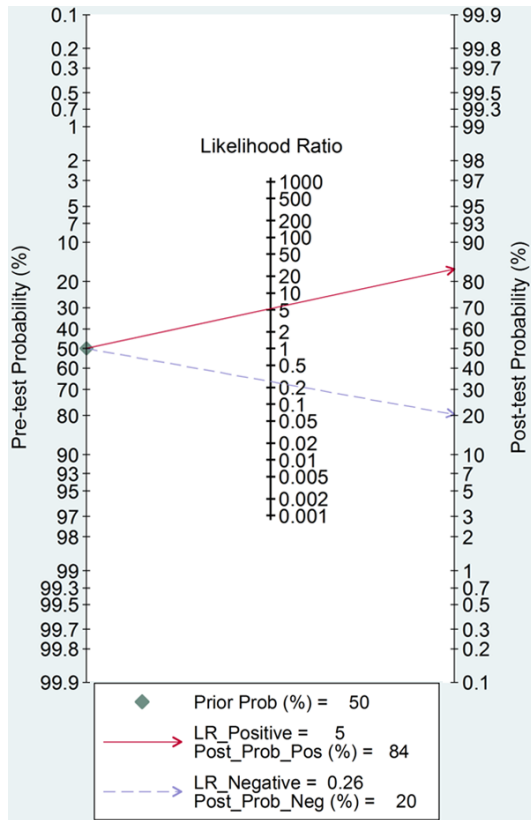


Figure 7. Fagan's nomogram for likelihood ratios.

and NLR, each individual study was relatively neatly arranged on the figure. *P* values of Cochrane Q tests were 0.41 and 0.31 ($P > 0.05$), while corresponding I^2 values were 1.78% and 16.09%. The above results suggest no statistically significant heterogeneity. This meta-analysis was quite small, only including 7 articles. Therefore, meta-regression analysis and subgroup analysis were not necessary.

Discussion

MicroRNAs have been identified as regulators in the life of cancer cells, affecting not only proliferation and migration but also differentiation and apoptosis [5]. Previous studies have reported that miRNAs can act as tumor suppressors or oncogenes. Abnormal expression of miRNAs often prompts development and progression of cancer [32, 33]. Moreover, circulating miRNAs can adapt to many unfavorable physiological conditions and maintain high stability. They can also be easily quantified in paraffin-embedded materials by PCR [34]. Therefore, microRNAs have potential for diagnosis and prediction of biomarkers in tissue

samples, such as serum, plasma, and urine, as routine pathological predictors.

Researchers have done a lot of work to explore the association between aberrant miR-143 expression and cancer. It has been confirmed that miR-143 is involved in the proliferation, invasion, and metastasis of cancer cells [18-21]. Inducing miR-143 expression can block the occurrence of many malignant tumors, such as cervical cancer, gastric cancer, and pancreatic cancer [35-37]. This conclusion has been verified both *in vitro* and *in vivo*. miR-143 is frequently downregulated in various cancers. In other words, miR-143 is expressed in tumor tissues at a lower level than in adjacent normal tissues. Apparently, miR-143 expression is negatively correlated with tumor occurrence and development. Recently, miR-143 has attracted more and more attention as a molecular marker of cancer. The present study is the first meta-analysis on results of individual studies, carefully exploring the accuracy of miR-143 in diagnosis of cancer. Through pooled analysis, some vital conclusions were obtained.

The final summary indexes, AUC of 0.88 (95% CI = 0.85-0.91), sensitivity of 0.78 (95% CI = 0.74-0.82), and specificity of 0.85 (95% CI = 0.81-0.88), indicated that miR-143 was a good biomarker for cancer. Pooled DOR was 20.25 (95% CI = 14.21-28.87), meaning that the level of diagnostic accuracy of miRNA-143 was relatively high. Additionally, more clinically meaningful information from the likelihood ratio (LR) was gathered. Pooled PLR of 5.17 (95% CI = 4.02-6.64) and NLR of 0.26 (95% CI = 0.21-0.30) suggest that cancer patients have a 5.17-fold higher possibility of being miR-143 positive than patients without cancer. The NLR value of 0.26 suggests that the probability of having a negative result for those with cancer is 0.26 times less likely than those without cancer [38].

Post-test probability, obtained by combining the likelihood ratio with pre-test probability, can help judge the application value of miR-143 in tumor diagnosis. Assume that after a clinical assessment, the pretest probability of a person having cancer was 50%. When using miR-143 to further diagnose cancer and getting a positive result, the person's post-test probability of having cancer would rise to 84%. Conversely, if the test result was negative, the probability of having cancer would reduce to 20%. These out-

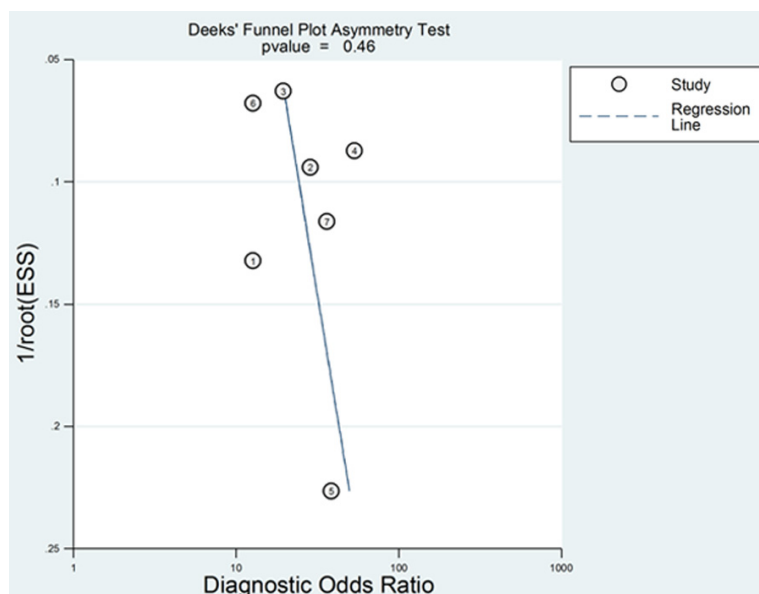


Figure 8. Deeks' funnel plot asymmetry test for assessing publication bias.

comes indicated that miRNA-143 has a stable value in the diagnosis of various tumors.

Heterogeneity is a crucial factor that must be considered, as it may affect the accuracy of this meta-analysis. According to results of Q tests and I^2 index, no obvious statistical heterogeneity was observed. However, Cochran Q test and I^2 index are underpowered in detecting heterogeneity of a small meta-analysis, only included 7 studies (fewer than twenty studies) [39]. Thus, the seven studies in this meta-analysis could not conclusively be proven homogeneous.

There were several limitations to this meta-analysis. First, the limited quantity of studies included might have potentially reduced the reliability of the diagnostic role of miR-143 in various cancers. Second, although no effort was spared in covering all relevant studies, some articles may have still been missed due to negligence. Third, the samples were not only small but often came from the same country. Therefore, more cancer types and more studies from different countries are necessary in the future to confirm the present results. Fourth, failure to obtain original data from the studies may have limited the reliability of miR-143 diagnostic values.

In summary, the present meta-analysis identified that miR-143 has moderate accuracy as a

novel noninvasive biomarker for cancer diagnosis. More extensive prospective studies should be conducted to further validate the diagnosis. In the future, miR-143 may be used as a clinical cancer screening tool, together with some other biomarkers, improving the efficiency of cancer diagnosis.

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Disclosure of conflict of interest

None.

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