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Evaluation of the Sensitivity and Specificity of Circulating MicroRNAs to Diagnose Breast Cancer: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: Today, scientists use cell-free circulating microRNAs (miRNAs) biomarkers to identify, control, and treat cancer, even in its early stages. The present study aimed to evaluate the sensitivity and specificity of circulating microRNAs to diagnose breast cancer.

Material and methods: The search was conducted based on keywords related to the study objectives in the international databases PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase between January 2015 and March 2023. Effect size (95% confidence interval) was calculated using the fixed effect model with the inverse-variance method. STATA/MP. V17 software was used for meta-analysis.

Results: In the present study, 31 articles were included in the meta-analysis. Sensitivity of circulating microRNAs to diagnose breast cancer was 85% (ES: 0.85 [95% CI: 0.74, 0.95]. Specificity of circulating microRNAs to diagnose breast cancer was 85% (ES: 0.85 [95% CI: 0.75, 0.96]. The AUC of miR-21 to diagnose breast cancer was 84% (ES: 0.84 [95% CI: 0.71, 0.97].

Conclusions: Based on the present meta-analysis, circulating microRNAs are promising biomarkers in breast cancer diagnosis.

1. Introduction

Breast cancer is the most common cancer in women; it is the main cause of death and a very important issue of women's health and treatment.[1] So in 2020, more than 2.3 million new cases were diagnosed, and there were 7.8 million living women with a history of breast cancer in the last five years.[2, 3] Risk factors such as age, family history of cancer, history of abortion, lifestyle, contraceptive drugs, and environmental factors have been attributed to breast cancer.[4] Today, one out of every eight women is infected, and one out of every 30 women with breast cancer dies.[5] The best way to reduce mortality from breast cancer is to detect it early to treat it.[6] Early detection of breast cancer is very important, and choosing an accurate and reliable diagnostic method is challenging; Among the various introduced methods, mammography has been highly welcomed, and this method is very common.[7] Systematic screening of the women's community using mammography devices and early detection of breast cancer in the early stages can reduce the chances of the patient's survival and the negative side effects caused by the necessary treatments.[8] Using mammography to diagnose breast cancer also has problems; there is a high possibility of damage to the film, or the image is not suitable for diagnosis; The observation is visual, and eye observations are used to detect the lesion, which leads to errors; The doctor's diagnosis may not be the same as the radiologists. Reports indicate that 3 to 20 percent of breast cancer cases are not detected by mammography.[9, 10] Also, mammography screenings are scheduled at fixed intervals that may occur between two screenings for unanticipated cancers.[11] Biomarkers are considered a suitable and minimally invasive method for breast cancer diagnosis. It can greatly help with early identification and screening planning.[12] In recent years, non-invasive biomarkers have been introduced, such as cell-free DNA, circulating cell-free, single nucleotide polymorphisms, and exosomal non-coding RNAs.[13-16] Today, scientists use cell-free circulating microRNAs (miRNAs) biomarkers to identify, control, and treat cancer, even in its early stages.[17] miRNAs, closely related to malignant phenotypes, can be helpful as diagnostic markers for early disease detection.[18] More than 2500 miRNAs have been identified in the human genome, which regulates more than 30% of protein-coding genes. Since the expression of miRNAs is related to a variety of clinical and biological

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characteristics of the tumor, such as tissue type, differentiation, invasion, and response to treatment, therefore, it is possible to detect miRNAs in the serum or blood plasma of patients without the need to use any type of invasive method. They used diagnostic markers of cancer cells. miRNAs are found in serum, plasma, saliva, or urine.[19-21] In diagnostic studies, circulating miRNAs have been investigated in different types of cancers, such as breast cancer,[22] and have been introduced as a diagnostic tool for tumor detection.[23] Another advantage of circulating cell-free miRNAs is their low cost and convenient analysis. Based on studies, circulating miRNAs are considered diagnostic biomarkers. However, conflicting results are observed in some studies.[24] In previous meta-analyses, it was observed that miRNAs have a promising diagnostic function in cancer diagnosis. However, the reviewed articles were very old, and very high heterogeneity between studies was observed.[25, 26] Unlike the meta-analyses performed in the present study, only newer studies with high methodological quality have been examined in order to provide stronger and newer evidence. Also, sensitivity and specificity were analyzed in all studies. This study aimed to evaluate the sensitivity and specificity of circulating microRNAs to diagnose breast cancer.

2. Material and methods

Search strategy

The present study was conducted based on the PRISMA 2020 checklist.[27] The search was conducted based on keywords related to the study objectives in the international databases PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase; all articles were reviewed between January 2015 and March 2023. The PICO framework (Population, Intervention, Comparison, and Outcomes) is summarized in Table 1. Keywords and the MeSH terms:

(((((("Neoplasms"[Mesh] OR "Early Detection of Cancer"[Mesh]) OR "Neoplasms/diagnosis"[Mesh]) OR "Breast Neoplasms"[Mesh]) AND "Circulating MicroRNA"[Mesh]) OR "MicroRNAs"[Mesh]) OR ("Biomarkers"[Mesh] OR "Biomarkers, Tumor"[Mesh])) AND "Diagnosis"[Mesh]) AND "Sensitivity and Specificity"[Mesh].

Table 1. PICO strategy.

PICO Strategy	Description
P	Population: breast cancer
I	Intervention: cell-free circulating microRNAs
C	Comparison: healthy controls
O	Outcome: Sensitivity and Specificity

Data collection

First, a checklist was prepared, including the author's name, publication year, study design, sample size, and sentinel lymph nodes. The study data were entered in this checklist and summarized in Table 2. The sensitivity and diagnostic specificity data of the studies were extracted and used for meta-analysis. Two independent, blinded reviewers screened each record, and a third person retrieved each report. The selection of articles was based on inclusion and exclusion criteria.

Inclusion and exclusion criteria

Only articles published in English, prospective and retrospective studies, case-control studies, miRNA models based on qRT-PCR data, and reported diagnostic performance data were included. Case studies, case reports, and review articles; studies without access to the full text were excluded from the study.

Risk assessment

The quality of studies was measured using diagnostic accuracy studies (QUADAS-2).[28] This tool examines four areas of patient selection, index test, reference standard, and schedule.

Data analysis

Potential heterogeneity between studies was reported with the I^2 coefficient. Values 50%< indicate low heterogeneity, 50% to 75% indicate moderate heterogeneity, and values >75% indicate high heterogeneity. Effect size (95% confidence interval) was calculated using the fixed effect model with the inverse-variance method. STATA/MP. V17 software was used for meta-analysis.

3. Results

Study selection

In the initial search, 659 articles were found based on keywords, and all articles were entered into EndNote X8 software. Duplicate articles with inappropriate and inconsistent titles, and other reasons were removed, then the abstracts of 624 articles were reviewed, 423 articles were removed (based on the inclusion and exclusion criteria). The full text of 201 articles was reviewed. Articles whose full text was incomplete had incomplete data, articles that were not in line with the objectives of the study were excluded, and finally, 31 articles were selected (Fig. 1). All the steps of searching and reviewing the articles were done by two blind observers and evaluated by a third observer.

Study characteristics

Six randomized control studies, nine retrospective, and two prospective studies were selected and included in the present meta-analysis. A total of 2827 patients (Experimental: 1169; control: 1658); the mean ages in the experimental and control group was 42.2 years and 37.12 years, respectively. Table 2 shows a summary of the data extracted.

Risk assessment

According to Cochrane Collaboration's tool, six randomized clinical trial studies had high quality (low risk of bias). According to the ROBINS-I tool, eight studies had a low risk of bias, and three studies had a Middle risk of bias (Tables 3 and 4).

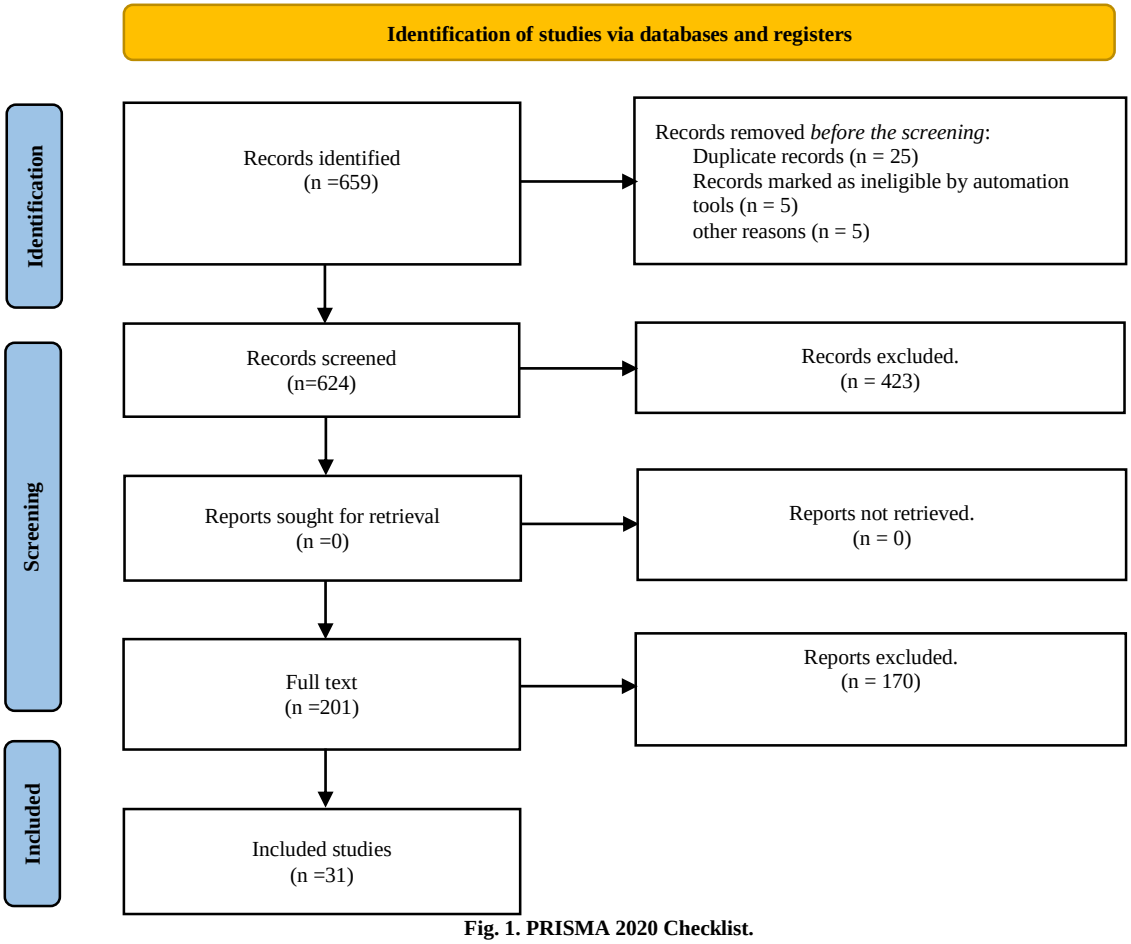

Fig. 1. PRISMA 2020 Checklist.

Table 2. Demographic information extracted from the full text of the selected studies.

No	Study. Years	Source of MiRNAs	Number of Patients		MiRNAs
			MiRNAs	Control	
1	Rasheed et al., 2023[29]	Whole Blood	75	50	miR-92a
2	Zou et al., 2022[30]	Serum	70	25	miR-301a-3p
3	Li et al., 2022[31]	Serum	49	49	miR-9-5p
					miR-17-5p
					miR-148a-3p
4	Sadeghi et al., 2021[32]	Whole Blood	70	60	miR-145
5	Swellam et al., 2021[33]	Serum	44	50	miR-27a
6	Zou et al., 2021[34]	Serum	100	296	miR-451a
					miR-126-5p
					miR-192-5p
					miR-195-5p

					miR423-3p
					miR-17-5p
7	Shaker et al., 2021[35]	Serum	180	270	miR-29
					miR-182
8	Diansyah et al., 2021[36]	Plasma	26	16	miR-21
9	Zou et al., 2021[37]	Serum	124	122	miR-16-5p
					miR-19a-3p,
					miR-19b-3p
					miR-20a-5p
					miR-223-3p
					miR-25-3p
					miR-425-5p
					miR-451a
					miR-92a-3p
					miR-93-5p
10	Nashtahosseini et al., 2021[38]	Serum	34	38	miR-660-5p
11	Jang et al., 2021[39]	Plasma	80	56	miR-1246
					miR-206
					miR-24
12	Hosseini Mojahed et al., 2020[40]	Serum	36	36	miR-155
13	Kim et al., 2020[41]	Plasma	30	30	miR-202
14	Pastor-Navarro et al., 2020[42]	Serum	45	45	miR-21
					miR-205
15	Han et al., 2020[43]	Serum	144	38	miR-1204
16	Ashirbkekov et al., 2020[44]	Plasma	30	33	miR-16-5p
					miR-21
					miR-210-3p
17	Ibrahim et al., 2020[45]	Plasma	30	20	miR-10b
					miR-181a
					miR-145
					miR-21-3p
18	Swellam et al., 2019[46]	Serum	96	86	miR-21

					miR-126
					miR-155
19	Pena-Cano et al., 2019[47]	Serum	50	50	miR-195-5p
20	Motamedi et al., 2019[48]	Plasma	23	24	miR-21
21	Swellam et al., 2019[49]	Serum	80	70	miR-17-5p
					miR-222-3p
					miR-155
22	Li et al., 2019[50]	Plasma	113	113	miR-122-5p
23	Fang et al., 2019[51]	Plasma	53	78	miR-324-3p
					miR-324-3p
					miR-21-3p
					miR-382-5p
					miR-30a-5p
24	Soleimanpour et al., 2019[52]	Plasma	30	30	miR-21
					miR-155
25	Heydari et al., 2018[53]	Serum	40	40	miR-140-3p
26	Li et al., 2018[54]	Plasma	146	146	miR-106a
27	Yu et al., 2018[55]	Serum	113	47	miR-21-5p
					miR-21-3p
					miR-99a-5p
28	Zhang et al., 2017[56]	Whole Blood	15	13	miR-30b-5p
					miR-96-5p
					miR-182-5p
					miR-374b-5p
					miR-942-5p
29	Zhang et al., 2017[57]	Plasma	75	50	miR-200c
					miR-141
30	Freres et al., 2016[58]	Plasma	88	88	miR-16
31	Antolin et al., 2015[59]	Whole Blood	44	20	miR-200c

Diagnostic accuracy

The sensitivity of circulating microRNAs on whole blood models to diagnose breast cancer was 79% (ES: 0.79 [95% CI: 0.67, 0.90], (I^2=0%; p =0.99; low heterogeneity) (Fig. 2). specificity of circulating microRNAs on whole blood models to diagnose breast cancer was 90% (ES: 0.90 [95% CI: 0.58, 1.22], (I^2=0%; p =0.99; low heterogeneity) (Fig. 3).

The sensitivity of circulating microRNAs on serum models to diagnose breast cancer was 83% (ES: 0.83 [95% CI: 0.68, 0.99], (I^2=0%; p =1.00; low

heterogeneity) (Fig. 4). specificity of circulating microRNAs on serum models to diagnose breast cancer was 82% (ES: 0.82 [95% CI: 0.67, 0.97], (I^2=0%; p =0.99; low heterogeneity) (Fig. 5).

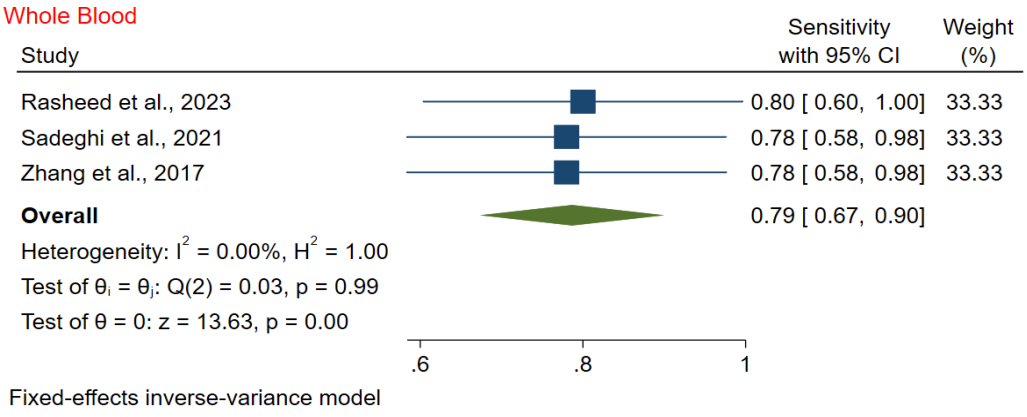

Fig. 2. Sensitivity of circulating microRNAs on whole blood models.

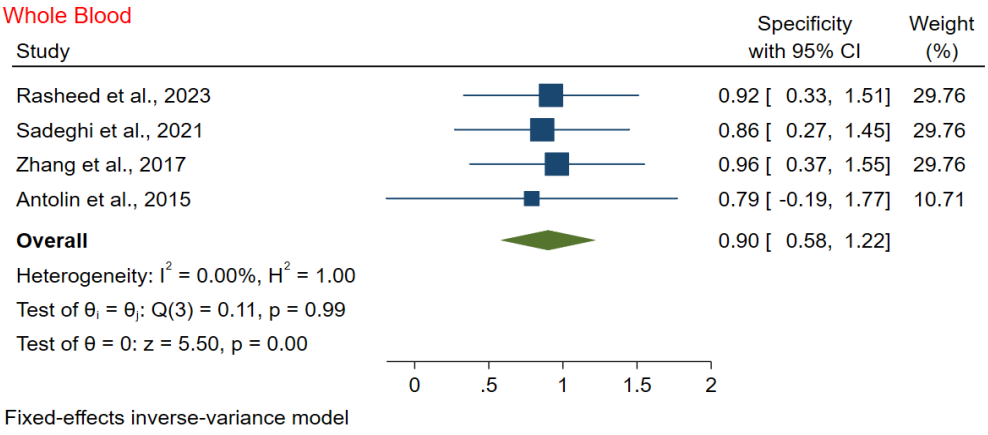

Fig. 3. Specificity of circulating microRNAs on whole blood models.

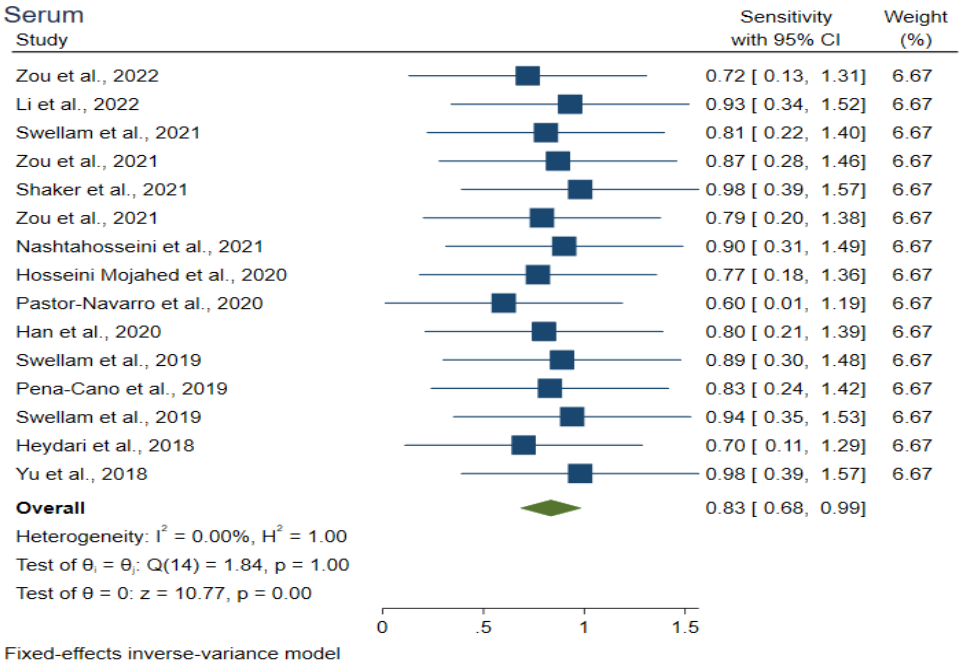

Fig. 4. Sensitivity of circulating microRNAs on serum models.

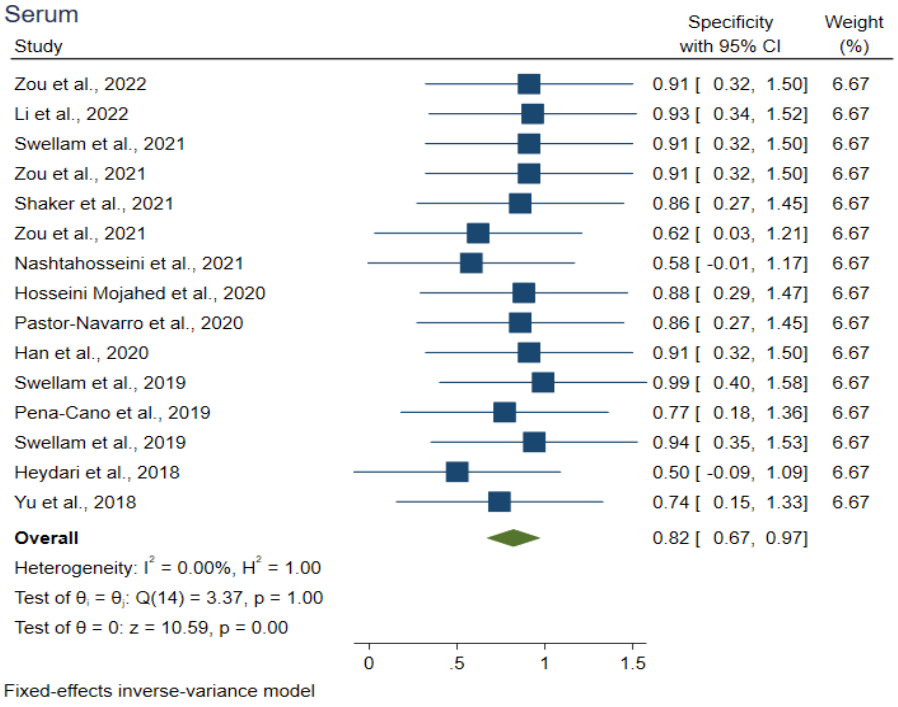

Fig. 5. Specificity of circulating microRNAs on serum models.

The sensitivity of circulating microRNAs on plasma models to diagnose breast cancer was 87% (ES: 0.87 [95% CI: 0.70, 1.04], (I^2=0%; *p* =1.00; low heterogeneity) (Fig. 6). Specificity of circulating microRNAs on plasma models to diagnose breast cancer was 88% (ES: 0.88 [95% CI: 0.71, 1.05], (I^2=0%; *p* =0.99; low heterogeneity) (Fig. 7).

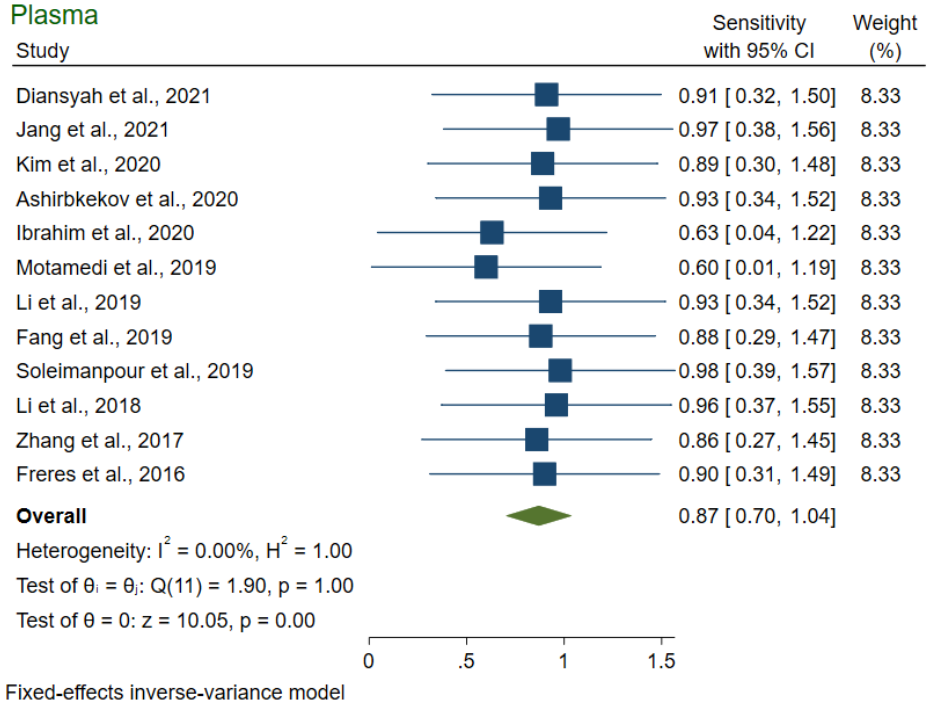

Fig. 6. Sensitivity of circulating microRNAs on plasma models.

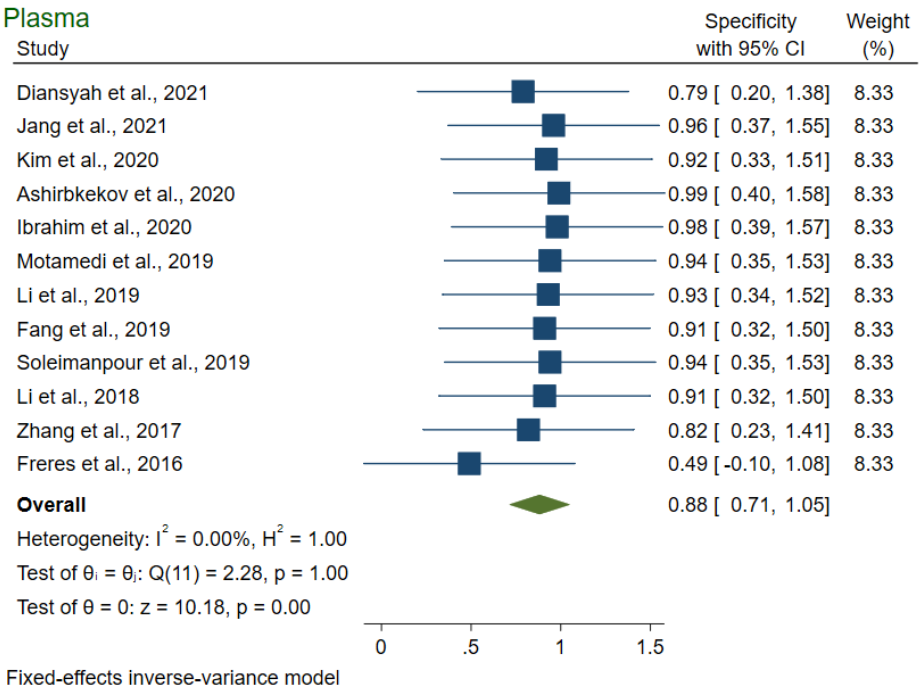

Fig. 7. Specificity of circulating microRNAs on plasma models.

Diagnostic accuracy of miR-21

MiRNA-21 was the most frequently analyzed miRNA in the selected studies; It was included in the meta-analysis for the same reason. The AUC of miR-21 to diagnose breast cancer was 84% (ES: 0.84 [95% CI: 0.71, 0.97], (I^2=0%; *p* =0.99; low heterogeneity) (Fig. 8).

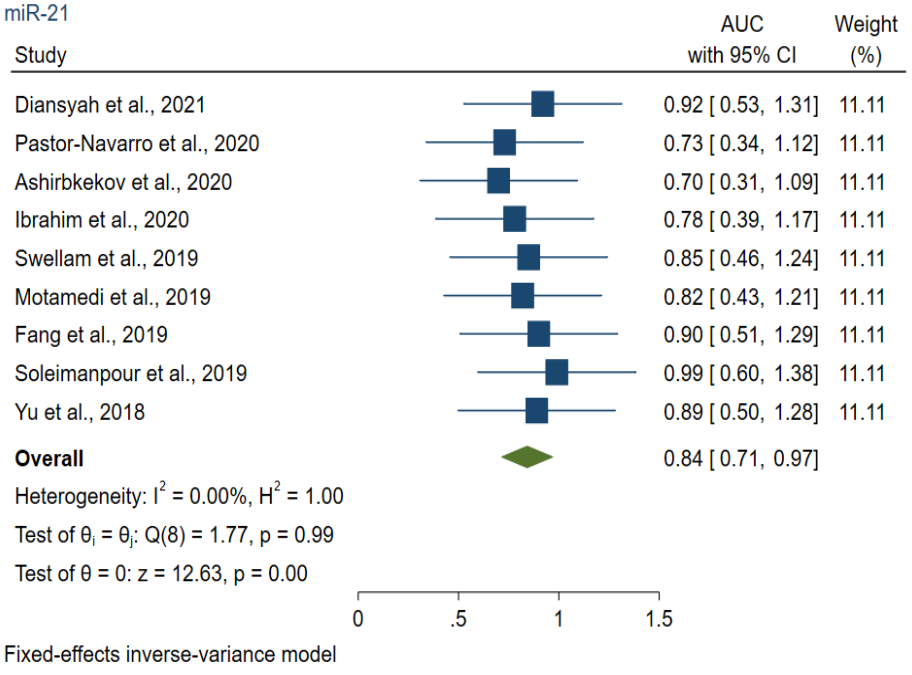

Fig. 8. AUC of miR-21 to diagnose breast cancer.

The sensitivity of circulating microRNAs to diagnose breast cancer was 85% (ES: 0.85 [95% CI: 0.74, 0.95], (I^2=0%; p =1.00; low heterogeneity) (Fig. 9). Specificity of circulating microRNAs to diagnose breast cancer was 85% (ES: 0.85 [95% CI: 0.75, 0.96], (I^2=0%; p =0.99; low heterogeneity) (Fig. 10).

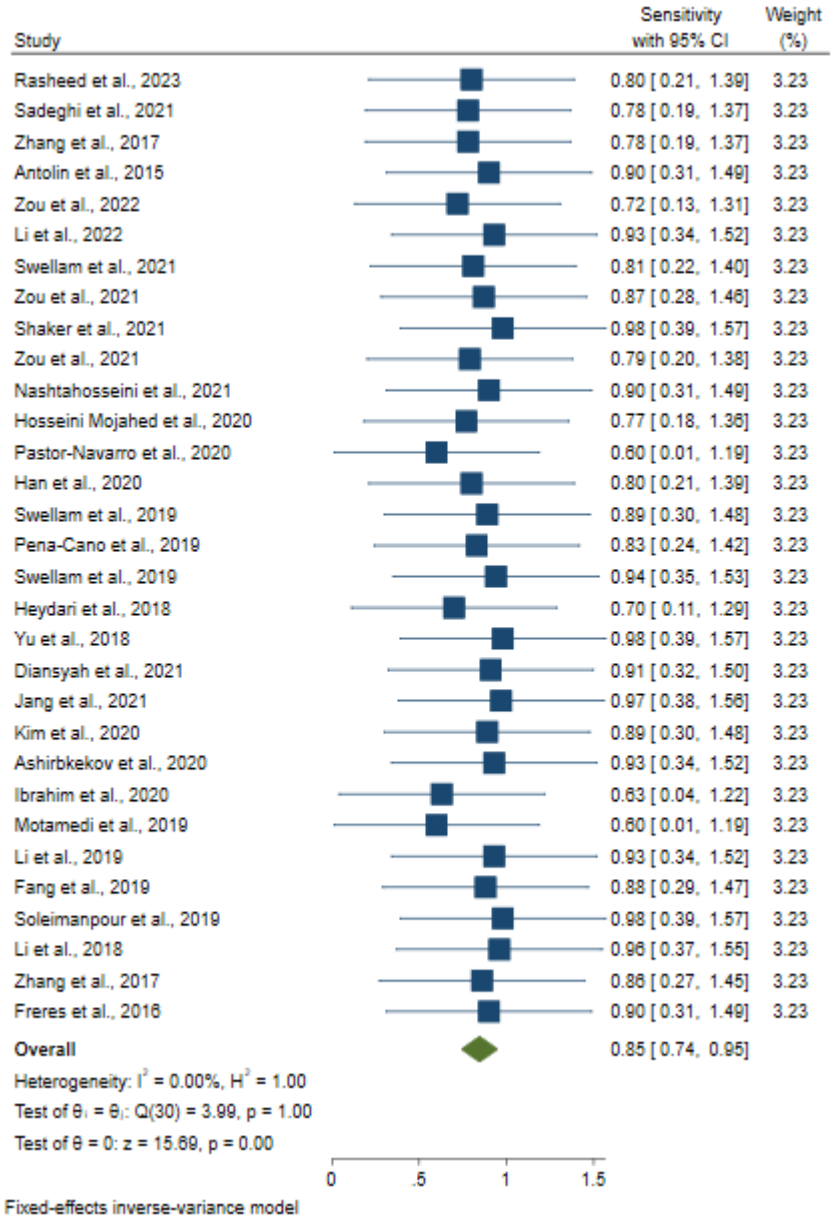

Fig. 9. Sensitivity of circulating microRNAs to diagnose breast cancer.

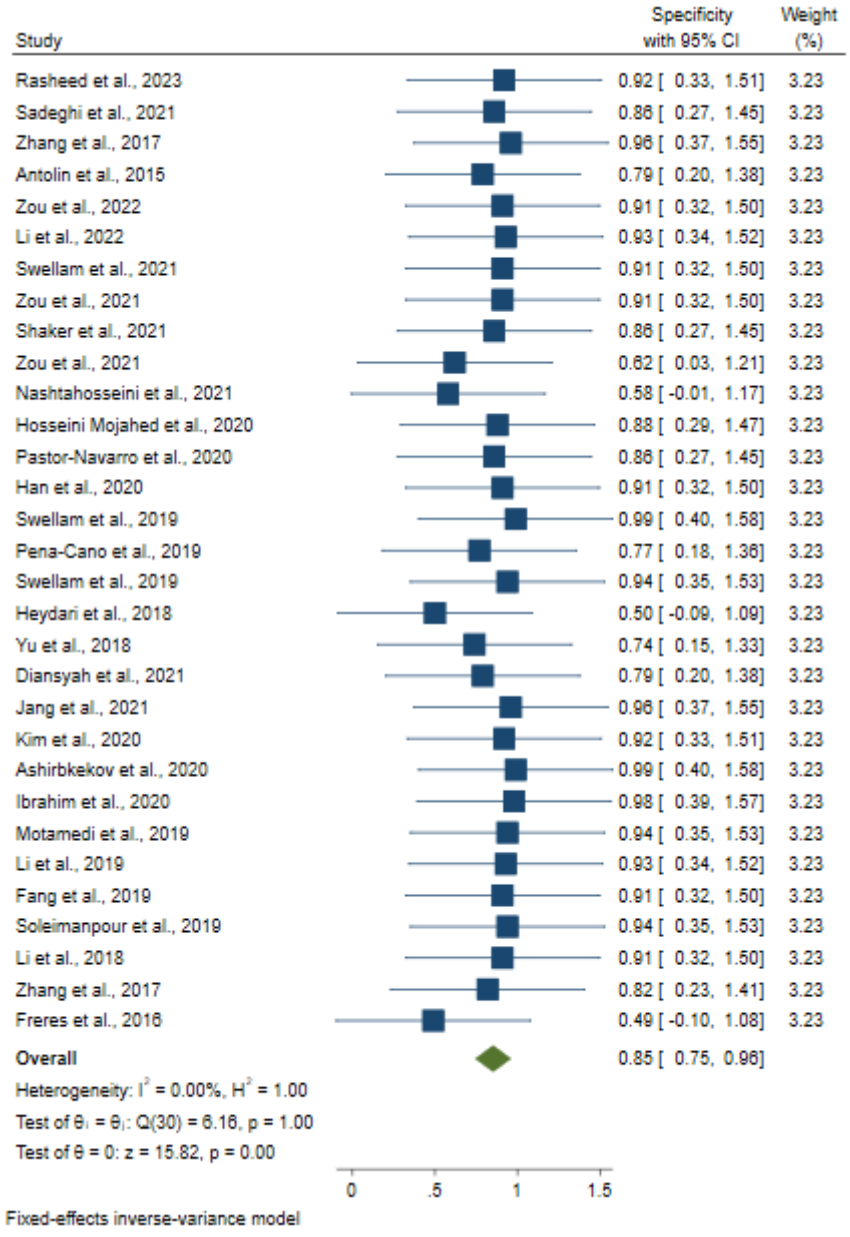

Fig. 10. Specificity of circulating microRNAs to diagnose breast cancer.

4. Discussion

In the case of breast cancer, mammography is one of the best diagnostic tools, although it has limitations, such as ionizing radiation and errors. On the other hand, using common markers such as estrogen and growth hormone receptors is not completely flawless.[60, 61] miRNA has a significant potential to be used as biomarkers for identifying, diagnosing, classifying, and treating cancer because they have the necessary sensitivity. In addition, they can show the stage of the tumor, the receptor status, and the survival of the patient.[62] Based on the meta-analysis of the present study, the sensitivity of circulating microRNAs to diagnose breast cancer in the plasma model was higher than the serum model, and these two were higher than the whole blood model. Also, the specificity of circulating microRNAs to diagnose breast cancer in a whole blood model was higher than plasma and serum. The present meta-analysis showed that, in general, the specificity and sensitivity of circulating microRNAs to diagnose breast cancer are completely satisfactory. The obtained sensitivity and characteristics were 85%, making this estimation strong and reliable. The heterogeneity between the studies was very low, which indicates the appropriate cognitive methodology of the studies, and the results of the present study provide good evidence. The results of a study showed that before biopsy, blood sampling could be effective on the level of circulating miRNAs.[63] The results of the studies indicate that the use of plasma samples may lead to hemolyzed samples, which can affect the miRNA content of the samples.[64, 65] In studies that have used a plasma model, hemolyzed samples need to be checked and removed.[66, 67] In using the serum sample, RNA molecules may be released and change the actual profile of circulating miRNAs; Therefore, it is very important to use a standard method to detect circulating miRNA.[64] It is better to use a standard laboratory protocol to obtain miRNAs. The present meta-analysis showed that the diagnostic accuracy of miR-21 in diagnosing breast cancer is high and significant. According to the published results of a meta-analysis in 2014,

miR-21 has been used as a cancer biomarker in more than 31 studies to investigate various malignancies. It confirms the high potential of this microRNA as a diagnostic tool for the early detection of breast cancer.[26] Another meta-analysis study in 2015 observed, by reviewing 15 articles, that sensitivity and specificity of 0.82. These findings are consistent with the present study. The difference between the present study and the previous studies is that in the present study, the articles that reported stage >4.5% were not included in the meta-analysis because it seems that stage IV cases can affect the accuracy of diagnosis. The present study had some limitations; firstly, laboratory and experimental differences were not investigated, some studies may not have been selected in the search stage, only articles published in English were selected and reviewed, and studies that were based on the whole blood model. They had used few. One of the advantages of the present study was the low heterogeneity between subjects.

5. Conclusion

Based on the present meta-analysis, the sensitivity and specificity of circulating microRNAs to diagnose breast cancer were estimated at 85%; these findings show that circulating microRNAs are promising biomarkers in breast cancer diagnosis. Also, the sensitivity of circulating microRNAs to diagnose breast cancer in serum, plasma, and whole blood models was 83%, 87%, and 79%, respectively. Moreover, specificity in serum, plasma, and whole blood models was estimated at 82%, 88%, and 90%, respectively. Circulating microRNAs have the potential to be used for breast cancer screening.

Conflict of Interest

The authors declared that there is no conflict of interest.

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References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca Cancer J Clin. 2018;68(6):394-424.

[2] El Sharif N, Khatib I. Healthy Lifestyle and Breast Cancer Risk in Palestinian Women: A Case-Control Study. Nutrition and Cancer. 2023:1-1. https://doi.org/10.1080/01635581.2023.2168022.

[3] Yuniastini Y, Murhan A, Purwati P, Pratiwi MD. Risk Factors for Breast Cancer: Hormonal Contraception. Jurnal Aisyah: Jurnal Ilmu Kesehatan. 2022;7(S1):349-54. http://dx.doi.org/10.30604/jika.v7iS1.1307.

[4] Singh R, kumar Sain MN. Etiology Of Breast Cancer. Journal of Pharmaceutical Negative Results. 2023:1427-34. https://doi.org/10.47750/pnr.2023.14.03.192.

[5] Ho AY, Barker CA, Arnold BB, Powell SN, Hu ZI, Gucalp Aet al. A phase 2 clinical trial assessing the efficacy and safety of pembrolizumab and radiotherapy in patients with metastatic triple ‐ negative breast cancer. Cancer. 2020;126(4):850-60. https://doi.org/10.1002/cncr.32599.

[6] Pashayan N, Antoniou AC, Ivanus U, Esserman LJ, Easton DF, French D, et al. Personalized early detection and prevention of breast cancer: ENVISION consensus statement. Nature Reviews Clinical Oncology. 2020;17(11):687-705. https://doi.org/10.1038/s41571-020-0388-9.

[7] Cai X, Li X, Razmjooy N, Ghadimi N. Breast cancer diagnosis by convolutional neural network and advanced thermal exchange optimization algorithm. Computational and Mathematical Methods in Medicine. 2021. https://doi.org/10.1155/2021/5595180.

[8] Balali GI. Breast cancer: a review of mammography and clinical breast examination for early detection of cancer. Open Access Library Journal. 2020;7(10):1. https://doi.org/10.4236/oalib.1106866.

[9] Heindel W, Weigel S, Gerß J, Hense HW, Sommer A, Krischke M, et al. Digital breast tomosynthesis plus synthesised mammography versus digital screening mammography for the detection of invasive breast cancer (TOSYMA): a multicentre, open-label, randomised, controlled, superiority trial. The Lancet Oncology. 2022;23(5):601-11. https://doi.org/10.1016/S1470-2045(22)00194-2.

[10] Iranmakani S, Mortezazadeh T, Sajadian F, Ghaziani MF, Ghafari A, Khezerloo D, et al. A review of various modalities in breast imaging: technical aspects and clinical outcomes. Egyptian Journal of Radiology and Nuclear Medicine. 2020;51(1):1-22. https://doi.org/10.1186/s43055-020-00175-5.

[11] Smith RA, Andrews KS, Brooks D, Fedewa SA, Manassaram-Baptiste D, Saslow D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. CA: a cancer journal for clinicians. 2019;69(3):184-210. https://doi.org/10.3322/caac.21557.

[12] Jusoh AR, Mohan SV, Ping TL, Bin TA, Din T, Haron J, et al. Plasma circulating mirnas profiling for identification of potential breast cancer early detection biomarkers. Asian Pacific Journal of Cancer Prevention: APJCP. 2021;22(5):1375-81. https://doi.org/10.31557/APJCP.2021.22.5.1375.

[13] Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, Lee A, et al. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. The American Journal of Human Genetics. 2019;104(1):21-34. https://doi.org/10.1016/j.ajhg.2018.11.002.

[14] Yu D, Tong Y, Guo X, Feng L, Jiang Z, Ying S, et al. Diagnostic value of concentration of circulating cell-free DNA in breast cancer: a meta-analysis. Frontiers in oncology. 2019;9:95. https://doi.org/10.3389/fonc.2019.00095.

[15] Lubowicka E, Przylipiak A, Zajkowska M, Piskór BM, Malinowski P, Fiedorowicz W, et al. Plasma chemokine CCL2 and its receptor CCR2 concentrations as diagnostic biomarkers for breast cancer patients. BioMed research international. 2018. https://doi.org/10.1155/2018/2124390.

[16] Khorrami S, Tavakoli M, Safari E. Clinical value of serum S100A8/A9 and CA15-3 in the diagnosis of breast cancer. Iranian Journal of Pathology. 2019;14(2):104-12. https://doi.org/10.30699/IJP.14.2.104.

[17] Mo MH, Chen L, Fu Y, Wang W, Fu SW. Cell-free circulating miRNA biomarkers in cancer. Journal of Cancer. 2012;3:432-48. https://doi.org/10.7150/jca.4919.

[18] Li C, Zhou T, Chen J, Li R, Chen H, Luo S, et al. The role of Exosomal miRNAs in cancer. Journal of translational medicine. 2022;20(1):1-5. https://doi.org/10.1186/s12967-021-03215-4.

[19] Davarinejad O, Mohammadi P, Ghavi D, Golmohammadi F, Foruzandeh Z, Alivand M, et al. Identifying miRNA signature for predicting and treatment of breast cancer using the transcriptomic data of 7,000 breast tumors. 2022. https://doi.org/10.21203/rs.3.rs-1551331/v1.

[20] Hasanoğlu S, Göncü BS, Yücesan E, Atasoy S, Kayali Y, Kandaş NÖ. Investigating differential miRNA expression profiling using serum and urine specimensfor detecting potential biomarkers for early prostate cancer diagnosis. Turkish journal of medical sciences. 2021;51(4):1764-74. https://doi.org/10.3906/sag-2010-183.

[21] Hoshino I. The usefulness of microRNA in urine and saliva as a biomarker of gastroenterological cancer. International Journal of Clinical Oncology. 2021;26:1431-40. https://doi.org/10.1007/s10147-021-01911-1.

[22] Chen H, Liu H, Zou H, Chen R, Dou Y, Sheng S, et al. Evaluation of plasma miR-21 and miR-152 as diagnostic biomarkers for common types of human cancers. Journal of cancer. 2016;7(5):490-99. https://doi.org/10.7150/jca.12351.

[23] Boeri M, Verri C, Conte D, Roz L, Modena P, Facchinetti F, et al. MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer. Proceedings of the National Academy of Sciences. 2011;108(9):3713-8. https://doi.org/10.1073/pnas.1100048108.

[24] Aggarwal V, Priyanka K, Tuli HS. Emergence of circulating MicroRNAs in breast cancer as diagnostic and therapeutic efficacy biomarkers. Molecular diagnosis & therapy. 2020;24(2):153-73. https://doi.org/10.1007/s40291-020-00447-w.

[25] Cui Z, Lin D, Song W, Chen M, Li D. Diagnostic value of circulating microRNAs as biomarkers for breast cancer: a meta-analysis study. Tumor Biology. 2015;36:829-39. https://doi.org/10.1007/s13277-014-2700-8.

[26] Liu L, Wang S, Cao X, Liu J. Analysis of circulating microRNA biomarkers for breast cancer detection: a meta-analysis. Tumor Biology. 2014;35:12245-53. https://doi.org/10.1007/s13277-014-2533-5.

[27] Tugwell P, Tovey D. PRISMA 2020. Journal of Clinical Epidemiology. 2021;134:A5-6. https://doi.org/10.1016/j.jclinepi.2021.04.008.

[28] Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155(8):529-36. https://doi.org/10.7326/0003-4819-155-8-201110180-00009.

[29] Rasheed NW. Circulating microRNA-92a as biomarkers for primary woman breast cancer Iraq population. Journal of Population Therapeutics and Clinical Pharmacology. 2023;30(1):344-54. https://doi.org/10.47750/jptcp.2023.1093.

[30] Zou R, Loke SY, Tang YC, Too HP, Zhou L, Lee AS, et al. Development and validation of a circulating microRNA panel for the early detection of breast cancer. British journal of cancer. 2022;126(3):472-81. https://doi.org/10.1038/s41416-021-01593-6.

[31] Li X, Tang X, Li K, Lu L. Evaluation of serum microRNAs (miR-9-5p, miR-17-5p, and miR-148a-3p) as potential biomarkers of breast cancer. BioMed Research International. 2022. https://doi.org/10.1155/2022/9961412.

[32] Sadeghi H, Kamal A, Ahmadi M, Najafi H, Sharifi Zarchi A, Haddad P, et al. A novel panel of blood-based microRNAs capable of discrimination between benign breast disease and breast cancer at early stages. RNA biology. 2021;18(sup2):747-56. https://doi.org/10.1080/15476286.2021.1989218.

[33] Swellam M, Zahran RF, Ghonem SA, Abdel-Malak C. Serum MiRNA-27a as potential diagnostic nucleic marker for breast cancer. Archives of Physiology and Biochemistry. 2021;127(1):90-6. https://doi.org/10.1080/13813455.2019.1616765.

[34] Zou R, Loke SY, Tan VK, Quek ST, Jagmohan P, Tang YC, et al. Development of a microRNA panel for classification of abnormal mammograms for breast cancer. Cancers. 2021;13(9):2130. https://doi.org/10.3390/cancers13092130.

[35] Shaker O, Ayeldeen G, Abdelhamid A. The impact of single nucleotide polymorphism in the long non-coding MEG3 gene on microRNA-182 and microRNA-29 expression levels in the development of breast cancer in Egyptian women. Frontiers in Genetics. 2021;12:683809. https://doi.org/10.3389/fgene.2021.683809.

[36] Diansyah MN, Prayogo AA, Sedana MP, Savitri M, Romadhon PZ, Amrita PN, et al. Early detection breast cancer: role of circulating plasma miRNA-21 expression as apotential screening biomarker. Turkish Journal of Medical Sciences. 2021;51(2):562-9. https://doi.org/10.3906/sag-2005-138.

[37] Zou X, Xia T, Li M, Wang T, Liu P, Zhou X, et al. MicroRNA profiling in serum: Potential signatures for breast cancer diagnosis. Cancer Biomarkers. 2021;30(1):41-53. https://doi.org/10.3233/CBM-201547.

[38] Nashtahosseini Z, Aghamaali MR, Sadeghi F, Heydari N, Parsian H. Circulating status of microRNAs 660‐5p and 210‐3p in breast cancer patients. The Journal of Gene Medicine. 2021;23(4):e3320. https://doi.org/10.1002/jgm.3320.

[39] Jang JY, Kim YS, Kang KN, Kim KH, Park YJ, Kim CW. Multiple microRNAs as biomarkers for early breast cancer diagnosis. Molecular and clinical oncology. 2021;14(2). https://doi.org/10.3892/mco.2020.2193.

[40] Hosseini Mojahed F, Aalami AH, Pouresmaeil V, Amirabadi A, Qasemi Rad M, Sahebkar A. Clinical evaluation of the diagnostic role of MicroRNA-155 in breast cancer. International Journal of Genomics. 2020. https://doi.org/10.1155/2020/9514831.

[41] Kim J, Park S, Hwang D, Kim SI, Lee H. Diagnostic value of circulating miR-202 in early-stage breast cancer in South Korea. Medicina. 2020;56(7):340. https://doi.org/10.3390/medicina56070340.

[42] Pastor-Navarro B, García-Flores M, Fernández-Serra A, Blanch-Tormo S, Martínez de Juan F, Martínez-Lapiedra C, et al. A tetra-panel of serum circulating mirnas for the diagnosis of the four most prevalent tumor types. International Journal of Molecular Sciences. 2020;21(8):2783. https://doi.org/10.3390/ijms21082783.

[43] Han S, Li P, Wang D, Yan H. Dysregulation of serum miR-1204 and its potential as a biomarker for the diagnosis and prognosis of breast cancer. Revista da Associação Médica Brasileira. 2020;66(6):732-6. https://doi.org/10.1590/1806-9282.66.6.732.

[44] Ashirbekov Y, Abaildayev A, Omarbayeva N, Botbayev D, Belkozhayev A, Askandirova A, et al. Combination of circulating miR-145-5p/miR-191-5p as biomarker for breast cancer detection. PeerJ. 2020;8:e10494. https://doi.org/10.7717/peerj.10494.

[45] Ibrahim AM, Said MM, Hilal AM, Medhat AM, Abd Elsalam IM. Candidate circulating microRNAs as potential diagnostic and predictive biomarkers for the monitoring of locally advanced breast cancer patients. Tumor Biology. 2020;42(10):1010428320963811. https://doi.org/10.1177/1010428320963811.

[46] Swellam M, Ramadan A, El-Hussieny EA, Bakr NM, Hassan NM, Sobeih ME, et al. Clinical significance of blood‐based miRNAs as diagnostic and prognostic nucleic acid markers in breast cancer: Comparative to conventional tumor markers. Journal of cellular biochemistry. 2019;120(8):12321-30. https://doi.org/10.1002/jcb.28496.

[47] Peña-Cano MI, Saucedo R, Morales-Avila E, Valencia J, Zavala-Moha JA, López A. Deregulated microRNAs and adiponectin in postmenopausal women with breast cancer. Gynecologic and Obstetric Investigation. 2019;84(4):369-77. https://doi.org/10.1159/000496340.

[48] Motamedi M, Hashemzadeh Chaleshtori M, Ghasemi S, Mokarian F. Plasma level of miR-21 and miR-451 in primary and recurrent breast cancer patients. Breast Cancer: Targets and Therapy. 2019:293-301.

[49] Swellam M, Zahran RF, Abo El-Sadat Taha H, El-Khazragy N, Abdel-Malak C. Role of some circulating MiRNAs on breast cancer diagnosis. Archives of Physiology and Biochemistry. 2019;125(5):456-64. https://doi.org/10.1080/13813455.2018.1482355.

[50] Li M, Zou X, Xia T, Wang T, Liu P, Zhou X, et al. A five-miRNA panel in plasma was identified for breast cancer diagnosis. Cancer medicine. 2019;8(16):7006-17. https://doi.org/10.1002/cam4.2572.

[51] Fang R, Zhu Y, Hu L, Khadka VS, Ai J, Zou H, et al. Plasma microRNA pair panels as novel biomarkers for detection of early stage breast cancer. Frontiers in physiology. 2019;9:1879. https://doi.org/10.3389/fphys.2018.01879.

[52] Soleimanpour E, Babaei E, Hosseinpour-Feizi MA, Montazeri V. Circulating miR-21 and miR-155 as potential noninvasive biomarkers in Iranian Azeri patients with breast carcinoma. Journal of Cancer Research and Therapeutics. 2019;15(5):1092-7. https://doi.org/10.4103/jcrt.JCRT_1227_16.

[53] Heydari N, Nikbakhsh N, Sadeghi F, Farnoush N, Khafri S, Bastami M, et al. Overexpression of serum MicroRNA-140-3p in premenopausal women with newly diagnosed breast cancer. Gene. 2018;655:25-9. https://doi.org/10.1016/j.gene.2018.02.032.

[54] Li M, Zhou Y, Xia T, Zhou X, Huang Z, Zhang H, et al. Circulating microRNAs from the miR-106a–363 cluster on chromosome X as novel diagnostic biomarkers for breast cancer. Breast cancer research and treatment. 2018;170:257-70. https://doi.org/10.1007/s10549-018-4757-3.

[55] Yu X, Liang J, Xu J, Li X, Xing S, Li H, et al. Identification and validation of circulating MicroRNA signatures for breast cancer early detection based on large scale tissue-derived data. Journal of breast cancer. 2018;21(4):363-70. https://doi.org/10.4048/jbc.2018.21.e56.

[56] Zhang K, Wang YW, Wang YY, Song Y, Zhu J, Si PC, et al. Identification of microRNA biomarkers in the blood of breast cancer patients based on microRNA profiling. Gene. 2017;619:10-20. https://doi.org/10.1016/j.gene.2017.03.038.

[57] Zhang G, Zhang W, Li B, Stringer-Reasor E, Chu C, Sun L, et al. MicroRNA-200c and microRNA-141 are regulated by a FOXP3-KAT2B axis and associated with tumor metastasis in breast cancer. Breast Cancer Research. 2017;19(1):1-13. https://doi.org/10.1186/s13058-017-0858-x.

[58] Frères P, Wenric S, Boukerroucha M, Fasquelle C, Thiry J, Bovy N, et al. Circulating microRNA-based screening tool for breast cancer. Oncotarget. 2016;7(5):5416-28. https://doi.org/10.18632/oncotarget.6786.

[59] Antolín S, Calvo L, Blanco-Calvo M, Santiago MP, Lorenzo-Patiño MJ, Haz-Conde M, et al. Circulating miR-200c and miR-141 and outcomes in patients with breast cancer. BMC cancer. 2015;15(1):1-15. https://doi.org/10.1186/s12885-015-1238-5.

[60] Heneghan HM, Miller N, Lowery AJ, Sweeney KJ, Newell J, Kerin MJ. Circulating microRNAs as novel minimally invasive biomarkers for breast cancer. Annals of surgery. 2010;251(3):499-505. https://doi.org/10.1097/SLA.0b013e3181cc939f.

[61] Iorio MV, Croce CM. MicroRNAs in cancer: small molecules with a huge impact. Journal of clinical oncology. 2009;27(34):5848-56. https://doi.org/10.1200/JCO.2009.24.0317.

[62] Wang H, Peng R, Wang J, Qin Z, Xue L. Circulating microRNAs as potential cancer biomarkers: the advantage and disadvantage. Clinical epigenetics. 2018;10(1):1-10. https://doi.org/10.1186/s13148-018-0492-1.

[63] Tiberio P, Callari M, Angeloni V, Daidone MG, Appierto V. Challenges in using circulating miRNAs as cancer biomarkers. BioMed research international. 2015. https://doi.org/10.1155/2015/731479.

[64] Felekkis K, Papaneophytou C. Challenges in using circulating micro-RNAs as biomarkers for cardiovascular diseases. International Journal of Molecular Sciences. 2020;21(2):561. https://doi.org/10.3390/ijms21020561.

[65] Kirschner MB, Edelman JJ, Kao SC, Vallely MP, Van Zandwijk N, Reid G. The impact of hemolysis on cell-free microRNA biomarkers. Frontiers in genetics. 2013;4:94. https://doi.org/10.3389/fgene.2013.00094.

[66] Pizzamiglio S, Zanutto S, Ciniselli CM, Belfiore A, Bottelli S, Gariboldi M, et al. A methodological procedure for evaluating the impact of hemolysis on circulating microRNAs. Oncology letters. 2017;13(1):315-20. https://doi.org/10.3892/ol.2016.5452.

[67] Yamada A, Cox MA, Gaffney KA, Moreland A, Boland CR, Goel A. Technical factors involved in the measurement of circulating microRNA biomarkers for the detection of colorectal neoplasia. PLoS One. 2014;9(11):e112481. https://doi.org/10.1371/journal.pone.0112481.

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