

## Original Article

# Significance of microRNA-183 family expression in cancer diagnosis: a meta-analysis

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**Abstract:** Cancer is the third major cause of death in the world and it has turned into an enormous threat to human health. MicroRNAs have been considered as novel and noninvasive biomarkers for human cancer detection. The microRNA-183 (miRNA-183, miR-183) family, consisting of miR-96, miR-182 and miR-183, is considered to be associated with various types of human cancer. However, the diagnostic performance of these miRNAs in human cancer detection failed to reach a consensus. Thus, a meta-analysis was carried out to consolidate the existing findings. Several electronic databases were searched systematically for relevant studies and the pooled results were obtained using the random-effects model. Heterogeneity among individual studies was assessed by the Chi-Square test. A total of 1659 cancer patients and 1457 healthy individuals from 17 articles were included in our meta-analysis. The pooled sensitivity and specificity was 0.69 (95% CI: 0.65-0.73) and 0.82 (95% CI: 0.77-0.86), respectively. The area under the curve (AUC) was 0.80 together with a partial AUC of 0.74. Subgroup analysis indicated that ethnicity, cancer, specimen types and quality score might be potential sources of heterogeneity. In conclusion, the relatively high specificity and AUC suggested that miR-183 family members can be adopted to screen human cancer. However, this conclusion should be confirmed by studies with large sample size and confounding factors should also be controlled in the study.

**Keywords:** microRNAs, microRNA-183 family, cancer, diagnostic value, meta-analysis

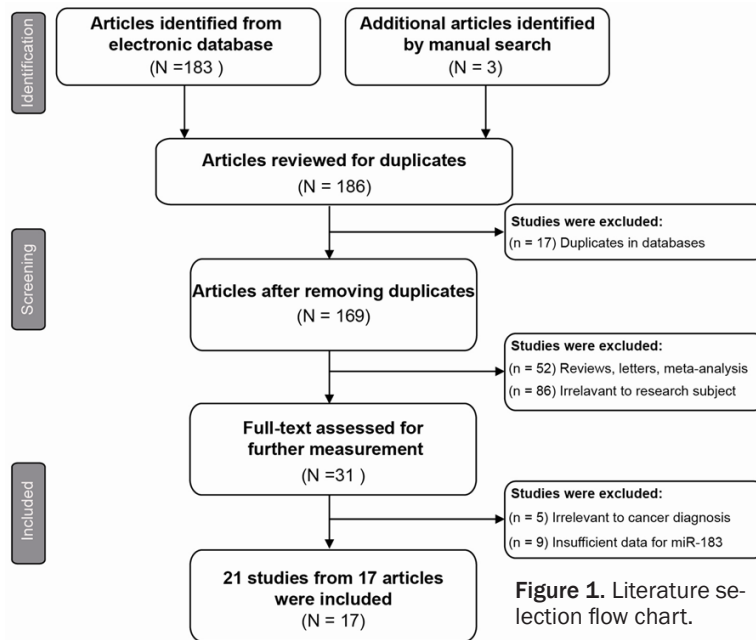
## Introduction

Cancer is the third leading cause of death worldwide and it has turned into a major public health issue [1]. It is estimated that 1,665,540 new cancer cases occurred in the US in 2014 with a number of 585,720 deaths [2]. The number of confirmed human cancer case was 12.7 million in which 7.6 million of people died in 2010 [3-5]. Although human cancer has been associated with high morbidity and mortality, they can be controlled and treated when they are detected at their stages [6]. Therefore, early detection and precise diagnosis of human cancer have significant impact on the survival status of cancer patients. The current gold standard for human cancer diagnose includes histopathological, imageological and microscopic examinations [7]. However, histopathological examination does not enable us to screen some cancer at its early stage such as liver cancer and it is always associated with

manpower issues and risk of patient injuries [8]. In addition, these diagnostic methods are invasive and expensive, particularly for cancer patients in developing countries [9]. Other diagnostic methodologies using biomarkers have not been proved to be as effective as the gold standard methods [10]. Although great achievements have been made in the understanding of tumorigenesis, the progression and development of new cancer diagnostic methods have not been overcome by scientists. As a result, increasing studies should be focused on unfolding novel and noninvasive diagnostic test for early detection of cancer.

According to emerging evidence, microRNAs (miRNAs) have been regarded as noninvasive and efficient biomarkers which could be useful in early cancer detection. MiRNAs are single-stranded RNAs with approximately 22 nucleotides and they constitute a novel class of gene regulators which are found in both animals and

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**Figure 1.** Literature selection flow chart.

Embase, Chinese National Knowledge Infrastructure (CNKI), Web of Science and other databases until July 1, 2015. The following key words were used to search eligible articles: (“microRNA-183” or “miR-183” or “microRNA-182” or “miR-182” or “microRNA-96” or “miR-96”) and (“cancer” or “tumor” or “neoplasms”) and (“diagnosis” or “ROC curve” or “sensitivity” or “specificity”). Apart from that, references of selected articles were screened manually to identify any additional relevant studies to be included in the meta-analysis.

### *Inclusion and exclusion criteria*

plants. The role of miRNAs is regulating gene expressions by binding with specific regions of target miRNAs [11]. MiRNA gene family is composed by the gene miRNA clusters with high homogeneity [12]. Moreover, miRNA can be obtained easily from common specimens such as tissue, plasma, serum and urine, making early cancer diagnose viable without invasion to human body [13].

Among these miRNAs, microRNA-183 (miRNA-183, miR-183) family, consisting of miR-96, miR-182 and miR-183, is considered to have connections with various types of human cancer. Several studies found that miRNA-183 family members directly involved in human cancer processes and they were abnormally expressed in various tumors, such as bladder cancer, breast cancer and lung cancer [14-17]. However, conclusions on the association between miR-183 and tumorigenesis were inconsistent due to the potential heterogeneity caused by different study characteristics. Therefore, this meta-analysis was conducted in order to calculate the pooled diagnostic accuracy of miR-183 for cancer detection.

## Materials and methods

### *Search strategy*

Relevant articles were searched, identified, screened and selected from electronic databases including PubMed, the Cochrane Library,

The following inclusion criteria were set to determine the eligibility of articles to be included in the meta-analysis: (1) studies must focus on the evaluation of miR-183 or miR-182 or miR-96 in cancer diagnosis; (2) Results of sensitivity and specificity must be summarized and presented in the study; and (3) studies must include a control group and a matched case group. Also, the following exclusion criteria were considered: (1) studies focused on survival or prognosis of cancer; (2) conference reports, editorials, letters or reviews; (3) studies containing duplicated or unqualified data.

### *Data extraction and quality assessment*

All the included studies were examined by two independent reviewers. Then relevant data was extracted from these literatures including publication year, author, ethnicity, number and age of patients, specimen types, sensitivity and specificity. If sensitivity and specificity were not given in the study, then relevant calculations were performed based on the receiver operator characteristic (ROC) curves.

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria were adopted to assess the quality of included articles [18]. There are 10 questions used in the QUADAS-2 tool to assess the overall quality of the included studies and all questions should be answered with “yes”, “no”, or “unclear”. Higher scores

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**Table 1.** Main characteristics of the articles included in the meta-analysis

First author	Year	Country	Ethnicity	Case		Control		miR-183 family	Cancer	Specimen	Diagnostic power				SEN	SPE	QUADAS
				N	Age	N	Age				TP	FP	FN	TN			
Hideki et al	2010	Japan	Asian	54	NR	42	NR	miR-96	Bladder cancer	Urine	38	4	16	38	70.40%	90.50%	5
Hideki et al	2010	Japan	Asian	54	NR	42	NR	miR-183	Bladder cancer	Urine	40	12	14	30	74.10%	71.40%	6
Yamada et al	2011	Japan	Asian	100	75	74	45	miR-96	Bladder cancer	Urine	71	8	29	66	71.00%	89.20%	7
Yamada et al	2011	Japan	Asian	100	75	74	45	miR-183	Bladder cancer	Urine	74	17	26	57	74.00%	77.30%	8
Zheng et al	2011	America	Caucasian	74	64	68	61	miR-182	Lung cancer	Plasma	30	6	44	62	40.20%	91.30%	8
Enokida et al	2012	Japan	Asian	85	NR	74	NR	miR-96	Bladder cancer	Urine	60	8	25	66	71.00%	89.20%	7
Enokida et al	2012	Japan	Asian	85	NR	74	NR	miR-183	Bladder cancer	Urine	63	17	22	57	74.00%	77.30%	8
Lee et al	2012	Korea	Asian	44	47	53	47	miR-182	Endometrial cancer	Tissue	32	9	12	44	72.70%	83.00%	7
Lee et al	2012	Korea	Asian	44	47	53	47	miR-183	Endometrial cancer	Tissue	35	12	9	41	79.50%	77.40%	7
Miah et al	2012	England	Caucasian	68	71	53	58	miR-183	Bladder cancer	Urine	36	26	32	27	52.60%	50.00%	7
Liu et al	2012	China	Asian	57	NR	59	NR	miR-183	Liver cancer	Tissue	33	18	24	41	57.90%	69.50%	6
Patterson et al	2012	America	Caucasian	27	39.8	42	46.6	miR-183	Pheochromocytoma	Tissue	22	4	5	38	79.70%	91.20%	7
Torres et al	2013	Italy	Caucasian	73	62.8	31	44.78	miR-182	Endometrial cancer	Tissue	51	8	22	23	70.00%	73.00%	8
Abd et al	2013	Egypt	African	65	54.1	37	50.1	miR-182	Liver cancer	Serum	65	5	0	32	100.00%	86.50%	8
Liang et al	2013	China	Asian	92	NR	49	NR	miR-183	Liver cancer	Tissue	55	4	37	45	59.80%	91.80%	7
Chen et al	2014	China	Asian	109	NR	50	NR	miR-182	Pancreatic cancer	Plasma	70	9	39	41	64.10%	82.60%	8
Marino et al	2014	Brazil	Caucasian	29	53.1	35	53.1	miR-183	Breast cancer	Tissue	22	7	7	28	75.00%	80.00%	8
Chen et al	2015	China	Asian	103	52	135	49	miR-182	Liver cancer	Serum	81	11	22	124	78.60%	91.60%	8
Eissa et al	2015	Egypt	African	94	NR	116	NR	miR-96	Bladder cancer	Urine	72	12	22	104	76.60%	89.40%	9
Eissa et al	2015	Egypt	African	188	NR	180	NR	miR-183	Bladder cancer	Urine	134	20	54	160	71.30%	88.90%	8
Matamala et al	2015	Spain	Caucasian	114	NR	116	NR	miR-96	Breast cancer	Plasma	83	39	31	77	72.40%	66.80%	7

NR, not reported; TP, true positive; FP, false positive; FN, false negative; TN, true negative; SEN, sensitivity; SPE, specificity.

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**Table 2.** Overall and subgroup analyses of the included studies

Subtype	SEN	95% CI	SPE	95% CI	AUC	Partial AUC
Overall	0.694	0.651-0.734	0.819	0.773-0.858	0.806	0.743
Ethnicity						
Asian	0.703	0.663-0.740	0.830	0.779-0.871	0.796	0.703
Caucasian	0.654	0.521-0.766	0.773	0.624-0.875	0.764	0.679
Cancer						
Bladder cancer	0.704	0.660-0.744	0.822	0.737-0.884	0.770	0.729
Other	0.691	0.615-0.758	0.821	0.761-0.868	0.825	0.700
miR183 family						
miR183	0.693	0.632-0.747	0.784	0.704-0.848	0.782	0.713
Other	0.698	0.632-0.758	0.851	0.799-0.892	0.843	0.741
Specimen (in other cancer)						
Circulating	0.730	0.484-0.886	0.842	0.733-0.912	0.868	0.775
Non-circulating	0.697	0.621-0.763	0.806	0.737-0.871	0.816	0.672

SEN, sensitivity; SPE, specificity; FPR, false positive rate; AUC, area under the curve; CI, confidence interval.

suggest lower risk of bias whereas lower scores indicate higher risk of bias.

### Statistical methods

The pooled sensitivity and specificity with their corresponding 95% CIs were calculated by the random-effects model or fixed-effects model. Apart from that, the summary receiver operator characteristic (SROC) curve was plotted and the area under this curve (AUC) together with partial AUC were calculated. A Chi-Square test was conducted to assess the heterogeneity in the included studies. A *P* value of less than 0.05 reveals the existence of significant heterogeneity as suggested by the Chi-Square test [19, 20]. Furthermore, subgroup analyses were carried out in order to detect potential sources of heterogeneity. All statistical analyses were implemented by the R 3.1.2 software.

### Results

#### Included studies

The selection flowchart of our literature research is presented in **Figure 1**. Initially, 186 articles were identified from the electronic databases and 17 of the articles were removed due to duplications. After the titles and abstracts were reviewed, another 138 articles were excluded: 52 of them were reviews, letters or meta-analysis and 86 of them were irrelevant to our research subject. After reviewing

the full text of the remaining 31 articles, 14 of them were further excluded: 5 of them were not related to cancer diagnosis and 9 articles did not have sufficient data. Eventually, 21 studies from 17 articles [21-39] were included in the meta-analysis based on the inclusion and exclusion criteria.

#### Baseline characteristics

**Table 1** shows the characteristics of all included articles by an order of publication date ranging from 2010 to 2015. A total of 1659 cancer patients and 1457 matched controls from these articles were included in the meta-analysis. Among these 17 researches, 8 of them were conducted in Asian population and 9 of them were conducted in Caucasian population (*n* = 6) or African population (*n* = 3). All the research studied the level of miRNA expression by the method of quantitative real-time polymerase chain reaction (qRT-PCR) assay in blood (*n* = 5), tissue (*n* = 6) and urine (*n* = 6). Moreover, 6 of the 21 studies focused on diagnostic performance of miR-182, 10 on miR-183, and the remaining 5 on miR-96. Quality assessment was conducted according to the QUADAS-2 guidelines and the majority of these articles achieved relatively high scores (**Figure 2**).

#### Diagnostic accuracy

The pooled estimates of the diagnostic accuracy of miR-183 family members in cancer detec-

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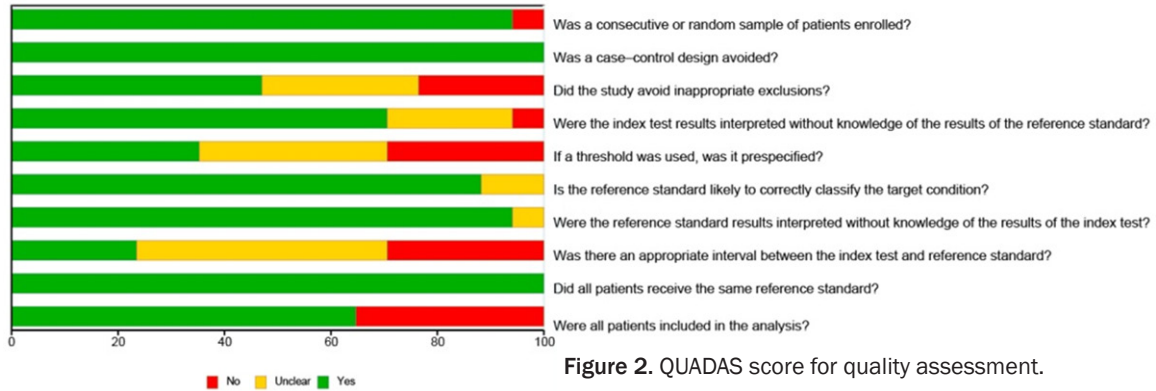


Figure 2. QUADAS score for quality assessment.

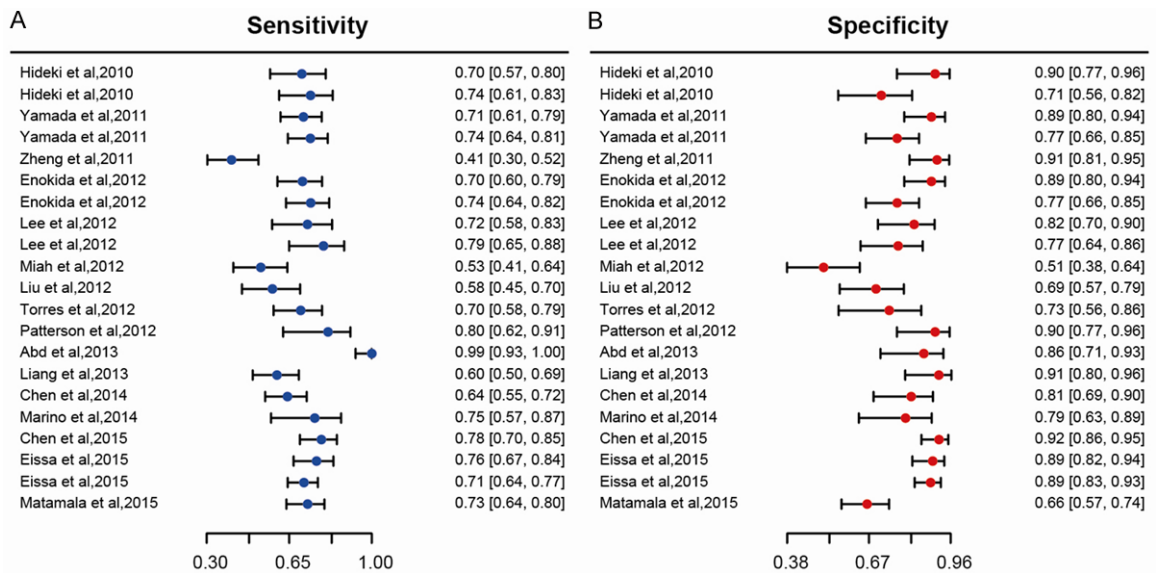


Figure 3. Forest plots of sensitivity and specificity by individual studies.

tion are revealed in **Table 2**. Forest plots of sensitivity and specificity for individual studies are shown in **Figure 3**. Since there was significant heterogeneity between individual studies in terms of sensitivity and specificity (Chi-Square test,  $P < 0.05$ ), a random-effects model was employed in the meta-analysis. The overall sensitivity and specificity were 0.69 (95% CI: 0.65-0.73) and 0.82 (95% CI: 0.77-0.86), respectively. Apart from that, the AUC and the partial AUC was 0.81 and 0.74 respectively as suggested by **Figure 4**.

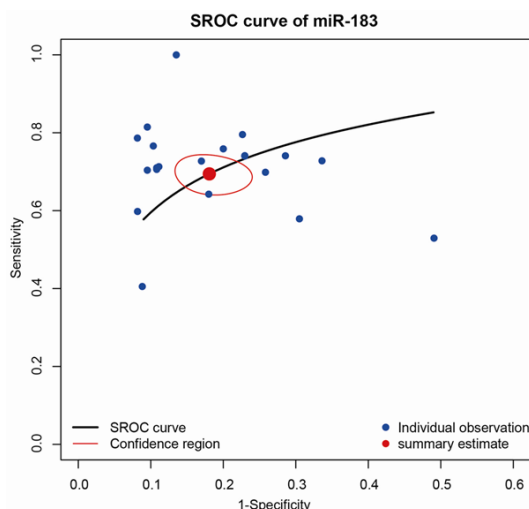
### Subgroup analyses

As shown in **Table 2** and **Figure 5A-D**, subgroup analyses based on ethnicity (Asian or Caucasian), cancer (bladder cancer or other), miR-183 family (miR183 or other), specimen type in

other types of cancer (circulating-based or non-circulating-based) and the quality scores were carried out to assess the heterogeneity between those studies.

Subgroup analysis by ethnicity (Asian:  $n = 12$ , Caucasian:  $n = 6$ , African = 3) indicates the diagnostic accuracy of miR-183 appeared to be higher in African than that in Asian and Caucasian. The sensitivity and specificity of those three groups were 0.74 (95% CI: 0.67-0.80) vs. 0.70 (95% CI: 0.66-0.74) vs. 0.65 (95% CI: 0.52-0.77), and 0.89 (95% CI: 0.85-0.92) vs. 0.83 (95% CI: 0.78-0.87) vs. 0.77 (95% CI: 0.62-0.88). The SROC curves of African, Asian and Caucasian subgroups are plotted in **Figure 5A**. AUC of the three subgroups were 0.90 vs. 0.80 vs. 0.76 and partial AUC were 0.76 vs. 0.70 vs. 0.68. It is obvious

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**Figure 4.** Overall diagnostic accuracy analysis for miR-183.

that the diagnostic accuracy of miR-183 in African was higher than that in Asian or Caucasian.

On the division based on cancer types, the included studies were divided into two groups: bladder cancer group ( $n = 9$ ) and other cancer group ( $n = 12$ ). The sensitivity and specificity of this two groups were 0.70 (95% CI: 0.66-0.74) vs. 0.69 (95% CI: 0.62-0.76), and 0.82 (95% CI: 0.74-0.88) vs. 0.82 (95% CI: 0.76-0.87). The SROC curves of those two groups are plotted in **Figure 5B**. The AUC were 0.77 vs. 0.83 and partial AUC were 0.73 vs. 0.70.

On the division based on miRNA type, two groups were obtained: miR-183 group ( $n = 10$ ) and other groups including miR-96 ( $n = 5$ ) and miR-182 ( $n = 6$ ). The sensitivity and specificity of this two groups were 0.69 (95% CI: 0.63-0.75) vs. 0.70 (95% CI: 0.63-0.76) and 0.78 (95% CI: 0.70-0.85) vs. 0.85 (95% CI: 0.80-0.89). The SROC curves of those two groups are plotted in **Figure 5C**. The AUC were 0.78 vs. 0.84, and partial AUC were 0.71 vs. 0.74. As a result, other miR183 family members (miR-96, miR-182) had more accurate diagnosis than that of miR-183.

Subgroup analysis by specimen type (circulating:  $n = 5$ , non-circulating:  $n = 7$  and 9 studies were removed for this subgroup analysis as bladder cancer used urine as specimens) suggested that circulating based miR-183 was

more accurate than non-circulating based miR-183 for cancer detection. The sensitivity and specificity of this two groups were 0.73 (95% CI: 0.48-0.89) vs. 0.70 (95% CI: 0.62-0.76) and 0.84 (95% CI: 0.73-0.91) vs. 0.81 (95% CI: 0.74-0.87). The SROC curves of those two groups are plotted in **Figure 5D**. The AUC were 0.87 vs. 0.82, and partial AUC were 0.78 vs. 0.67. Based on the quality score, five subgroup were gained (5 score:  $n = 1$ , 6 score:  $n = 2$ , 7 score:  $n = 8$ , 8 score:  $n = 9$ , 9 score:  $n = 1$ ). The sensitivity of these five groups were 0.70 (95% CI: 0.57-0.81) vs. 0.66 (95% CI: 0.49-0.80) vs. 0.69 (95% CI: 0.63-0.75) vs. 0.70 (95% CI: 0.62-0.78) vs. 0.77 (95% CI: 0.67-0.84), correspondingly, the specificity of these five groups were 0.91 (95% CI: 0.96-0.77) vs. 0.70 (95% CI: 0.79-0.61) vs. 0.81 (95% CI: 0.89-0.71) vs. 0.84 (95% CI: 0.88-0.79) vs. 0.90 (95% CI: 0.94-0.83). The SROC curves of these groups were presented in **Figure 6**. The AUC were 0.89 vs. 0.72 vs. 0.78 vs. 0.85 vs. 0.91, and partial AUC were 0.70 vs. 0.65 vs. 0.72 vs. 0.69 vs. 0.76.

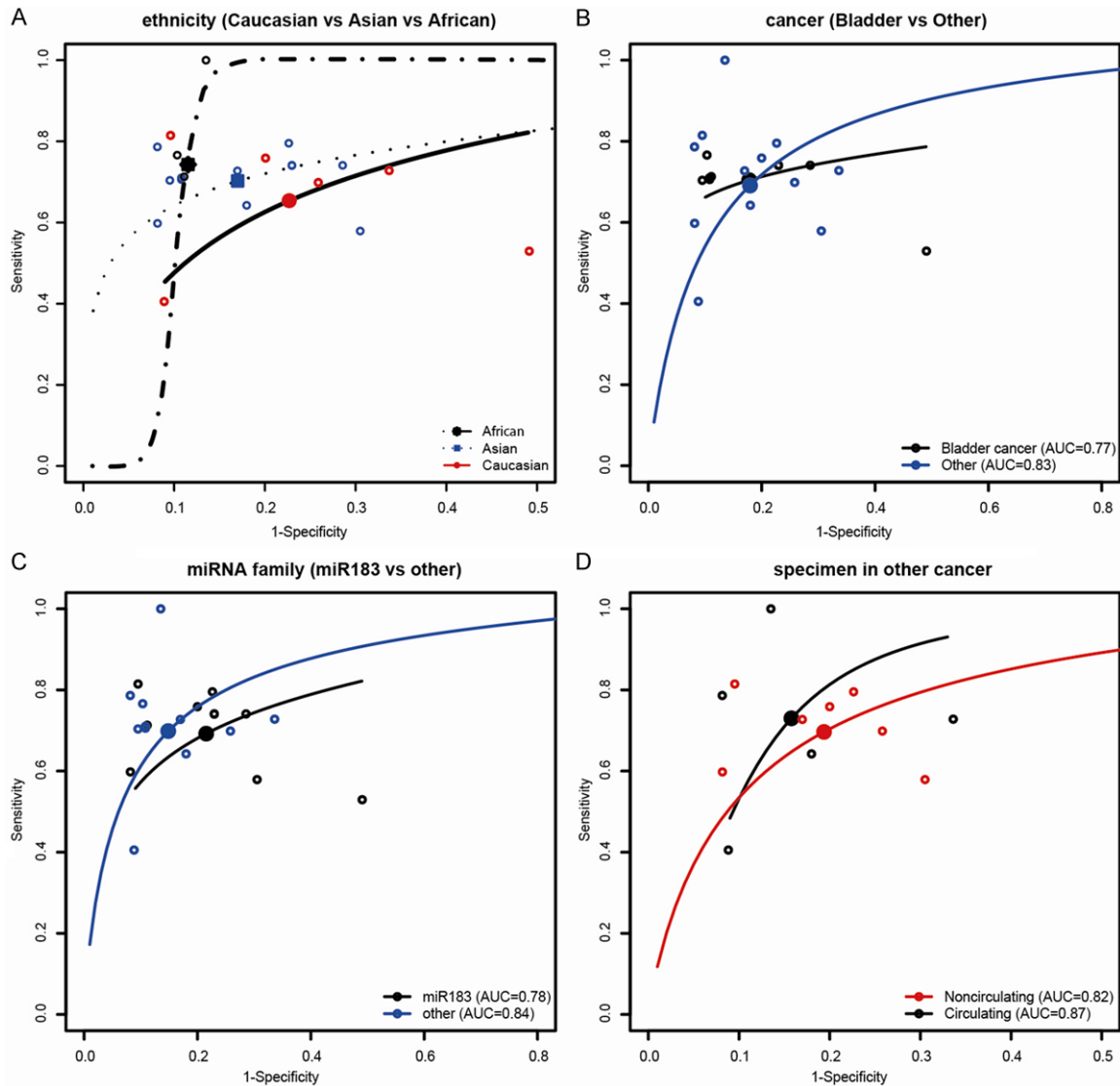
### Discussion

Sensitive and specific tumor biomarkers are essential to early detection and diagnose of cancer. In recent years, the aberrant expression of miRNAs in various types of cancer has been widely reported [14-17, 21-39] and miR-183 has been suggested to have potential diagnostic significance for cancer detection [14-17, 21-39]. As the underlying diagnostic value of miR-183 has not been discovered, a comprehensive meta-analysis was performed in order to evaluate the diagnostic accuracy of miR-183 family members.

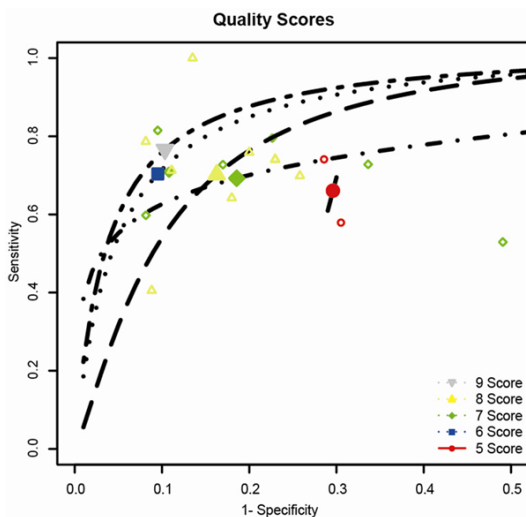
In accordance with the meta-analysis results, the pooled sensitivity, specificity, AUC and partial AUC were 0.69 (95% CI: 0.65-0.73), 0.82 (95% CI: 0.77-0.86), 0.8 and 0.74. Apart from the pooled sensitivity, the relatively high specificity and AUC of miR-183 implied a significant advantage over other biomarkers.

Heterogeneity should be taken into account as it significantly affects the diagnostic value of miR-183 family members. Subgroup analysis by ethnicity suggested that the sensitivity, specificity, AUC and partial AUC of miR-183 family in African populations were higher than those in Asian and Caucasian populations. Therefore, miR-183 may be more suitable for

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**Figure 5.** Subgroup analysis of diagnostic accuracy by ethnicity, types of cancer, miR-183 family and specimen.



**Figure 6.** Subgroup analysis of diagnostic accuracy by quality score.

the African population to detect and diagnose cancer.

The subgroup analysis based on miR-183 family members indicated that miR-183 showed lower sensitivity, specificity, AUC and partial AUC compared with other miR-183 family members (miR-92 and miR-182). It suggested that other miR-183 family members may have superior diagnostic value than miR-183.

The subgroup analysis based on cancer types and specimen types revealed that circulating-

based miRNA specimen had significantly higher sensitivity and specificity compared with urine-based and other non-circulating-based specimen. Therefore, circulating-based specimen may be more appropriate than non-circulating based miR-183 for cancer detection. It is speculated that miRNA have great stability and was abundant in blood, which facilitates the extraction for cancer detection.

Compared with individual studies, the meta-analysis has several advantages. First of all, we incorporated 17 articles consisting of 21 studies, which enhanced the reliability of the pooled evaluation of diagnostic performance of miR-183 family members. In addition, we adopted comprehensive methods including subgroup analysis to further assess the impact of heterogeneity on the diagnostic accuracy. However, there are still several limitations in this meta-analysis. Firstly, the included studies were mostly conducted in Asian and Caucasian population, which results in population selection bias. Therefore, more African-based studies should have been incorporated to improve the reliability of the results of this meta-analysis. Secondly, the patients in early stages or advanced stages of cancer were absent in the included articles. Accordingly, it is difficult to evaluate the capability of miR-183 family members for early cancer detection. Finally, the relative small sample size of the meta-analysis may reduce statistical power and produce biased results. Therefore, it is recommended that further studies with large sample size should be carried out to confirm the diagnostic value of miR-183 for cancer detection.

In summary, our results evaluated the diagnostic value of miR-183 family members for cancer diagnose. It is encouraged that miR-183 family could be used as an ancillary cancer-screening tool because of its noninvasive nature. MiR-183 may be more appropriate in African population with blood as a better specimen for cancer diagnose. Nevertheless, more studies should be incorporated in our meta-analysis to enhance the clinical feasibility of miR-183 family members.

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### Disclosure of conflict of interest

None.

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