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Evaluation of the Potential of the MicroRNAs to Predict Chemotherapy Resistance in Breast Cancer Patients: A Systemic Review with Meta-analysis

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ABSTRACT

Background and aim: Breast cancer is the most common cancer diagnosed in women. In predicting the survival rate of breast cancer patients, factors such as age, race, spread of the disease, stage of diagnosis, and involvement of lymph nodes are involved. In this study, the potential of the microRNAs to predict chemotherapy resistance in breast cancer patients has been investigated.

Material and methods: In the present systematic review and meta-analysis, information about microRNAs to predict chemotherapy resistance in breast cancer patients in all articles published until the end of May 2023 through searching in databases PubMed, Scopus, Science Direct, ISI, Web of Knowledge, Elsevier, Wiley, and Embase and Google Scholar search engine were extracted using keywords and their combinations by two trained researchers independently. Data analysis was done using the fixed effects model in the meta-analysis by STATA (version 17); a p-value less than 0.05 was considered significant.

Results: Eight studies with a sample size of 509 breast cancer patients were included in the meta-analysis. The chemotherapeutic response of miRNAs in breast cancer patients receiving chemotherapy was 0.56 (ES, 95% CI: -1.30, 2.42; 0.03. I2 =0(p=1.00)).

Conclusions: The meta-analysis of the present study shows that there is a statistical relationship between predicting chemotherapy resistance and miRNA expression in breast cancer patients.

1. Introduction

Breast cancer is the second cause of death caused by cancer and is the most common cause of death in women.[1] Breast cancer includes 23% of all cancers in women, so it is considered the most common and deadly malignancy and is one of the most important factors concerning women's health worldwide.[2] The future burden of breast cancer will increase to over 3 million new cases and 1 million deaths in 2040.[3] Breast cancer is a disease in which malignant cells originate from the breast tissue and multiply irregularly.[4] Breast cancer originates from breast tissues, lining cells, milk ducts, and lobules around the ducts.[5] Breast cancer is a heterogeneous disease with different metastatic behaviors (multiple and often more than one organ location).[6] Predicting the probability of metastasis is very important in diagnosing the disease and its treatment. The most important achievement in cancer treatment will be inhibition of metastasis.[7] Bone is the most common site of distant breast cancer metastasis (56.4%), followed by lung, liver, lymph nodes, chest, subcutaneous tissues, and brain.[8] Breast cancer

metastasis, in other words, the tumor spread to the lymph nodes around the chest and chest, is an important complication of this disease, leading to treatment failure and reduced patient survival.[9] Chemotherapy treats metastatic breast cancer; However, chemoresistance remains a major obstacle to treatment success.[10]

Metastasis is a multi-step process that separates cancer stem cells from the primary tumor, destroys the basement membrane and extracellular matrix by proteinases, enters the vessels next to the tumor, is transported by proteinases, enters the vessels next to the tumor, and is transported. In a vascular system, getting stuck in a vascular bed and out of it is a secondary tumor.[11] Since metastasis is a multi-step process, each step must be carefully regulated. The discovery of microRNAs (miRNAs), small non-coding RNA molecules (19-25 nucleotides), as the primary gene regulators have created the hope of developing more powerful and effective strategies in the field of inhibiting metastasis in cancers.[12] miRNAs whose expression levels increase in metastasis help the progression of metastasis by decreasing the expression

of metastasis inhibitors, and those whose expression decreases by increasing the expression of metastasis activators cause metastasis. Cancer-related miRNAs are downstream of the main metastasis, inhibiting or promoting genes.[13] Using miRNAs in treatment has advantages over other methods; for example, using a small molecule to target a protein or enzyme can cause compensatory mechanisms to occur in the same pathway. In the use of miRNAs, the possibility of such a mechanism being created is less because miRNAs can affect multiple pathways simultaneously or target different components of a pathway. Also, miRNAs are small molecules with less antigenicity than peptides and proteins.[14] Considering the importance of the topic and the lack of comprehensive studies in this field, according to our knowledge, the present study is the first meta-analysis that aims to evaluate the potential of microRNAs for chemoresistance in patients with breast cancer.

2. Material and methods
Search strategy

In order to obtain documents and scientific evidence related to the role of microRNAs in breast cancer, articles published in international databases such as PubMed, Scopus, Science Direct, ISI, Web of Knowledge, Elsevier, Wiley, and Embase and Google Scholar search engine were used. The search process in these databases is done using keywords until May 2023: (((((("Breast Neoplasms"[Mesh]) OR ("Breast Neoplasms/diagnosis"[Mesh]

OR "Breast Neoplasms/therapy"[Mesh])) AND "Neoplasm Metastasis"[Mesh]) OR ("Neoplasm Metastasis/diagnosis"[Mesh] OR "Neoplasm Metastasis/prevention and control"[Mesh] OR "Neoplasm Metastasis/therapy"[Mesh])) OR ("Neoplasm Metastasis/drug therapy"[Mesh] OR)) OR ("Breast Neoplasms/drug therapy"[Mesh] OR)) AND "MicroRNAs"[Mesh]) OR "MicroRNAs/therapeutic use"[Mesh]. In addition, the reference list of the obtained articles was checked to identify the articles that were not obtained using the above methods. Articles were searched by two researchers independently. Then, during the study of the abstracts of the articles, duplicate and unrelated items were removed, and the information on the related articles was extracted by two researchers independently and evaluated by the relevant checklist in terms of quality. In case of disagreement between the first and second researchers, the third researcher evaluated the article.

Study selection criteria
Inclusion criteria

Use of the PECO (patient/population, exposure, comparison, and outcome) strategy to construct the research question is specified in Table 1; availability of the full text of the article; and published in English. Studies with incomplete results, case studies, case reports, and review articles were excluded.

Table1. PECO strategy.

PECO Strategy	Description
P	Population: patients with breast cancer
E	Exposure: Chemotherapy
C	Comparison: Control group
O	Outcome: neoadjuvant chemotherapy response

Data collection

From all articles related to the purpose of the present study, required information such as sample size, overall response rate, disease progression, partial response, and other demographic and clinical variables were extracted.

Risk assessment

The quality of the studies was evaluated using the Newcastle-Ottawa Scale (NOS).[15] This scale evaluates the articles in terms of the selection process (in 4 parts including representativeness of the samples, sample size, non-response, and measurement tools), comparability (one part includes investigation of confounders and other influencing factors), and results (from two aspects: evaluation of the result and statistical tests). Articles are scored from 1 (weakest study) to 9 (strongest study). Studies with a score of less than three are considered low quality, scores between 4 and 6 indicate average quality, and a score above 6 indicates high quality.

Data analysis

Meta-analysis was performed using an odd ratio and effect size with a 95% confidence interval. To estimate the heterogeneity of the studies, the index I^2 (<25%: weak heterogeneity, 25-75%: moderate heterogeneity, and more than 75%: high heterogeneity) was used. The results were combined using the random and fixed effects models in meta-analysis. The Egger test

checked the publication bias and Beggs funnel plot, and data analysis was done using STATA/MP. v17 software. A p-value of less than 0.05 was considered significant.

3. Results

After searching with related keywords, 481 studies were obtained. Endnote.X8 software was used to organize the studies. By using the mentioned software and reviewing the title and abstract of the articles, 184 duplicate studies were eliminated. Then, the abstracts of 266 articles were examined by the researchers. One hundred ninety-four 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 72 articles; 4 articles were removed due to low quality, one article was removed due to repetitive content and re-reporting of information in the form of a new article, and 59 studies were excluded due to the inconsistency of study objectives; Finally, eight articles were selected.
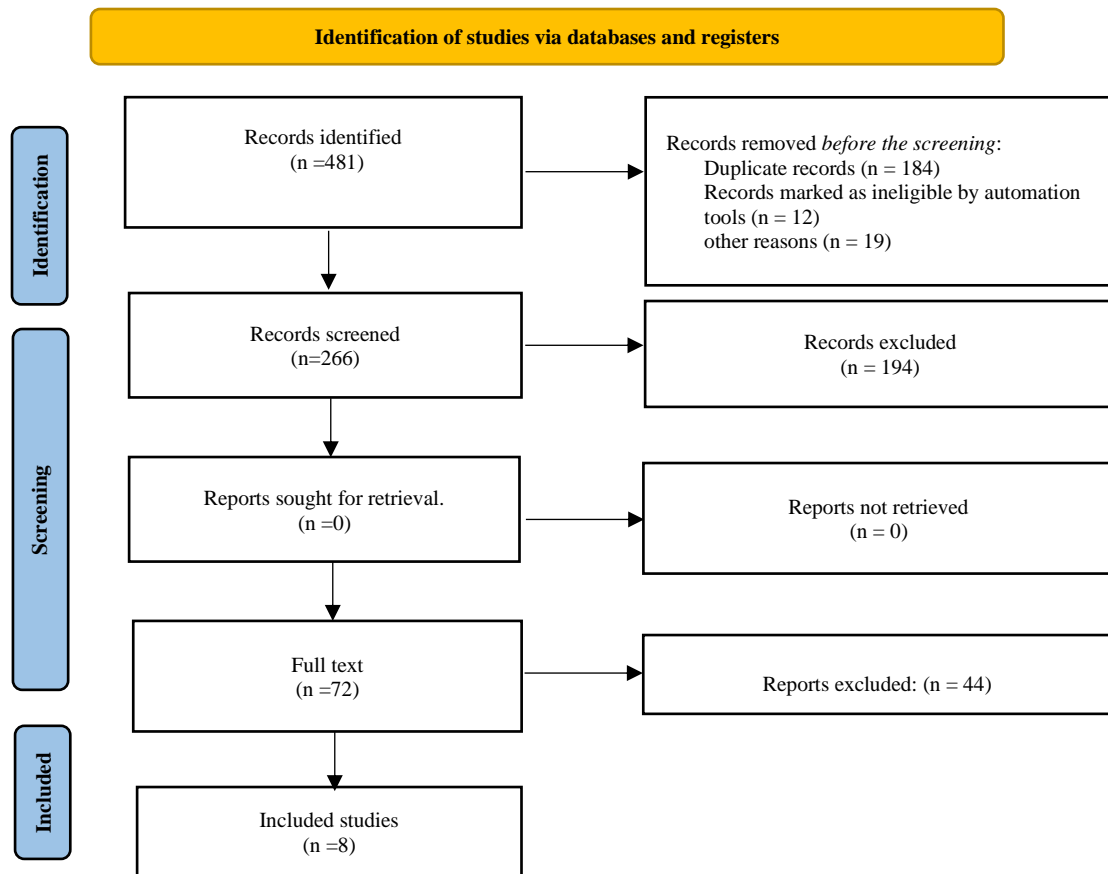
Fig. 1. PRISMA 2020 Checklist.

Characteristics of patients

In total, 509 breast cancer patients were included in this study. All the patients received chemotherapy. One study investigated chemoresistance in patients with metastatic breast cancer,[16] and other studies were conducted in patients with breast cancer. The clinical characteristics of 509 breast cancer patients are presented in Table 2.

Table 1. Characteristics of the patients with breast cancer.

Study. Years	Number of Patients	Source	MiRNAs	MiRNA Profiling Platform
Yang et al., 2021[17]	24	Serum	miR-378a-3p, miR-378d	qRT-PCR
Salvador et al., 2020[18]	34	Plasma	miR-185, miR-4283, miR-5008, miR-3613, miR-1302, miR-4715, miR-3144	qRT-PCR
Shao et al., 2019[16]	143	Plasma	miR-150, miR-145, miR-155, miR-21, miR200a, miR-200b, miR-200c, miR-210, miR-203, miR-221, miR-375, miR-451, miR-34a, and miR-122	qRT-PCR
Guo et al., 2018[19]	79	Biopsy	miR-let-7a	qRT-PCR
Yu et al., 2018[20]	110	Tissue	miR-200a	qRT-PCR
Raychaudhuri et al., 2017[21]	64	Tissue	miR-7, miR-21, miR-29a, miR-29b, miR-34a, miR-125b, miR-155, miR-200c, miR-340, miR-451	qRT-PCR
Sha et al., 2016[22]	20	Tissue	miR-18a	qRT-PCR
Zhu et al., 2013[23]	35	Plasma	miR-181a	qRT-PCR

Chemotherapeutic response

Chemotherapeutic response of miRNAs in breast cancer patients receiving chemotherapy was 0.56 (ES, 95% CI: -1.30, 2.42; 0.03. I^2 =0(p=1.00)); this result showed that expression of miRNAs is increased in breast cancer patients receiving chemotherapy and is associated with chemoresistance (Fig. 2). Yang et al., 2021[17] reported that miR-378a-3p and miR-378d levels were increased in the serum of patients after neoadjuvant chemotherapy compared with before chemotherapy, and this difference was greater in the chemo-insensitive group and is associated with chemoresistance. Salvador et al., 2020[18] reported low circulating blood

eMDSCs levels significantly associated with complete neoadjuvant chemotherapy response. Shao et al., 2019[16] showed that plasma miR-200a expression and miR-210 levels were identified as independent factors for chemotherapeutic response. Guo et al., 2018[19] reported that lower let-7a levels were associated with inferior treatment response (p< 0.001). Yu et al., 2018[20] showed that miR-200a plays a role in chemoresistance. Raychaudhuri et al., 2017[21] reported that After chemotherapy, the overall survival of patients with residual invasive tumors was better for those demonstrating low miR-7 or high miR-125b (p = 0.01). Figure 3 shows the bias of published studies (Fig. 3).
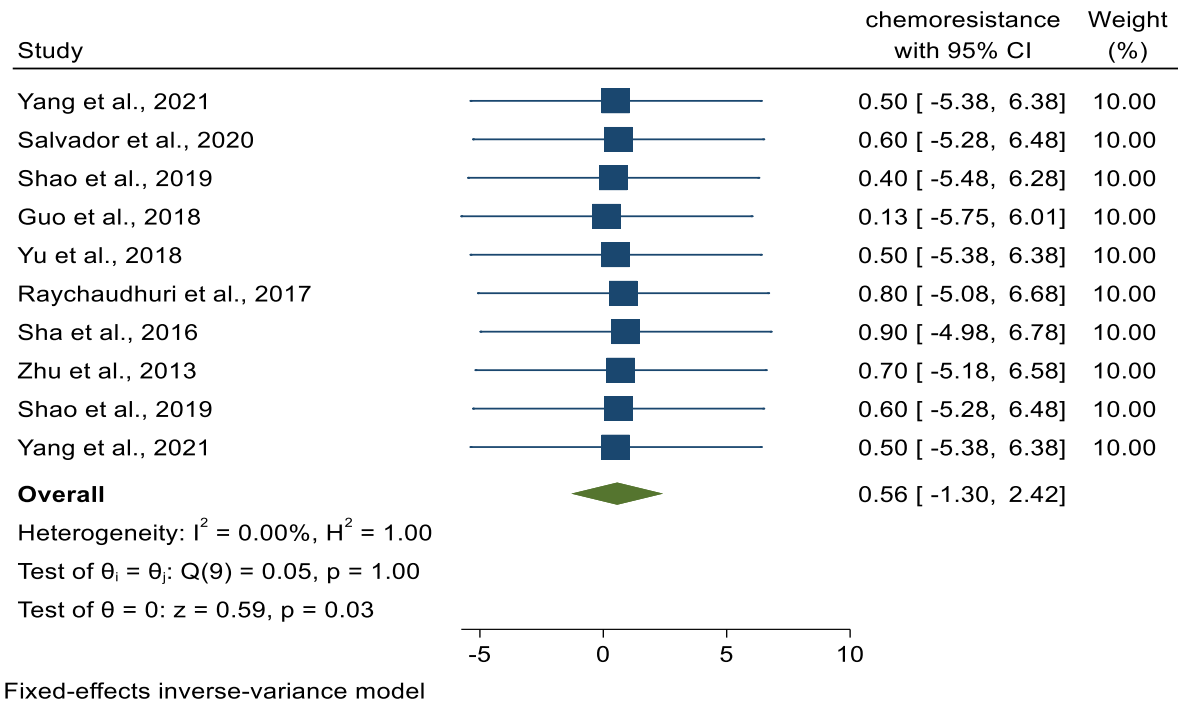

Fig. 2. The forest plot showed miRNA and chemotherapy response in breast cancer patients.
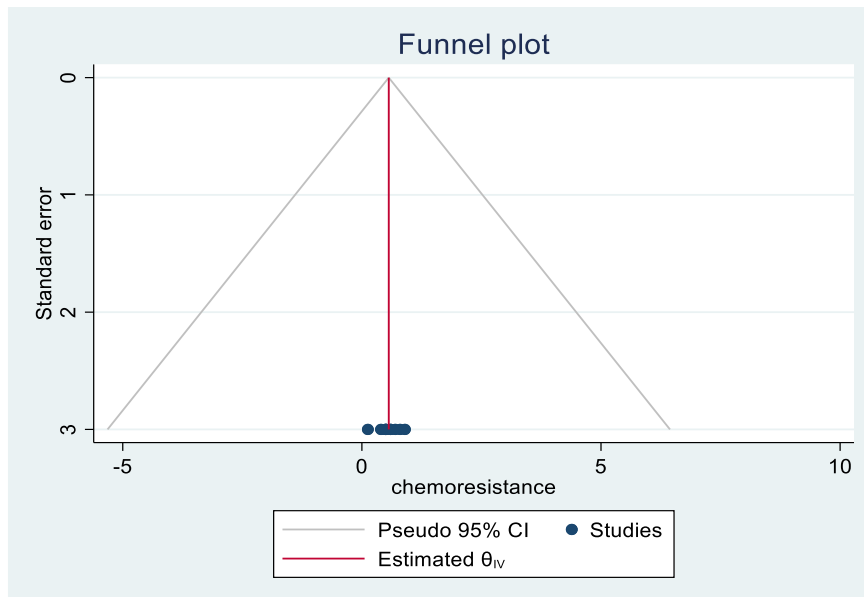

Fig. 2. A funnel plot is the effect size on the horizontal axis and each study's sample size, variance, or weight on the vertical axis.

4. Discussion

In the clinical examination, the predictors of chemotherapy response are of great importance. Evidence suggests that miRNAs can play an important role in chemoresistance in cancer patients, especially breast cancer. In recent years, many studies have been conducted regarding evaluating miRNAs on patient responses to treatment. Research shows that miRNAs are directly related to tumor size, metastasis, and overall survival.[24] Studies have shown that plasma miRNAs accurately predict and diagnose breast cancer.[25-27] In the present study, despite having differences in the methodology of the selected studies, the meta-analysis showed that some miRNAs have an excellent predictive function in breast cancer chemoresistance. The findings of selected studies show that high levels of miRNAs in breast cancer patients are directly related to resistance to chemotherapy; Therefore, miRNAs can be used as therapeutic options. A study has reported that high levels of miR-200a are associated with metastasis in breast cancer.[28] MiR-200a and miR-210 in plasma are effective biomarkers and can predict resistance to chemotherapy in patients with metastatic breast cancer.[16] Also, another study has shown that the prognostic value of miR-200a is higher in metastatic breast cancer patients.[29] A meta-analysis study showed that the high expression level miR-210 can predict poor survival in cancer patients.[30]

Unfortunately, in the current study, there was a high heterogeneity between the studies about the type of miRNA, and this limitation can affect the results of the current study. More studies must be done in line with each other. Based on consensus, patients who show polymerase chain reaction (PCR) are usually at very low risk of relapse and death.[31, 32] The samples were taken from tissue, serum, plasma, and biopsy in the selected studies. Therefore, it is necessary to conduct more studies in each sample to confirm the results of the present study so that subgroup meta-analysis can be performed and stronger evidence can be provided. Another limitation of the present study was that the studies did not classify or report the molecular and histological subtypes. The present study tried to select studies that reported OR and HR values or could calculate OR and HR values from full-text data; Therefore, few studies were selected. Future studies need to report OR and HR values to provide stronger evidence. Another limitation of the present study was that the miRNA list published by the studies was incomplete, usually including miRNAs that were not statistically significantly regulated. A more complete list of dysregulated miRNAs and standardized miRNA nomenclature are necessary for future more extensive research. The present study can be suitable for clinical research and study design in the relationship between microRNAs and predicting chemotherapy resistance.

5. Conclusion

The meta-analysis of the present study shows that there is a statistical relationship between predicting chemotherapy resistance and miRNA expression in breast cancer patients. It was also observed through a systematic review that breast cancer prognosis is related to miRNA expression. More studies with a more detailed design and clinical trials are needed to confirm the findings of the present study and previous studies.

Conflict of Interest

The authors declared that there is no conflict of interest.

Acknowledgements

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