

Diagnostic value of microRNAs in breast cancer: a meta-analysis

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Abstract. – OBJECTIVE: To explore the value of diagnosis accuracy of aberrant microRNAs in breast cancer.

MATERIALS AND METHODS: We searched PubMed, Embase, EBSCO and the Cochrane Library, accessing to the case of articles about microRNA expression in breast carcinoma patients after literature screening and quality assessment, extracting data from included studies and using Stata 14.0 analysis data for meta-analysis.

RESULTS: 14 English studies met the inclusion criteria. After meta-analysis for included studies obtained high sensitivity and specificity and diagnostic odds ratio, the combined OR value is 17.96 (95% CI: 11.42-28.42), sensitivity is 0.85 (95% CI: 0.81-0.88), specificity is 0.77 (95% CI: 0.69-0.82), diagnostic odds ratio is 18 (95% CI: 12-29), operating characteristic area under the curve is 0.88 (95% CI: 0.85-0.91).

CONCLUSIONS: The microRNAs can be used as a clinical auxiliary reference index for diagnosis of breast cancer.

Key Words:

Breast cancer, microRNA, Meta-analysis.

Introduction

Breast cancer ranks the highest not only in the carcinoma incidence in the females all over the world, but also in the mortality in all diseases. Among all the tumors of female, breast cancer has accounted for 25%, while in the death cases caused by tumors, it also takes up to 15%¹. Currently, surgery and chemotherapy are the major clinical therapies for breast cancer. As one of mitotic inhibitor frequently applied for the chemotherapy of breast cancer, Taxol can be used for other kinds of tumors: ovarian cancer, prostatic cancer and non-small cell lung cancer (NSCLC)^{2,3}. However, many patients have been found to be resistant to the chemotherapy dru-

gs, leading to the poor prognosis for the treatment of patients with cancer⁴. Thus, an early diagnosis of breast cancer has become an important prerequisite for improving the efficacy of breast cancer. Various conventional methods have been proved to be beneficial to the diagnosis of breast cancer, such as image examination as well as the receptor examination of the hormone. The focus of various studies⁵⁻⁸ has been shifted to the newly identified marker for the early diagnosis of breast cancer: micro-RNA.

Micro-RNA, a kind of small non-coding RNA molecule (containing about 22 nucleotides), can regulate the gene expression by degrading the mRNA or suppressing the translation process after transcription⁹. The binding regions (2-7nt) on the micro-RNA are short enough to regulate the expression of multiple loci on the gene. Some micro-RNA can affect the occurrence and development of various diseases^{10,11}. Generally, micro-RNA can impact the differentiation, growth and apoptosis of normal cells through various pathways; while the abnormally expressed micro-RNA can alter the physiological and morphological features of different kinds of cells, and induce the abnormal hyperplasia of tissues or the tissues to be differentiated into the tumors. Thus, the abnormally expressed micro-RNA can be served as a specific marker for diagnosis of some tumors^{12,13}. In the microenvironment of breast cancer, significant changes occur in the specific micro-RNA in the cells of a tumor or its excretion, and we can predict the occurrence and development of tumor by detecting such changes of the specific micro-RNA. There have been more and more investigations as well as clinical experiments focusing on the influences of micro-RNA on the diagnosis and prognosis of breast cancer. In this work, we conducted a meta-analysis of diagnostic accuracy of breast cancer using micro-RNA for, and explored the application value of micro-RNA in the diagnosis of breast cancer.

Materials and Methods

Literature Retrieval Strategy

PubMed, Embase, EBSCO and Cochrane Library were searched using the following key words: breast cancer, breast carcinoma, breast tumor, microRNA, miRNA, miR. The search with random combination of key words was also performed, e.g. “breast cancer” and “microRNA”, “breast carcinoma” and “microRNA”, “breast tumor” and “microRNA” or “miR”.

Inclusion and Exclusion Criteria for Literature

Inclusion criteria of literature were set as follows: a) literature with enrolled cases which were clinically confirmed as breast cancer and with the control group which was constituted by patients with no breast cancer; b) literature which included a case-control study; c) literature which was the original article in English published in recent years; d) literature with real and intact data; e) literature which was evaluated as high-quality literature through the quality assessment. Exclusion criteria of literature were set as follows: a) literature which were repeatedly published; b) literature that were review articles, case report or meeting documents; c) literature which could not provide intact data; d) literature which was not a case-control study.

Criteria of Quality Assessment for Literature

The quality assessment was performed for the enrolled literature using QUADAS-2 developed by Cochrane collaborate websites. In the assessment, the reviewers answered to 11 items with “yes”, “no” or “unclear”, and the literature was scored by following protocols: “yes”, 1 point; “no”, -1 point; “unclear”, 0 point. Literature with the score not less than 7 points was considered as the high-quality literature.

Data Extraction

The data required for the study were extracted from the enrolled literature by 2 or 3 researchers, mainly including: author, published date, article source, the type of detected micro-RNA and the relevant detection method, number of cases in the case group and the control group, and increase or decrease in the expression of micro-RNA. For any doubt, researchers should work out by negotiation or acquisition of the original material through contacting the author of literature.

Statistical Analysis

Meta-analysis was applied to the extracted data using Stata 14.0. Firstly, we evaluated the publication bias and tested the heterogeneity for the enrolled literature. Literature with publication bias was all removed. While for the literature with higher heterogeneity, meta-regression analysis was performed to identify the major source of heterogeneity, a subgroup analysis was performed for the enrolled literature to minimize the influence of heterogeneity on the results. We analyzed and acquired the sensitivity (SENS), specificity (SPEC), positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and area under the receiver operating characteristic curve (AUC) of the enrolled subjects.

Results

Results of Literature Search

In the preliminary results of literature search, there were 1014 works of literature on the breast cancer and micro-RNA. Of these, 145 repeatedly published works of literature were excluded. In the remaining 869, 313 of article reviews, case reports or correspondences and 379 not related to the clinical diagnosis experiment of micro-RNA were all rejected after a brief review. For the rest of the literature (177) that needed to review the whole text, 3 researchers extracted the relevant data after the literature screening to exclude the non-case control literature or the non-breast cancer literature. Finally, 14 work of literature were enrolled¹⁴⁻²⁷ (Figure 1).

Basic Information of the Enrolled Literature

In this study, we enrolled 14 English work of literature containing 18 independent case-control experiment (Table I). In these experiments, there were a total of 4581 patients: 2351 in the case group and 2230 in the control group. The sources where micro-RNA was collected included the plasma, serum, tissue and urine. This literature was from Europe, Asia and America.

Quality Assessment of Literature

The researchers conducted the quality assessment for the enrolled literature using the scoring system recommended by Cochrane Collaborate Websites. According to the reference of 11 items, the scores of all enrolled literature were not less than 6 points, suggesting that literature met the quality requirement.

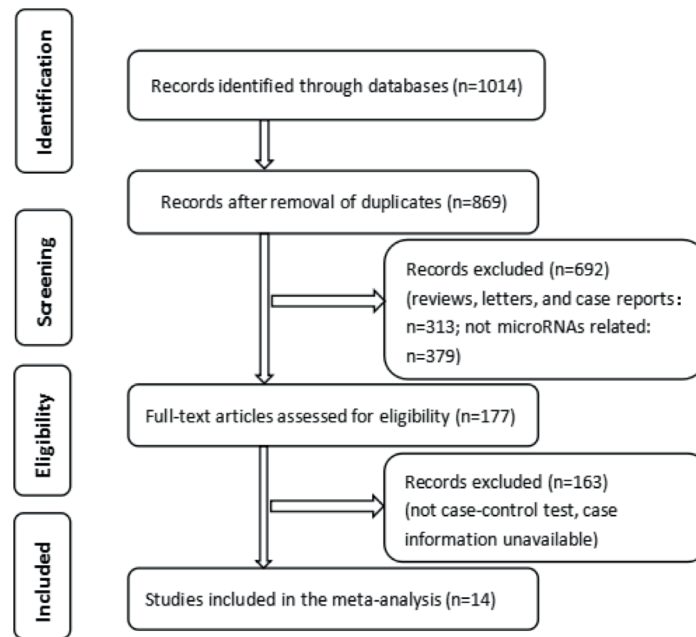


Figure 1. Literature searching process.

Table I. Summary of included studies. (*undetected; #unmentioned).

ID	Author	Year	Country	microRNAs	Specimen	Cancer	Control	SENS	SPEC	Method	Level
1	Shimomura A	2016	Japan	miR-1246	serum	1260	1343	0.91	0.883	Taqman	up
2	Fu L(a)	2016	China	miR-598-3p	serum	100	40	0.95	0.85	SYBR	down
3	Fu L(b)	2016	China	miR-1246	serum	100	40	0.93	0.75	SYBR	up
4	Fu L(c)	2016	China	miR-184	serum	100	40	0.875	0.71	SYBR	down
5	Freres P	2016	Belgium	miR-16/103/107/148a/19b/22,let-7i,let-7d	plasma	108	88	0.91	0.49	#	*
6	Zheng R	2015	China	miR-106b	plasma	173	70	0.882	0.601	#	up
7	Zhang H	2015	China	miR-205	serum	58	93	0.862	0.828	#	down
8	Toraih EA	2015	Egypt	miR-21	serum	30	60	0.667	0.867	Taqman	up
9	Matamala N(a)	2015	Spain	miR-505-5p	plasma	114	116	0.75	0.6	#	up
10	Matamala N(b)	2016	Spain	miR-96-5p	plasma	114	116	0.73	0.66	#	up
11	Erbes T	2015	Germany	miR-21/125b/155/451	urinary	24	24	0.833	0.875	Taqman	up
12	Eissa S	2015	Egypt	miR-221	tissue	76	36	0.816	0.972	SYBR	up
13	Antolin S(a)	2015	Spain	miR-141	blood	57	20	0.9	0.702	#	up
14	Antolin S(b)	2015	Spain	miR-200c	blood	57	20	0.9	0.795	#	down
15	Zhao FL	2014	China	miR-195	serum	102	210	0.69	0.892	SYBR	down
16	Shen J	2014	USA	miR-133a/148b	plasma	50	50	0.87	0.7	SYBR	up
17	Deng ZQ; Yin JY	2014	China	miR-98	tissue	98	40	0.827	0.538	SYBR	up
18	Deng ZQ; Qian J	2014	China	miR-93	tissue	101	40	0.85	0.875	SYBR	up

Test of Publication Bias and Heterogeneity

Symmetry test ($p=0.07$) and heterogeneity test ($I^2=89.3\%$, $p=0.00$) were performed for the enrolled literature (Figure 2c-d), and a very high heterogeneity was identified in intergroup comparison. SENS analysis revealed that the research of Shimomura had the highest influence on the overall enrollment of subjects (Figure 2a), and that no lite-

rature with poor SENS was found in this research after research scope was removed (Figure 2b). Heterogeneity was found to be very high even though the random effect model was selected for combined analysis of enrolled subjects ($I^2=72.6\%$). Hence, we performed a meta-regression analysis for this study, and found that the heterogeneity was primarily from the specimen source of the micro-RNA

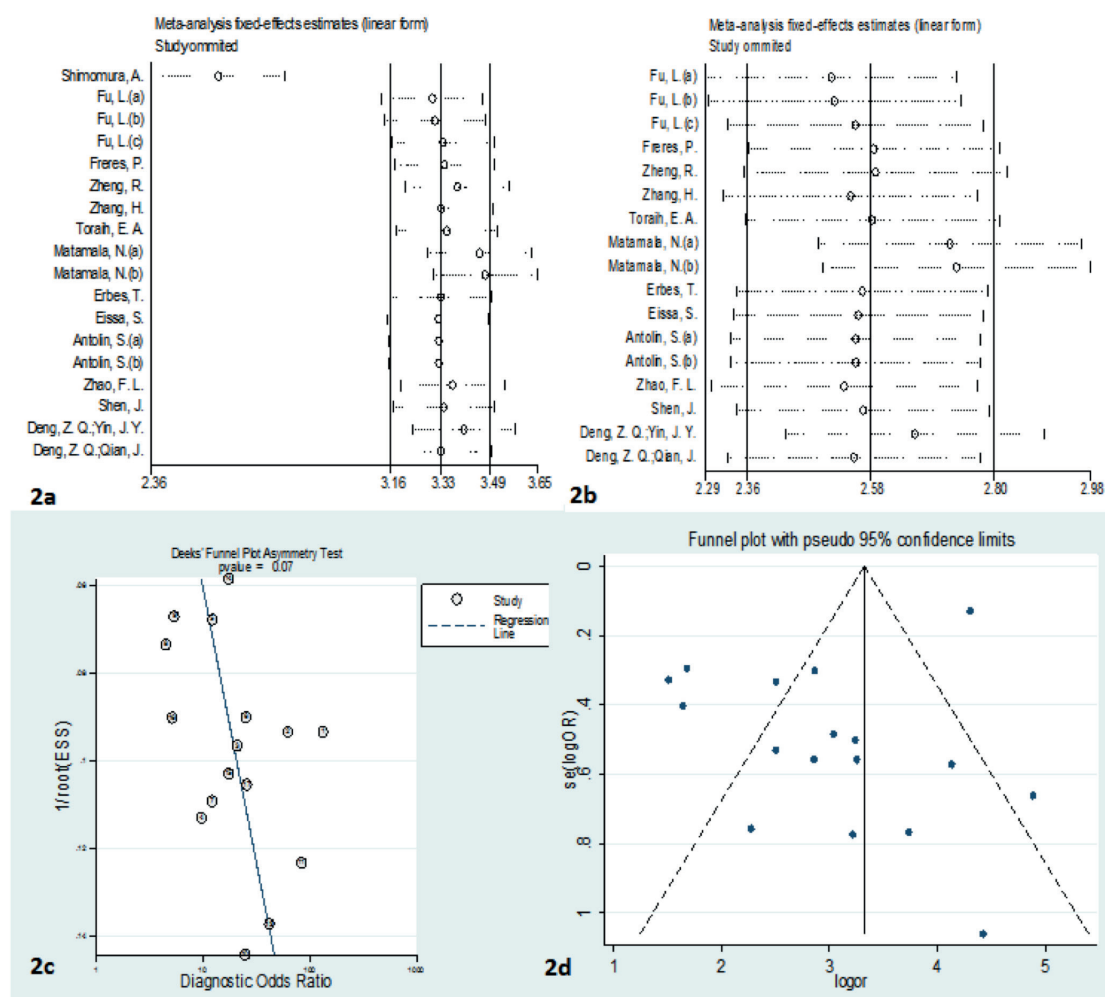


Figure 2. Summary of included studies: (a-b) pre and post sensitivity analysis; (c) publication bias test; (d) funnel plot.

followed by the detection method. Therefore, we conducted the subgroup analysis for different specimens of subjects.

Results

According to the distribution of SENS and SPEC in the contour map (Figure 3a) and the di-

splay of PLR and NLR in the matrix of all the enrolled subjects (Figure 3b), we found that the uniformity of these analysis results was affected by 3 studies from Freres et al²³, Eissa et al²⁷ and Deng et al^{25,26}.

Based on the above results, we applied the random effect models to the enrolled studies (Table II, Figure 4). Subgroup analysis results indicated that the combined OR was 17.96 (95% CI: 11.42-

Table II. Subgroups' analysis results.

	OR	Sens	Spec	PLR	NLR	DOR	AUC
Serum	28.38(15.37-52.40)	0.87(0.79-0.95)	0.86(0.82-0.89)	6.2(4.8-8.0)	0.15(0.09-0.25)	41(22-77)	0.90(0.87-0.92)
Plasma	7.90 (4.75-13.15)	0.83(0.75-0.89)	0.61(0.54-0.68)	2.1(1.8-2.5)	0.28(0.19-0.4)	8(5-12)	0.76(0.72-0.79)
Tissue	18.32 (3.91-85.88)	0.83(0.78-0.87)	0.70(0.60-0.79)	4.2(1.1-15.8)	0.22(0.16-0.32)	18(4-86)	0.90(0.87-0.93)

(OR: odds ratio; Sens: sensitivity; Spec: specificity; PLR: positive likelihood ratio; NLR: negative likelihood ratio; DOR: diagnostic odds ratio; AUC: area under the curve).

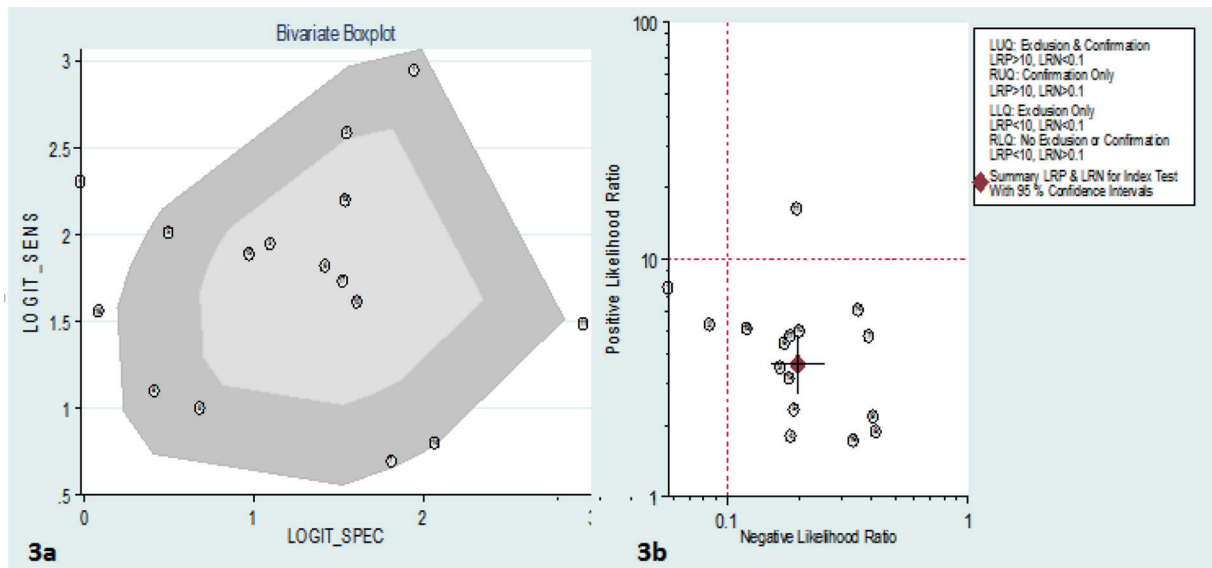


Figure 3. Contour plot for SENS/SPEC and Matrix plot for PLR/NLR.

Forest plots for subgroup

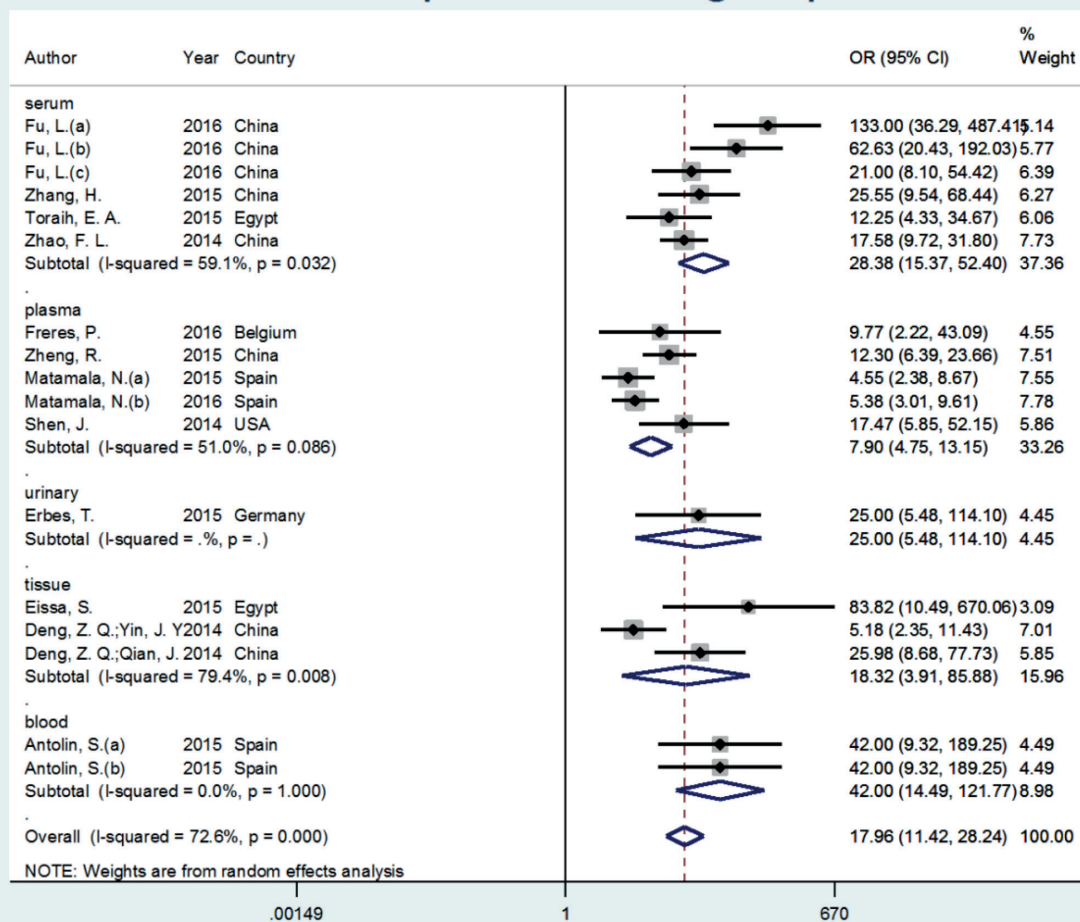


Figure 4. Forest plots for subgroup.

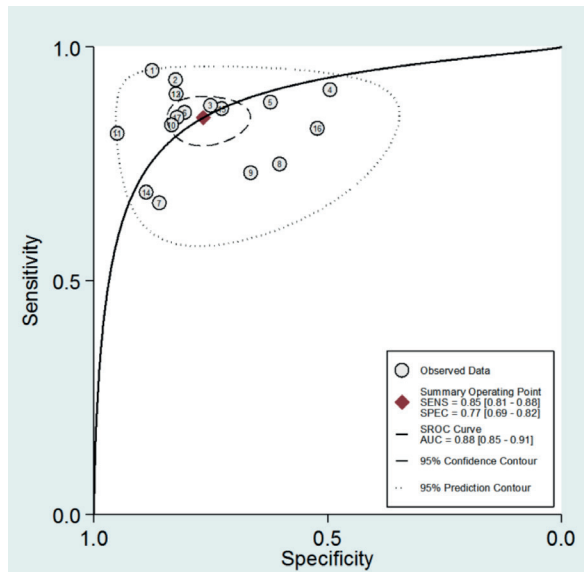


Figure 5. Summary receiver operator characteristic curve (SROC).

28.42), SENS was 0.85 (95% CI: 0.81-0.88), SPEC was 0.77 (95% CI: 0.69-0.82), PLR was 3.6 (95% CI: 2.7-4.8), NLR was 0.20 (95% CI: 0.15-0.26), DOR was 18 (95% CI: 12-29), and the area un-

der the receiver characteristic-operating curve was 0.88 (95% CI: 0.85-0.91). Summary receiver operator characteristic curve (SROC) could better evaluate the accuracy of the detection method. Area under curve (AUC) was a major index to determine the value of diagnosis. The closer the value was to 1, the higher value it had. Besides, as shown in Figure 5, no threshold effect was identified in this study ($z=0.74$, $p=0.47$).

Discussion

According to the above results of the meta-analysis, we could discover the advantage of micro-RNA in the diagnosis of breast cancer with a higher SENS, SPEC and DOR. However, the heterogeneity among studies remained very high in the subgroup analysis, largely affecting the uniformity of micro-RNA in the diagnosis of breast cancer and the combined effect size. Through the separated ROCs (Figure 6a), SENS was 0.849, SPEC was 0.765 and DOR was 18.37 ($z=0.74$, $p=0.46$). Also, the criterion for detecting the diagnostic rate was set as 0.5 (Figure 6b), the positive diagnostic rate and negative diagnostic rate were

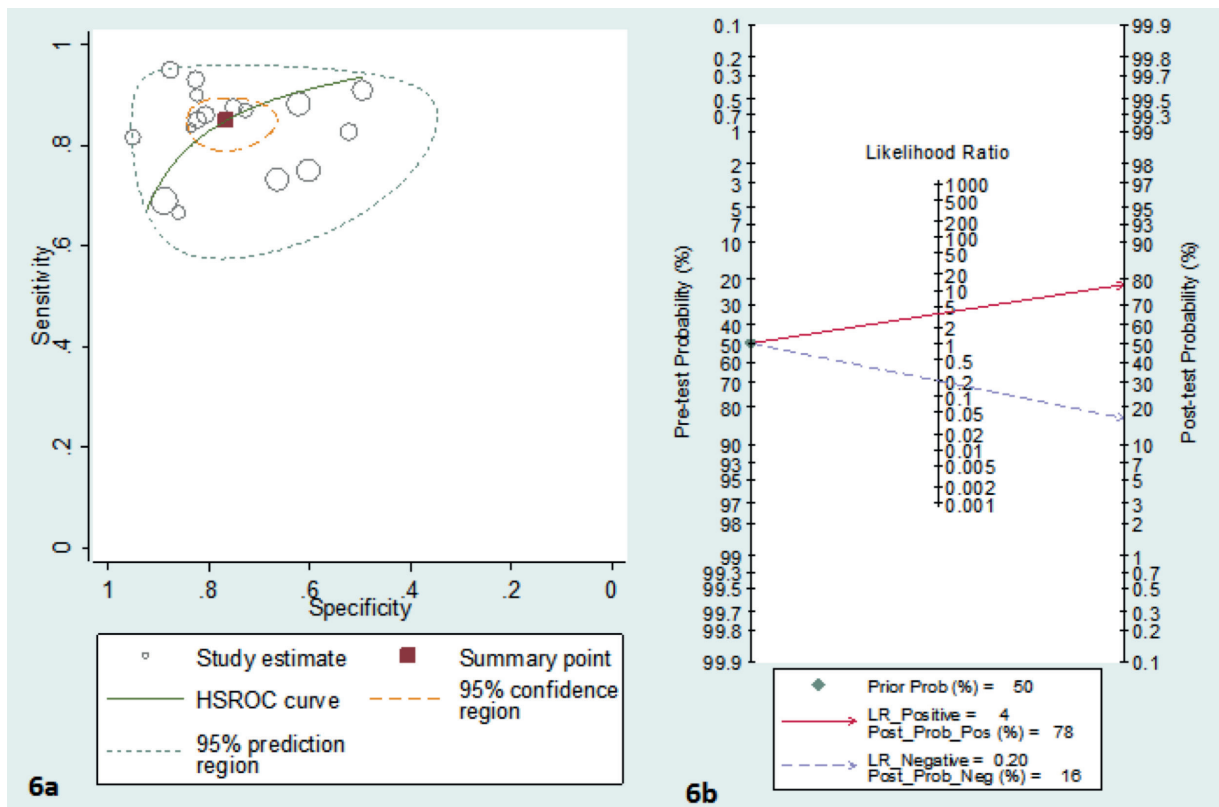


Figure 6. Hierarchical summary receiver operator characteristic curve (HSROC) and post-diagnose probability.

0.78 and 0.16, respectively. This suggested that the detection method was reliable for detecting the accuracy of breast cancer diagnosis.

Besides, there remains some limitation in this meta-analysis: the heterogeneity among the enrolled literature could not be fully eradicated. There were some key factors affecting the heterogeneity of literature, including the bias in the process that clinical physicians enrolled the patients into the case group and control group, and the detection methods of micro-RNA as well as the tissue sources.

The breast cancer has ranked the top of the female tumors. Thus, to increase the early diagnostic rate and reduce the morbidity and mortality of breast cancer has become a priority in the clinical practice. Currently, estrogen receptor (ER) and human epidermal growth factor receptor-2 (HER2) have been served as common indexes for determining the efficacy of endocrine therapy and biological chemotherapy for breast cancer include, but the best positive diagnostic rate can hardly be attained. Moreover, some patients with tumors show no response to these detection methods^{28,29}. Also, biological markers are also adopted, such as carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE), but these markers show a poor sensitivity and specificity, and are limited in clinical application^{30,31}.

Conclusions

At present, the research result of micro-RNA can be served as a new clue for the early diagnosis of breast cancer, and plays an important role in pathological and physiological characteristics, metastasis and prognosis of breast cancer^{32,33}.

It can provide the theoretical basis for micro-RNA used as a new biological marker for diagnosis of breast cancer³⁴, and it is expected to be a key method for the diagnosis and treatment of the early-stage breast cancer in the future.

Conflict of interest

The authors declare no conflicts of interest.

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