Article
JOURNAL OF UNIVERSITY OF BABYLON
For Pure and Applied Sciences (JUBPAS)
Vol. 34 ; No.1 | 2026

Evaluation the Role of MIRNA-21 AND MIRNA-205 in Patients with Breast Cancer

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تقييم دور الحمض النووي الرايبي المايكروي 21 و 205 لدى مرضى سرطان الثدي

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Accepted: 2/3/2026 **Published:** 31/3/2026

ABSTRACT

Background: Breast cancer is one of the most serious health problems and challenges facing women, as it is one of the most widespread tumors among women worldwide, and understanding molecular aspect is essential for improving diagnosis and treatment.

Objective: The aim of this research to investigate the impact of microRNAs (miR-205, miR-21) in breast cancer patients . and Comparing gene expression results between the breast cancer patients group and the control group and explains the influence of increased or decreased gene expression of these parameters on tumor progression.

Materials and Methods: A total of 80 individuals, 40 from the healthy group and 40 from the control group, all females aged 30 to 50 and older, were sampled. Two milliliters of blood were collected in an EDTA tube for RNA extraction and genomic study.

Results: Achieved results indicated that the gene expression of miR-205 was decreased significantly ($P<0.01$) in patients group which was (0.508±0.17 fold) in comparison to control group which was (1±0 fold) with the area under the curve (AUC) was found to be 0.826. while Achieved results indicated that the gene expression of miR-21 was increased significantly ($P<0.05$) in patients group which was(1.72±0.43 fold) in comparison to control group which was (1±0fold)with thr area under the curve (AUC) was found (0.478).

Conclusion: The gene expression of miRNA-205 is decreased significantly in patients with breast cancer compared to the control group, ROC for miRNA-205 showed a good prognostic indicator for breast cancer patients with good sensitivity. while the gene expression of miR-21 is significantly higher in patients group compared to the healthy group. ROC for miRNA-21 demonstrated a good prognostic indicator for breast cancer patients with weak sensitivity.

Key words: Breast cancer, miR-205,miR-21

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INTRODUCTION

Breast cancer is one of the biggest and most important health problems facing women worldwide, and it is very widespread among women, with large numbers diagnosed annually, as 2.2 million cases were diagnosed in 2020 [1]. A large number of women are diagnosed with breast cancer each year, approximately 2.09 million, while breast cancer deaths number around 627,000 women [2]. In Iraq, breast cancer is one of the leading causes of death among women and is widespread among them [3]. There are several internal and external factors that affect the growth and development of breast cancer, including hereditary predisposition, environmental exposures, lifestyle choices, and psychosocial stressors [4],[5]. Established risk factors include female age, parity, family history of breast cancer—particularly in first-degree relatives—radiation exposure, smoking, and genetic mutations such as BRCA1 and BRCA2 [2],[6]-[7]. Chronic inflammation is a risk factor for breast cancer, as supported by a study that found a link between recurrent inflammation at a young age and breast cancer, particularly among breastfeeding women. The study also concluded that women with a history of mastitis face a significantly elevated risk of developing breast cancer[8].Clinical procedures currently exist to identify high-risk breast cancer patients, such as those with early-onset disease or pathogenic mutations in genes like BRCA1 and BRCA2. However, precise guidance for low-risk patients is limited. Recent genomic studies suggest that genetic profiling, including polygenic risk scores (PRS), could help identify low-risk individuals. One study defined low-risk women based on two criteria ,First criterion no known or uncertain variations in significant susceptibility genes, including BRCA1, BRCA2, PALB2, ATM, and CHEK2, and The second criterion a PRS within the lowest decile based on 313 validated single-nucleotide variations [9],[10]. The interaction between breast cancer cells and the immune system is highly complex and dynamic. Tumor cells can evade immune surveillance by creating immunosuppressive microenvironments and expressing checkpoint proteins that inhibit immune activity. Conversely, the immune system can mount effective anticancer responses under certain conditions, particularly when stimulated by immunotherapy [11],[4]. there key role of immune system to identifying and eliminating cancerous cells, utilizing diverse cellular components and molecular pathways that can recognize and attack abnormal cells before tumor formation. Breast cancer cells can escape immune detection by downregulating antigens, releasing inhibitory cytokines, or activating immune checkpoint pathways [12]. miRNA consists of 17-27 nucleotides , it is a short-stranded , non-coding RNA that are found in viruses, animals, plants, and this miRNA can play an major role in negative mRNA gene expression[41],[42]. Tumors with a low level of differentiation have lower levels of miRNA than tumors with a high level of differentiation, suggesting that changes in miRNA expression reflect the degree of cell differentiation. This theory was confirmed by a study showing that miRNA expression is lower in human tumor-derived cell lines compared to corresponding tissues[43].miRNA has been characterized in breast cancer as a tumor suppressor, miRNA-205 is expressed paradoxically between species, being expressed inconsistently in ER+/PR+ (less aggressive) and highly aggressive (stage III negative breast cancer) species. This has been demonstrated by numerous studies. In HER2+ breast cancer, miR-205 expression is low compared to ER+/PR+ breast cancer, where miR-205 expression is elevated, but in (TNBC) its expression is low compared to other subtypes[13]. It was found that down regulation of miRNA-205 is not jast observed in tumors compared to normal tissues, but it has also been reported that in metastases, expression of MiR-205 is lower compared to normal tissues, and expression is also reduced in lymph nodes compared to primary tumors[14]-[15]. MicroRNA 21 targets several tumor suppressor genes, including TIMP3, TPM1, RECK, Cdc25A, p53 network, PDCD4,

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PTEN, and Maspin, therefore, it regulates cell proliferation, migration, invasion, and programmed cell death[16]-[17]. miRNA-21 also modulates key signaling pathways involved in tumorigenesis, such as Ras/MAPK and RTK/PI3K/Akt/mTOR, where downregulation of PTEN and other negative regulators leads to hyperactivation of mTOR, enhancing tumor cell proliferation and survival[18]-[20]. Given its multifaceted roles, miRNA-21 represents a promising therapeutic target, where inhibition of miRNA-21 could restore tumor suppressor activity and sensitize tumors to mTOR inhibitors, offering potential synergistic antitumor effects[21]. miRNA-21 is central to breast cancer pathogenesis, particularly in aggressive subtypes like TNBC, and is a candidate for early detection, prognosis, and targeted therapy[22]-[23]. This work aimed at the evaluation role of MIR-21 AND MIR-205 in patients with breast Cancer.

MATERIALS AND METHODS

Study group

A case control study have been conducted based on 40 patients diagnosed with breast cancer in addition to 40 apparently healthy control volunteers from the period (2/12/2024- 5/1/2025), their age range from (30–39), (40–49),50 years and over .

Blood samples

two ml of blood from 40 patients and 40 healthy women has been collected by vein puncture under aseptic condition and have been collected with EDTA for RNA extraction and genomic study.

Inclusion Criteria

The included cases in this study were all women patients with breast cancer.

Exclusion Criteria

Pregnant women, women with other malignancies or chronic illnesses, people with autoimmune diseases, and all males with breast cancer were excluded.

Primers design:

The primers for MiR_205 and MiR_21 target markers and U6 housekeeping gene were used from abm company, Canada. as following table(1)**:.**

Table(1):primers sequences for gene expression utilized in this study

Primer	Sequence (5'-3')		Product Size	NCBI Reference Sequence
MiR_205	F	TCCTTCATTCCACCGGA	~60-80bp	MI0000285
	R	GAACATGTCTGCGTATCTC		
MIR_21	F	GCTTATCAGACTGATGTTG	~60-80bp	MI0000077
	R	GAACATGTCTGCGTATCTC		
U6	F	CTCGCTTCGGCAGCACAT	~90bp	NR_004394.2
	R	TTTGCGTGTCATCCTTGCG		

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Total RNA extraction

Total RNA were extracted from blood samples by using (GENEzol™ reagent kit) and done according to company instructions as following steps:

1. For each 250ul of blood sample, 750 µl of GENEzol™ reagent was added . cells in the sample suspension were analyzed by passing the suspension several times through a pipette or vortexing.
2. Two hundred µl chloroform was added to per 1ml of GENEzol™ reagent and shake vigorously for 15 seconds.
3. The mixture was incubated on ice for 5 minutes. Then centrifuged at 12000 rpm, 4C°, for 15 minutes.
4. Supernatant was transferred into a new Eppendorf tube ,and equal volume of isopropyl alcohol was added. Then, mixture was mixed by inverting the tube 4-5 times and incubated at -20℃ for 10 minutes. Then, centrifuged at 12,000 rpm , 4C° for 10 minutes.
5. - Supernatant was discarded, and 1ml 80% Ethanol was added and mixed well by inverting or vortexing. Then, centrifuged at 12000 rpm, 4C° for 5 minutes.
6. The supernatant was discarded and the RNA pellet was left to air to dry.
7. RNA was dissolved in RNase-free water, and incubated for 10 minutes at 55 to 60℃ and stored at -70℃.

Estimation of extracted total RNA yield

Using a Nanodrop spectrometer, the total extracted RNA was measured and evaluated (THERMO. USA), Two quality tests were performed on the RNA to determine quantity and purity, using absorbance readings in the spectrometer at 260 and 280 nm, as follow:

1- After opening up the Nanodrop software, chosen the appropriate application (Nucleic acid, RNA).
2- A dry wipe was taken and cleaned the measurement pedestals several times. Then carefully pipeted 2µl of free nuclease water and put on the surface of the lower measurement pedestal to blanking of Nanodrop.
3- Then, for measurement purposes, 1µl of RNA was withdrawn and the bases were cleaned.

cDNA synthesis

Total RNA was conversely translated to complementary DNA (cDNA) by miRNA All-in-One cDNA Synthesis Kit as following tables(2).

Step 1

RT master mix	Volume
2X MIRNA CDNA Synthesis SuperMix	10 ul
RNA Template	6 ul
Enzyme mix	2ul
Nuclease-free water	2 ul
Total	20 ul

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Step 2

	Temperature	Time
Mixture incbated	**37 C°**	**30 min**
cDNA synthesis (RT step)	**50 c**	**15 min**
Heat inactivation	**85 c**	**5 min**

All micDNA kept in freezing at -20c

Quantitative real-time PCR (qPCR)

Quantitative real-time polymerase chain reaction (qPCR) was used to quantify gene expression of the target markers miRNA-205 and miRNA-21.

Table (3):- qPCR Thermocycler conditions

qPCR step	Temperature	Duration	Cycle
Enzyme Activation	**95 °C**	**3 min**	**1**
Denaturation	**95 °C**	**15 sec**	**40**
Annealing/Extension	**60 °C**	**1 min**	

qPCR master mix preparation

qPCR master mix was prepared by using BlasTaq™ 2X qPCR MasterMix based on SYBER green dye detection of target and housekeeping genes amplification in RealTime PCR system and include the following table(4):

Table(4): qPCR master mix preparation

qPCR master mix	Volume
BlasTaq™ 2X qPCR MasterMix	**10 µL**
Forward primer(10um)	**0.5 µL**
Reverse primer (10um)	**0.5 µL**
cDNA template	**1 µL**
Nuclease-free H_2O	**8 µL**
Total	**20 µL**

Then we mixed the qpcR components using a centrifuge for 3 min.

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qPCR Thermocycler conditions

Table (5) :-qPCR Thermocycler conditions

qPCR step	Temperature	Duration	Cycle
Enzyme Activation	95 °C	3 min	1
Denaturation	95 °C	15 sec	40
Annealing/Extension	60 °C	1 min	

Ethical Approval

This work was done meeting all the formal regulations University of ALQadisyah and the Ministry of Health of iraq,also all patients were informed consent and formal acceptance were obtained.

Statistical analysis

Using the Statistical Package for the Social Sciences (IBM-SPSS) version 27 and Microsoft Office 2010, all obtained data was managed, summarized, and analyzed by this software. To assess the nature of the distribution of numerical variables, the Kolmogorov-Smirnov test was used. The data are normally distributed and presented as a mean± standard deviation (SE). by using student's t-test The group mean were compared. Pearson's correlation coefficient was calculated to examine linear relationships between numeric variables. To determine the optimal cutoff point for achieving the highest level of sensitivity and specificity, a receiver operating characteristic (ROC) curve analysis was performed.Where the statistical significance is indicated as P-value of <0.05 ,and The high statistical significance is refer as P-value of <0.01 (24).

RESULTS

MiRNA 205 gene expression

Achieved results indicated that the gene expression of MiR-205 was decreased significantly (P<0.01) in patients group which was (0.508±0.17fold) in comparison to control group which was (1±0fold) as shown in Table (6) and (Figure 1) .

Table (6) miRNA205 gene expression in the patients and control

Groups	miRNA205(mean ±SE)
Control	1±0
Patients	0.508±0.17
T value	2.86
P value	0.009(HS)

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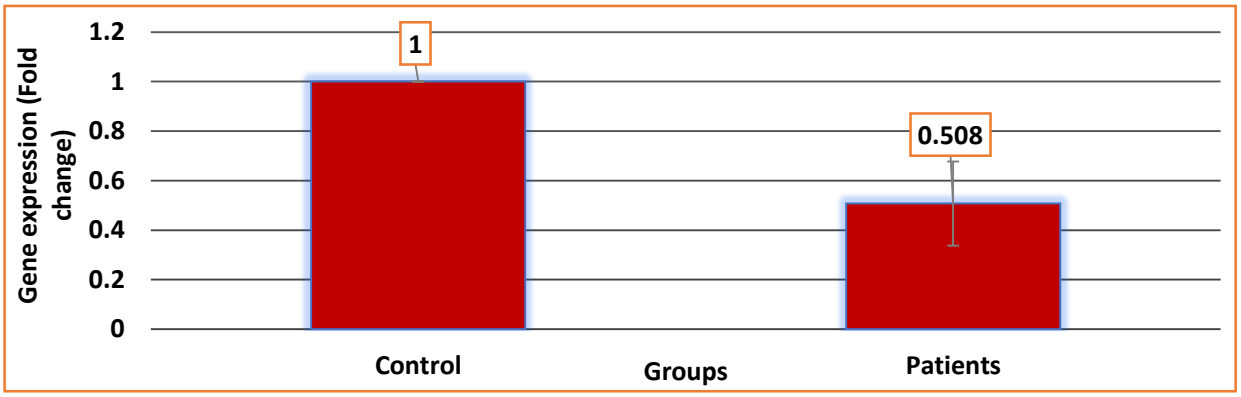

Figure (1):-The means of miRNA205 gene expression

The receiver operating characteristics curve of miRNA205 gene expression

According to the analysis of the miRNA205 gene expression ROC curve results (Figure2), the area under the curve (AUC) was found to be 0.826, which is a good indicator for prognostic breast cancer, as the sensitivity was 0.826 and the specificity was 1, as shown in the table(4). The miRNA205 gene expression cutoff value was 0.867.

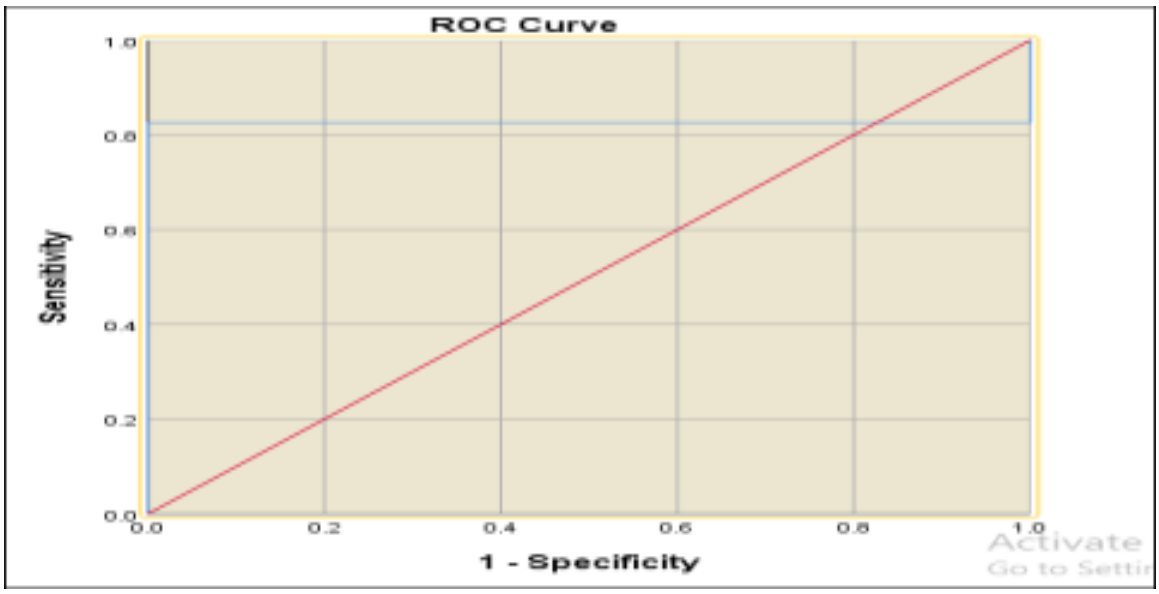

Figure (2):The receiver operating characteristic curve of the miRNA205 gene expression

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Table(7) the criteria of the Receiver operating characteristic curve of miRNA205 gene expression

Marker	Patients	Control
Number	40	40
AUC	0.826	
Standard error	0.079	
P value	0.001	
95% CI	0.025-0.322	
Sensitivity	0.826	
Specificity	1	
Cut-off point	0.867	
	True positive=39	True negative=36
	False positive=1	false negative=4
	Total positive cases=40	Total negative cases=40

MiRNA-21 gene expression

Achieved results indicated that the gene expression of MiRNA-21 was increased ($P<0.05$) in patients group which was (1.72±0.43fold) in comparison to control group which was 1±0(fold) as shown in(Table 8) and (Figure 3) .

Table (8): miR-21 gene expression in the patients and control

Groups	miRNA-21(mean ±SE)
Control	**1±0**
Patients	**1.72±0.43**
T value	**1.66**
P value	**0.109(NS)**

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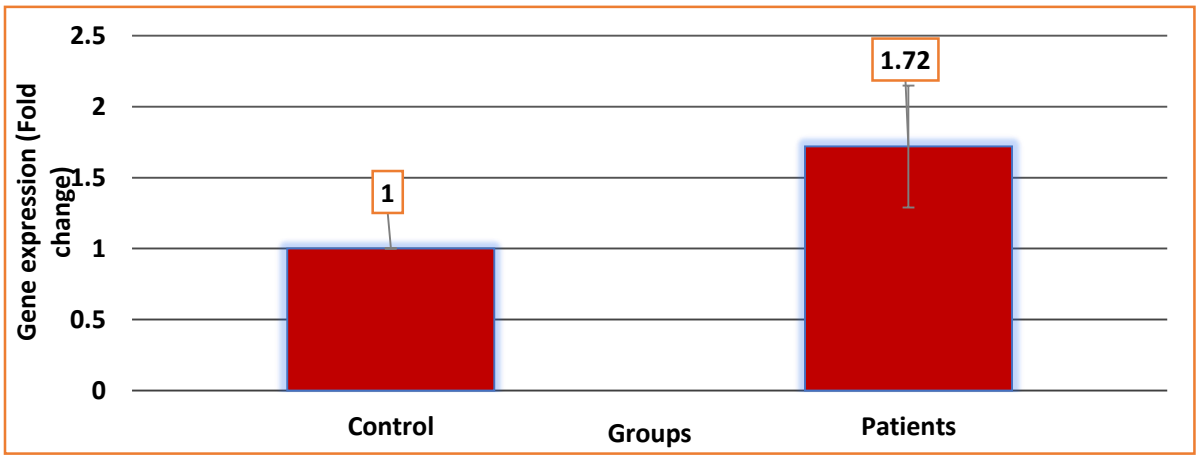

Figure (3) :-The means of MiRNA-21 gene expression

the Receiver operating characteristics curve of MiRNA-21 gene expression

According to the analysis of the miRNA-21 gene expression ROC curve results (Figure 4), the area under the curve (AUC) was found to be 0.478, which is a good indicator for prognostic breast cancer, as the sensitivity was 0.478 and the specificity was 1, as shown in the (table 6). The miRNA-21 gene expression cutoff value was 0.919.

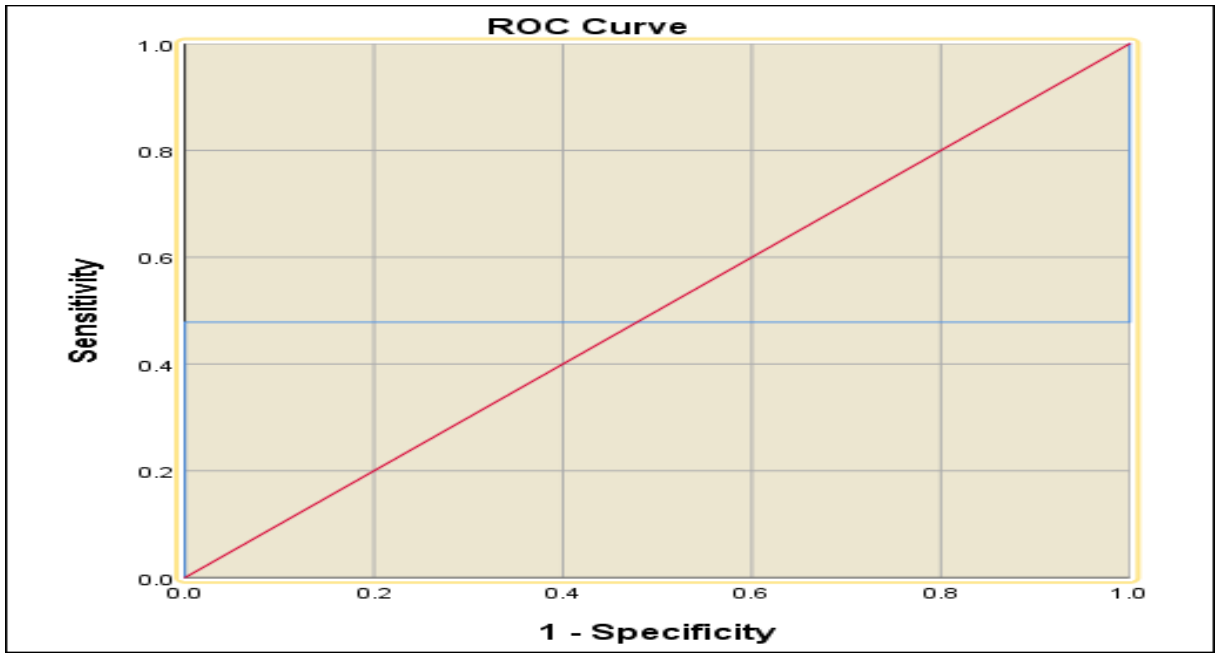

Figure (4) :The receiver operating characteristic curve of the miRNA21 gene expression.

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Table (9): The criteria of the receiver operating characteristic curve of miRNA-21 gene expression

Marker	Patients	Control
Number	40	40
AUC	0.478	
Standard error	0.104	
95% CI	0.225-0.728	
Sensitivity	0.478	
Specificity	1	
Cut-off point	0.919	
	True positive=39	True negative=37
	False positive=1	false negative=3
	Total positive cases=40	Total negative cases=40

DISCUSSION

Collected data showed a significant decrease in miRNA-205 in the patient group compared to the control group. This is consistent with the findings of study who found that miRNA-205 expression is significantly reduced in breast cancer and other types of cancer[13]. The role of miR-205 varies depending on the subtype within the same cancer; it has a tumor-suppressive role in triple-negative breast cancer, while its role is more complex in hormone receptor-positive breast cancer[25]. miR-205 specifically targets ZEB1 and ZEB2, leading to inhibition of the EMT process and thus exerting tumor-suppressive effects[26]. miR-205 regulates the expression of ErbB3 and mediates apoptosis by regulating the P13k-AKT signaling pathway, thus mediating apoptosis in cancer[27]. This pathway is hyperactive, causing increased cell proliferation, decreased apoptosis, and an rise likelihood of tumor formation and metastasis[28]. A study found that miR-205 expression is higher in patients with estrogen receptor-positive cells compared to those with estrogen receptor-negative cells. One study showed that patients with low levels of microRNA 205 had a better five-year survival rate compared to patients with higher expression of microRNA 205[29]. There are parts of the phosphatidylinositol 3-kinase (P13K) signaling pathway that can be regulated by microRNA. study on miR-205 and found that MCF7 cells(Michigan Cancer Foundation-7) exhibit reduced growth and colonization capacity due to the induction of apoptosis at elevated levels of miRNA-205 expression. They also observed inhibition of MCF7 cell migration and invasion capacity through miR-205 overexpression, suggesting its role in preventing invasion and tissue transformation. Furthermore, they noted that this gene reduces the expression of the HER3 protein, which supports cell survival and growth, through the binding of miR-205 to UTR'3[30]. A study conducted on miR-205 in Endometrioid Endometrial Cancer also noted elevated expression of miRNA-205 in EEC(Endometrioid

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Endometrial Carcinoma) tissue specimens compared to normal endometrium[31]. In a study conducted on miR-205 it was observed that VEGF-A (vascular endothelial growth factor A) is targeted by miR-205, and VEGF-A It plays a fundamental and very important role in cancer metastases[32]. While Based on the data we obtained in this research, MiRNA-21 levels were significant elevated in the patient group compared to group of healthy. This finding is matches with study, which found that Tumor progression, relapse, and tumor grade are closely associated with the overexpression of MiR-21[27].As study confirmed, the carcinogenic role of the miRNA-21 gene in breast cancer[33]. study also found reduced cell growth and tumor growth in mice when miRNA-21 was inhibited in MCF7 breast cancer cell lines[34]. Also found that most cancers show overexpression of MiR-21, which supports its activity as an oncomiR and targets the tumor suppressor gene PREN[35]. Study they found an inverse association between decreased miR-205 expression and TNM stage in breast cancer. This study also found that tumor growth can be inhibited by targeting CLDN11 with miR-205, as elevated expression of miR-205 inhibits the translation and formation of CLDN11, which plays a role in tumor development by promoting mesenchymal transformation, inhibiting apoptosis, and increasing migration and invasion[36]. In results similar to ours results, a study showed that high levels of miR-21 expression are related to relapse and reduced survival rates [37]. Our findings are further supported by the results of the study which concluded that a decrease in survival rate is closely associated with increased expression of miRNA-21 in TNBC [38]. Similarly, other studies on miR-21 have focused on Overexpression of miRNA-21 is considered a marker of relapse in breast cancer, as elevated miR-21 reduces its capacity to Disrupting the molecular pathway involved in tumor and regulating tumor suppressor genes[39]. In a study on miRNA-205 the idea of adopting miR-205 as an indicator for diagnosing breast cancer was supported. A target of miRNA was identified as LZTFL1 (Leucine zipper transcription factor-like 1), where they concluded that inhibiting miR-21 inhibits the proliferation and spread of breast cancer cells through EMT in vivo and in vitro by enhancing the gene expression of LZTFL1[40]. Previous studies have shown that miRNA expression is involved in carcinogenesis and is also a notable regulator of PI3K/AKT [45]-[46].Therefore, changes in miRNA levels are often described as a key factor in the initiation of cancer development and many other diseases[44].

Conflict of interests:

the article was done as part if Msc theis. no confect of interest

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