

RESEARCH ARTICLE

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The Role of Long Non-Coding RNAs and MicroRNAs in Breast Cancer: Implications for Early Diagnosis, Prognosis, and Axillary Lymph Node Metastasis

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Abstract

Background: The presence of axillary metastases is a critical factor for the diagnosis and prognosis of breast cancer. This study aimed to investigate the feasibility of detecting axillary metastases using preoperative serum samples as a non-invasive alternative to tissue samples, focusing on the expression profiles of *BLACAT1*, *miR-150*, *miR-503*, *BCL-2*, and *CCR-2*. **Methods:** The study enrolled 61 patients with primary breast cancer who underwent surgical intervention without neoadjuvant treatment. Serum expression levels of the target molecules were analyzed by RT-qPCR and compared between patients with benign and malignant sentinel lymph nodes (SLN), as well as across different molecular subtypes. **Results:** Serum *BLACAT1* expression was significantly upregulated (2.37-fold, $p=0.002$) in patients with malignant SLNs compared to those with benign SLNs. *miR-150* and *miR-503* showed a trend of downregulation in the malignant group ($p=0.058$ and $p=0.089$, respectively). In terms of molecular classification, *CCR2* was significantly upregulated in Triple-Negative Breast Cancer (TNBC) ($p=0.001$), while *miR-503* was significantly upregulated in *HER2+* tumors ($p=0.010$). **Conclusions:** Circulating *BLACAT1* demonstrated significant potential as a non-invasive biomarker for the detection of axillary metastases. While *miR-150* and *miR-503* showed distinct differential expression patterns among molecular subtypes, their diagnostic value for axillary metastasis requires validation in larger cohorts. These findings suggest that serum-based molecular profiling could support standard histopathological methods in breast cancer management.

Keywords: Breast cancer, axillary metastasis, lncRNAs, miRNAs, molecular biomarkers

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Introduction

Breast cancer remains one of the most prevalent and challenging malignancies in women worldwide [1]. The involvement of axillary lymph nodes is a critical prognostic factor that influences both staging and treatment strategies for patients with breast cancer [2]. When there is axillary metastasis, patients often need more aggressive treatments, like axillary lymph node dissection or radiation therapy, which are necessary to improve their outcomes [3]. In recent years, microRNAs (miRNAs) have emerged as significant regulators of gene expression and play a crucial role in various cellular processes, including proliferation, differentiation, apoptosis, and metastasis [4]. Multiple miRNAs have been demonstrated to influence tumor progression, metastasis, and response to therapy in breast cancer [5]. Of particular note, circulating miRNAs

in serum have been identified as potential non-invasive biomarkers for early detection, prognosis, and prediction of treatment response [6]. Given the potential clinical significance of miRNAs, this investigation aimed to examine whether specific miRNAs, in conjunction with other molecular markers, could be utilized to detect axillary metastases in patients with breast cancer using serum samples. This study looked at important molecules like *BLACAT1*, *miR-150*, *miR-503*, *BCL-2*, and *CCR-2* to see if there was a link between molecular expression patterns and metastasis. The goal was to find a way to diagnose cancer that does not involve a tissue biopsy. Additional research is necessary to corroborate these findings in larger cohorts and elucidate the mechanistic role of these miRNAs in breast cancer metastasis. In any case, our results show that serum-based molecular profiling could be a less invasive and easier way to

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diagnose and treat breast cancer, especially for the detection of axillary metastases.

Materials and Methods

Study design and population

Sixty-one patients who underwent surgery for primary breast cancer without distant metastasis or benign breast disease were enrolled in this study. Patients were included if they had no history of other types of cancer and had not received neoadjuvant treatment.

Data collection

Serum samples were stored at -80 °C. Total RNA was extracted from 200 µL serum samples utilizing the MiRNeasy Mini Kit (Qiagen) in accordance with the manufacturer's protocol. *BLACAT1*, *miR-150*, *miR-503*, *Bcl2*, and *Ccr2* expression levels were quantified using RT-qPCR. RNA was reverse-transcribed into cDNA employing a cDNA Synthesis Kit system (Qiagen) as per the manufacturer's protocol at 37 °C for 60 min and subsequently at 95 °C for 5 min. The qPCR reaction was conducted using 2X qPCR SYBRGreen MasterMix (Qiagen), and qPCR amplification was performed utilizing a Rotor-Gene Q system (Qiagen). The thermocycling conditions for qPCR were as follows: 40 cycles of 15 s at 95 °C, 30 s at 60 °C, and 30 s at 72 °C. Relative mRNA expression levels were calculated using the $2^{-\Delta\Delta C_q}$ method. *GAPDH*, *U6*, and 18S RNA served as internal controls.

Data management and statistical analysis

Data and privacy management adhered to the guidelines established by the country's legislative body, and all data were reported anonymously to the study coordinator. Data collection was conducted by SY and TYB and BEU in a two-stage process utilizing Microsoft Excel. Statistical analyses were performed using StataIC 16.1 (64-BIT) (StataCorp, 4905 Lakeway Drive, College Station, Texas 77845 USA). For descriptive statistics, the mean and standard deviation were calculated for the variables. Further statistical comparisons between groups were conducted using Student's t-test, χ^2 , or Kruskal-Wallis test. Spearman or Pearson correlation analyses were employed to examine the relationships between continuous variables. GraphPad Prism 9 was utilized for the graphics. The suitability of the data for normal distribution was assessed using the Shapiro-Wilk test. Statistical significance was defined as a two-sided p-value < 0.05.

Results

Patient characteristics

Patient demographics and tumor characteristics were analyzed for 61 patients. The analysis revealed that 57.4% of breast cancer patients were between the ages of 45-65 (n=35). Regarding Body Mass Index (BMI) status, 36.7% of the patients were classified as overweight (n=22) and 35% as obese (n=21). The study found that 48.3% of the included breast cancer patients had T1cN0M0 stage 1A (n=28), and 57.4% presented with benign sentinel lymph

nodes (n=35). Twenty-five patients (41%) had between 4-9 lymph nodes. Additionally, 25 patients had more than 10 resected lymph nodes without tumors. Patient demographics and tumor characteristics are presented in Table 1.

Tumor characteristics

When stratified by patient demographics and tumor characteristics, benign sentinel lymph nodes were

Table 1. Patient Demographics and Tumor Characteristics of Breast Cancer Patients

Characteristics	No. of Patients	%
Age status		
25-35	3	4.9
35-45	15	24.6
45-65	35	57.4
>65	8	13.1
BMI status		
Underweight	1	1.7
Healthy weight	16	26.7
Overweight	22	36.7
Obesity	21	35.0
TNM		
T1aN0M0 stage 1A	1	1.7
T1bN0M0 stage 1A	5	8.6
T1cN0M0 stage 1A	28	48.3
T2N0M0 stage 2A	19	32.8
T2N1aM0 stage 2A	1	1.7
T3N0M0 stage 2B	2	3.5
TisN0M0 stage 0	2	3.5
Sentinel lymph node		
Benign	35	57.4
Malign	25	41.0
NA	1	1.6
No. Of resected lymph nodes		
1-3	15	24.6
4-9	25	41.0
≥10	21	34.4
No. Of resected lymph nodes without tumor		
1-3	18	30.0
4-9	28	46.7
≥10	14	23.3
NA	1	1.7
ER status		
Positive	53	86.9
Negative	7	11.5
NA	1	1.6
PR status		
Positive	51	83.6
Negative	9	14.8
NA	1	1.6

BMI, Body mass index; TNM, Classification of Malignant Tumors; ER, estrogen receptor; PR, progesterone receptor; NA, not available.

more prevalent than malignant sentinel lymph nodes in breast cancer patients aged 45-65 who participated in the study, and this finding was statistically significant ($p=0.038$). Moreover, the total number of lymph nodes was significantly higher in patients with breast cancer and malignant sentinel lymph nodes ($p=0.001$). Similarly, the number of tumor-free lymph nodes was significantly higher in patients with breast cancer with benign sentinel lymph nodes ($p=0.001$). When breast cancer patients participating in the study were stratified according to sentinel lymph node type, no statistically significant difference was observed in BMI status, TNM stage system, ER, and PR status. Patient demographics and tumor characteristics of breast cancer patients stratified

by sentinel lymph node status are presented in Table 2.

Gene expression

Gene expression levels were analyzed with respect to differences in molecular classifications. Correlation analysis revealed a statistically significant positive correlation between $\Delta CT\ bcl2$ and $\Delta CT\ CCR2$ levels in the Luminal A, Luminal B, and $HER\ 2$ groups ($p<0.05$, $r=0.53$). A statistically strong negative correlation ($p<0.05$, $r=-1$) was observed between $\Delta CT\ miR-503$ and $\Delta CT\ miR-150$ levels; however, this correlation was attributable to the limited number of groups ($n<5$). (Figure 1) Furthermore, the gene expression levels were analyzed with respect to sentinel lymph node differences. Correlation analysis demonstrated a statistically significant positive correlation between $bcl2$ and $CCR2$ levels in patients with benign sentinel lymph nodes ($p<0.05$, $r=0.56$). (Figure 2).

Table 2. Patient Demographics and Tumor Characteristics of Breast Cancer Patients Stratified by Sentinel Lymph Nodes Status

Characteristics	Benign N=35		Malign N=25		P value
Age status					
25-35	2	5.7	1	4.0	0.038
35-45	4	11.4	11	44.0	
45-65	24	68.6	10	40.0	
>65	5	14.3	3	12.0	
BMI status					
Underweight	0	0.0	1	4.2	0.48
Healthy weight	8	22.9	8	33.3	
Overweight	14	40.0	8	33.3	
Obesity	13	37.1	7	29.2	
TNM					
T1aN0M0 stage 1A	0	0	1	4.2	0.297
T1bN0M0 stage 1A	3	8.8	2	8.3	
T1cN0M0 stage 1A	14	41.2	14	58.3	
T2N0M0 stage 2A	13	38.2	6	25.0	
T2N1aM0 stage 2A	0	0.0	1	4.2	
T3N0M0 stage 2B	2	5.9	0	0	
TisN0M0 stage 0	2	5.9	0	0	
No. Of resected lymph nodes					
1-3	13	37.1	2	8.0	0.001
4-9	21	60.0	19	76.0	
≥ 10	1	2.9	4	16.0	
No. of resected lymph nodes without tumor					
1-3	14	41.2	4	16.0	0.001
4-9	19	55.9	12	48.0	
≥ 10	1	2.9	9	36.0	
ER status					
Positive	32	91.4	21	84.0	0.377
Negative	3	8.6	4	16.0	
PR status					
Positive	31	88.6	20	80.0	0.289
Negative	4	11.4	5	20.0	

BMI, Body mass index; TNM, Classification of Malignant Tumors; ER, estrogen receptor; PR, progesterone receptor; NA, not available; One ($n=1$) NA variable was removed from the analysis. (Pearson χ^2).

Expression analysis of patients according to Sentinel lymph node involvement

A total of 60 patients were included in the sentinel lymph node analysis, as one patient was excluded due to missing data. Among them, 35 patients (mean age: 54.94 ± 12.01 years) exhibited benign sentinel lymph nodes, while 25 patients (mean age, 50.6 ± 13.48 years) presented with malignant sentinel lymph nodes. LncRNA *BLACAT1* expression was upregulated by 2.37-fold in patients with at least one malignant sentinel lymph node ($p = 0.002$). *miR-503* and *miR-150* showed a trend of downregulation (2.57 and 3.05 times, respectively) in patients with at least one malignant sentinel lymph node, although this did not reach statistical significance ($p = 0.058$, 0.089). *Bcl2* expression was downregulated by 2.55-fold in patients with at least one malignant sentinel lymph node ($p = 0.223$). No significant changes in *Ccr2* expression were observed (Table 3).

Expression Analysis of Patients According to Their Molecular Classifications

The expression levels of lncRNA *BLACAT 1* were significantly elevated in Luminal B, *HER2*, and TNBC subtypes. *miR-150* expression was downregulated in the Luminal B and TNBC subtypes, whereas it was

Table 3. Relative expression changes of target genes in patients with malignant sentinel lymph nodes compared to those with benign sentinel lymph nodes. Fold change values were calculated using the $2^{-\Delta\Delta Ct}$ method, with the benign group used as the reference. Positive values indicate upregulation, while negative values indicate downregulation. P values were obtained using appropriate statistical tests as described in the Methods section.

	Benign lymph node	Malignant lymph node Fold Change	P value
<i>BLACAT1</i>	Ref.	2.37	0.002
<i>miR-150</i>	Ref.	-2.57	0.058
<i>miR-503</i>	Ref.	-3.05	0.089
<i>Bcl2</i>	Ref.	-2.55	0.223
<i>Ccr2</i>	Ref.	1.67	0.114

Table 4. Relative Expression Changes of Target Genes Across Breast Cancer Molecular Subtypes. Fold change values were calculated using the $2^{-\Delta\Delta Ct}$ method, with Luminal A subtype used as the reference group. Positive values represent upregulation and negative values represent downregulation relative to the reference group. Statistical significance was determined as described in the Methods section.

Luminal A		Luminal B		HER2		TNBC	
		Fold Change	P value	Fold Change	P value	Fold Change	P value
<i>BLACAT1</i>	Ref.	2.02	0.02	5.14	0.002	27.6	0.006
<i>miR-150</i>	Ref.	-3.13	0.156	1.98	0.655	-20.35	0.005
<i>miR-503</i>	Ref.	3.67	0.206	54.29	0.010	-48.14	0.006
<i>Bcl2</i>	Ref.	2.60	0.061	1.47	0.583	-1.59	0.336
<i>Ccr2</i>	Ref.	1.21	0.753	1.01	0.412	13.24	0.001

significantly upregulated in the *HER2* subtype. *miR-503* expression was upregulated in Luminal B and *HER2* subtypes, whereas it was downregulated in the TNBC subtype. *Bcl2* expression showed an upregulation trend (2.60-fold) in the Luminal B subtype, although this did not reach statistical significance ($p = 0.061$). *Ccr2* expression is significantly upregulated in TNBC cells (Table 4).

Discussion

Histology remains the gold standard for diagnosing breast cancers. Despite advancements in molecular and genetic understanding, histological typing has been a

primary focus since the initial World Health Organization classification in 1968, owing to the similarities and differences in the histological appearance of cancers. This approach continues to serve as the foundation for breast cancer classification [7, 8].

In recent years, following the elucidation of miRNA roles in breast cancer pathogenesis, research has increasingly focused on miRNAs with potential applications as diagnostic, predictive, and prognostic markers [5, 9].

The utilization of miRNAs as novel biomarkers, which are readily accessible, non-invasive, and exhibit high sensitivity and specificity for tumor formation, is

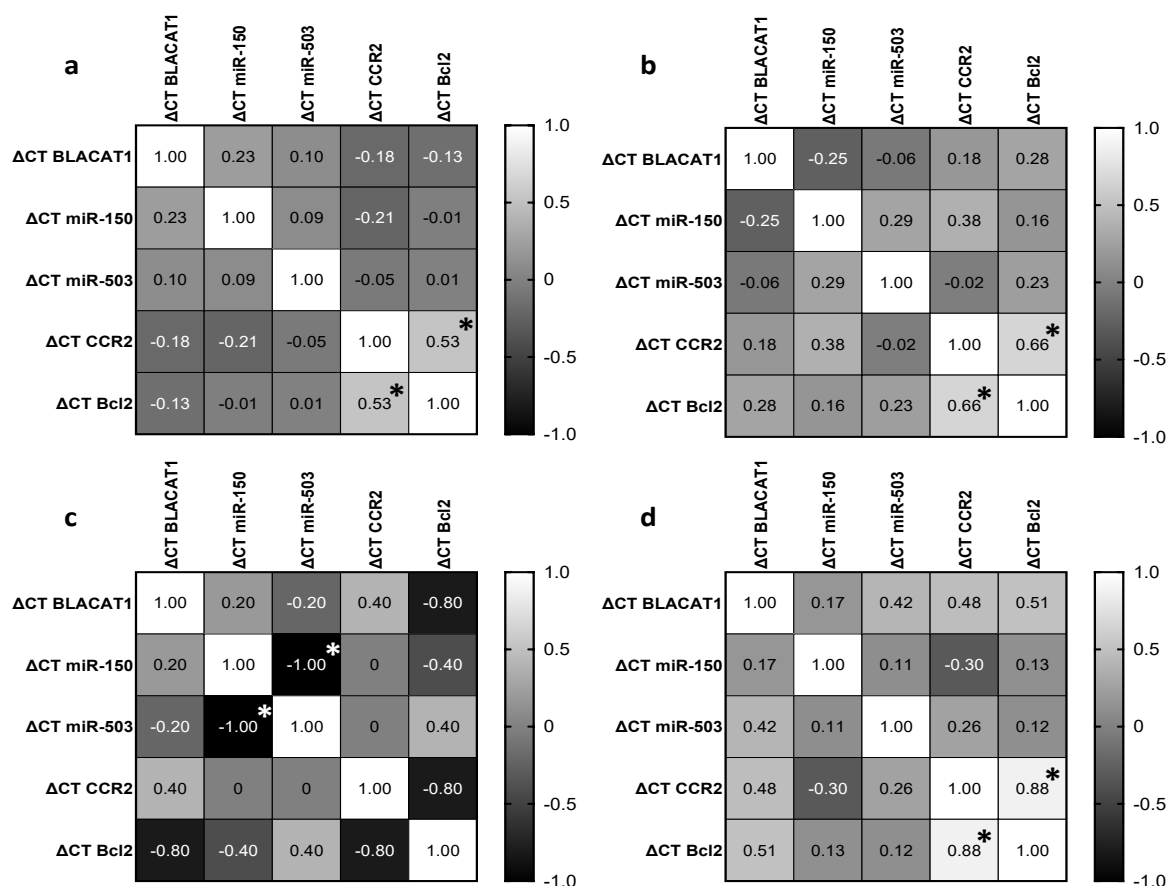


Figure 1. Correlation analysis of ΔCt gene expression levels (*BLACAT1*, *miR-150*, *miR-503*, *BCL2*, and *CCR2*) stratified by molecular subtypes of breast cancer. Correlations were evaluated using Spearman/Pearson analysis, and significant associations ($p < 0.05$) are indicated. Subgroups include (a) Luminal A, (b) Luminal B, (c) TNBC, and (d) *HER2*-positive tumors. ΔCt values were calculated relative to internal controls (*GAPDH*, *U6*, and *18S RNA*).

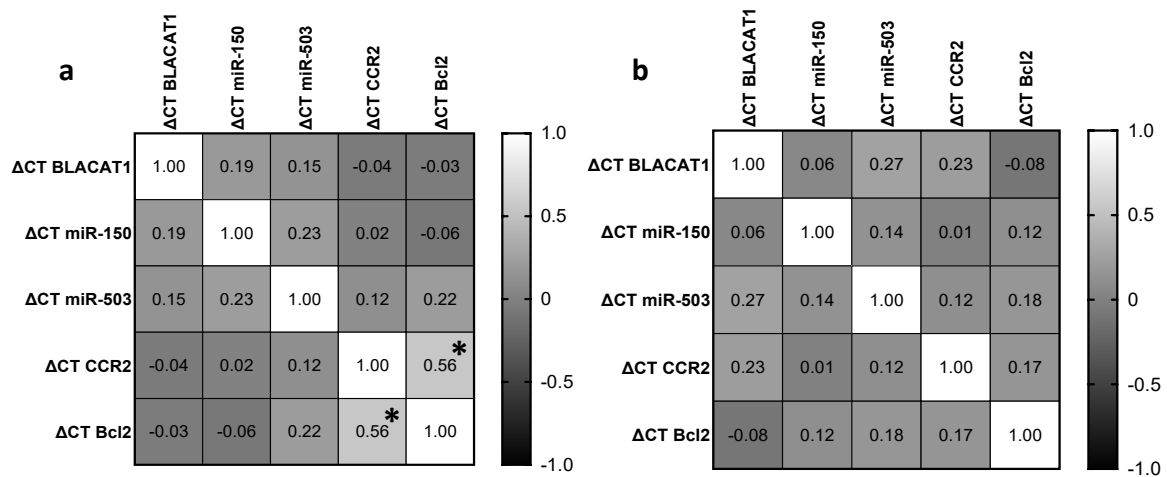


Figure 2. Correlation analysis of ΔC_t gene expression levels according to sentinel lymph node status. Correlations between target genes (*BLACAT1*, *miR-150*, *miR-503*, *BCL2*, and *CCR2*) were analyzed using Spearman/Pearson correlation methods. Statistically significant correlations ($p < 0.05$) are indicated. (a) Benign sentinel lymph node group, (b) malignant sentinel lymph node group.

anticipated to facilitate the diagnosis and monitoring of the disease and provide a more accurate predictive assessment of treatment response [10]. miRNAs are considered ideal biomarkers due to their high specificity, stability, and distinct expression profiles [11].

Long noncoding RNAs (lncRNAs) constitute a large heterogeneous class of transcripts exceeding 200 nucleotides in length with limited protein-coding potential. Circulating lncRNAs in serum/plasma exhibit relative stability owing to their resistance to RNase degradation, even within the complex in vivo environment [12].

There is increasing consensus that lncRNAs function as novel biomarkers and/or key regulators of toxicological responses in human and animal models [13]. Sentinel Lymph Node Biopsy (SLNB) is an invasive procedure that serves as the gold standard for detecting axillary metastases. Preoperative identification of metastases through histopathological examination is preferable as it facilitates a definitive procedure for known axillary metastasis. Furthermore, it has been reported that SLNB is accurate for staging the axilla in women with clinically node-negative disease at initial presentation, even following chemotherapy [14, 15].

During SLNB, 3-5 mL of blue dye (isosulfan blue dye) is administered via subdermal injection near the cancer site or in the subareolar location, either into the breast parenchyma or the subareolar area, in the operating room. The lowest false-negative rates for SLNB were achieved when all blue lymph nodes were excised. Studies have demonstrated that the removal of four SLNs captures 98% of all positive SLNs; thus, excision of more than four SLNs is not necessary for accurate axillary staging [16].

Zitong Zhao et al. detected significantly elevated levels of *miR-503-3p* in the circulation of breast cancer patients and demonstrated that the overexpression of *miR-503-3p* correlated with lymph node metastasis [17]. Jianting Long et al. demonstrated that *miR-503* expression in tissue samples was downregulated in breast cancer tissues and cell lines. Furthermore, *miR-503* inhibits breast cancer

cell proliferation [18].

In the present study, *miR-503-5p* expression in plasma samples was observed to be 2.33 times lower in patients without sentinel lymph node involvement, showing a borderline trend towards significance. Xiaopeng Hu et al. demonstrated through *BLACAT1* expression analyses conducted on tissue samples that *BLACAT1* levels were elevated in breast cancer tissues compared to normal tissues. Furthermore, they established that higher *BLACAT1* expression correlates with tumor staging in breast cancer tissues. Patients exhibiting high *BLACAT1* expression in breast cancer present shorter survival times. Moreover, the aforementioned study observed that *BLACAT1* inhibits *miR-150-5p* expression in breast cancer cells and enhances breast cancer cell survival and metastasis via the *miR-150-5p* pathway [19]. Consistent with these tissue-based findings, our study extended the investigation to serum samples. We observed that the expression of lncRNA *BLACAT1* was 2.37 times higher in patients with sentinel lymph node involvement compared to those without sentinel lymph node involvement ($p = 0.002$).

Xiaopeng Hu et al. observed that *miR-150-5p* suppressed *CCR2* expression in breast cancer cells. This investigation demonstrated that the *BLACAT1*-*miR150-5p*-*CCR2* pathway exhibits increased expression in tissue samples, contributing to breast cancer metastasis [19].

Bruna M. Sugita et al. conducted an evaluation of *miR-150-5p* expression levels in breast cancer and normal tissues utilizing RT-qPCR. The results indicated that *miR-150-5p* was significantly upregulated in tumor tissues in comparison to normal tissues. Furthermore, analysis of paired samples demonstrated that *miR-150-5p* exhibited upregulation in both triple-negative breast cancer and non-TNBC tissues when compared to their corresponding normal tissues [20].

Qingfu Lu et al. in 2019, in a study conducted at Soochow University in China, demonstrated that *miR-150-5p* expression increased in breast cancer patients

in tissue samples [21]. Anna Kawiak et al. observed that *BCL-2* overexpression was present in various breast cancer subtypes, with *BCL-2* being most prominently upregulated in luminal-type breast cancers. *BCL-2* is a significant prognostic marker in patients with breast cancer and is associated with favorable outcomes [22]. In the present study, serum analyses revealed that *BCL-2* expression was 2.55 times lower in patients with sentinel lymph node involvement than in those without involvement in early stage breast cancers.

While previous studies have established a connection between lncRNA *BLACAT1* and breast cancer, no investigation has examined its association with molecular classification. In the present study, lncRNA *BLACAT1* expression was elevated 2.02-fold in Luminal B tumors, 5.14-fold in *HER2* tumors, and 27.6-fold in TNBC tumors, relative to other molecular subtypes.

Rolf Søkilde et al. identified a total of 655 microRNAs that were significantly differentially expressed among breast cancer molecular subtypes. They focused on the most prominent miRNAs and identified 73 miRNAs that were differentially expressed between subtypes. As anticipated, luminal clusters were associated with ER positivity, whereas the majority of Basal-like and *HER2* tumors were classified as ER-negative. ER+ tumors were primarily characterized by the high expression of *miR-26*, *miR-5681a*, *miR-5695*, *miR-887*, *miR-149*, *miR-375*, *miR-342*, *miR-190b*, *miR-29c*, *miR-29b*, and *miR-499a*. Downregulation of *miR-455-3p*, *miR-934*, *miR-135b*, and *miR-577* was observed, and these miRNAs were upregulated in ER tumors. ER-tumors were also characterized by the overexpression of *miR-18a*. Additionally, *miR-34a*, *miR-2115*, *miR-4728*, and *miR-7158* are upregulated in *HER2* tumors. Notably, microRNA-4728 is encoded within the *HER2* oncogene itself and has been demonstrated to be co-upregulated with its host gene [23].

Various miRNAs have been associated with molecular classification. However, no studies have demonstrated the relationship between *miR-150* and *miR-503* and molecular classification.

We examined *miR150*, *miR503*, lncRNA *BLACAT1*, *CCR2*, a chemokine receptor protein, and *BCL-2*, an apoptosis regulator, which may be associated with sentinel lymph node metastasis in preoperative serum samples of patients with newly diagnosed early-stage breast cancer and potentially possess predictive and prognostic value. The objective of this study was to non-invasively assess the detectability of axillary metastasis from preoperative serum samples of early-stage breast cancer patients and to contribute to existing clinical studies.

In our investigation, *miR-503* expression was 3.67-fold higher in Luminal B tumors ($p = 0.6734$), 54.29-fold higher in *HER2* tumors, and 48.14-fold lower in TNBC tumors than in other tumor types. Furthermore, *miR-150* was downregulated 3.13-fold in Luminal B tumors and 20.35-fold in TNBC tumors.

The current literature lacks studies demonstrating a relationship between *CCR2* expression and molecular classification. In our investigation, *BCL-2* expression was 2.60-fold higher in Luminal B tumors, while *CCR2*

expression was 13.24-fold higher in TNBC tumors. In conclusion, this study elucidates the potential of circulating miRNAs and other molecular markers to detect axillary metastasis in patients with breast cancer. Specifically, the differential expression of *BLACAT1* and *miR-150-5p* in older patients indicates age-related variations in the molecular pathways that may influence metastatic progression. The significant overexpression of *miR-150-5p* in patients aged > 50 years could function as a valuable biomarker for identifying patients at higher risk of metastasis, thereby providing an opportunity for earlier and more targeted interventions.

Taken together, our findings demonstrate that, the potential utility of circulating molecular markers, specifically *BLACAT1*, *miR-150*, and *miR-503*, in the non-invasive detection of axillary metastases in breast cancer patients. Our findings indicate that *BLACAT1* expression is significantly elevated in patients with malignant sentinel lymph nodes, whereas *miR-150* and *miR-503* exhibit downregulation in this patient group. These results suggest that circulating RNA molecules could serve as promising biomarkers for early detection and prognosis, offering a less invasive alternative to conventional histopathological approaches.

Furthermore, the differential expression patterns of these markers across different molecular subtypes highlight their potential role in refining breast cancer classification and risk stratification. While our data support the clinical relevance of these molecular markers, further validation in larger, independent cohorts is essential to establish their diagnostic and prognostic utility. Future studies should also explore the mechanistic pathways underlying these molecular interactions to better understand their role in tumor progression and metastasis.

Our findings contribute to the growing body of evidence supporting the integration of circulating RNA-based biomarkers into clinical practice, potentially improving patient outcomes through earlier detection and more tailored therapeutic approaches.

Author Contribution Statement

Taha Yasin Baran, Sevda Yılmaz and Ergün Erdem conceived and designed the experiments. Buket Er Urgancı and Selda Şimşek performed the experiments. Taha Yasin Baran and Sevda Yılmaz collected the patient samples and performed clinical analysis. Pathological evaluations were performed by Yeliz Arman Karakaya. Taha Yasin Baran, Buket Er Urgancı and Sevda Yılmaz wrote and completed the paper. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on

reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee for Non-Interventional Clinical Research of Pamukkale University (Approval No: 94107, Date: 26.04.2021).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest Disclosure

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

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