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Coordinated Rise of miR-155-5p and Regulatory T Cells in Peripheral Blood Mononuclear Cells: An Early Event in Newly Diagnosed Breast Cancer Pathogenesis

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ABSTRACT

miR-155-5p is a well-established oncomiR upregulated in a variety of human malignancies, including breast cancer, where its aberrant expression has been documented in both tumor tissue and serum. Given its role as a key modulator of immune-inflammatory pathways and regulatory T cell (Treg) expansion, we aimed to investigate its expression in the peripheral blood mononuclear cells (PBMCs) of breast cancer patients.

This study enrolled sixty (n=60) breast cancer patients and forty (n=40) age-matched healthy controls. The relative expression of *miR-155-5p* in PBMCs was quantified using qPCR, and Treg cell frequency (defined as $CD4^+CD25^+Foxp3^+$) was assessed by flow cytometry.

The expression of *miR-155* was significantly increased in PBMCs of breast cancer patients compared with that of the control group, especially in patients with high tumor grade. The number of Treg cells was also increased in PBMCs of patients than in the healthy group, however, no significant correlation was found between the expression levels of *miR-155* and Treg cell count (r=-0.16).

Our findings demonstrate a significant up-regulation of *miR-155-5p* and a concomitant increase in Treg frequency in breast cancer patients, suggesting its potential role in shaping an immunosuppressive microenvironment. Consequently, *miR-155-5p* emerges as a promising non-invasive prognostic biomarker, warranting further validation in larger studies.

Keywords: Breast cancer; MicroRNA-155; Peripheral blood mononuclear cell; Regulatory T cell

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INTRODUCTION

Breast cancer represents the most frequently diagnosed cancer among women globally, accounting for approximately 12% of all female cancer cases and resulting in around 450 000 annual fatalities.[1] The most documented risk factors are age, family history of the disease, menstrual history, or the use of hormone-based medications.[2] The diagnostic process typically involves a combination of a physical examination, clinical breast exam (CBE), and imaging techniques such as mammography—which serves as the primary screening tool—ultrasound, and magnetic resonance imaging (MRI), complemented by blood tests and confirmatory biopsy.[3,4] The standard therapeutic approach usually begins with surgical intervention, which is often followed by adjuvant treatments including chemotherapy, radiation, or hormonal therapy, depending on the individual patient's profile.[5] The study of molecular pathways involved in breast cancer tumorigenesis can reveal an increasing number of novel targets for the development of more effective therapeutic agents.[6]

MicroRNAs (miRNAs) are small noncoding RNAs that function as critical regulators of fundamental biological processes, including cell cycle progression, proliferation, and differentiation.[7,8] Release 22.1 of MiRBase (https://www.mirbase.org/) has reported 1917 annotated miRNA precursors in humans that are processed into approximately 2656 mature miRNA sequences. Notably, nearly half of all miRNA genes are located within genomic regions associated with cancer or fragile sites, underscoring the strong link between miRNA dysregulation and human tumorigenesis.[9,10] Altered expression of miRNAs has been reported in most cancers, and few cancers exist in which these small molecules have not been reported.[11–14] Since the initial association between miRNAs and breast cancer was established in 2005, subsequent research has consistently identified these molecules as pivotal modulators of the disease.[15] In breast cancer, numerous miRNAs exhibit aberrant expression, functioning either as oncogenic drivers (oncomiRs) or tumor suppressors (tsmiRs).[16,17] Among these, human *miR-155* has been specifically implicated in promoting telomere fragility and genomic instability within the breast cancer context.[18–20]

MicroRNA-155 (miR-155), processed from the noncoding B-cell integration cluster (BIC) transcript in humans,[21] is a key regulator of diverse physiological and pathological processes, including hematopoiesis, immunity, and inflammation.[22,23] *MicroRNA-155* regulates the development of regulatory T cells (Tregs). It also regulates the mRNA level of the *FOXP3 (forkhead box P3)* gene.[24,25] The FOXP3 protein is a critical factor in developing Tregs.[26]

Regulatory T cells, which are also known as suppressive T cells, suppress excessive immune responses and prevent autoimmunity. Increased numbers of Tregs are associated with a poor outcome in some tumors.[17–20] In fact, Treg cells play an important role during tumorigenesis through inhibition of antitumor immunity.[27] The *miR-155* regulates Treg cell count through various targets such as the *SOCS1* transcript.[28]

The present study was designed to analyze the expression of miR-155 in peripheral blood mononuclear cells (PBMCs) and to evaluate the frequency of Tregs in patients with breast cancer. Additionally, this study investigated the potential correlation between *miR-155* expression and the frequency of Tregs.

MATERIALS AND METHODS

This case-control study was conducted at the Department of Medical Immunology and received ethical approval from the Ahvaz Jundishapur University of Medical Sciences (Ethics Code: IR.AJUMS.REC.1398.690; Grant No. CMRC-9814). Written informed consent was obtained from all participants prior to their inclusion in the study.

A total of 60 patients with a primary diagnosis of breast cancer (mean age ± SD: 53 ± 11.83 years) were enrolled from affiliated sonography and radiology centers in Ahvaz, Iran, between July 2019 and October 2020. Enrollment occurred prior to the initiation of any oncological therapy. The diagnosis was confirmed by clinical examination, a positive biopsy result, and a Breast Imaging-Reporting and Data System (BI-RADS) assessment of category 4C or 5. Individuals with unrelated pathological findings or cystic symptoms were excluded from the study. The control group consisted of 40 age-matched healthy individuals (n = 40; mean age ± SD: 51 ± 10.5 years) with no personal or family history of breast cancer. Demographic and

clinicopathological characteristics of all participants are summarized in Table 1.

Isolation of Peripheral Blood Mononuclear Cells

Peripheral blood samples (10 mL) were collected from all participants into heparinized tubes. PBMCs were isolated by density gradient centrifugation using Ficoll-Paque (Lymphodex, Inno-train, Germany). The isolated cells were washed twice with phosphate-buffered saline (PBS; Sigma, Germany) and subsequently prepared for gene expression analysis and Treg cell quantification.

RNA Extraction and Quantitative Real-time PCR

Total RNA was extracted from PBMCs using TRIzol reagent (Thermo Fisher Scientific, USA), following the manufacturer's instructions. Complementary DNA (cDNA) was synthesized from the RNA using the BON-miR QPCR Kit (Stem Cell Technology, Tehran, Iran). The expression levels of *miR-155* and the reference gene *U6* were quantified by quantitative real-time PCR (qRT-PCR) using universal specific primer sets provided in the BON-miR QPCR Kit (Stem Cell Technology, Tehran, Iran). The sequences of the primers used are listed in supplementary table. The relative expression of miR-155 was calculated using the $2^{-\Delta\Delta Ct}$ method.

Table 1. The clinicopathological presentation of breast cancer patients.

Variables	Breast Cancer Patient (n = 60)
Average of Age, y	53 ± 11.83
BMI	28.1 ± 3.9
Tumor grade	
G1	55% (n = 33)
G2	26.6% (n = 16)
G3	18.3% (n = 11)

BMI, body mass index.

Flow Cytometry Analysis

Flow cytometry was performed using 1×10^5 cells per sample. Isolated PBMCs were first washed with PBS and subsequently stained with surface antibodies against *CD4* and *CD25* for 30 minutes at 4°C in the dark. For intracellular *FOXP3* staining, cells were fixed and permeabilized using a commercial fixation/permeabilization kit (eBioscience, California, USA) according to the manufacturer's instructions. After permeabilization, cells were incubated with a fluorochrome-conjugated anti-*FOXP3* antibody (5 µL) diluted in 1× permeabilization buffer for 30 minutes at 25°C in the dark. Cells were then washed with 1× permeabilization buffer and finally resuspended in staining buffer for acquisition.

Statistical Analysis

All experiments were done in triplicate. SPSS ver. 26.0 (SPSS Inc., Armonk, NY, USA) was used for statistical analysis. One-way analysis of variance was used to compare data expressed as the median ± SEM. Mann-Whitney U test was applied for non-normally distributed data, and a *t* test was conducted for the analysis of normally distributed data. The Kruskal-Wallis statistical test was also used to compare the obtained data across the different tumor grades. Associations between variables were calculated by Spearman correlation. A p value of$\leq$0.05 was considered statistically significant.

RESULTS

The Expression Level of miR-155 Was Highly Up-regulated in Breast Cancer Patients

Figure 1A compared the expression level of *miR-155* transcript in PBMCs of breast cancer patients and healthy individuals. As indicated, the *miR-155* expression level has been significantly up-regulated in breast cancer patients (6.96 ± 1.52) than in the control counterpart (1.56 ± 0.47) (p<0.001). The fold change was 4.55 ± 1.01. Furthermore, the expression level of *miR-155* was measured in patients for whom different

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tumor grades had been determined based on pathology results. The results showed that the expression of *miR-155* in the PBMCs of breast cancer patients with high tumor grade was 23.160 ± 2.61 (G3). The *miR-155* expression level showed a statistically significant increase compared to patients with low tumor grade (G1, G2), which were 1.21 ± 0.221 and 7.155 ± 1.85, respectively (p<0.001). This difference is illustrated in Figure 1B.

The Percentage of Treg Cells in Breast Cancer Patients Was Significantly Higher Than the Control

Using FACS analysis (as shown in Figure 2), we found that the percentage of Treg cells *($CD4^+CD25^+FOXP3^+$)* in PBMCs of breast cancer patients was 2.21 ± 0.304 while the corresponding value in control individuals was 1.289 ± 0.248. Statistical analysis showed the difference as significant (p=0.034) (Figure 3A). However, there was no significant correlation between the number of Treg cells and the expression of *miR-155* (r=−0.16, p=0.94). Additionally, there was no statistically significant increase in the percentage of Treg cells in the PBMCs of patients with grade 3 breast cancer (3.345 ± 0.459) compared to patient subjects with low-grade variants grade 2 and 1 (2.36 ± 0.464 and 1.77 ± 0.459; respectively) (p=0.185) (Figure 3B).

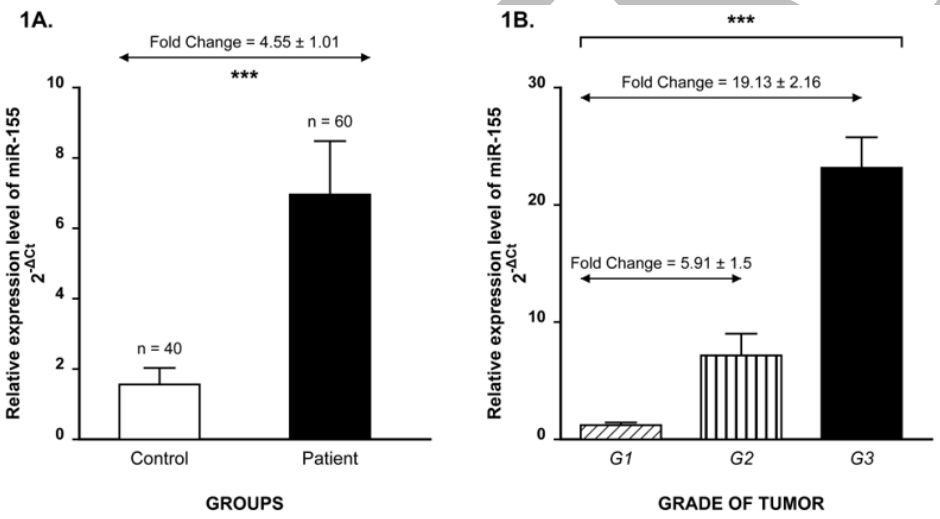
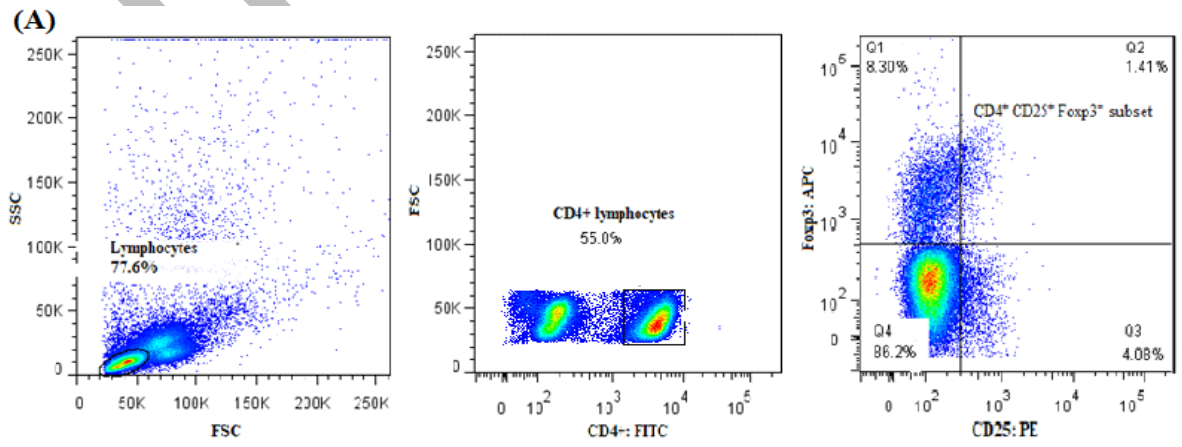


Figure 1. The relative expression level of *miR-155-5p* in breast cancer patients and control. The expression level of *miR-155-5p* in breast cancer patients was significantly higher than the control group (p<0.001) (A). Also, the expression level of *miR-155-5p* showed a significant difference across the different grades of breast tumor (p<0.001) (B). The * indicates the p value less than 0.001.**



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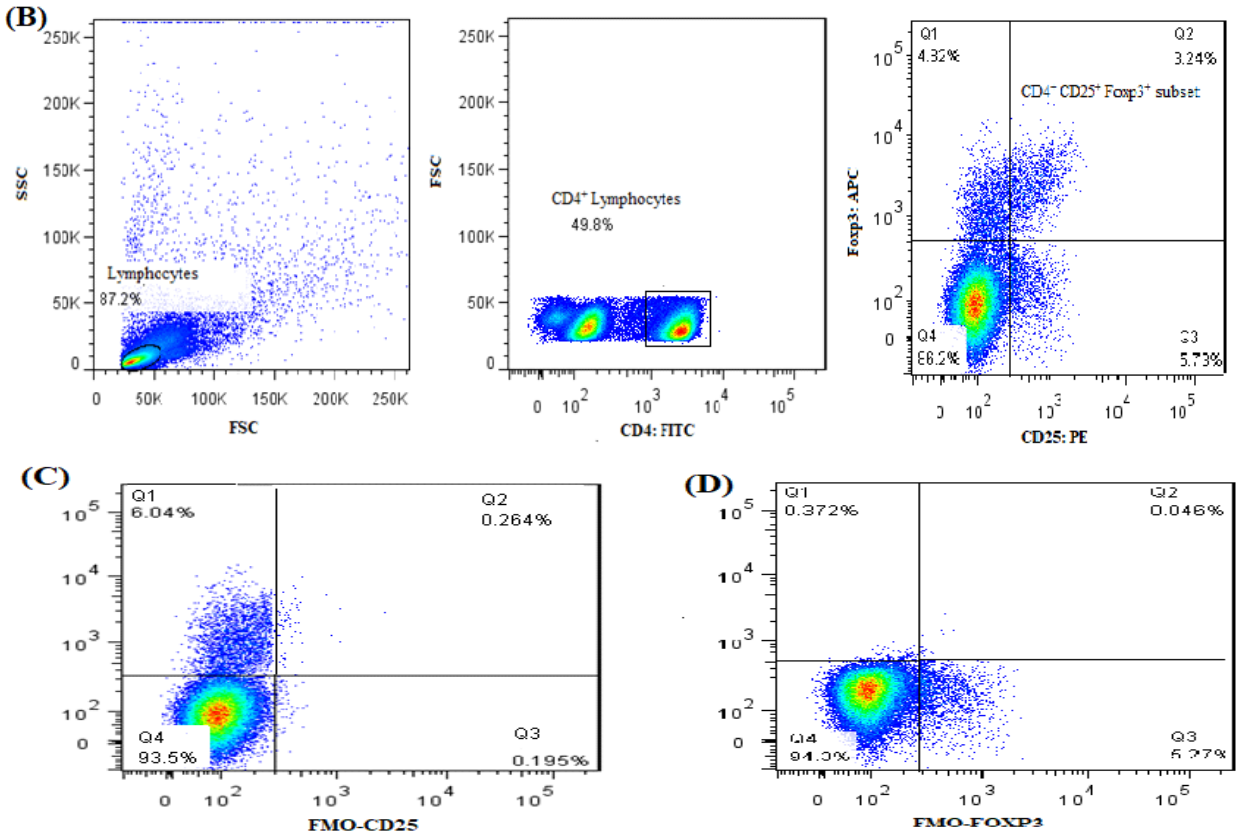

Figure 2. Representative graphics from flow cytometry for Treg measurements. These graphs show the percentage of Treg cells in Control (A) and patient group (B). FMO-*CD25* and FMO-*FOXP3* images are also shown in C and D sections.

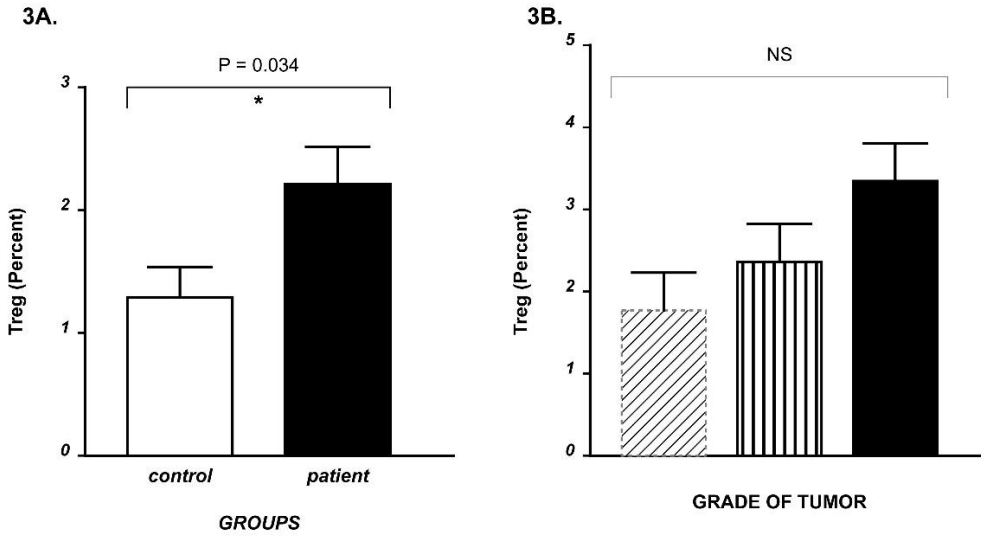

Figure 3. The percentage of Treg lymphocytes in breast cancer patients and control individuals. The percentage of Treg cells in breast cancer patients was significantly higher than the control (*p*=0.034) (A). However, the frequency of regulatory T cells did not show a significant difference across the different grades of breast tumor (*p*=0.185) (B). The * indicates the *p* value less than 0.05; NS, no significant.

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DISCUSSION

Chronic inflammation is now widely recognized as a pivotal driver in the initiation and progression of breast cancer. Sanguinetti et al[29] previously demonstrated the activation of inflammatory pathways during breast tumorigenesis. In this study, *miR-155* has been identified as a key upstream regulator linking inflammatory processes to malignancy.[30]

In the present study, the expression level of miR-155 was examined in PBMCs of breast cancer patients. Our findings revealed a significantly higher transcript level of this noncoding RNA in patients compared to healthy controls. A notable strength of our study design was the enrollment of treatment-naïve patients who had not undergone any surgical intervention or initiated pharmacological therapy. This approach minimized potential confounding factors that could influence gene expression levels and reduced the risk of obtaining artifactual results—a methodological consideration often overlooked in previous studies in this field. Furthermore, our sample size was statistically robust, enhancing the validity and generalizability of our findings. Notably, the majority of patients (55%, n = 33) presented with grade 1 tumors, representing an early disease stage. These results align with existing literature documenting upregulated *miR-155* expression across various human malignancies, including breast cancer,[31,32] and further substantiate its potential role as a clinically relevant biomarker in breast oncology.[30,33,34] However, in most of these studies the expression level of miR-155 was examined in tumorous tissues or plasma of patients. As indicated before, we traced the expression level of *miR-155* in PBMCs of breast cancer patients. This is a part of the novelty of the present study. The main reason for selecting these cells to analyze gene expression, was the role of *miR-155* in immune system responses and inflammatory pathways.[35–37]

Our finding that *miR-155* is markedly upregulated in the PBMCs of breast cancer patients, particularly those with high-grade tumors, aligns with and extends the existing literature. Sun et al[38] previously reported a significant increase of *miR-155* in breast cancer tissues, highlighting its potential prognostic value. Furthermore, Vladimir Cherny and colleagues provided evidence that *miR-155* can be served as a prognostic molecular marker forlymph node metastasis in breast cancer patients. They also showed that *miR-155* could be considered a prominent target for breast cancer treatment and for controlling the process of cancer progression.[39] Consolidating this role, Petrović et al[40] also observed that *miR-155* is instrumental in the early stages of tumorigenesis and lymphatic spread, suggesting its utility in screening for micrometastases undetectable by conventional diagnostics. However, the role of *miR-155* appears to be context-dependent across different cancers. For instance, conflicting reports exist where, in contrast to breast cancer, decreased expression of *miR-155-5p* was associated with tumor progression and metastasis in gastric cancer.[41] This underscores the tissue-specific nature of miRNA function and necessitates careful interpretation of its role in distinct malignancies.[39]

We further quantified the frequency of Tregs a specialized immunosuppressive subset characterized by the $CD4^+CD25^+FOXP3^+$ phenotype[42]- within the PBMC population of breast cancer patients. The accumulation of Tregs in the tumor microenvironment is a well-established indicator of disease progression and poor prognosis.[43] Consistent with this, our analysis revealed a significant increase in circulating Treg levels in breast cancer patients compared to healthy controls.

This finding aligns with previous studies: Ohara et al[44] implicated Tregs in tumor onset and progression in early-onset breast cancer, while Bates et al[45] reported elevated *FOXP3* expression and Treg numbers within breast tissue of high-grade tumors. The expansion of Tregs is known to be regulated by specific miRNAs.[46] Notably, a more detailed analysis within our patients showed that the percentage of Tregs was elevated in newly diagnosed patients with high-grade (G3) tumors compared to those with low-grade (G1 and G2) tumors; however, this comparison did not reveal a significant difference. This suggests a potential correlation between Treg abundance and tumor aggressiveness.

The critical role of *miR-155* in Treg biology is further evidenced by studies in murine models, where *miR-155* deficiency led to a reduced number of Tregs in the thymus, peripheral blood, and lymph nodes, despite normal expression of surface markers.[25,47] This specific link between Treg-derived *miR-155* and Treg frequency (as opposed to serum *miR-155*) has also been observed in human rheumatoid arthritis.[46] In the context of breast cancer, a positive correlation has been reported between *miR-155* and *FOXP3* expression. Mechanistically, *FOXP3* was found to induce *miR-155* expression in

cultured cancer cells, a process that is suppressed by the tumor suppressor BRCA1. This investigation into the *FOXP3-BRCA1-miR-155* axis suggests that plasma miR-155 levels could serve as a diagnostic biomarker for early-stage breast cancer.[48] Beyond cancer, the immunosuppressive function of *miR-155* is conserved, as demonstrated in sepsis, where increased *miR-155* expression promotes immunosuppression by expanding the population of $CD39^{+}$ Tregs.[49] Collectively, these findings underscore a conserved mechanism whereby *miR-155* enhances immunosuppressive capacity by modulating Treg frequency and/or function across various pathological conditions. No significant correlation was observed between *miR-155* expression levels and Treg cell frequency in our study. Indeed, even this weak relationship could be entirely random. Both variables could be activated through different signaling pathways and contexts influenced by cancer progression. The relationship might differ across various tumor grade levels. For instance, a positive correlation might be observed in lower grades, while a negative correlation may be seen in higher grades.

This lack of association may be attributed to the predominance of low-grade (Grade I) tumors in our study population, as both parameters may be more substantially altered in advanced disease stages. It is important to note that the relationship between miR-155 and Tregs in treatment-naïve, primary breast cancer patients remains largely uncharacterized in the existing literature, highlighting the exploratory nature of this analysis.

In conclusion, our study provides two key findings regarding the systemic immune landscape in breast cancer patients. First, we demonstrate a significant upregulation of the oncomiR *miR-155* within PBMCs, highlighting its potential as a noninvasive biomarker. Second, we confirm an elevated frequency of immunosuppressive Tregs in the circulation of these patients.

The absence of a correlation between *miR-155* levels and Treg counts, while initially surprising, suggests a more complex relationship than a simple linear pathway. This discrepancy may be attributed to several factors, including the predominant enrollment of patients with early-stage (Grade I) disease, where such interactions might not yet be fully established. It is also possible that *miR-155's* role in Treg biology is indirect, acting through intermediary molecules or being more critical in the tumor microenvironment than in the peripheral circulation.

Therefore, while our data firmly establish *miR-155* and Tregs as key players in breast cancer-associated immunology, they also reveal a nuanced picture. Future studies are warranted to investigate this relationship in advanced-stage cancers, within the tumor microenvironment itself, and to elucidate the precise molecular mechanisms connecting oncogenic miRNAs to immune cell populations.

STATEMENT OF ETHICS

The research was approved by ethical board of Ahvaz Jundishapur University of medical sciences with the following code of ethics: IR.AJUMS.REC.1398.690.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The raw data supporting the findings of this study cannot be publicly shared due to confidentiality restrictions. However, the primer sequences are available within the supplementary. The authors declare that no artificial intelligence (AI) tools were used in any part of the preparation of this manuscript.

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