

Original Article

MicroRNA-18a as a promising biomarker for cancer detection: a meta-analysis

Shan Jin, Shi-Sheng Tan, Hang Li

Department of Oncology, People's Hospital of Guizhou Province, No. 83 East Zhongshan Road, Guiyang 550002, Guizhou Province, China

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Abstract: Patients with cancer discovered at an early stage have relatively high survival rates. Increasing researches have shown the potential of detecting dysregulated microRNA-18a (miR-18a) to diagnose cancer. However, non-uniform results in previous studies were found. Thus, this meta-analysis was conducted to further explore the clinical applicability of miR-18a as an ideal biomarker for cancer detection. Suitable articles were obtained from online databases like PubMed, Embase, Cochrane, CBM and Wanfang. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool was used to evaluate the quality of our meta-analysis. The pooled diagnostic parameters like specificity, sensitivity, diagnostic odds ratio (DOR), positive and negative likelihood ratios (PLR and NLR) and area under the summary receiver operator characteristic curve (SROC) were pooled to assess the entire test accuracy. Overall, 10 studies from 9 articles, including 979 patients with cancer and 713 healthy controls were involved in our meta-analysis. The pooled sensitivity was 0.78 (95% CI: 0.70-0.84) and the corresponding specificity was 0.82 (95% CI: 0.73-0.89). The merged PLR was 4.3 (95% CI: 2.8-6.8), NLR was 0.27 (95% CI: 0.20-0.37), and DOR was 16 (95% CI: 8-31). The pooled AUC was 0.86 (95% CI: 0.83-0.89). Our meta-analysis suggested that miR-18a might open up a new field for novel clinical cancer screening with the merits of high accuracy, non-invasiveness, convenience and cheap cost. However, more reliable studies in larger cohort should be conducted before it is used.

Keywords: microRNA-18a, cancer biomarker, meta-analysis, diagnostic accuracy

Introduction

Cancer accounts for the highest mortality in developed countries and it is also the leading cause of death ranked only second to angiocardopathy in developing countries, making it a worldwide healthy problem [1]. It is estimated that about 16.6 million new cancer cases and 5.8 million new deaths have come up in 2013 worldwide [1]. In general, cancers are easier to treat and control, respectively, when detected at an early stage of disease progression. Whereas, due to its aggressive invasion and early metastasis to lymph nodes, adjacent tissue or organs, the majority of cancer patients are diagnosed at a relatively late stage, and the overall 5-year survival rate were extremely dismal [2, 3]. For example, with complete surgical resection, 90% of gastric cancer patients in stage I got an excellent prognosis. However, for patients in stage IV, about 80% of the patients die within a short time [4]. Meanwhile, for

esophageal cancer patients diagnosed at a relatively late stage, the overall survival rate remains low, only 3-5% of diagnosed patients survive for 5 years [5]. In contrast, the survival rate increases to 90% in patients diagnosed with Stage I disease [6]. Therefore, cancer patients can significantly improve the awful survival rates only if they are diagnosed at an early stage.

Currently, the reference gold standards for cancer diagnosis mainly consist of biopsy and imaging examination. Although the biopsy yields an excellent accuracy, the invasiveness and uncomfortable nature for patients limit its clinical practicability. Imaging examinations, such as computed tomography, X-ray computed tomography and magnetic resonance imaging, can significantly improve the accuracy of early diagnosis, but they are limited by low-resolution and radioactivity. Other detection methods like chromoendoscopy for gastric cancer patients

and fine-needle aspiration biopsy for thyroid cancer indicated a relatively ideal diagnostic accuracy [7, 8]. However, the invasiveness of these diagnostic procedures and potential sampling errors limit their routinely use for clinic. Beyond that, these detection methods are also limited by its unbearable price. Hence, the development of highly accurate tests with a minimal invasiveness for the early detection of cancers is urgently needed. Recently, numerous studies were focused on the utility of molecular biomarkers, such as mutation analysis in tumor samples and identification of gene panels [9, 10]. However, these biomarkers are still far from ideal, for moderate accuracy and inconvenience of detection all restricted their practicability. Unusually, microRNAs (miRNAs) have caught increasing attention recently with their satisfying benefits.

Several studies have shown that the specific dysregulated expression level of miRNAs was connected with tumorigenesis [11-13]. Given this, specific miRNA may have the potential to serve as a promising biomarker for cancer detection. MiRNAs are a group of 18-22 nucleotide non-coding RNAs which regulate gene expression by influencing mRNAs in post-translational process [14]. Researches demonstrated clearly that by interfering the function of specific cell cycle-gene, miRNAs play a vital role in a wide variety of physiologic cellular processes, including differentiation, proliferation, apoptosis and tumorigenesis [15]. Furthermore, miRNAs also exhibited the characteristics of high stability, easy extraction and quantification, non-invasiveness and tumor-specific characteristics. These findings will bring about a new and promising field for early diagnosis of cancer.

Among all of these miRNAs, accumulative studies have indicated the feasibility of detecting dysregulated miR-17-92 cluster (miR-17-5p, -17-3p, -18a, -19a, -19b, -20a and -92a) to diagnose cancer patients. MicroRNA-18a (miR-18a) is one of the most highly expressed miRNAs in the miR-17-92 cluster, which has been found to be significantly up-regulated in various human cancers. Komatsu et al. studied the diagnostic utility of plasma miR-18a and found a significantly higher concentration in esophageal and pancreatic cancer patients than that in healthy controls [16]. Morimura et al. extracted plasma

RNA and discovered that the expression of miR-18a was increased specifically in pancreatic cancer [17]. Calvano et al. also found an extreme overexpression of miR-18a in luminal breast invasive ductal carcinoma patients compared with normal controls [18].

Numerous previous studies have focused on miR-18a utility in field of cancer diagnosis. However, there exist conflicting results in these researches. Morimura et al. reported a good diagnostic characteristic for miR-18a with 95.0% sensitivity and 80.0% specificity in pancreatic cancer [17]. Hirajima et al. studied the diagnosis with miR-18a for oesophageal squamous cell carcinoma and found that this method had an excellent diagnostic accuracy with 86.8% sensitivity and 100% specificity [18]. However, Luo et al. reported a much lower accuracy with 58.0% sensitivity and 58.0% specificity in colorectal cancer detection [19]. Differences in cancer types, study design, sample type and ethnicity may result in the inconsistent conclusion of these related studies. Therefore, this meta-analysis was aimed to further explore the clinical applicability of miR-18a as novel and ideal biomarkers in cancer detection.

Materials and methods

Search strategy and study selection

Suitable articles were searched from PubMed, Embase, Cochrane, Chinese Biomedical Literature Database (CBM) and Wanfang database until June 13, 2014 without language limit and low data limit. ("Neoplasms" or "cancer" or "tumor" or "neoplasm"), and ("microRNA-18a" or "miRNA-18a" or "miR-18a") and ("diagnoses" or "ROC curve" or "sensitivity" or "specificity") were used as the MeSH and key words for our literature retrieval. We also manually retrieve the reference lists of review articles and selected papers to gain any additional eligible studies.

Relative studies would be included if they conform to the following inclusion criteria: (1) the study must concern the use of miR-18a for cancer diagnosis; (2) all the study objects were confirmed by currently golden standard test; (3) sufficient data should be gained to fill up the two-by-two tables [i.e. true positive (TP), false positive (FP), true negative (TN) and false nega-

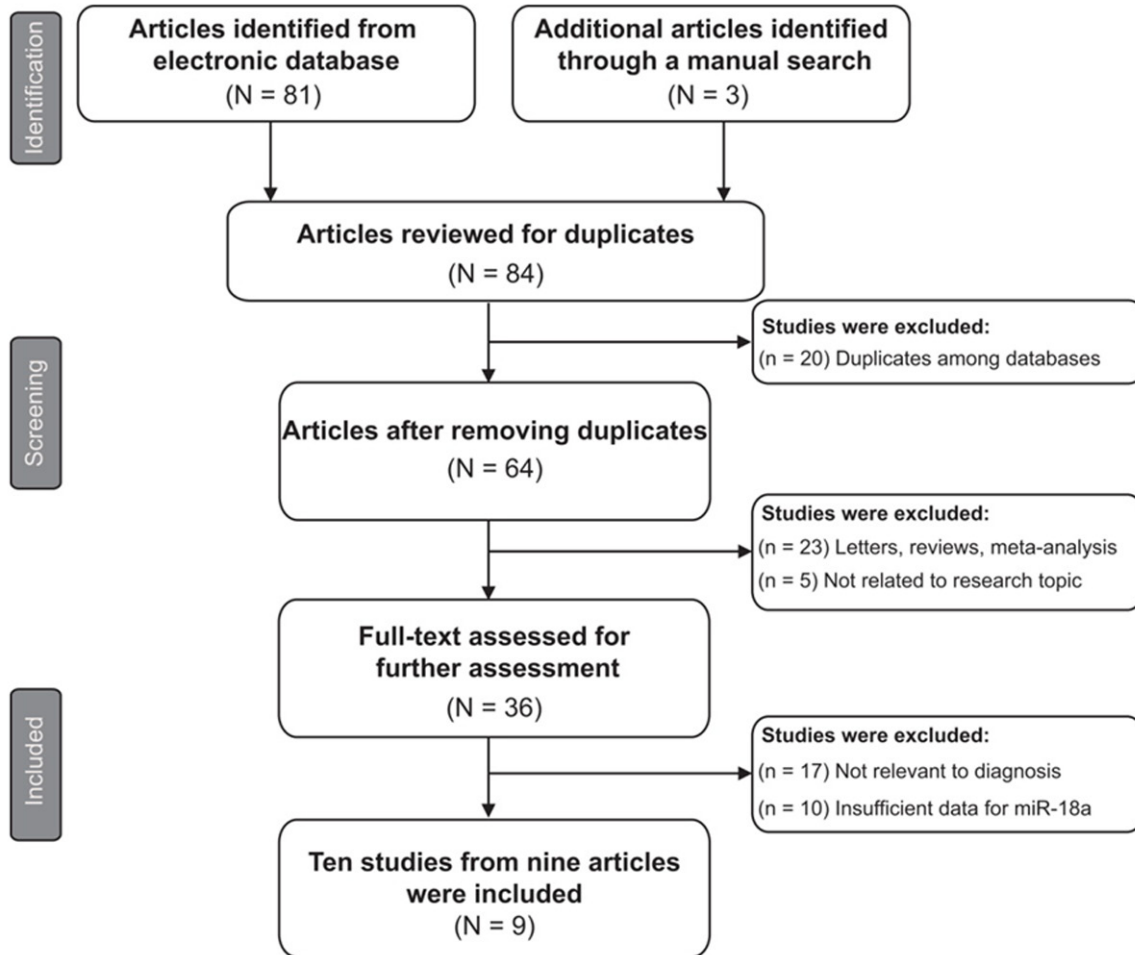


Figure 1. Flow diagram of the study selection process.

tive (FN)]. Articles would be excluded (1) if they focus on survival or prognosis of cancer; (2) if they are conference reports, editorials, letters or reviews; (3) if they report duplicated data and unqualified data. Two reviewers judged study eligibility independently while screening the citations.

Data extraction

The full texts of included studies were independently reviewed by two investigators. Data were extracted from these studies including trial features (first author, published year, and country of publication), research object’s general features (ethnicity, number of subjects, gender ratio, mean age of subjects, cancer sites, and source of control), data for our final meta-analysis (specimen, detection method, sensitivity, specificity, TP, FP, FN, and TN) and information

needed for methodological quality assessment.

Statistical methods

Diagnostic studies were performed on the basis of two-by-two contingency table and by means of the recommended standard methods. While heterogeneity caused by differences in clinical studies and standard methods may result in inconsistent conclusions. Therefore, we use Chi-square test and inconsistency index (I^2) test to estimate the heterogeneity exist in our meta-analysis. P value less than 0.1 and I^2 value more than 50% implied a significant heterogeneity existing in our studies [20, 21]. Furthermore, meta-regression of our meta-analysis based on the different features was conducted to explore the potential sources of between-study heterogeneity. The sensitivity,

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Table 1. Main characteristic of all the included literatures in this meta-analysis

Author, year	Country	Ethnicity	Case			Control			Cancer	Specimen	Expression	Diagnostic power				QUADAS
			N	Age	Male	N	Age	Male				TP	FP	FN	TN	
Koga Y, 2010 [26]	Japan	Asian	197	63	0.67	119	60	0.44	CRC	Feces	Up	113	7	84	112	4
Morimura R, 2011 [17]	Japan	Asian	36	68	0.58	30	n.a.	n.a.	PaC	Plasma	Up	34	6	2	24	4
Wu CW, 2011 [27]	China	Asian	93	n.a.	n.a.	101	n.a.	n.a.	CRC	Feces	Up	60	30	33	71	5
Li L, 2012 [28]	China	Asian	101	54	0.75	60	52	0.77	HCC	Serum	Up	87	15	14	45	4
			101	54	0.75	30	51	0.77	HCC	Serum	Up	78	9	23	21	
Hirajima S, 2013 [18]	Japan	Asian	106	n.a.	0.82	54	n.a.	n.a.	ESCC	Plasma	Up	92	0	14	54	4
Luo X, 2013 [19]	Germany	Caucasian	80	68	0.56	144	62.5	0.42	CRC	Plasma	Down	46	60	34	84	5
Ulivi et al, 2013 [29]	Italy	Caucasian	86	68.1	n.a.	24	65	n.a.	NSCLC	Blood	Up	58	5	28	19	4
Zhang GJ, 2013 [30]	China	Asian	78	61.4	0.55	86	60.3	0.62	CRC	Plasma	Up	57	18	21	68	4
Tsujiura M, 2014 [31]	Japan	Asian	104	65.6	0.64	65	n.a.	n.a.	GC	Plasma	Up	88	20	16	45	4

CRC: colorectal cancer. PaC: pancreatic cancer. HCC: hepatocellular carcinoma. ESCC: oesophageal squamous cell carcinoma. NSCLC: non-small cell lung cancer. GC: gastric cancer. QUADAS: quality assessment of diagnostic accuracy studies.

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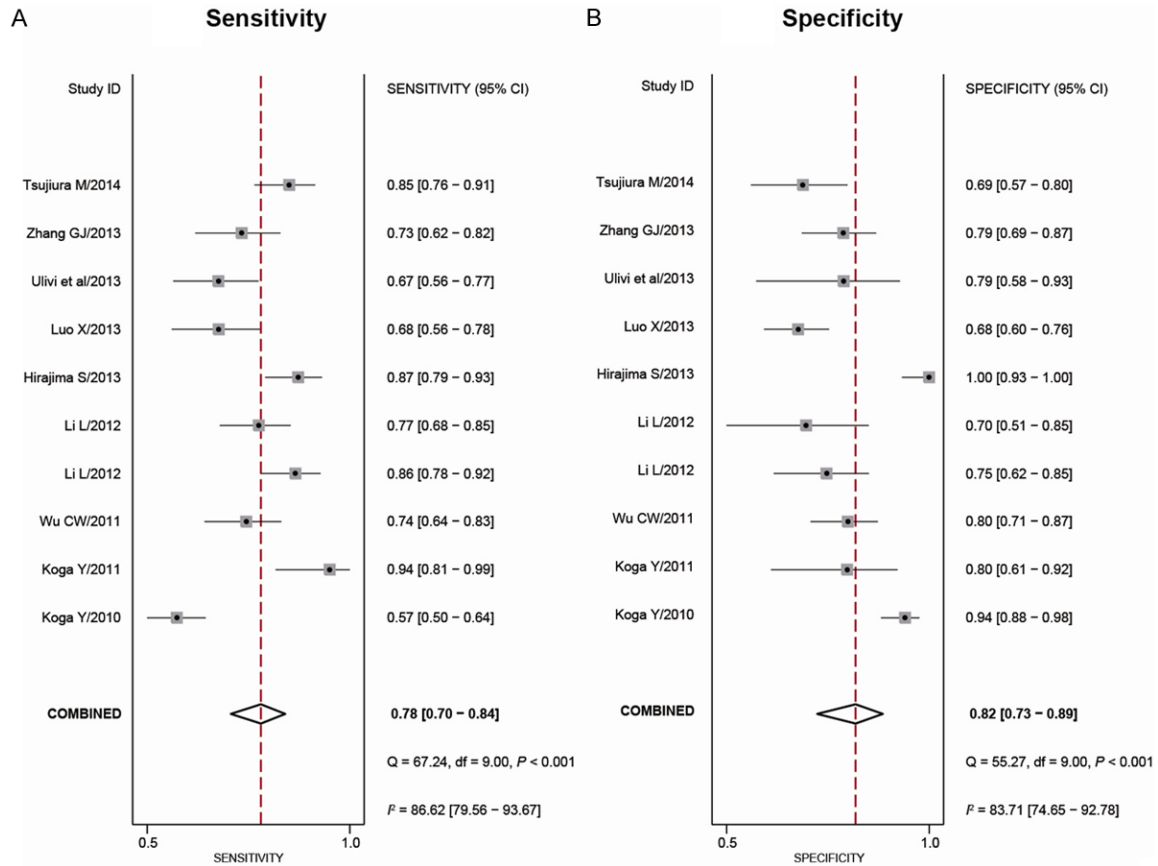


Figure 2. Forest plots of sensitivity (A) and specificity (B) with corresponding heterogeneity statistics.

specificity, positive and negative likelihood ratios (PLR and NLR) and diagnostic odds ratio (DOR) were summarized by performing the bivariate meta-analysis model [22]. Synchronously, a SROC curve was constructed according to the sensitivity and specificity of our meta-analysis. The AUC which indicated the summary of our analytical test was calculated [23]. Deeks' funnel plot was used to explore the potential publication bias in our meta-analysis [24]. Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) was a standard quality-evaluating tool [25]. We use the QUADAS-2 criteria to evaluate the qualities of involved studies in our meta-analysis. All the analyses were undertaken using Stata software (version 12.0, College Station, TX).

Results and discussion

Included studies

The results of our literature research are presented in **Figure 1**. The initial search gained a

total of 84 research papers (81 from electronic database searches, 3 from manually search), of which 20 were excluded for being duplications among databases. The remaining 64 research articles were subject to the next stage of evaluation. After titles and abstracts were reviewed, 28 were excluded, of which 23 were reviews, letters and meta-analysis, and 5 were not related to search topic. Next, 36 articles were suitable for further assessment. After full-text assessment, 17 research papers were excluded for they were not related to diagnosis and 10 without sufficient data for miR-18a. Finally, 9 articles were left for final meta-analysis [17-19, 26-31].

Study characteristics

The clinical features of the included articles were extracted and listed in **Table 1** by order of publication year. Overall, 1,692 subjects (979 cancer patients and 713 healthy controls) were included in the 10 studies. The publication years of the included articles range from 2010

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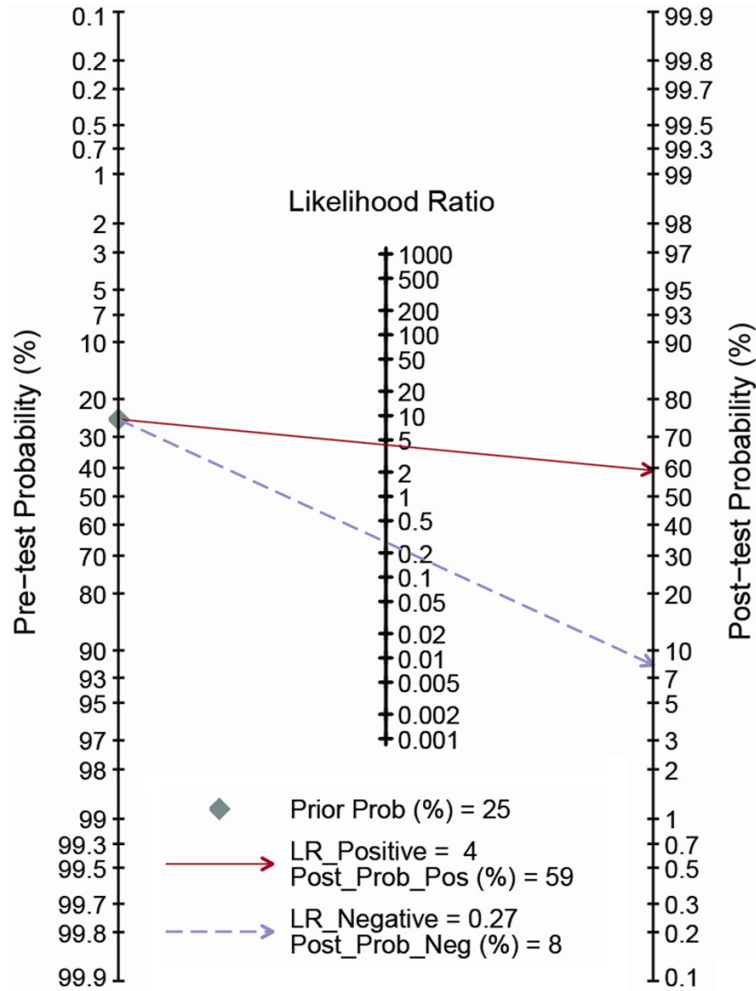


Figure 3. Summary ROC curve with confidence and prediction regions around mean operating sensitivity and specificity point.

to 2014. Colorectal cancer (n = 4), pancreatic cancer (n = 1), hepatocellular carcinoma (n = 2), oesophageal squamous cell carcinoma (n = 1), non-small cell lung cancer (n = 1) and gastric cancer (n = 1) constitute of our studied cancer types. Among the 10 diagnostic studies, 8 studies were conducted in Asian and 2 in Caucasian. The sample types contain blood (n = 1) feces (n = 2), serum (n = 2) and plasma (n = 5). All studies used the method of quantitative reverse transcription PCR (qRT-PCR) to measure the expression of miR-18a.

Diagnostic accuracy

Figure 2 indicated the forest plots of summational sensitivity and specificity of miR-18a in the cancer detection. The sensitivity varied from 0.57 to 0.94 and the specificity from 0.68

to 1.00. Significant heterogeneity between studies in sensitivity and specificity data were observed ($I^2 = 86.62\%$ and $I^2 = 83.71\%$). Hence, the pooled estimates in our meta-analysis were figured up by using the random effects model. The pooled sensitivity and specificity were 0.78 (95% CI: 0.70-0.84) and 0.82 (95% CI: 0.73-0.89), which were calculated via bivariate random effects model (**Figure 2**). The pooled DOR was 16 (95% CI: 8-31). We also measured the diagnostic accuracy of miR-18a by calculated PLR and NLR which were regarded as more clinically meaningful parameters than sensitivity and specificity. The pooled PLR and NLR of our meta-analysis were 4.3 (95% CI: 2.8-6.8) and 0.27 (95% CI: 0.20-0.37), indicating an encouraging diagnostic characteristic (**Figure 3**). The SROC curve of miR-18a was showed in **Figure 4**, and the AUC was 0.86 (95% CI: 0.83-0.89).

As shown in **Table 1**, there were only two studies that were conducted with feces. Therefore, in this meta-analysis,

we deleted these two studies to further identify the diagnostic performance of circulating miR-18a for cancers. The results revealed a pooled sensitivity of 0.80 (95% CI: 0.73-0.86), specificity of 0.80 (95% CI: 0.69-0.87), PLR of 3.9 (95% CI: 2.4-6.3), NLR of 0.25 (95% CI: 0.17-0.36), DOR of 16 (95% CI: 7-34), and AUC of 0.87 (95% CI: 0.83-0.89), which had only minimal changes compared with overall results.

Influence analysis and publication bias

The random-effect bivariate model was robust for the calculation of the pooled estimates by performing the goodness of fit and bivariate normality analyses (**Figure 5A** and **5B**). Influence analysis and outlier detection detected only one outlier studies (**Figure 5C** and **5D**). After exclusion of the outlier studies, the pooled

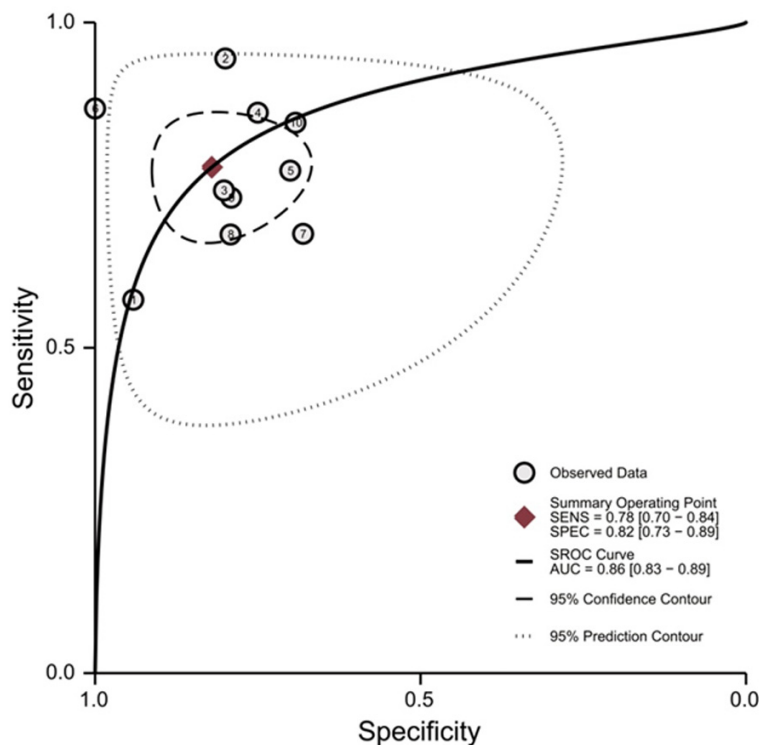


Figure 4. Fagan's nomogram with PLR and NLR.

sensitivity, specificity, PLR, NLR, DOR and AUC were 0.78 (95% CI: 0.72-0.84), 0.75 (95% CI: 0.70-0.79), 3.1 (95% CI: 2.6-3.7), 0.29 (95% CI: 0.22-0.39), 11 (95% CI: 7-17), and 0.83 (95% CI: 0.80-0.87), respectively. The results indicated a minimal influence which did not significantly affect the overall estimates.

Finally, publication bias of our meta-analysis was evaluated by the Deeks' funnel plot asymmetry test. The funnel plots presented symmetry data, and the overall studies' *P*-value was 0.75 suggesting a low likelihood of publication bias in our meta-analysis (Figure 6).

Discussion

According to the GLOBOCAN 2008 and cancer statistics, an estimated 12.7 million new cancer cases occur in 2008 compared with 16.6 million new cases in 2013 [32]. Cancer incidence rates increased about 6% per year. Interestingly, cancer death rates indicated a decrease by about 4.7% per year [1]. We speculate this phenomenon may be caused by the development of cancer detection methods and implementation of intensive treatment. Based

on the latest cancer detection, comparatively speaking, many cancer patients were diagnosed at an early stage. However, these latest detection methods are still far from ideal. Cancer still accounts for the highest mortality disease worldwide. Like fine-needle aspiration biopsy, magnetic resonance imaging and gastroscopic screening were the current golden detection methods to diagnose thyroid cancer, nervous system cancer and gastric cancer, respectively. These methods are still confined by the drawbacks of low diagnostic accuracy, invasiveness and exorbitant price. Above all, many patients were diagnosed still at an advanced stage. For patients with advanced cancer, it frequently relapses due to the lymphatic and haematogenous metastases which consequently lead to extremely poor survival rates. Therefore, it becomes urgent and necessary to find novel ideal detection methods.

Recently, accumulative researches have focused their emphasis in molecular biomarkers. Looming large among these, miRNAs have been carried out as the most promising ideal biomarkers for cancer diagnosis. MiRNAs have the unique merits of tumor specificity, stable, extracted easily and non-invasive. All these prompted us to discover more useful miRNAs as ideal biomarkers for cancer diagnosis with a clinically satisfactory accuracy. Numerous researches have reported upregulated expression level of miR-18a in various cancers, including esophagus cancer [33], colorectal cancer [34], and non-small cell lung cancer [29]. In our meta-analysis, we focus on the diagnostic performance of miR-18a for cancer patients. Through our meta-analysis, miR-18a may open up a promising field of diagnosis by virtue of miRNA.

Statistical significant difference of miRNA expression was found between cancer patients and healthy controls in these included studies.

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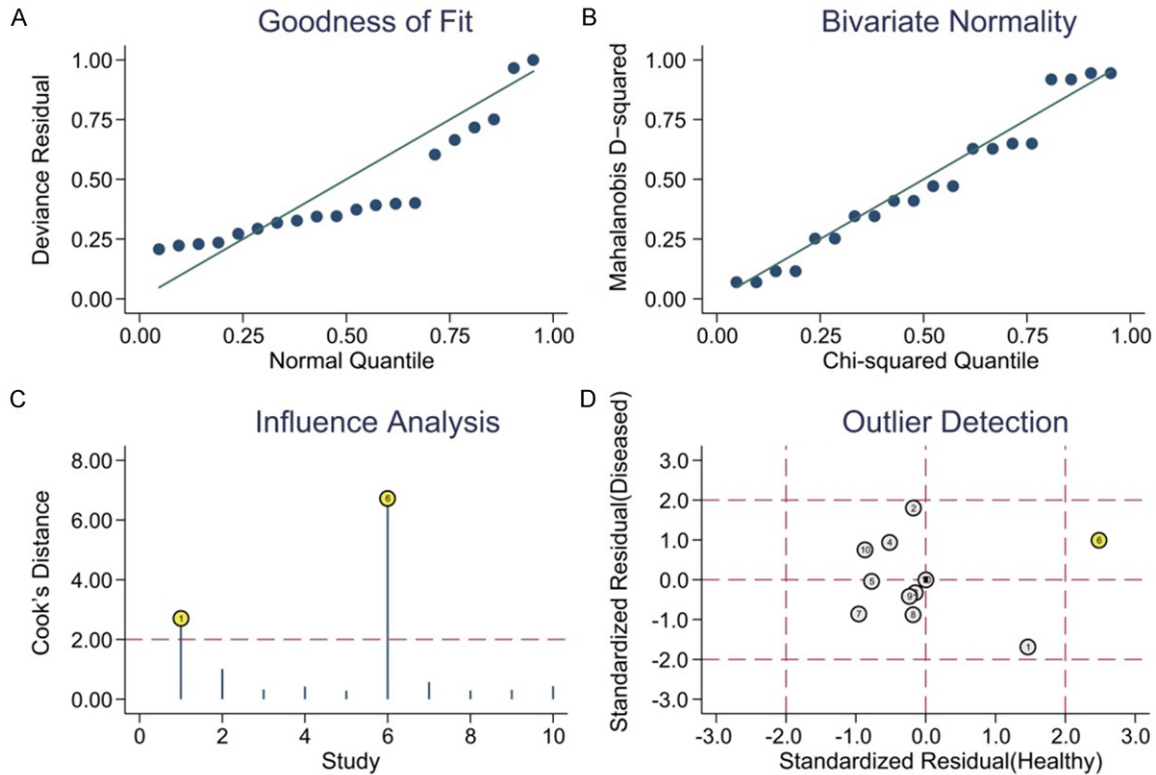


Figure 5. Graphical depiction of residual-based goodness-of-fit (A), bivariate normality (B), influence and outlier detection analyses (C and D, respectively).

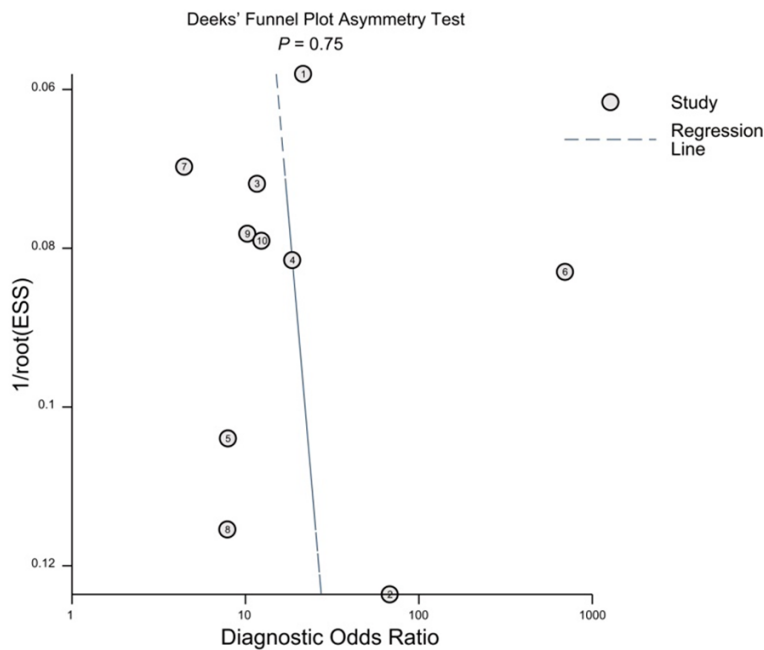


Figure 6. Funnel plot with superimposed regression line.

Our meta-analysis yield an AUC of 0.86 (95% CI: 0.83-0.89) with a 0.78 (95% CI: 0.70-0.84) sen-

sitivity and 0.82 (95% CI: 0.73-0.89) specificity, respectively. Our results showed an excellent diagnostic accuracy of miR-18a for cancer detection. These results may differ due to various cancer types. For pancreatic cancer and oesophageal squamous cell carcinoma, miR-18a indicated an excellent diagnostic sensitivity and specificity. As for other cancer types included in our meta-analysis, the diagnostic function was not optimistic. With regard to miRNAs' characteristic of tumor specificity, this result makes sense. Given the tumor specificity, numerous studies convinced that tumorigenesis was a complex cell processes which a panel of certain miRNAs were involved. Therefore, a panel of miRNA may serves as a better profile for cancer detec-

tion. Therefore, subgroup analysis based on the cancer type and more included studies are needed to further confirm the exact function of miR-18a and miRNA panels in cancer detection.

In spite of the promising satisfying diagnostic characteristic of miR-18a for cancer detection, little is known about the exact role of miRNAs in the carcinogenesis of tumors. Research indicated that the miRNAs might function as oncogenes and suppressor genes such as phosphatase and tensin homolog (PTEN) and regulates its expression [35]. Other studies surmised that miR-18a acts as a known oncomir, and it promotes cell proliferation, suppresses apoptosis, induces tumor angiogenesis and accelerates tumor progression [36, 37]. As for the mechanism of miRNAs analysis, further studies are needed to make certain all these doubts.

For all we know, our meta-analysis first arrived at the conclusion that miR-18a analysis may do duty for an ideal cancer biomarker. And the meta-analysis also suggested agreeable results. Despite of the promising prospect of miR-18a analysis list above, several problems need to be handled before clinical application. First, some factors which might influence the diagnosis accuracy of miR-18a haven't been taken into our meta-analysis, like surgical removal of tumors, the control plasma concentration of miR-18a, specific cancer type, and combination with other miRNA profiles or not. Second, to reflect the entire tumor dynamics, we should conduct three different analyses: the comparison of miR-18a levels in circulating and primary tumor tissue, the comparison of miR-18a concentration before and after surgery, the difference between the tissues miR-18a expression level in vivo and in vitro. Third, studies included in our meta-analysis are still far from enough, we need more reliable articles in a larger search scale. Lastly, all studies were performed based on Caucasian and Asian population, whereas African population should have been included.

Conclusions

In conclusion, miR-18a might open up a new field for the next-generation cancer screening and detection. Compared with the existing methods, diagnosis by virtue of miR-18a is non-invasive, convenient, and cheap. Besides, after improvements on the methods and operation,

it will certainly reach the clinically satisfactory diagnostic effects. However, larger, preciser and problem-oriented researches are should be carried out before it is put into practice.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Shi-Sheng Tan, Department of Oncology, People's Hospital of Guizhou Province, 83 East Zhongshan Road, Guiyang 550002, Guizhou Province, China. Tel: +86-851-5922979; E-mail: tssh18018@yeah.net

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