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The Evaluation of Circulating Micro RNA-21 As the Potential Role of Biochemical in Females with Breast Cancer

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ABSTRACT

Background: Breast carcinoma, a malignant neoplasm originating from breast tissue, exhibits a remarkable pathological diversity that underscores its complexity. However, the pathological manifestations of this disease are multifaceted, encompassing various histological subtypes and molecular classifications. In 2018, over 2 million new cases of breast cancer were estimated to occur globally, accounting for nearly 12% of all new cancer cases. Circular RNAs (microRNAs) have recently gained attention as a novel class of non-coding RNAs with diverse gene regulatory functions among the various epigenetic regulators.

Subjects and methods: The study includes 100 women with age range 23 to 80 years old. They were divided into two groups: Group A included 48 women with newly diagnosis breast cancer. And group B include 52 women without breast cancer or any other cancers. Laboratory investigation included measurement of miR-21, CA 15-3, HbA1c, Lipid profile, liver function, renal function.

Results: The mean ± SD for women without breast cancer was 8.64 ± 2.17, while for women with breast cancer patients, it was 46.32 ± 11.28. The p-value was 0.000, indicating statistical significance. In conclusion, our study has proven an increase in micro RNA-21 with breast cancer compared to individuals without cancer. Micro RNA-21 used as a biochemical marker for breast cancer. CA 15-3, also increased with the presence of breast cancer.

Keywords: microRNA-21, Breast cancer, Metastasis, CA 15-3, CEA.

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Introduction

Breast carcinoma, a malignant neoplasm originating from breast tissue, exhibits a remarkable pathological diversity that underscores its complexity. At its core, breast carcinoma involves the uncontrolled proliferation of abnormal cells within the breast, leading to the formation of tumors. However, the pathological manifestations of this disease are multifaceted, encompassing various histological subtypes and molecular classifications [1]. Breast cancer is the most frequently diagnosed cancer among women worldwide, representing about 25% of all new cancer cases in the female population. In 2018, over 2 million new cases of breast cancer were estimated to occur globally, accounting for nearly 12% of all new cancer cases. Although incidence rates have been rising worldwide, breast cancer death rates have declined in many regions, including North America and parts of Europe, due to improvements in early detection through mammography screening and adjuvant therapy [2].The complex molecular mechanisms underlying breast cancer development and progression are not fully understood, hindering the development of more effective personalized therapies. Epigenetic dysregulation has emerged as a key hallmark of cancer, enabling the acquisition of malignant capabilities such as sustained proliferation, evasion of growth suppressors, and activation of invasion and metastasis [3]. Circular RNAs (circRNAs) have recently gained attention as a novel class of non-coding RNAs with diverse gene regulatory functions among the various epigenetic regulators. Aberrant circRNA expression has been implicated in various cancers, including breast cancer [4]. Moreover, breast carcinoma exhibits a diverse array of molecular classifications, reflecting the intricate interplay of genetic and epigenetic alterations that drive tumor development and progression [5].The pathological diversity of breast carcinoma underscores the importance of accurate diagnosis and subtyping, as these factors significantly impact treatment strategies and patient outcomes. Comprehensive pathological evaluation, including histological examination, immunohistochemical staining, and molecular profiling, is essential for tailoring personalized treatment plans and optimizing patient care [6]. The Oxford Group conducted a combined analysis to present a summary of the results related to alcoholic beverage consumption of data from 53 epidemiologic studies. Women who had an average daily consumption of 4 or more drinks a day had a 50% higher breast cancer risk than those who did not drink alcohol [7]. Age remains one of the most critical risk factors for breast cancer. A global

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rise in breast cancer incidence has been noted across all age groups, with the most pronounced increase occurring in women under the age of 50 [8]. The incidence of breast cancer increases significantly with age, with the majority of cases occurring in women over 50 years old. This observation underscores the importance of age as a crucial risk factor and highlights the need for targeted screening and prevention strategies for older women [9]. Age-related changes in the breast tissue microenvironment may play a pivotal role in the development of breast cancer in older women. Specifically, increased inflammation and altered immune response within the breast tissue microenvironment could create a conducive environment for the initiation and progression of breast cancer [10]. Estrogen is a key hormone involved in the regulation of breast tissue development and function, but prolonged exposure to estrogen has been associated with an increased risk of breast cancer. Estrogen can contribute to breast cancer development through mechanisms such as stimulating cell proliferation, promoting angiogenesis (the formation of new blood vessels), and inducing DNA damage via oxidative stress and other pathways [11]. Breast cancer is divided into in situ (ductal and lobular) and invasive disease. There are more than 21 subtypes of invasive breast carcinoma [12]. Molecular classification provides a more comprehensive understanding of breast cancer biology and has the potential to guide personalized treatment strategies [13]. the four main molecular subtypes: luminal A, luminal B, HER2-enriched, and basal-like (triple-negative). Each subtype is characterized by distinct gene expression profiles, clinical features, and therapeutic implications [14]. Gene expression analysis has enabled the classification of breast cancer into five molecular subtypes: luminal A, luminal B, HER-2 positive non-luminal, basal-like, and certain special histological variants. These molecular categories align with the immunophenotypic profiles of tumor cells, which are defined based on established pathological criteria [15]. A groundbreaking study explores the potential of a microRNA signature as a prognostic biomarker in triple-negative breast cancer (TNBC), a particularly aggressive and challenging subtype of breast cancer [16]. The development of breast malignant tumors is a complex multistep process associated with numerous genetic alterations. MicroRNA (miRNA) is a small noncoding RNA gene product known to post-transcriptionally modulate gene expression by negatively regulating the stability or translational efficiency of its target mRNAs, which modulate the expression of target genes and play essential roles in the biological and pathological processes of diseases [17]. MiRNAs control a wide array of biological processes, such as cell differentiation, proliferation, and apoptosis. Aberrant

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expressions of miRNAs have been widely reported in human cancers with both up- and down-regulation detected in neoplastic cells compared with their normal counterparts. miRNAs are stably detectable in plasma and serum [18]. MicroRNA-21 (miR-21) is one of the most extensively studied microRNAs due to its significant role in various physiological and pathological processes, particularly in cancer, cardiovascular diseases, and inflammation. It is a small, non-coding RNA molecule approximately 22 nucleotides in length, transcribed from the MIR21 gene located on chromosome 17q23.2 [19]. miRNA-21 (miR-21), one of the first identified and most prevalent miRNAs in human cells, has been studied in various diseases, including cardiovascular diseases as well as cancers. Particularly, since the miR-21-targeted genes identified till now are mostly tumor suppressors, miR-21 is closely related to various types of cancers, including hepatocellular cancer, glioblastoma, glioma, and laryngeal carcinoma and has been designated as an oncomir [20]. Clinical research has revealed that the expression of miR-21 is elevated in a wide range of cancers, including brain, breast, cervix, lung, liver, prostate, pancreas, and colon. Due to the association with cancers, the potential of miR-21 as a cancer biomarker has also been widely studied for the past few years. [21] miR-21 functions primarily as a post-transcriptional regulator of gene expression. It binds to complementary sequences in the 3' untranslated region (3' UTR) of target messenger RNAs (mRNAs), leading to translational repression or mRNA degradation. Through this mechanism, miR-21 modulates the expression of multiple genes involved in cell proliferation, apoptosis, migration, and differentiate[19]. The aim of this study is to evaluate the expression levels of circulating miRNA-21 in whole blood samples of breast cancer patients compared to age-matched healthy controls, and to assess its potential utility as a diagnostic biomarker for breast cancer.

Subjects and Method

It was case – control study conducted at Oncology Teaching Hospital in Medical city in Baghdad, Iraq. The study included (100) females with age ranged between 23 to 80 years old. They were divided into two groups: group A include 48 women with newly diagnosis breast cancer and group B include 52 women without breast cancer or any other cancers. The inclusion criteria include all women with breast cancer before treatment and the exclusion criteria from this study was based on factors that may influence miRNA expression such as a previous

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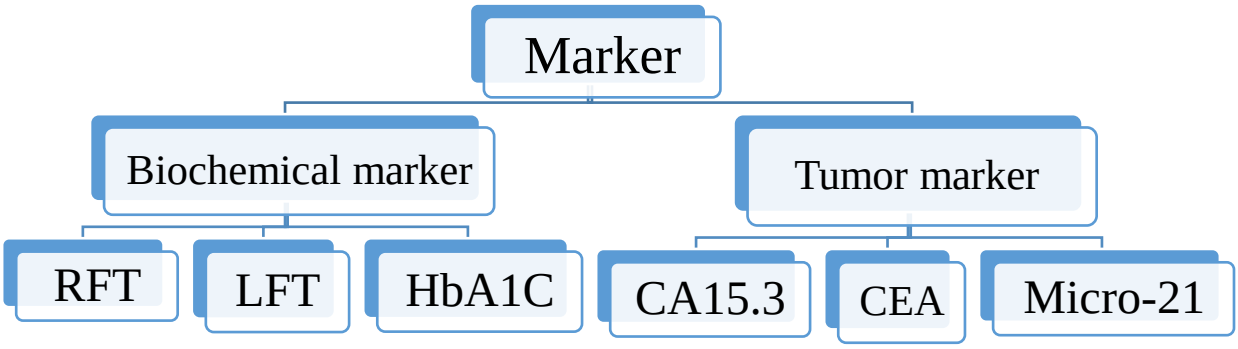
diagnosis of any cancers other than breast cancer like ovary, uterus, bone and others. The study chemical markers were applied in Scheme1.



Scheme 1: The study chemical markers

Blood samples were collected from participants at 8:00 a.m. to 12:00 a.m from January 2025 to March 2025. Blood was drawn from a vein using a 4 mL disposable syringe. A total of 2 mL of the sample was transferred into an EDTA tube for microRNA analysis, and the remaining 2 mL was placed into a gel, then, the tubes were centrifuged. The resulting serum separated and stored at -80˚ C to measure the laboratory biochemical markers. The biochemical markers include: Cancer antigen (CA 15-3), HbA1c, lipid profile, liver function, and renal function. miRNA qPCR is a powerful method for quantifying specific microRNAs in biological samples like serum, plasma, or tissues. Its significance in mRNA research stems from the regulatory functions of miRNAs. qPCR is used for miRNA detection due to its high sensitivity, allowing for the identification of low-abundance miRNAs. It also offers high specificity, capable of distinguishing miRNAs that differ by just a single nucleotide. The human microRNA q RT–PCR is provided by Thermo Fisher Scientific (USA)

Results: MicroRNA-21 (ng/µL): The mean ± SD for women without breast cancer was 8.64 ± 2.17, while for women with breast cancer patients, it was 46.32 ± 11.28. The p-value was 0.000, indicating statistical significance (Table 1).

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Table (1): Statistical significance between breast cancer patients and healthy individuals

Biochemical Markers	Breast Cancer Patients (n= 48)	Healthy Individuals (n=50)	P-Value
	Mean ± SD	Mean ± SD	
CA 15-3 (U/mL)	49.6 ± 8.22	18.23 ± 0.84	0.001**
CEA (µg/L)	16.77 ± 1.69	3.62± 0.84	0.001**
microRNA-21 (ng/µL)	46.32 ± 11.28	8.64 ± 2.17	0.000**

** Statically highly significant.

In table 2 there was positive correlation (0.881) between microRNA-21(ng/µL) and CA15-3 (U/mL) with p-value of 0.003. Also, a positive correlation (0.965) between microRNA-21(ng/µL) and CEA (µg/L) with p-value of 0.003 was found, while, a negative correlation (-0.089) between microRNA-21(ng/µL) and HbA1c % was found with p-value of 0.008. Furthermore, in table (2) there was positive correlation (0.089) between microRNA-21(ng/µL) and cholesterol (mg/dL) with p-value of 0.008. Also, a positive correlation (0.068) between microRNA-21(ng/µL) and ALP (U/L) with p-value of 0.005 was found, while, a negative correlation (-0.03) was found between microRNA-21(ng/µL) and ALT(U/L) with p-value of 0.0008. Moreover, a negative correlation (-0.048) was found between microRNA-21(ng/µl) and AST(U/L) with p-value of 0.002. In table 2 also there was a negative correlation (-0.083) was found between microRNA-21(ng/µL) and urea (mg/dL) with p-value of 0.007, and a negative correlation (-0.029) was found between microRNA-21(ng/µL) and Creatinine (mg/dL) with p-value of 0.0008.

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Table (2): Correlation between microRNA-21(ng/µL) with other markers

microRNA-21 Marker	Correlation (r)	P-Value
CA 15-3 (U/mL)	0.881	0.003**
CEA (µg/L)	0.965	0.003**
HbA1c %	-0.089	0.008**
Cholesterol (mg/dL)	0.089	0.008**
ALT (U/L)	-0.030	0.0008**
AST (U/L)	-0.048	0.002**
ALP (U/L)	0.068	0.005**
Urea (mg/dL)	-0.083	0.007**
Creatinine (mg/dL)	-0.029	0.0008**

** Statically highly significant.

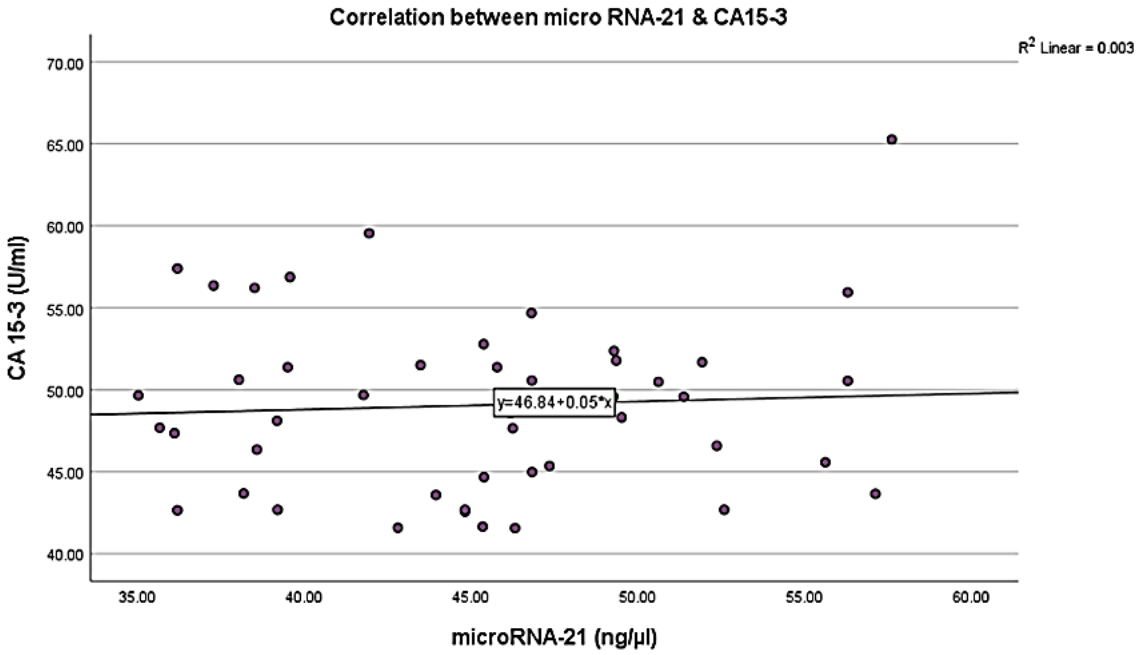

Figure 1. The correlation between microRNA-21 (ng/µL) and CA15-3 (U/mL).

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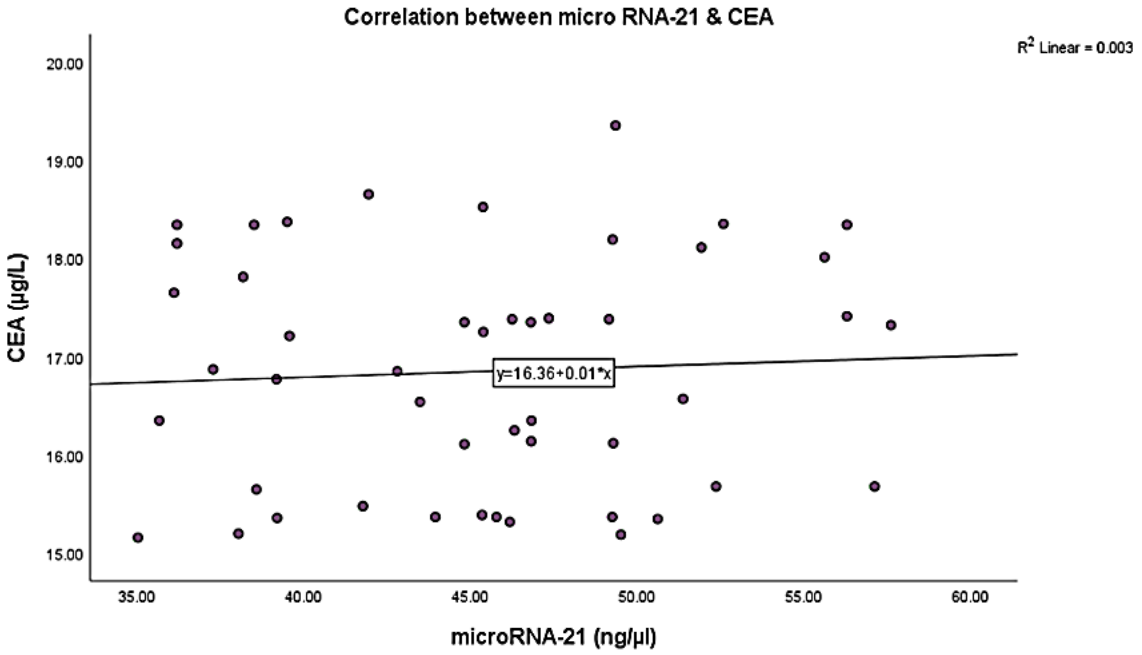

Figure 2. The correlation between microRNA-21 (ng/µL) and CEA (µg/L).

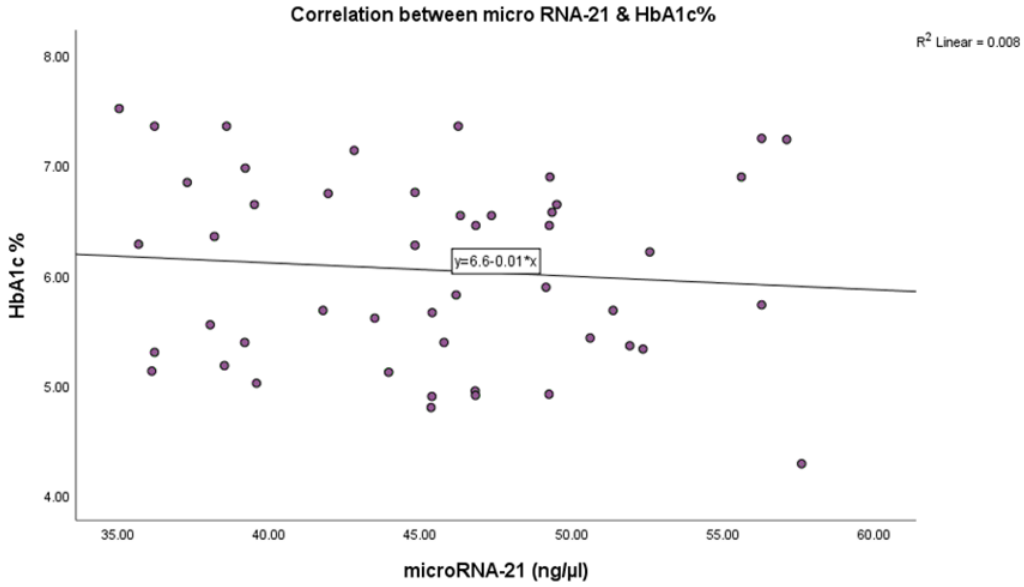

Figure 3: The correlation between microRNA-21 (ng/µL) and HbA1c%.

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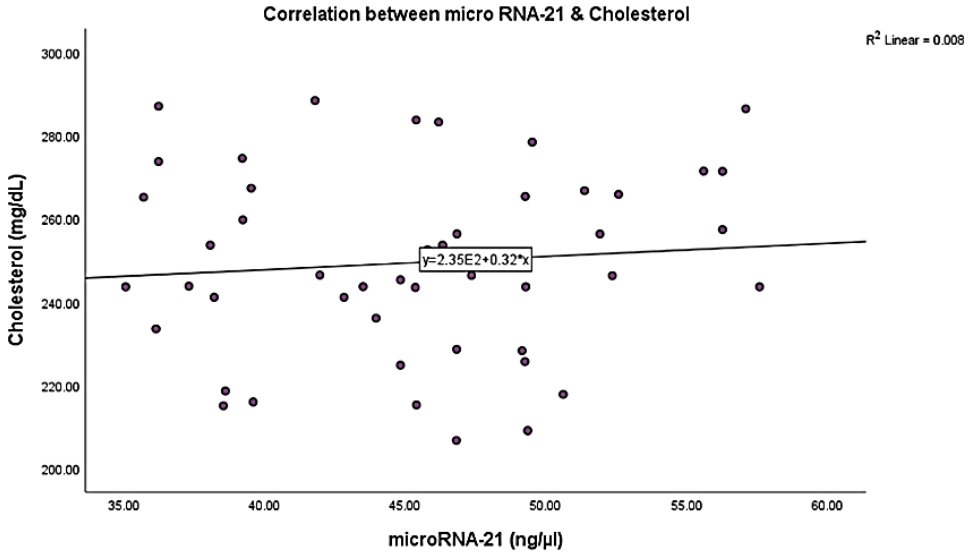

Figure 4: The correlation between microRNA-21 (ng/µL) and Cholesterol (mg/dL).

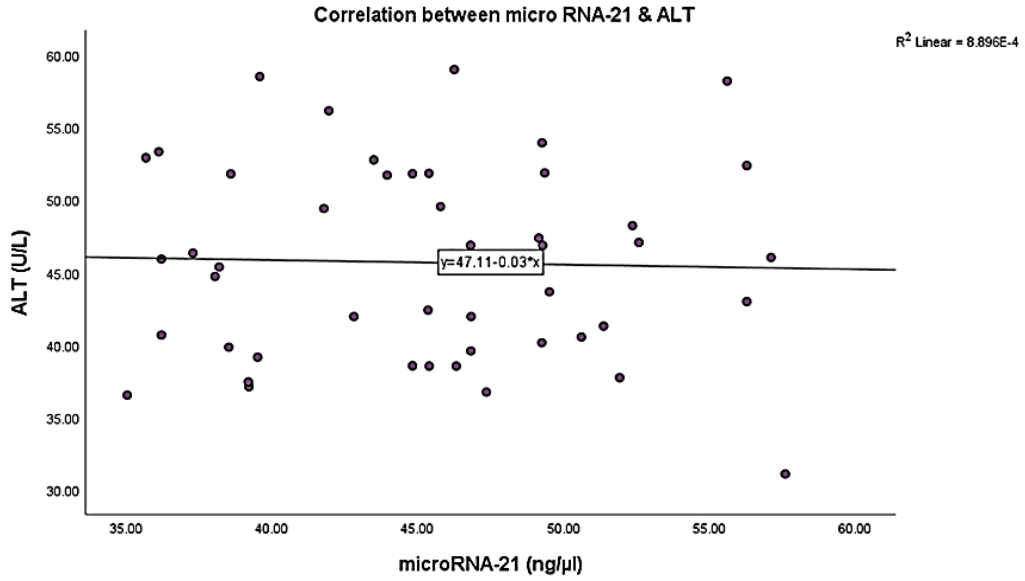

Figure 5: The correlation between microRNA-21 (ng/µL) and ALT (U/L).

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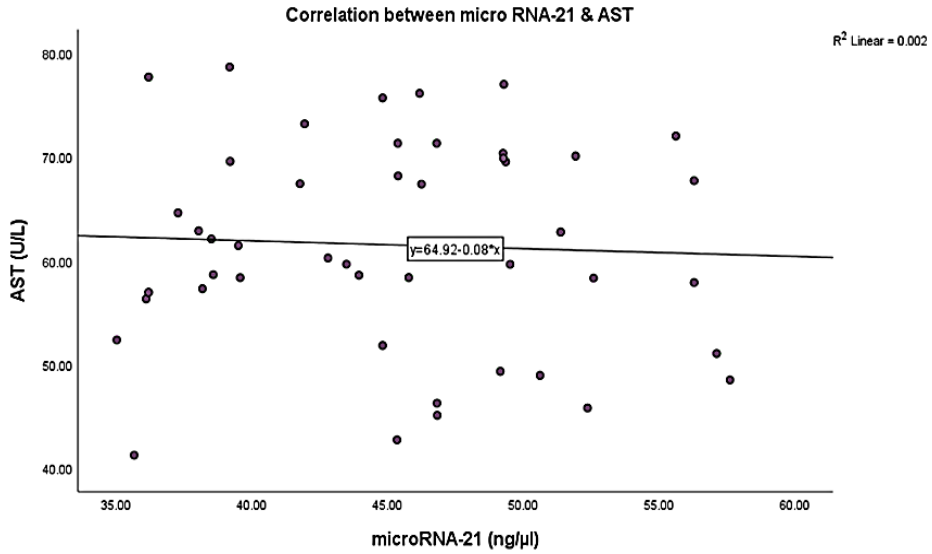

Figure 6: The correlation between microRNA-21 (ng/µL) and AST (U/L).

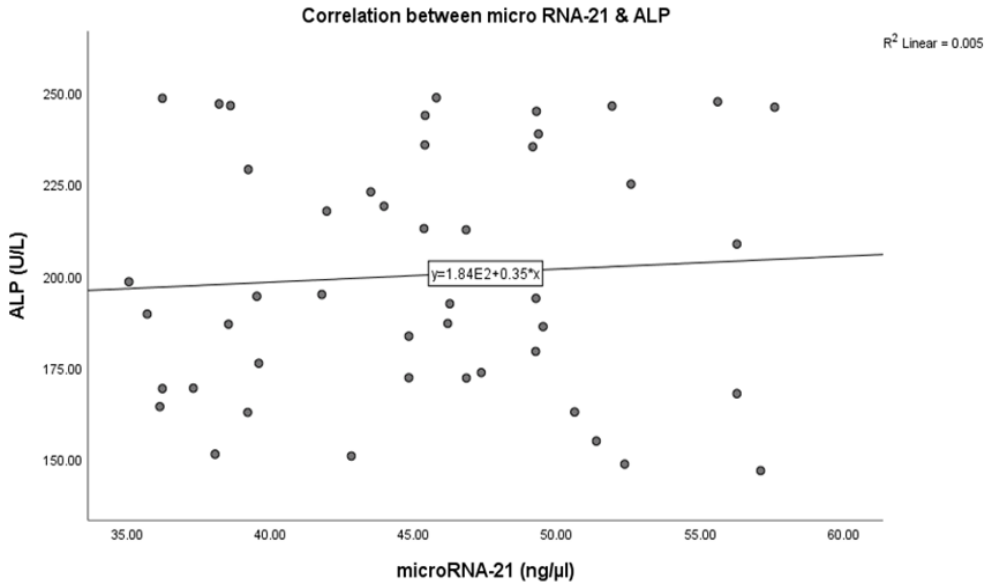

Figure 7: The correlation between microRNA-21 (ng/µL) and ALP (U/L).

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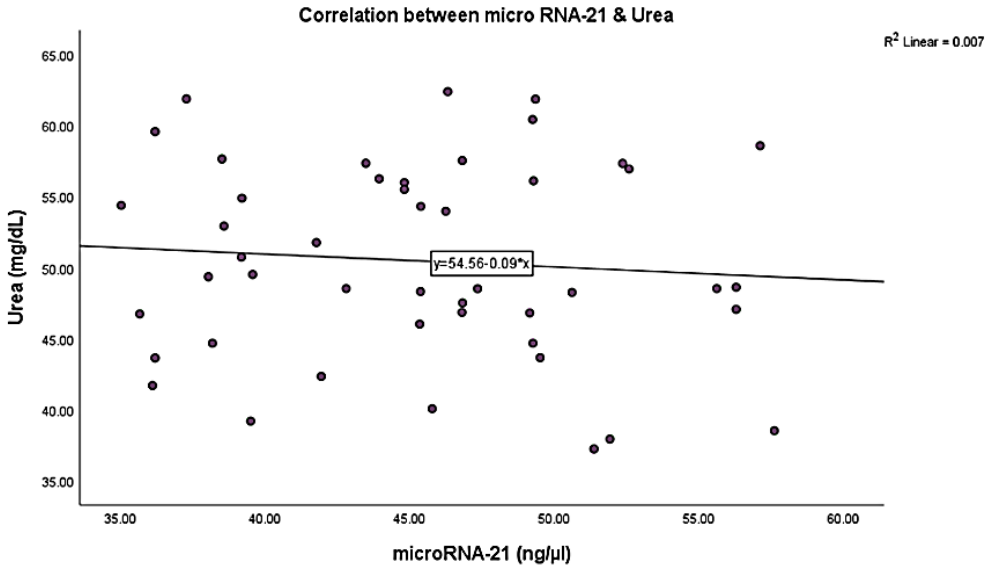

Figure 8: The correlation between microRNA-21 (ng/µL) and Urea (mg/dL).

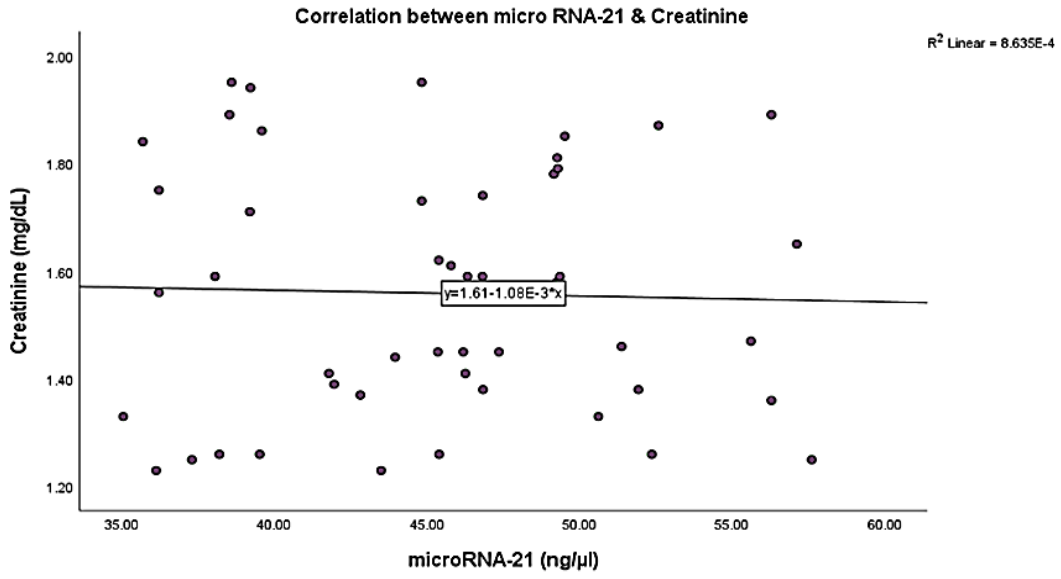

Figure 9: The correlation between microRNA-21 (ng/µL) and Creatinine (mg/dL).

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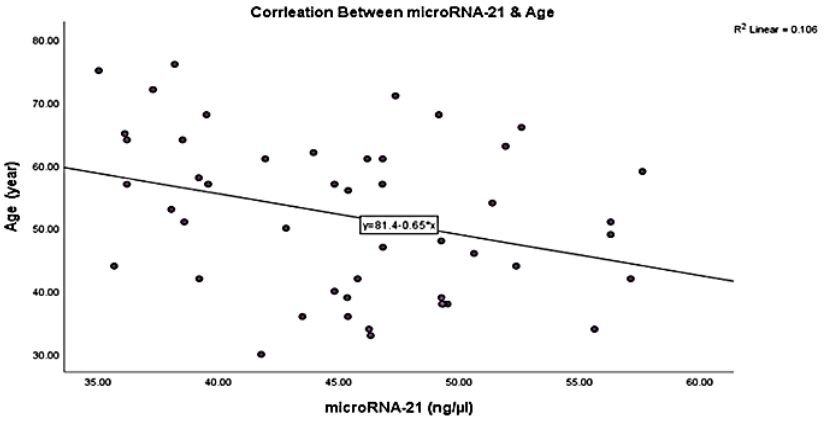

Figure 10: The correlation between microRNA-21 (ng/µL) and age (year).

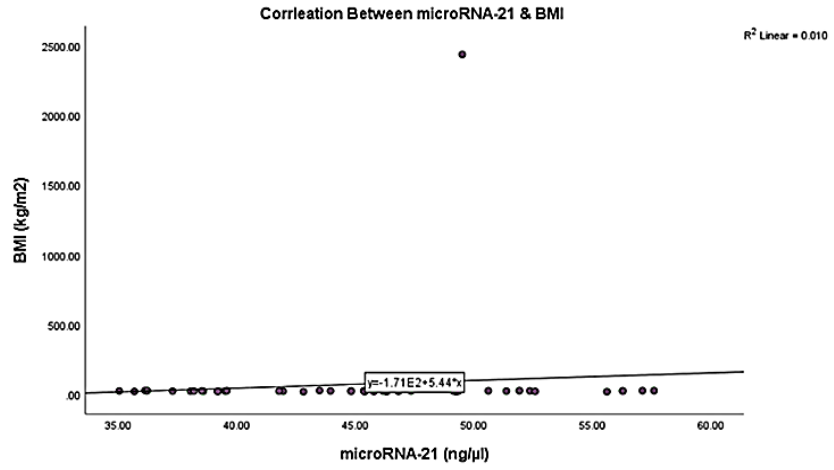

Figure 11: The correlation between microRNA-21 (ng/µL) and BMI (kg/m^2).

Discussion

This study provides important evidence supporting the diagnostic value of circulating microRNA-21 and tumor markers such as CA 15-3 and CEA in breast cancer patients. The microRNA-21 was found to be significantly elevated in breast cancer patients compared to healthy individuals suggesting that microRNA-21 could serve as a minimally invasive and

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reliable biomarker for early detection of breast cancer. These findings are consistent with previous literature highlighting the clinical relevance of microRNAs due to their stability in circulation and their regulatory role in gene expression [22, 23]. MicroRNAs, particularly miR-21, are known to promote tumorigenesis through their effect on target mRNAs, facilitating cancer progression by downregulating tumor suppressor genes. The marked increase in microRNA-21 levels in patients with breast cancer supports its oncogenic role and diagnostic potential [24]. As a kind of miRNA, the expression level of MiRNA-21 was first reported to be related to cancer in 2005 [25]. MicroRNA modulate gene expression primarily through their association with the miRNA- induced silencing complex (miRISC). This complex binds to specific mRNAs. Leading to outcomes such as inhibition of translation and m RNA degradation via deadenylation, decapping, and decay. The regulation of miRNA functions can be influenced by post-translational modifications of argonaute protein, the presence of RNA binding proteins, and the subcellular localization of miRNA pathway components highlighting the complexity of miRNA-mediated repression [26]. Kidney function markers such as urea and creatinine also showed statistically significant increases in breast cancer patients, which may reflect systemic effects of the disease, treatment-related nephrotoxicity, or underlying comorbidities. The mean creatinine level was nearly double that of the control group, indicating a possible impact on renal function in this patient population [27]. The relationship between body mass index (BMI) and breast cancer outcomes has been a subject of extensive research, yet many studies indicate that BMI does not significantly correlate with clinical outcomes such as recurrence or survival rates. This lack of statistical significance suggests that BMI may not be a reliable prognostic factor in breast cancer [28]. In addition to tumour markers, liver function tests such as ALT, AST, and ALP were significantly elevated in the patient group. This could suggest hepatic involvement or paraneoplastic effects in breast cancer. ALP in particular showed a highly significant increase potentially indicating bone metastases, a common site for breast cancer dissemination. Liver function protein levels should be considered as potential indicators when screening for liver metastasis in patients with breast cancer. With the new treatment options available, it could lead to prolonged life. [29]. The type of lipoprotein to which cholesterol is associated with, may alter cancer risk. A more recent meta-analysis suggested a small inverse association between total cholesterol and HDL-cholesterol levels and the risk of breast cancer. [30] In conclusion, our study proven an increase in micro RNA-21 with breast cancer compared to individuals without

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