Systematic Review and Meta-Analysis

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Diagnostic value of microRNA-25 in patients with non-small cell lung cancer in Chinese population

A systematic review and meta-analysis

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Abstract

Objective: Previous studies have shown that microRNA-25 (miR-25) plays a key role in the occurrence and development of non-small cell lung cancer (NSCLC). Many studies have shown that there is a significant increment of miR-25 in circulating blood of patients with NSCLC. The meta-analysis aims to explore diagnostic value of miR-25 in NSCLC in Chinese population.

Methods: PubMed, Web of science, Excerpta Medica Database, China national knowledge infrastructure and China Wanfang database were searched to collect studies upon correlation between miR-25 and diagnosis of the patients with NSCLC until April 2020. Combined sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio and area under receiver operating characteristic curve were calculated by Stata 15.0 software. Literature assessment was conducted according to quality assessment of diagnostic accuracy studies, and documents with scores above or equal to 11 were included in this meta-analysis.

Results: Six studies were included, including 480 cases with NSCLC and 451 healthy controls. The combined sensitivity (0.75, 95% confidence interval [CI]: 0.69~0.80), specificity (0.81, 95% CI: 0.76~0.86), positive likelihood ratio (4.04, 95% CI: 3.14~5.20), negative likelihood ratio (0.31, 95% CI: 0.25~0.37), diagnostic odds ratio (13.09, 95% CI: 9.37~18.29) and area under curve (0.85, 95% CI: 0.82~0.88) indicated that miR-25 had desirable diagnostic accuracy for NSCLC.

Conclusion: MiR-25 can be applied in diagnosis of NSCLC and has potential of becoming a biomarker for detection of patients with early NSCLC in Chinese population.

Abbreviations: AUC = area under curve, CI = confidence interval, DOR = diagnostic odds ratio, miR-25 = microRNA-25, NLR = negative likelihood ratio, NSCLC = non-small cell lung cancer, PLR = positive likelihood ratio, QUADAS = quality assessment of diagnostic accuracy studies, SROC = summary receiver operating characteristic curve.

Keywords: diagnosis, meta-analysis, microRNA-25, non-small cell lung cancer

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Ethical approval was not needed because this is a meta-analysis.

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article [and its supplementary information files, http://links.lww.com/MD/F328].

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study. The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.; The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Globally, lung cancer remains the leading cause of cancer morbidity and mortality, with nearly 2.1 million new lung cancer cases and 1.8 million deaths in 2018, accounting for nearly 1/5 of total cancer deaths.[1] In male population, lung cancer is the leading cause of death in Eastern Europe, West Asia (especially the former Soviet Union), North Africa, and some countries in East Asia (China) and Southeast Asia (such as Myanmar, the Philippines and Indonesia). The region that has the highest incidence of lung cancer among men is Micronesia / Polynesia, East Asia (China, Japan and South Korea with an incidence of over 40/ 100000), and most part of Europe, particularly Eastern Europe (with an incidence of 77.4/ 100000 in males in Hungary). Among women, the regions with the highest incidence are North America, Northern and Western Europe and Australia / New Zealand, with Hungary at the top of the list.[1] Lung cancer is classified according to the type of disease, into small cell 1 with the English full name "small cell lung cancer," abbreviated as small cell lung cancer, and non-small cell 1, with the English full name "non-small cell lung cancer," abbreviated as non-small cell lung cancer (NSCLC). NSCLC makes up a substantial proportion of these 2 types of lung cancer, roughly more than 80% of them.[2] Improvement of living standards, accelerated pace of life, changes in eating habits and other aspects life, lead to yearly increasing incidence of lung cancer.[3,4]

Although with continuous progress of biological research, medical technology has been greatly improved, yet treatment of lung cancer has not been significantly improved. Prognosis of lung cancer is still not satisfactory, and 5-year survival rate is at a relatively low level.[5,6] To accurately evaluate the prognosis of patients with lung cancer, determination of individualized and effective treatment for different patients is 1 of the effective ways for improvement of survival rate of patients with lung cancer. Early detection, early diagnosis and early treatment are rather crucial for patients with lung cancer. Hence, the determination of effective biomarkers related to diagnosis is of great help for clinical application, which can guide treatment of patients, and improve survival status of patients. Therefore, it has drawn considerable attention from clinic.[7–9] Low-dose helical CT scanning is the main means to diagnose asymptomatic lung cancer at present, but it has some disadvantages, including tedious operation, high false positive rate and radiation damage to human body.[10] Non-invasive tumor markers can detect tumors early or predict progress of tumors,[11] which may become an effective tool for early diagnosis of lung cancer.

MicroRNA-25 (miRNA) is of great diagnostic value for many diseases, and early diagnosis and early treatment is of great significance.[12,13] Current main clinical tumor markers of lung cancer will facilitate diagnosis and pathological classification of lung cancer to some extent, but their sensitivity and specificity are relatively low. Circulating miRNA, which is the miRNA in serum or plasma, can stably exist in clinical samples. Abnormal expression of miRNA may be earlier than appearance of clinical symptoms,[14] which therefore may become a new tumor marker. However, not all miRNA abnormally expressed in cancer tissues can be detected in blood. Nad et al[15] compared expression of 334 types of miRNA in sera of patients with NSCLC and healthy people, and found that only 91 miRNA expressed abnormally, of which only 24 miRNA had the same changes in cancer tissues and serum, which was probably related to the source of serum. MiR-25 is not only highly expressed in tumor tissues of patients with NSCLC,[16,17] but also increases in serum or plasma samples, indicating that miR-25 is qualified to be a diagnostic marker of NSCLC. So far, a number of researchers have published studies on diagnostic value of miR-25 in NSCLC and raised concerns about effectiveness of miR-25 as a biomarker. Therefore, in this research, studies on the relationship between blood miR-25 levels and diagnostic value of patients with NSCLC were collected in Chinese population, and corresponding statistical model was used to calculate combined sensitivity, specificity, positive likelihood ratio, negative likelihood ratio (NLR) and diagnostic ratio, in order to evaluate diagnostic value of miR-25 in Chinese patients with NSCLC.

2. Materials and methods

2.1. Retrieval strategy

PubMed, Web of science, Excerpta Medica Database, China national knowledge infrastructure and China Wanfang database were searched to evaluate diagnostic value of miR-25 in NSCLC. The retrieval strategy was as follows: (microRNA-25 OR miRNA-25 OR microRNA25, OR miR-25 OR miRNA25 OR hsa-miR-25) AND (lung tumor OR NSCLC OR NSCLC OR lung neoplasms OR lung cancer). The retrieval time was from the establishment of the databases to April 2020. The language was limited to English and Chinese. A comprehensive database search was carried out independently by 2 researchers.

2.2. Literature selection criteria

2.2.1. Inclusion criteria:. The inclusion criteria were as follows:

(1) The literatures were studies of miR-25 in NSCLC;
(2) 2)Human specimens must be used;
(3) The relationship between miR-25 and diagnostic accuracy was studied;
(4) The subjects were Chinese.

2.2.2. Exclusion criteria:. The exclusion criteria were as shown below:

(1) The literatures studied the relationship between the expression of miR-25 and diagnostic accuracy, with a receiver operating characteristic curve (ROC), but without report of the specific values of sensitivity and specificity;
(2) Letters, case reports, reviews, conference summaries, animal or laboratory studies were excluded;
(3) Pathological subtype of NSCLC was conducted to calculate the relevant indicators of diagnostic accuracy;
(4) The quality assessment of diagnostic accuracy studies (QUADAS) score was lower than 11.

2.3. Quality evaluation

The QUADAS was applied to assess diagnostic value of the study.[18] The QUADAS criteria included 14 evaluation items for systematic review of diagnostic accuracy studies, each of which was rated as yes (score 1), no (score-1) or unclear (score 0). If the QUADAS score was 11 or above, the quality of the study was defined as high-quality. Any differences between the 2 researchers were resolved through discussion by a third researcher.

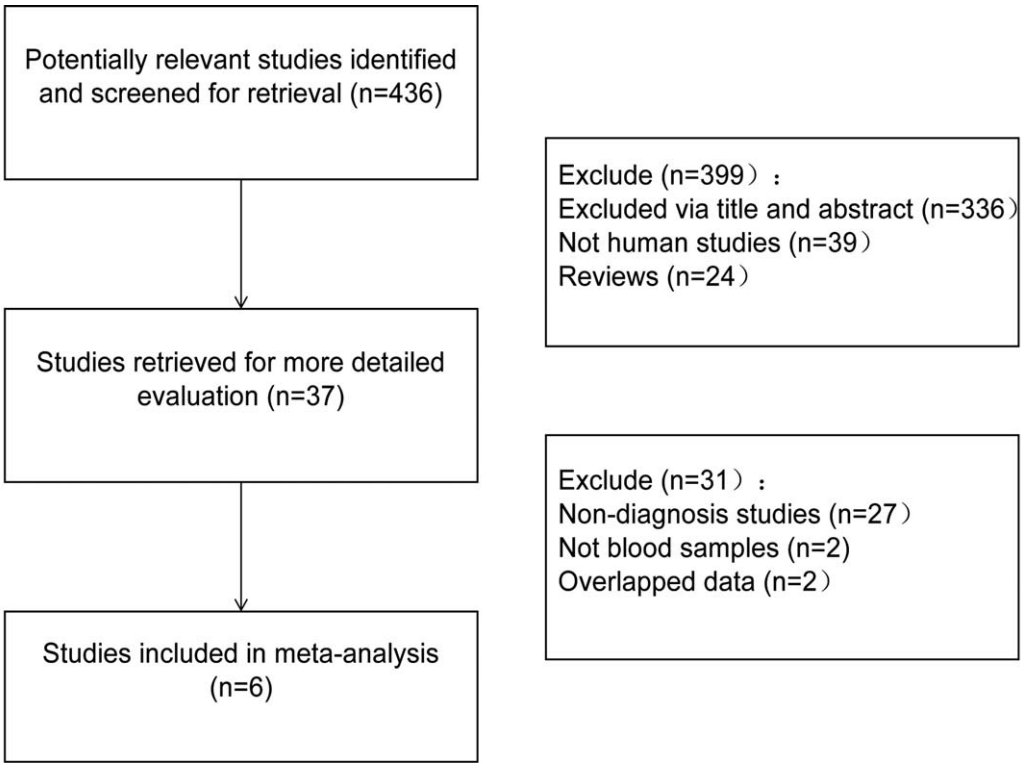

Figure 1. A flow diagram of the study selection process.

2.4. Data extraction

The following information was extracted in this study:

(1) first author, year of publication, tumor grade, detection method and cut-off value;
(2) sensitivity, specificity, number of true positive cases, number of false positive cases, number of false negative cases, and number of true negative cases.

The table was designed according to the information extracted.

2.5. Statistical analysis

Stata 15.0 software was used to analyze the data. The inconsistency index (I^2) and its *P*-value test were applied to evaluate the heterogeneity among studies. The bivariate mixed effect regression model was used to analyze the pooled diagnostic indicators.[19] Regarding the study of diagnostic value, the diagnostic threshold effect was evaluated by the ROC and the spearman correlation coefficient between sensitivity and specificity. The typical shoulder-arm-shaped representation in ROC space and the strong positive correlation between the logarithm of sensitivity and the logarithm of 1-specificity indicated the existence of threshold effect. In the bivariate mixed effect regression model, the pooled sensitivity, specificity, positive likelihood ratio (PLR), NLR, diagnostic odds ratio (DOR) and their forest maps were calculated using the corresponding 95% confidence interval (CI). The area under summary receiver operating characteristic (SROC) curve (AUC) was obtained. With AUC values ranging from 0.5 to 1.0, AUC values close to 0.5, it indicated poor diagnostic performance, and AUC values close to 1.0, it indicated good diagnostic performance. Deeks funnel diagram was applied to evaluate publication bias.

3. Results

3.1. Literature research and characteristic of studies

Initially, 436 articles were retrieved by keywords, of which the titles and abstracts were all reviewed, and 399 of which were excluded. Subsequently, the full text and data integrity of all the articles left were reviewed, 31 of which were excluded afterwards. Finally, 6 studies[13,20–24] that meet all the inclusion criteria were included in this study, including 480 patients with NSCLC and 451 healthy controls. The detailed screening flow diagram is shown in Fig. 1. The basic characteristics of the included literatures and the quality of the methods are shown in Table 1. The detailed evaluation of QUADAS is shown in supplementary table 1, http://links.lww.com/MD/F328. All the QUADAS score included in this study was equal to or above 11.

3.2. Meta-analysis

The results of diagnostic accuracy analysis showed that the heterogeneity was low in the studies of sensitivity ($P=.07$, $I^2=51.37\%$), specificity ($P=.09$, $I^2=47.27\%$), PLR ($P=.26$, $I^2=0.00\%$) and NLR ($P=.11$, $I^2=44.29\%$), while high heterogeneity was found in DOR ($P=.00$,$I^2=80.84\%$). There was no obvious threshold effect in the current meta-analysis, for the ROC curve was not a typical "shoulder-arm" pattern (Fig. 2). The Spearman correlation coefficient was 0.257($P=.623$)

Table 1

The basic characteristic and quality score of the studies included in this meta-analysis.

First author	Year	Patients (control)	Country	Tumor stage	Sample	cut-off	Normalizer	Detection method	TP	FP	FN	TN	QUADAS
Wang P	2015	94 (111)	China	IA–IIB	Serum	0.551	cel-miR-39	qRT-PCR	78	28	16	83	12
Zhi SY	2016	30 (30)	China	I–IV	Serum	1.854	U6 snRNA	qRT-PCR	17	3	13	27	11
Zhong JS	2018	82 (82)	China	I–IV	Serum	0.006	Let-7d/g/i	qRT-PCR	58	16	24	66	11
Li SR	2019	32 (20)	China	I–IV	Serum	NA	cel-miR-39	qRT-PCR	26	1	6	19	11
Zhang YL	2019	114 (80)	China	I–IV	Serum	0.832	cel-miR-39	qRT-PCR	85	20	29	60	12
Li J	2019	128 (128)	China	I–IV	Serum	0.670	U6 snRNA	qRT-PCR	98	20	30	108	12

FN = false negative, FP = false positive, qRT-PCR = Quantitative Real-time Polymerase Chain Reaction, QUADAS = Quality Assessment of Diagnostic Accuracy Studies, TN = true negative, TP = true positive.

between the logarithm of sensitivity and the logarithm of 1-specificity, so the difference was not statistically significant. In general, the results were the combined sensitivity (0.75,95%CI: 0.69~0.80), specificity (0.81,95%CI: 0.76~0.86), PLR (4.04,95%CI: 3.14~5.20), NLR (0.31,95%CI: 0.25~0.37), and DOR (13.09,95%CI: 9.37~18.29). The forest plot of DOR is as shown in Fig. 3A; the forest plot of sensitivity and specificity is shown in Fig. 3B; and the forest plot of PLR and NLR is demonstrated in Fig. 3C. The SROC curve is shown in Fig. 2, with AUC (0.85,95%CI: 0.82~0.88). The result of Fagan Nomogram suggested that the probability ratio of pre-test is 20%; the post-test probability of PLR is 50%, and the post-test probability of NLR is 7% (Fig. 3D), which indicates that miR-25 has an advanced diagnostic performance for NSCLC. The Deeks funnel plot in Fig. 4 illustrated a *P* value of .37, indicating that there was no publication bias.

3.3. Sensitivity analysis

The sensitivity analysis of diagnostic value is shown in Fig. 5. Through sensitivity analysis and outlier detection, a deviation study[13] which might affect the robustness of meta-analysis was determined. After excluding the study, there was no significant change in sensitivity (0.75 vs 0.77), specificity (0.81 vs 0.80), PLR (4.04 vs 3.80), NLR (0.31 vs 0.29), DOR (13.09 vs 13.00), and AUC (0.85 vs 0.83) between overall analysis with or without outlier. This showed that the meta-analysis of diagnostic value in this study was robust.

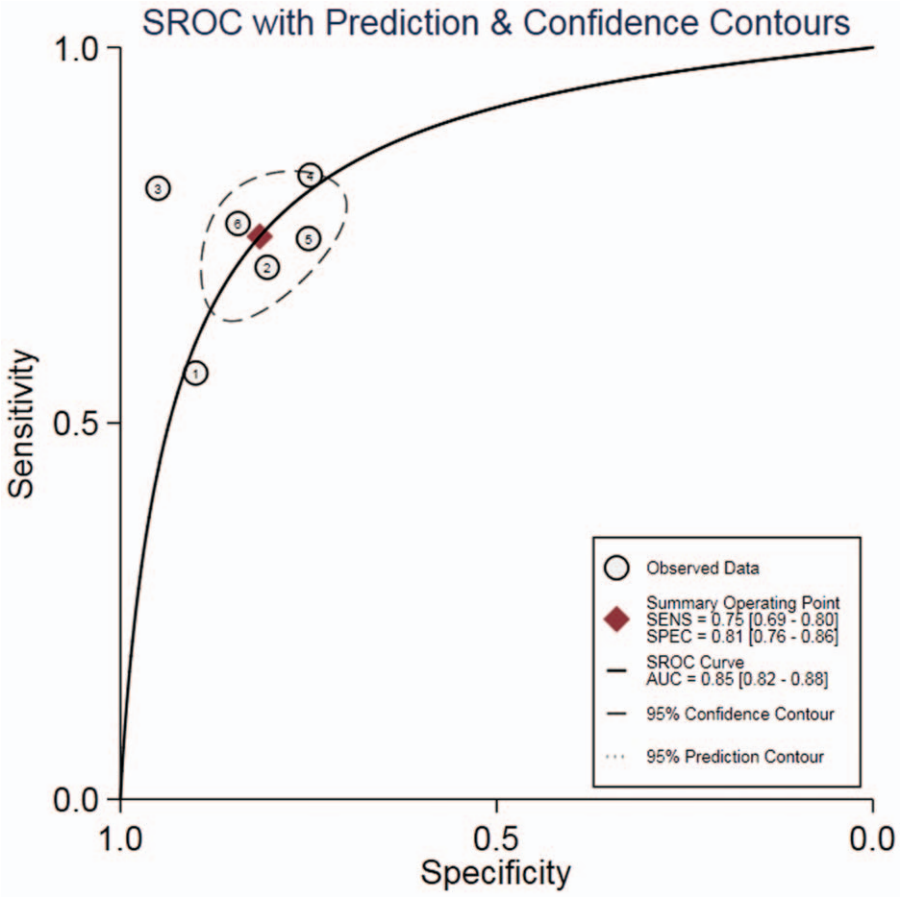

Figure 2. SROC curve for the accuracy of miR-25 in the diagnosis of NSCLC.

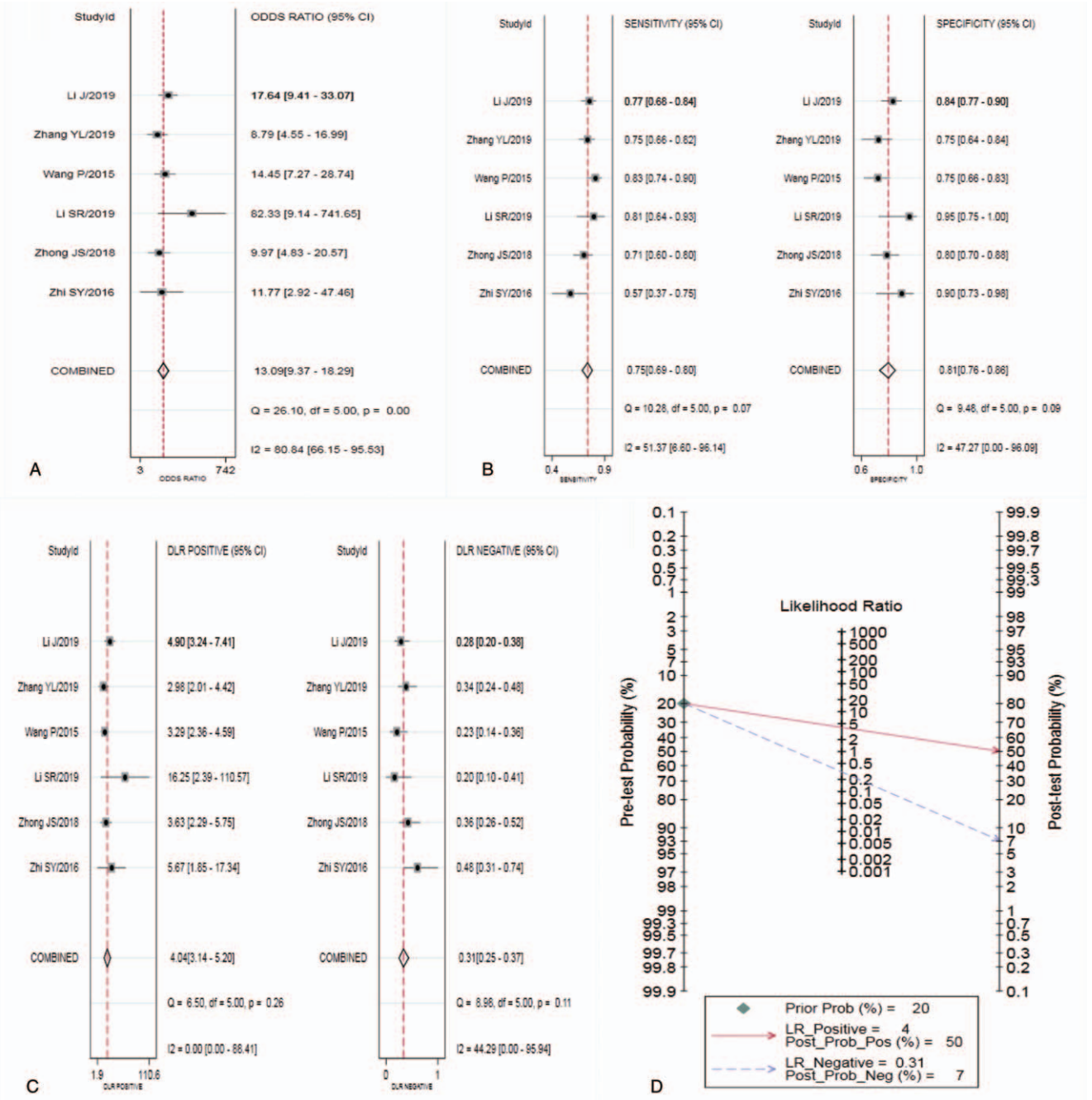

Figure 3. Plot of miR-25 for the diagnosis of NSCLC (A:DOR;B:Sensitivity and specificity;C:PLR and NLR;D: Fagan's Nomogram).

4. Discussion

Mortality rate of lung cancer is very high in the world. Due to difficulty of early diagnosis and rapid metastasis of lung cancer, many patients had already developed blood or lymph node metastasis when they were diagnosed, which results in a significant reduction in survival rate of patients with lung cancer. Therefore, seeking biomarkers for early diagnosis of lung cancer is the key to improve the survival rate of patients with lung cancer. MiRNA is a kind of endogenous non-coding small RNAs composed of 18 to 24 nucleotides, which widely exists in eukaryotes. MiRNA can be completely or incompletely complementary to bases in the 3 'untranslated region (3'UTR) of the target messenger RNA (mRNA), to induce the degradation of the target mRNA or inhibit its translation, and achieve the purpose of regulating the expression of the target gene at the post-transcriptional level.

More than 1000 mature miRNA have been discovered in human genes. Although the proportion of miRNA in human genome is only 1% to 3%, it regulates the expression of more than 30% of the protein-coded genes in human body.[25] Studies have shown that 50% of miRNA coding genes identified are

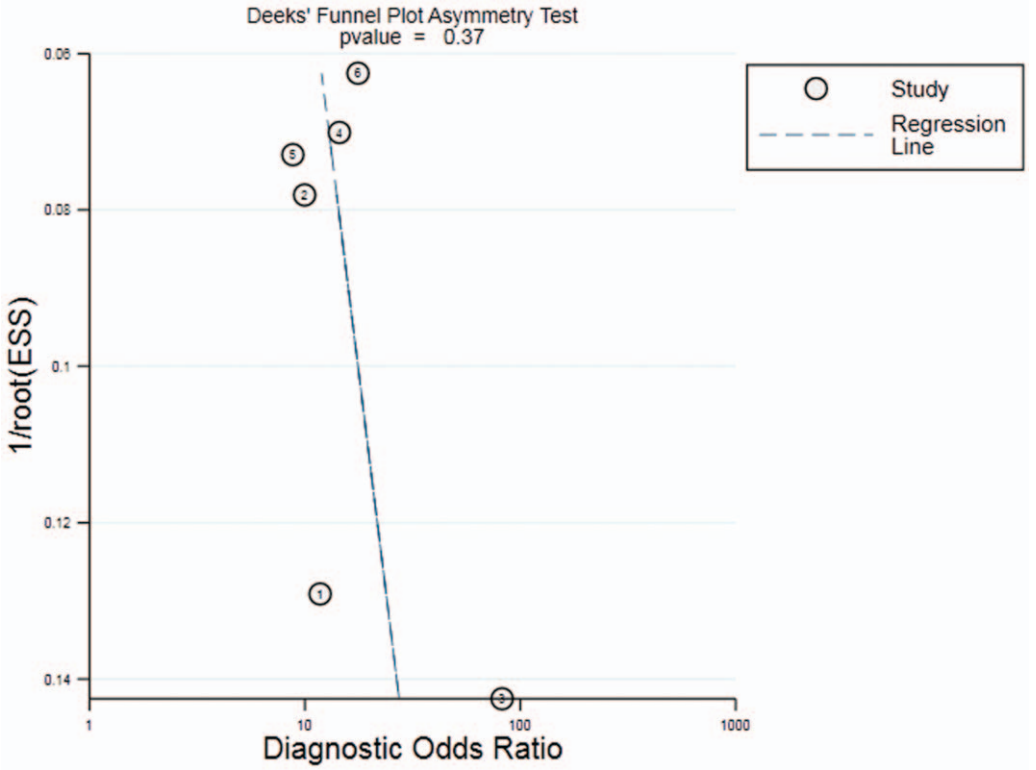

Figure 4. Funnel plot of miR-25 for the diagnosis of NSCLC.

located in tumor-related gene regions or fragile sites,[26] and there is a significant difference in expression of these microRNA between tumor cells and corresponding normal cells, which indicates that miRNA may play an critical role in occurrence and development of human tumors. The discovery of miRNA, especially serum miRNA, has opened up a new way for early diagnosis of cancer. Studies have found that not only can abnormal expression of miRNA be in lung cancer tissues, but also abnormal expression of miRNA in blood circulation, and miRNA can stably exist in serum .[27–29] Chen et al detected differential expression of serum miRNA of 400 patients with NSCLC and 220 healthy controls with Taqman probe quantitative RT- PCR. The study found that there was differential expression among 10 miRNAs (miR-20a, miR-24, miR-25, miR-145, miR-152, miR-199a-5p, miR-221, miR-222, miR-223, miR-320) in serum of NSCLC patients compared with the control groups. Then they evaluated diagnostic value of these serum miRNAs via risk score analysis, which suggested that this group of miRNAs could distinguish NSCLC patients from the control groups with high sensitivity and specificity.[30]

Foss et al. analyzed miRNA expression profiles in serum samples of 11 patients with early NSCLC and 11 healthy

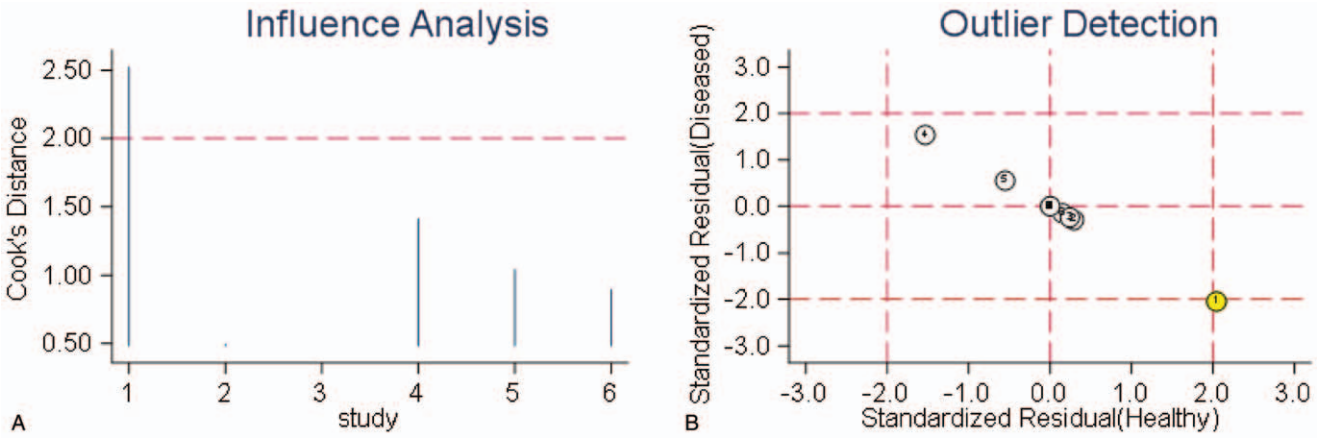

Figure 5. The results of sensitivity analysis.

controls, and found that the expression levels of has-miR-1254 and has-miR-574–5p in serum of early NSCLC patients were significantly higher than those of the control samples. In verification group, the sensitivity and specificity were 73% and 71%, respectively.[31] Saitoh et al found that miR-375 can promote tumorigenesis by up-regulating the target gene FZD8 to activate the β-catenin-TCF signal pathway.[32] Zeng et al. found that the expression of miR-205 is up-regulated in lung cancer tissues and it can target suppression of SMAD4 to promote proliferation of lung cancer cells.[33] Yi et al.found that miR-375 is highly expressed in lung adenocarcinoma and small cell lung cancer, but low in lung squamous cell carcinoma, elucidating that miR-375 can promote growth of small cell lung cancer cell lines by directly down-regulating the target gene ITPKB.[34] In addition to typical miRNAs, miR-545[35] and miR-25[36–38] are also closely related to proliferation and apoptosis of lung cancer cells.

Six studies were included in the study, including 480 patients with NSCLC and 451 healthy controls. The results showed that the sensitivity, specificity, PLR, NLR, DOR and AUC were 0.75, 0.81, 4.04, 0.31,13.09, and 0.85, respectively. From the spearman correlation test of logarithm of sensitivity and logarithm of 1-specificity, as well as the shape of the SROC curve, a conclusion can be drawn that there was no significant threshold effect between the included studies. In terms of the sensitivity, specificity and the area under the SROC curve, miR-25 has diagnostic value for NSCLC. Combining + LR and-LR, + LR was less than 10 and-LR was greater than 0.1, thus the miR-25 in diagnosing NSCLC is still limited. The results of publication bias analysis showed that the publication bias of this meta-analysis was well controlled. The results of sensitivity analysis also confirmed the robustness of circulating miR-25 in diagnosis of NSCLC. In terms of sensitivity, specificity, PLR, NLR and diagnostic ratio, diagnostic value of circulating miR-25 in NSCLC is advanced. In practice, miR-25 can be combined with other biomarkers to improve its diagnostic accuracy in NSCLC. Wang et al[39] combined 5 markers, miR-483–5p, miR-193a-3p, miR-25, miR-214 and miR- 7, to diagnose NSCLC, and the area under the ROC curve was as high as 0.976 (95%CI:0.939~1.000).

However, this study also has some limitations.

(1) In terms of diagnostic accuracy, only 6 studies met the conditions of combined analysis, and the insufficient sample size may affect the overall estimation;
(2) The population included in the study was relatively narrow, all of which were Chinese, so it may have some limitations for the generalization of the conclusion;
(3) The study only focused on meta-analysis of diagnostic value of miR-25 in NSCLC, while no joint analysis was performed with other potential biomarkers.

In conclusion, miR-25 is a promising biomarker for the diagnosis of NSCLC in Chinese population, with advanced sensitivity and specificity. It provides a faster and less invasive assessment of NSCLC than other markers that require histopathological analysis. In addition, it is more valuable in finding circulatory prognostic markers than tissue markers in cancer patients. On the other hand, considering the effects of gender, age and race on large-scale studies, it is necessary to further evaluate the relationship between mir-25, NSCLC prognosis and chemotherapy sensitivity. In conclusion, our results proved the valuable diagnostic function of miR-25 in NSCLC, which may eventually contribute to a better understanding of the role of miR-25 in development of NSCLC and may enable it to become a biomarker in early diagnosis of NSCLC.

Author contributions

JG Chen: Critical revision of the manuscript; C Li, L Sun,HB Zhou: Substantial contribution to the conception and design of the work, manuscript drafting; Y Yang and Y Wang: Acquisition, analysis, and interpretation of the data; JG Chen, C Li and M She: Revising the manuscript critically, final approval of the version to be published. All authors have read and approved the final manuscript.

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