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RESEARCH ARTICLE

Serum miR-34a-5p Expression as a Potential Diagnostic Biomarker in Iraqi Women with Breast Cancer

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Abstract

Background: MicroRNAs are small non-coding RNAs that are imperative in regulating gene translation. One of them is miR-34a-5p, which is reported to be a potent tumor suppressor, particularly in breast cancer. **Aim:** The research aims to examine the potential connection of the level of expression of miR-34a-5p with the clinical characteristics of older people with breast cancer tissue. **Methods:** RT-qPCR was used to measure levels of serum miRNA -34a -5p in 50 female breast cancer patients and 50 healthy controls. **Results:** Patient data, comprising body mass index, family history, hormonal profile, breast cancer (BC) type, and subtype, exhibited significant differences between the BC group (mean age 50.16 ± 10.63) and the control group (35.96 ± 11.93). There were no significant variation in miR-34a-5p expression among BC patients with respect to family history, HER2 positivity, progesterone expression, or estrogen detection ($p > 0.05$). However, a notable elevation in miR-34a-5p expression was noted in BC patients compared to controls ($P < 0.02$), with higher mean (34.03 ± 2.86 vs. 27.25 ± 5.64) and median (33.82 vs. 31.48) expression levels in the BC group. **Conclusion:** The findings indicate that there is a great enhancement in miR-34a-5p in the serum of older Iraqi women with breast cancer compared to the healthy controls, which implies that miR-34a-5p can serve as a non-invasive biomarker for diagnosis. Further studies are needed to explore its tumor-suppressive mechanisms and clinical utility in the prognosis or treatment of breast cancer in adult individuals.

Keywords: Breast cancer- miR-34-5p- elderly women- gene expression

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Introduction

The most prevalent malignancy in women and the primary cause of cancer-related mortality for women globally is breast cancer (BC), particularly in older demographics [1]. Recognizing the molecular mechanisms behind the onset and progression of BC in older women is essential for enhancing early detection and treatment approaches, as the disease's incidence rises with age [2]. MicroRNAs (miRNAs) are considered small RNA molecules that don't code for proteins but control gene expression after transcription. They have become very important in cancer biology. One of these, miR-34-5p, has drawn a lot of interest because of its ability to stop the growth of tumors., including in breast cancer [3]. Protein p53 directly regulates miR-34-5p family, which belongs to miR-34 family, which is a well-known regulator of cellular responses to stress such as DNA damage and apoptosis [4]. It is believed that the miR-34 family can regulate such essential processes like cell cycle arrest, apoptosis, and metastasis inhibition due to the targeting of many tumor-related oncogenes and pathways [5]. It is widely acknowledged that miR-34a-5p is a powerful tumor suppressor. in comparison to normal tissues, its expression is frequently downregulated (reduced) in a wide range of human malignancies [6]. Breast cancer among women is a big problem because of the immunological functioning with age, cellular senescence and the presence of hormone

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receptors which makes it difficult to treat and prognose [7]. weaker immune surveillance and immunotherapy efficacy, cellular senescence leading to a pro-tumorigenic microenvironment, and the common characteristics of hormone receptor-positive tumor in this population group often require tailored hormonal treatment, which is less effective because of physiological changes with age [8]. Consequently, the expression levels of miR-34-5p in this cohort may elucidate the molecular differences that influence breast cancer development in older compared to younger individuals [9]. In addition, checking the levels of circulating miR-34-5p could be a non-invasive way to find and forecast breast cancer in its early stages. It could also help improve patients' results in a clinical setting [10]. the principal objective of the present research is to evaluate the miR-34-5p concentration in the groups of adult Iraqi women with breast cancer compared to healthy women, hoping to determine whether it may serve as a diagnostic biomarker, as well as to verify how it interacts with clinical characteristics.

Materials and Methods

Study Population and Sample Collection

The present study was conducted from March 2024 to November 2024, involving 100 women, including 50 breast cancer (BC) patients and 50 healthy controls. Patients in Baghdad, Iraq, were recruited from Al-Andalus Specialist Oncology Hospital and Al-Amal National Oncology Hospital. The (BC) patients were women with histologically proven invasive breast cancer (BC) who had not received chemotherapy, radiation, or hormonal therapy. Patients with subsequent cancer or acute/chronic inflammatory disorders were excluded. The control group included fifty healthy Iraqi women who had no personal or family history of cancer and no chronic inflammatory or infectious diseases. From each participant, blood was drawn from a vein (5 mL) and placed into gel tubes. They were then spun in a centrifuge at ambient temperature for 15 minutes to separate the serum, which would be used for molecular tests. Serum samples were kept at -80°C, and RNA extraction was performed within 24 hours of serum separation using TRIzolTM Reagent to ensure RNA stability.

MicroRNA Extraction Protocol

TRIzol® Reagent was used to get total RNA out of 250 µL of serum (Thermo Fisher Scientific, USA). The serum was mixed with 750 µL of TRIzol. After sitting for five minutes, 0.2 mL of chloroform was added. The samples were blended for 15 seconds and then left alone for 3 minutes. Then, they were spun at 12,000 × for 15 minutes at 4°C. We put 0.5 mL of isopropanol into the water phase, let it rest for 10 minutes, and then spun it at 12,000 × g for 10 minutes at 4°C to get the RNA to drop to the bottom. 0.5 mL of 75% ethanol was used twice to wash the particle, centrifuged at 7,500 × g for 5 minutes at 4°C, left to dry in the air, and then rehydrated in 50 µL of nuclease-free water at 55–60°C for 10–15 minutes. NanoDrop 2000 was used to measure the amount of RNA, and it was kept at -80°C.

Reverse Transcription (R.T) for Complementary DNA (cD.NA) Synthesis

For cDNA synthesis, 4 µL of RNA was combined with 1 µL of miR-let-7-5p stemloop reverse transcription primers. Primers were designed and synthesized using the NCBI Gene Bank database and miRBASE, and selected from the Macrogene (South Korea) primer set (Table 1). To disrupt hairpin loop structures, the mixture had been incubated for five minutes at 70°C and then for ten minutes at 4°C.

Quantitative Real-Time Po1ymerase Chain Reaction (R.T-qPCR)

We followed the manufacturer's instructions to conduct the RT-qPCR using the SYBR Green PCR Kit from Synthol, Russia. The following components were utilized in a 10 µL reaction: 5 µL of SYBR Green Master Mix, 0.5 µL of particular miRNA forward and reverse primers, 2 µL of RNase-free water, and 2 µL of cDNA. The reaction was conducted using a Real-Time PCR system (Synthol, Russia) with the following cycling conditions: first, a one-minute cycle at 95°C; second, forty-five cycles of twenty seconds each at 95°C, 55°C, and 72°C. The levels of miRNA expression were determined as fold change, adjusted to the housekeeping gene miR-16-1, using the $2^{-\Delta\Delta CT}$ algorithm [11].

Statistical analysis

GraphPad Prism (v. 9) and IBM SPSS (v. 27) were used for statistical analysis. The Shapiro-Wilk test was used to assess normality. The Independent Samples t-test (for normally distributed data) or the Mann-Whitney U test (for non-normally distributed data) was used to compare continuous variables. Categorical variables were analyzed with the Chi-square test. Significance was defined as $P < 0.05$.

Table 1. Primer Sequences and Thermal Cycler Protocol for miR-34a-5p Gene Expression

Primer Name	Sequence	Thermal Cycler Protocol	Degrees Celsius	Time (min: sec)	Cycle
MiR34-5P R	5'-GTTGGCTCTGGTG CAGGGTCCGAGGTATTCGCACCAGAGCCAACACAACC-3'	Priming annealing	70	5:00	1
MiR34-5P F	5'-GGTTTTTTTTGGCAGTGTCTTAGCT-3'	Hold	4	10:00	-
Universal Reverse	5'-GTGCAGGGTCCGAGGT-3'	Spin after cooling in ice	-	-	-
MiR-16-1 R	5'-GTTGGCTCTGGTGCAGGGTCCGAGGTATTCGCACCAGAGCCAACCGCCAAT-3'	-	-	-	-
MiR-16-1 F	5'-GGTTTTTTTTAGCAGCACGTAAAT-3'	-	-	-	-

Results

Demographic characteristics of breast cancer patients

Table 2 gives an overview of demographics and other attributes of the study participants. The BC group included 50 female patients with a mean age of 49.16 ± 10.63 years, significantly older than the control group of 50 healthy females with a mean age of 35.96 ± 11.93 years ($p < 0.001$). Body mass index (BMI) (29.86 ± 6.349 kg/m^2) of the BC group was also significantly higher than that of controls (24.39 ± 2.682 kg/m^2, $p < 0.001$). On stratification by BMI subgroups, there were still significant age differences between the patients and controls in the normal BMI subgroup (50.18 ± 9.55 vs. 33.03 ± 9.54 years, $p < 0.001$). There was a significant difference in mean BMI between patients (35.50 ± 4.18 kg/m^2) and controls (30.64 ± 0.24 kg/m^2, $p < 0.05$) in the obese subgroup only, with no significant differences in the normal ($p > 0.0.5$) or overweight ($p > 0.05$) subgroups. The categories of BC patients included 27 who had a family history of breast cancer, 21 who were HER-2 positive, 36 who were progesterone receptor positive, and 37 who were estrogen receptor positive, and there was no equal counterpart of this in the controls.

Table 3 displays the results of the RT-qPCR analysis of miR-34a-5p expression levels in serum. Compared to healthy controls, BC patients showed a significantly higher level of miR-34a-5p expression ($p < 0.03$). The BC group exhibited a higher median expression level (32.26 vs. 31.48) than the control group. The BC group also had more variation in expression, with an interquartile range (IQR) of 2.54 and a range of 29.85 to 41.80. The control group had an IQR of 1.57 and a range of 30.09 to 33.35.

Table 4 shows the miR-34-5p expression levels in BC patients, using family history, HER-2 status, progesterone receptor status, and estrogen receptor status as stratification variables. There were no noticeable differences in miR-34-5p expression across these categories ($p > 0.05$ for any comparison). Particularly:

• Family History: Patients with a family history (n=27) had a median expression of 32.71 (IQR: 2.14, range: 29.88–41.80), while those without (n=23) had a median of 31.92 (IQR: 3.18, range: 26.23–35.99).

• HER-2 Status: Patients who were HER-2 positive (n=21) had a median expression of 33.02 (IQR: 2.26, range: 28.50–36.58), while patients who were HER-2 negative (n=29) had a median expression of 32.79 (IQR: 3.77, range: 28.36–34.99).

• Progesterone Receptor Status: Patients with positive progesterone receptors (n=36) had a median expression of 32.33 (IQR: 2.51, range: 29.85–36.09), whereas patients with negative progesterone receptors (n=17) demonstrated a median of 32.26 (IQR: 3.185, range: 30.03–41.80).

• Estrogen Receptor Status: Patients with positive estrogen receptors (n=37) had a median expression of 32.47 (IQR: 2.59, range: 29.85–36.19), while patients with negative estrogen receptors (n=13) had a median expression of 32.12 (IQR: 3.56, range: 30.99–41.60).

Table 2. Demographic Distribution of Parameters According to Groups of Participants

Parameter	Patients (n.=50)	Controls (n.=50)	P-value.
Age (years, mean±SD)	49.16±10.63	35.96±11.93	<0.001
BMI (mean±SD)	29.86±6.349	24.39±2.682	<0.001
Age by BMI Subgroup (years, mean±SD)			
Normal (n=12/33)	50.18±9.55	33.03±9.54	<0.001
Obese (n=23/2)	49.30±11.82	56±1.41	-
Overweight (n=15/13)	48.20±10.05	40.31±14.29	-
Mean BMI by Subgroup			
Normal	22.70±1.73	23.01±1.69	>0.05
Obese	35.50±4.18	30.64±0.24	<0.05
Overweight	26.45±1.86	26.92±1.37	>0.05
Family History (Yes/No)	27/23	N/A	-
HER-2 (Yes/No)	21/29	N/A	-
Progesterone (Yes/No)	36/14	N/A	-
Estrogen (Yes/No)	37/13	N/A	-

N/A = non-applicable

Table 3. Expression of miR-34-5p in Breast Cancer Patients and Hea1thy Controls

	Patients (n=50)	Controls (n.=50)	P-value.
Mean ± SD	34.03 ± 2.86	27.25 ± 5.64	<0.01
Median	33.82	31.48	-
Interquartile Range	4.38	1.57	-
		23.45–33.35	

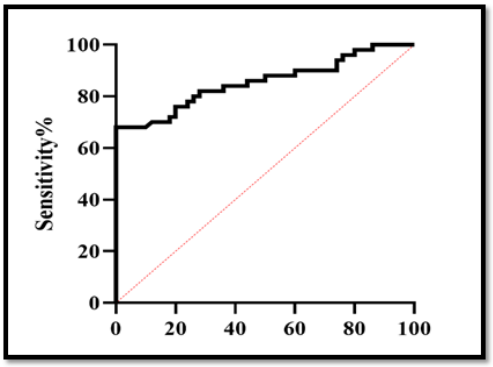

Figure 1. Receiver Operating Characteristic (ROC) Curve for miR-34a-5p in Women with Breast Cancer

Discussion

The present study involved a comparison between serum miR-34a-5p expression in breast cancer (BC) in old Iraqi women and healthy controls, including demographic and clinical features. The results of Tables (2-4) highlight the significant differences between the age, body mass index (BMI), and miR-34a-5p expression of breast cancer (BC) patients and controls, as well as the prevalence of hormone receptor-positive tumors. The results can improve the understanding of the potential role of miR-34a-5p in breast cancer and its importance as a diagnostic and therapeutic biomarker, as well as focusing on the role of age, body mass index, and familial history as risk factors [12].

Older people are more prone to breast cancer, and it is no secret that age is one of the biggest risk factor of breast cancer [13]. According to previous research [14], the age of the patients with BC under investigation (mean age: 49.16 ± 10.63 years) was significantly higher than that of the controls (35.96 ± 11.93 years, $p < 0.001$, Table 2), which shows that aging has a significant effect on the susceptibility to diseases. Old age can increase the risk of cancer due to the progressive genetic and epigenetic modifications [15]. Though these mechanisms were not directly assessed here. Similarly, BC patients exhibited a higher BMI (29.86 ± 6.349 kg/m²) than controls (24.39 ± 2.682 kg/m², $p < 0.001$, Table 2), particularly in the obese subgroup ($p < 0.05$). High BMI is a predisposing factor to BC, which may be explained by the exponential secretion of estrogens in fat-tissue, chronic inflammation, and insulin resistance [16, 17]. The predominance of hormone receptor-positive BC among older women (high prevalence of estrogen (37/49) and progesterone (36/49) receptors in this cohort (Table 2) is consistent with the high prevalence of hormone receptor-positive tumors in older women. [18]. These receptors enhance tumor growth by increasing cyclin G1 and creating an inflammatory tumor microenvironment [19], which an increased BMI can increase.

One of the main conclusions of this research is that mi.R-34a-5p is much more expressed in the serum of patients with BC (mean: 34.03 ± 2.86, median: 33.82) than in healthy controls (mean: 27.25 ±. 5.64, median: 31.48, $p < 0.0.1$, Table 3). This higher expression indicates that miR-34a-5p may play a role in the progression of BC in old women in Iraq, possibly due to a compensatory effect of oncogenic stress or a change in the regulatory mechanism in the low-stage disease [20, 21]. Despite

Table 4. miR-34-5p Expression in Breast Cancer Patients by Subgroups

Subgroup	Positive	Negative	P-value
Family History (n=27/23)	33.69 ± 2.77	34.43 ± 3.09	<0.04
Mean ± SD Median Interquartile Range Minimum Maximum	33.14	34.52	
	3.35	4.13	
	29.08	28.97	
	40.42	39.31	
HER-2 (n=21/29)	34.09 ± 2.57	33.99 ± 3.09	>0.05
Mean ± SD Median Interquartile Range Minimum Maximum	33.57	33.94	
	4.01	4.95	
	30.43	28.97	
	40.42	39.31	
Progesterone (n=36/17)	34.08 ± 3.50	33.91 ± 1.99	>0.05
Mean ± SD Median Interquartile Range Minimum Maximum	34.01	33.75	
	4.89	2.72	
	28.97	30.7	
	40.42	37.19	
Estrogen (n=37/13)	34.00 ± 3.14	34.09 ± 1.92	>0.05
Mean ± SD Median Interquartile Range Minimum Maximum	33.7	33.94	
	5.02	2.26	
	28.97	30.7	
	40.42	37.19	

the popularity of mi.R-34a-5p as a tumor suppressor that suppresses tumor proliferation by targeting the oncogenes and inducing apoptosis [22] that its serum levels in BC patients are high could be a sign that cancer biology is complex in some way, e.g., an effort to counter tumor progression or an escape of tumor cells into the blood. This observation is against other studies that have found downregulated miR-34a-5p in aggressive BC [23]. The age, early-stage diagnosis, or regional genetic variations should be suggested as cohort-specific factors that can affect its expression. Addressing mi[R-34a-5p as a non-invasive biomarker to screen BC, the ROC curve analysis (Figure 1) additionally highlights the great diagnostic performance of miR-34a-5p (AUC = 0.855, sensitivity = 92%, specificity = 72%, p = 0.00.1). These findings conform to the existing literature that has indicated the usefulness of mi.R-34a-5p in the early detection of BC. [24].

It is important to note that the expression of miR-34a-5p was significantly different between BC patients with and without a family history ($p < 0$ 04, Table 4), but the expression of miR-34a-5p in patients with no family history (mean: 34.43 ± 3..09 vs. 33.69 ± 2.77) was somewhat higher. This result indicates that genetic predisposition can adjust the expression of miR-34a-5p, and this can affect tumor-suppressive response in familial cases of BC [23]. Nevertheless, significant variations were not found between HER-2, progesterone, or estrogen receptor status ($p > 0..05$, Table 4), which means that the identified clinical factors might not have a strong effect on miR-34a-5p expression in this group of patients. To verify these findings and investigate the effects of a combination of both family history and mi.R-34a-5p regulation, larger studies are required [25].

The clinical significance of miR-34a-5p expression is huge. It has been proposed in the literature that miR-34a-5p increases chemosensitivity through cell cycle arrest and apoptosis caused by p53 signaling and decreases tumor invasion caused by Notch1 [26]. An increase in miR-34a-5p in BC patients over controls ($p < 0.01$) could be an indication of its tumor-suppressive effect, as has been described in earlier studies [27]. More studies should be conducted to establish whether this upregulation can be utilized therapeutically, including in combination with chemotherapeutic agents like doxorubicin [28]. The advantage of serum-based miR-34a-5p measurement is non-invasive, coupled with the high diagnostic accuracy (Figure 1), making the serum-based miR-34a-5p measurement a potential diagnostic or prognostic biomarker [29]. But it is too narrow and lacks enough prognostic value to be clinically useful without precedent in bigger, longitudinal studies [30].

The current study's major limitation is that its cross-sectional approach does not allow for causation or time-based inference of miR-34a-5p expression. Moreover, the stages of the disease in the BC were not provided, which restricted our potential to determine the association between the miR-34a-5p expression and disease progression in various stages. In future research, there is a priority on BC stage stratification in order to examine the stage-specific pattern of expression and its implications in clinical practice. Also, the investigation of the molecular processes behind the expression difference, which is related to the family history, might shed light on the individualized treatment of BC.

In conclusion, in this investigation, it was discovered that serum levels of microRNA-34a- 5p (miR-34a-5p) were much greater in adult Iraqi breast cancer patients than in similar healthy individuals. The expression was found to be elevated with great diagnostic accuracy with an Area Under the Curve (AUC). This result highlights its great potential as an ultra sensitive and non-invasive diagnostic biomarker of breast cancer screening and diagnosis in this specific group of patients.

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Statement of Ethics

The scientific and ethics committee of the Iraqi Centre for Cancer and Medical Genetic Research at Mustansiriyah University approved the study with reference No (361) (21-2-2024).

Competing Interests

The authors have no relevant financial or non-financial interests.

Author contributions

"All of the authors helped come up with the idea for the study and how it would be set up. [AS], [MA], [AH], [AS], [AJ], and [BS] did the work of preparing the materials, gathering the data, and analyzing it. [As] wrote the first draft of the text, and all of the writers gave feedback on earlier drafts. All of the authors read and agreed to the final manuscript."

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