International Journal of Scientific Research in Dental and Medical Sciences

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Evaluation of the Role of Exosome-derived MiRNA in Breast Cancer Diagnosis: A Systematic Review and Meta-analysis

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ARTICLE INFO

Article history:
Received 07 September 2023
Received in revised form 29 October 2023
Accepted 25 November 2023
Available online 01 December 2023

Keywords:
Area Under Curve
Breast Neoplasms
Exosomes
Sensitivity and Specificity

ABSTRACT

Background and aim: Considering the importance of early detection of breast cancer and the use of non-invasive methods, the present study was conducted to evaluate the role of exosome-derived miRNA in breast cancer diagnosis.

Material and methods: In the present systematic review and meta-analysis, information about exosome-derived miRNA in breast cancer diagnosis in all articles published up until the end of July 2023 was collected by two trained researchers individually using keywords and combinations of keywords from databases PubMed, Scopus, Science Direct, ISI, Web of Knowledge, Elsevier, Wiley, and Embase and Google Scholar. STATA (version 17) was used to analyze data using the fixed effects model in meta-analysis; p values less than 0.05 were considered significant.

Results: A total of six studies were included in the meta-analysis process. The sensitivity and specificity of plasma-based exosomal miRNAs were 68% (ES, 95% CI: 0.39, 0.97) and 82% (ES, 95% CI: 0.52, 1.11), respectively. The sensitivity and specificity of serum-based exosomal miRNAs were 67% (ES, 95% CI: 0.33, 1.01) and 88% (ES, 95% CI: 0.54, 1.22), respectively.

Conclusions: Exosomal miRNAs have high sensitivity and specificity in breast cancer diagnosis and can be considered a valuable and promising tool for early detection of breast cancer non-invasively.

1. Introduction

Breast cancer is one of the most common cancers among women and is the first cause of cancer-related death in women.[1] Breast cancer is a type of malignant tumor that arises from the cells of this organ. In breast cancer, the disease usually starts in the lobules or ducts of the breast, and then it can penetrate through the ducts and walls of the glands and attack the surrounding fatty tissues or even other parts of the person's body.[2] Early diagnosis of this disease helps doctors prevent the progression of cancer despite the lack of a method to prevent cancer and no definitive treatment. The number of cancer patients in the world is increasing. The best way to reduce mortality from breast cancer is to detect it early in order to treat it.[3] Early diagnosis requires an accurate and reliable diagnostic method.[4] MicroRNA (miRNA) is a group of non-coding RNAs that are about 21-23 nucleotides long and affect gene expression after transcription.[5] Evidence has shown that the expression and disruption of miRNA activity can lead to various problems and diseases, the most important of which is cancer. In cancer, miRNA can affect tumor suppressors, carcinogenesis, and Oncomir.[6] Exosomes are abundantly present in blood, urine, breast milk, and cerebrospinal fluid and contain protein and RNA. Their diameter is 30 to 150 nm.[7] By targeting the surface of the vesicles, exosomes can bind to the target cells and combine with them, and then change the physiological state of the recipient cells by releasing their cargo to the target cells.[8] Studies have shown that exosomal miRNAs are more stable than free miRNAs in body fluids.[9] Also, studies have shown that exosomal miRNA can perform better in diagnosing various cancers.[10-12] Considering the importance of early detection of breast cancer and the use of non-invasive methods, the present study was conducted to evaluate the role of exosome-derived miRNA in breast cancer diagnosis.

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https://doi.org/10.30485/IJSRDMS.2023.424322.1546

2. Material and methods

Search strategy

The present study used articles published in international databases such as PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase, and Google Scholar search engines to collect scientific documents and evidence related to exosome-derived miRNA on breast cancer diagnosis. The search process until July 2023 in PubMed database was done using MeSH keywords: (((((((("Neoplasms"[Mesh]) OR "Neoplasms/therapy"[Mesh]) OR "Breast Neoplasms"[Mesh]) OR "Breast Neoplasms/therapy"[Mesh]) AND "MicroRNAs"[Mesh] AND "EXOSC1 protein, human" [Supplementary Concept] AND ("Diagnosis"[Mesh] OR "Early Diagnosis"[Mesh]) OR "Sensitivity and Specificity"[Mesh] and search process in other database was done until July 2023 using English keywords: neoplasm, cancer, breast neoplasm, breast cancer, diagnosis, diagnosis accuracy, sensitivity, specificity, MicroRNAs, Exosomal microRNAs. In addition, the reference list of the obtained articles was checked to identify the articles that were not obtained using the above methods. Databases were searched with high sensitivity. The search was done independently by two researchers to avoid bias.

Study selection criteria

Inclusion and exclusion criteria

Table 1 specifies the PECOS (patient/population, exposure, comparison, outcome, and study design) strategy for constructing the research question. Human samples, serum, plasma or blood samples, exosomal miRNA, studies reported sensitivity and specificity, and availability of the full text of the article. We excluded incomplete studies, case reports, in vitro and in vivo studies, and review articles.

Table 1. PECO strategy.

PECO Strategy	Description
P	Population: Breast Cancer Cells
E	Exposure: exosomal miRNA
C	Comparison: Control group
O	Outcome: Detection accuracy
S	Study design: RCT and Non-RCT

Data collection

The information from the selected articles was entered into a checklist based on the objectives (Table 2).

Risk assessment

The quality of the studies was evaluated using the Newcastle-Ottawa Scale (NOS).[13] This scale evaluates the articles in terms of the selection process: representativeness of the samples, sample size, non-response and measurement tools (four parts), comparability (one part includes investigation of confounding factors and other influencing factors), and results (two aspects: statistical tests and evaluation of the results). Articles are scored from 1 (weakest study) to 9 (strongest study). Low-quality studies have a score of less than three. A score between 4 and 6 indicates average quality, while a score above 6 indicates high quality.

Data analysis

An effect size with a 95% confidence interval was used in the meta-analysis. Heterogeneity was determined by the Index I2 (less than 25%: weak heterogeneity, 26-75%: moderate heterogeneity, and more than 75%: high heterogeneity). The results were combined using the random effect model (REML method) in meta-analysis. The Egger test checked the publication bias and Beggs funnel plot (Fig. 7), and data analysis was done using STATA/MP. V17 software. A p-value of less than 0.05 was considered significant.

3. Results

The search with related keywords turned up 291 studies. The studies were organized using Endnote.X8 software. With the mentioned software, 13 duplicate studies were eliminated after reviewing their titles and abstracts. Researchers then examined abstracts from 265 articles. Two hundred twenty-three studies that did not meet the inclusion criteria or were excluded due to weak or unrelated relevance to the study objective (if, after reading the title and abstract, it was impossible to decide on the article, the full text was referred to). Two independent researchers carefully reviewed the full text of 42 articles; 36 articles were removed due to low quality and inconsistency of study objectives. Finally, six articles were selected (Fig. 1).

Characteristics of patients

In total, 327 breast cancer patients and 157 healthy controls were included in this study. The clinical characteristics are presented in Table 2.

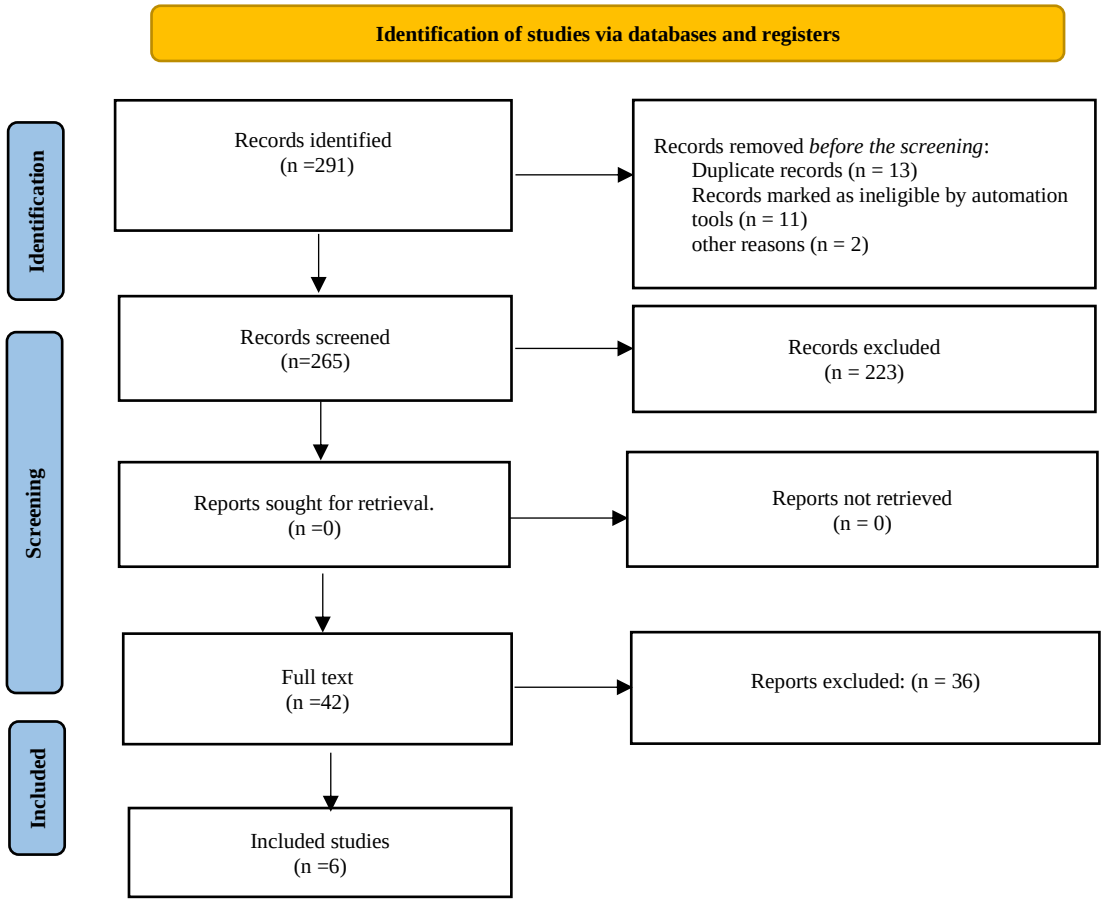

Fig. 1. PRISMA 2020 Checklist.

Table 2. Characteristics of the patients with breast cancer.

Study. Years	Number of Patients		Source	Exosome MiRNA	Test	Area Under the Curve
	Intervention	Control				
Asgari et al., 2022[14]	7	7	Serum	miR-21, miR-155, miR-182, miR-373, and miR-126	qRT-PCR	NR
Zhou et al., 2021[15]	41	18	Plasma	MiR-494	qRT-PCR	0.72
Zhou et al., 2021[16]	41	18	Plasma	MiR-6886, MiR-6819	qRT-PCR	0.69
Liu et al., 2021[17]	30	30	Plasma	miR-21-5p	qRT-PCR	0.96
Li et al., 2020[18]	125	50	Serum	miR-148a	qRT-PCR	0.80
Lv et al., 2020[19]	83	34	Serum	miR-17-5p	qRT-PCR	0.78

Sensitivity of exosome-derived miRNAs in breast cancer

The sensitivity of exosome-derived miRNAs in breast cancer was 67% (ES, 95% CI: 62%, 100%; I^2 =0% (p=0.95), low heterogeneity); The sensitivity of exosome-derived miRNAs in breast cancer diagnosis is high and acceptable (Fig. 2).

Specificity diagnostic accuracy of exosome-derived miRNAs in breast cancer

The specificity of exosome-derived miRNAs in breast cancer was 84% (ES, 95% CI: 45%, 90%; I^2 =0% (p=0.99), low heterogeneity); The specificity of exosome-derived miRNAs in breast cancer diagnosis is high and acceptable (Fig. 3).

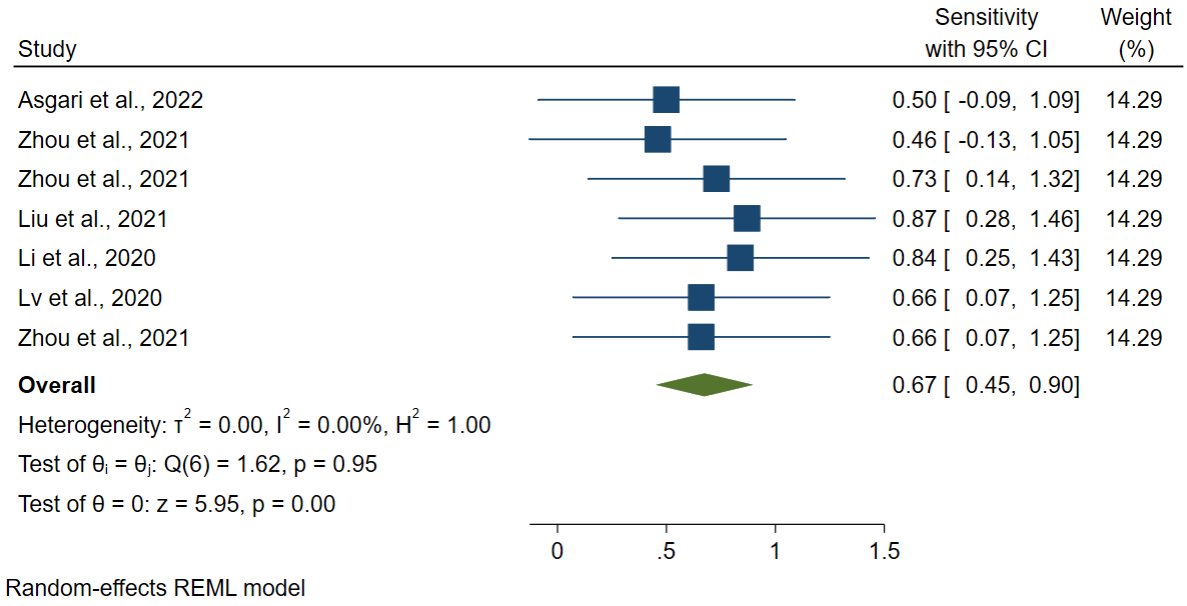

Fig. 2. Forest plot showed sensitivity of exosome-derived miRNAs in breast cancer diagnosis.

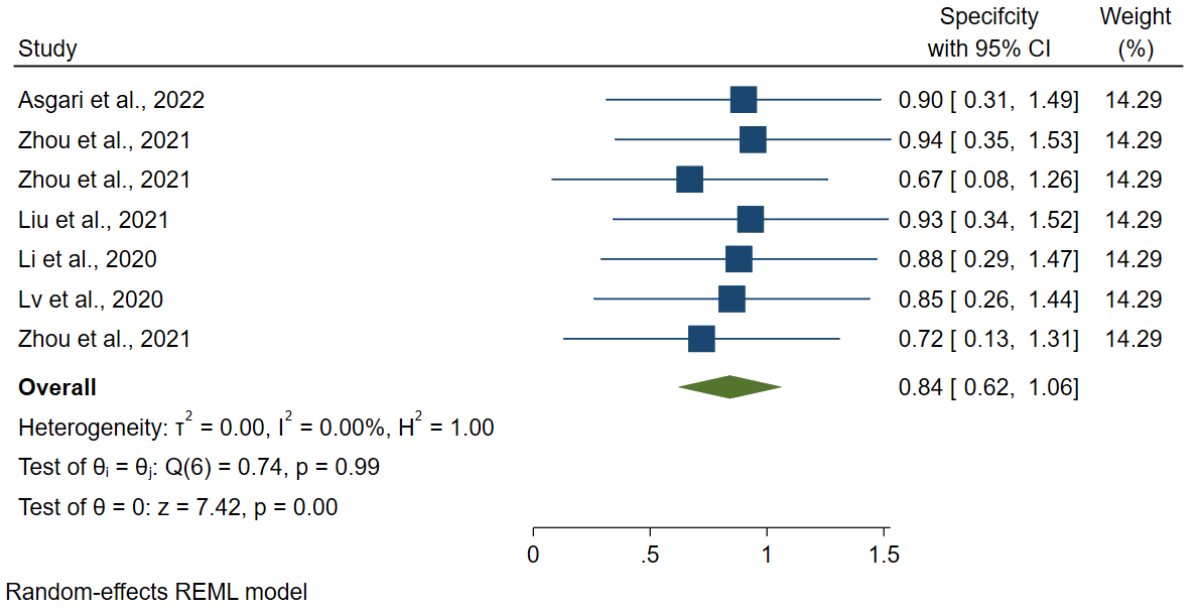

Fig. 3. Forest plot showed specificity of exosome-derived miRNAs in breast cancer diagnosis.

The odds ratio of diagnostic accuracy of exosome-derived miRNAs in breast cancer was 23.10 (OR, 95% CI: -3.68, 49.88; I2 =99.99% (p=0.00), high heterogeneity) (Fig. 4).

Subgroup meta-analysis by source

The sensitivity and specificity of serum-based exosomal miRNAs were 67% (ES, 95% CI: 0.33, 1.01) and 88% (ES, 95% CI: 0.54, 1.22), respectively (Figs. 5 and 6).

The sensitivity and specificity of plasma-based exosomal miRNAs were 68% (ES, 95% CI: 0.39, 0.97) and 82% (ES, 95% CI: 0.52, 1.11), respectively (Figs. 5 and 6).

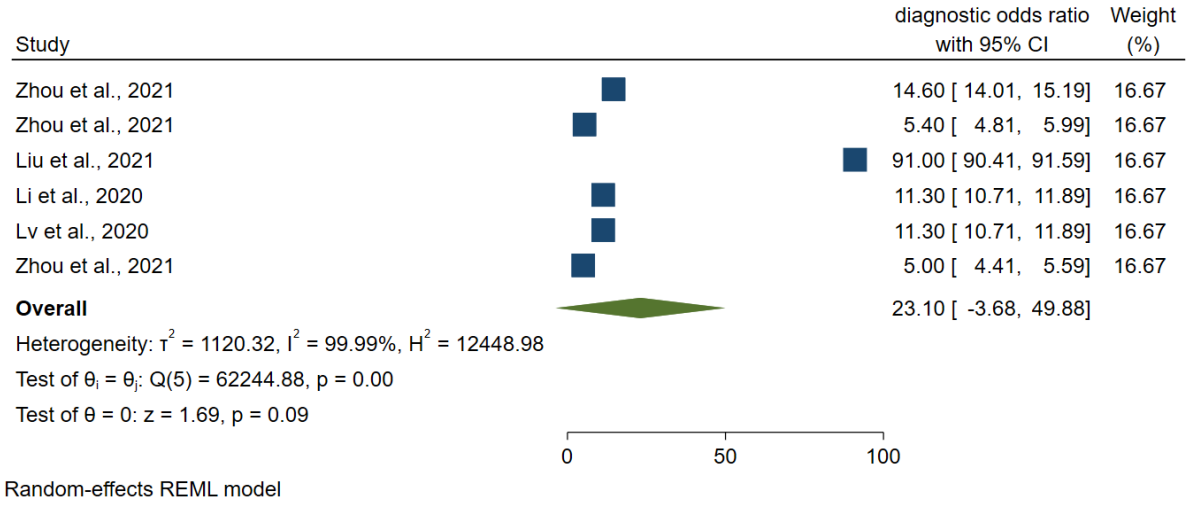

Fig. 4. The forest plot showed the odds ratio of diagnostic accuracy of exosome-derived miRNAs in breast cancer.

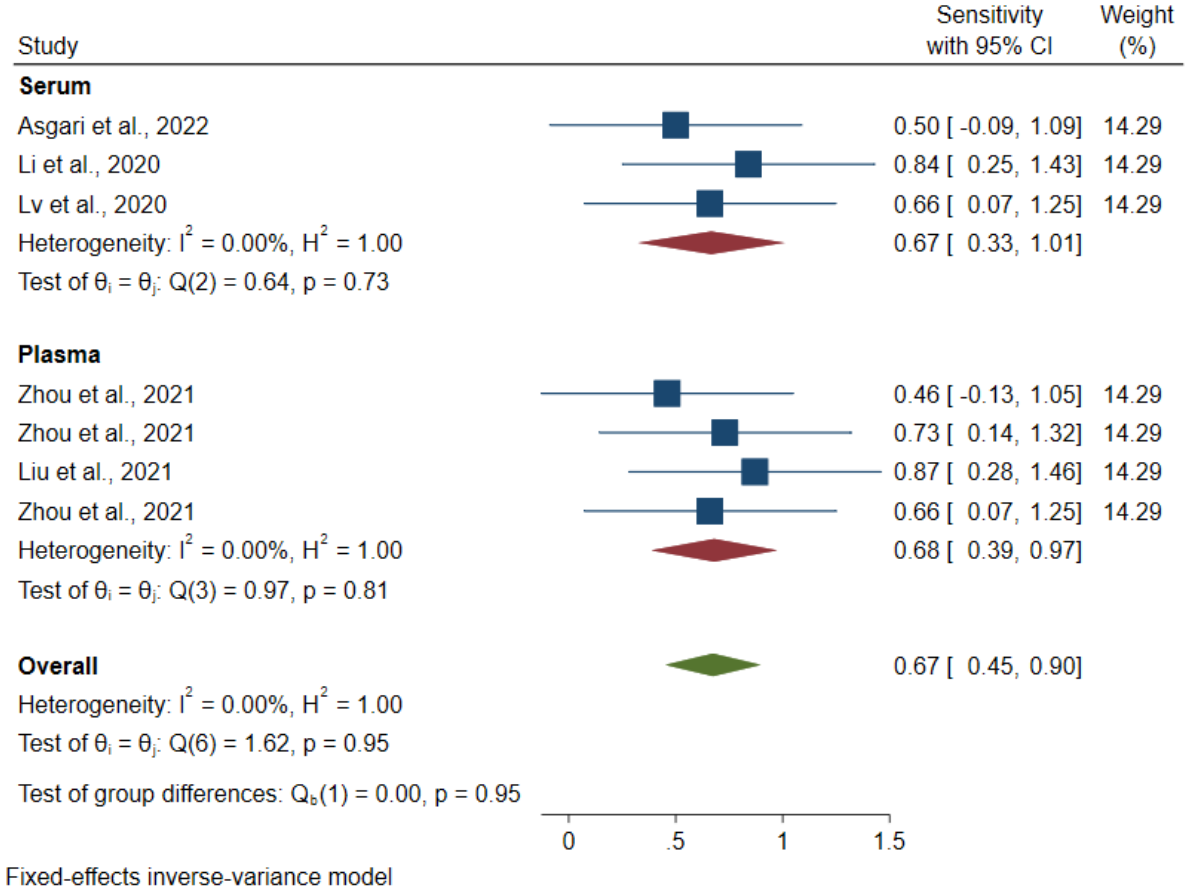

Fig. 5. forest plot showed a subgroup meta-analysis of serum-based exosomal miRNAs.

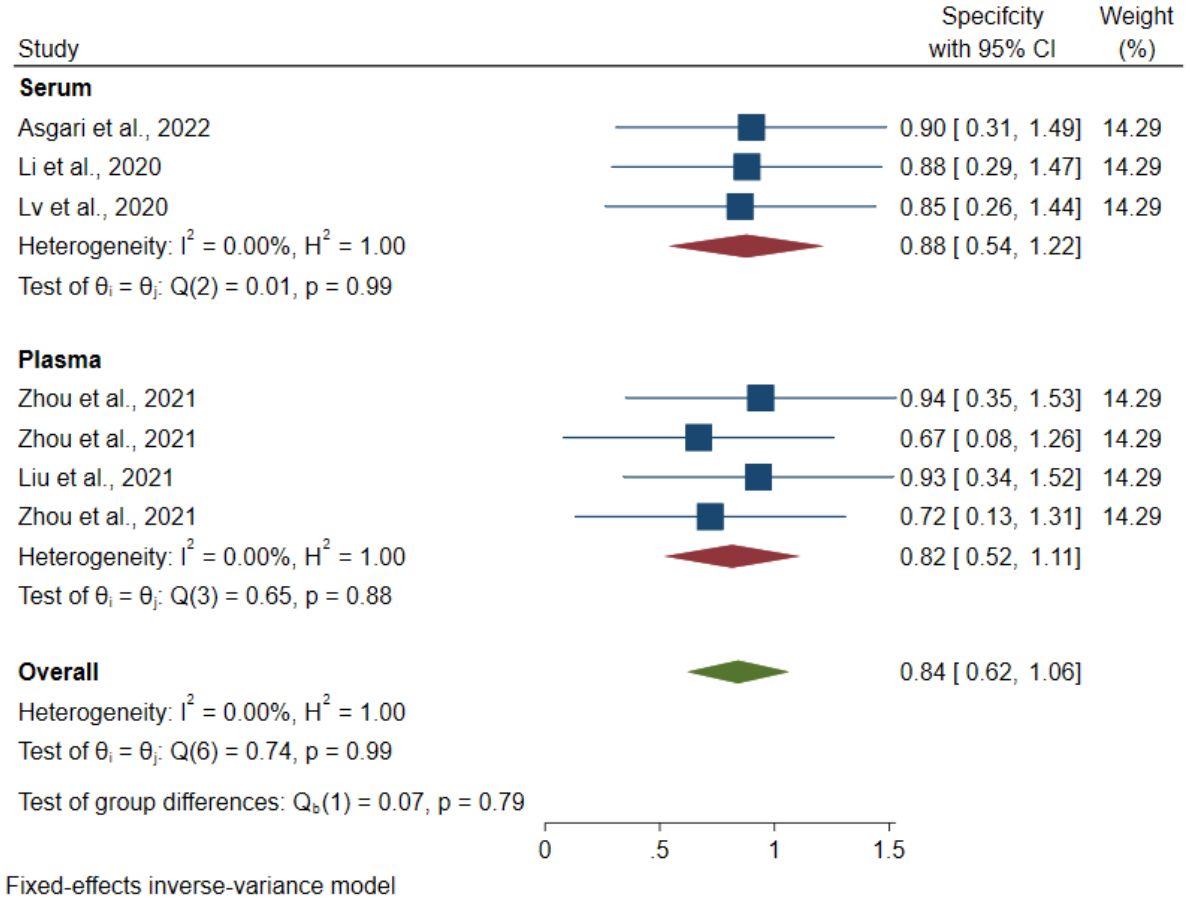

Fig. 6. The forest plot showed subgroup meta-analysis of plasma-based exosomal miRNAs.

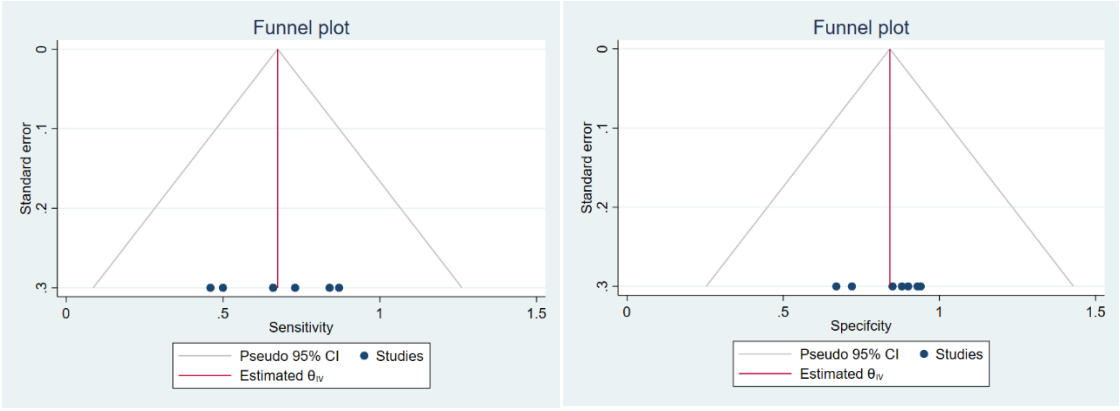

Fig. 7. Funnel plot showing publication bias of studies.

4. Discussion

In recent years, exosomes and the discussion of breast cancer diagnosis have received much attention, so recent studies have shown that exosomes can play an essential role in the diagnosis, prognosis, and treatment of breast cancer.[20] The present meta-analysis investigated exosomal miRNAs in breast cancer diagnosis. Meta-analysis showed that exosomal miRNAs have high sensitivity and specificity in breast cancer diagnosis. Subgroup meta-analysis by source also showed that the sensitivity and specificity of plasma and serum-based exosomal miRNAs are similar, and both sources have good sensitivity and specificity for breast cancer diagnosis. The present study observed that exosomal miRNA can potentially be used in the diagnosis of breast cancer. However, few studies were found, so more studies must be done to confirm the current evidence. As reported in studies, miRNAs play an essential role in breast cancer progression and metastasis.[21] Evidence also shows that miRNAs are a suitable diagnostic tool for cancer diagnosis. Therefore, the use of biomarkers is considered a non-invasive method, and due to its high sensitivity and specificity, the use of exosome-derived miRNA is suggested for breast cancer diagnosis. The present study has limitations;

firstly, the number of articles found was small, which requires more studies to be designed with appropriate cognitive methodology. Also, various factors can affect the accuracy of the test, which need to be carefully investigated in future studies. The heterogeneity among the current studies was small and insignificant, and a high heterogeneity was observed only in the odds ratio report. It is necessary to design the cognitive methodology of the studies well. Future studies are suggested to investigate the role of exosomal miRNAs on the progression, cell migration, and metastasis of breast cancer and consider using exosomal miRNAs in therapeutic approaches.

5. Conclusion

The present meta-analysis showed that exosomal miRNAs have high sensitivity and specificity in breast cancer diagnosis and can be considered a valuable and promising tool for the early detection of breast cancer non-invasively. Also, plasma-based and serum-based exosomal miRNAs have almost the same sensitivity and specificity in breast cancer diagnosis, and both sources can be used.

Conflict of Interest

The authors declared that there is no conflict of interest.

Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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How to Cite this Article: Ghadami P, Mehrafar N, Hassanpour Amnieh M, Rabiee F, Ebrahimi M, Rouzbahani H. Evaluation of the Role of Exosome-derived MiRNA in Breast Cancer Diagnosis: A Systematic Review and Meta-analysis. International Journal of Scientific Research in Dental and Medical Sciences. 2023;5(4):207-213. https://doi.org/10.30485/IJSRDMS.2023.424322.1546.