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Original Article

Prevalence of Cancer-Related Biomarkers in Breast Cancer Patients in Northern Iran

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Background: Breast cancer is the most common malignancy among women and a leading cause of cancer-related mortality. Molecular biomarkers, including estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67, play a crucial role in prognostic assessment and therapeutic decision-making. The prevalence and expression patterns of these biomarkers may vary across populations, underscoring the importance of evaluating their characteristics in local settings

Materials and Methods: This descriptive cross-sectional study was conducted on 117 patients with breast cancer who were referred to healthcare centers in Babol, northern Iran, between 2019 and 2023. Data were obtained from medical records and a researcher-developed questionnaire encompassing demographic characteristics, tumor features, and molecular biomarker status (ER, PR, HER2, and Ki-67). Statistical analysis was performed using descriptive methods, including frequencies, percentages, and means.

Results: The mean age of the patients was 56.23 years (SD = 10.88). Biomarker analysis showed that 66.7% of patients were ER-positive, 59.0% were PR-positive, 23.1% were HER2-positive, and 66.7% were Ki-67–positive. No cases of distant metastasis (M1) were identified, and all patients were classified as M0. ER and PR positivity increased with advancing age, whereas Ki-67 positivity was more prevalent among younger patients. Higher Ki-67 expression was also associated with more advanced tumour stage and lymph node involvement.

***Conclusion*:** This study emphasizes the prognostic value of molecular biomarkers in breast cancer. The findings indicate that older patients are more likely to have hormone receptor-positive tumors, while younger patients tend to exhibit higher tumor proliferative activity. Assessment of ER, PR, HER2, and Ki-67 expression may support personalized treatment approaches and contribute to improved clinical outcomes.

Keywords: Breast Cancer, Biomarkers, Tumor Markers, Prognosis

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Introduction

Breast cancer is the most common malignancy among women worldwide and the second leading cause of cancer-related mortality. In 2020, more than 2.3 million new cases of breast cancer were diagnosed globally, making it the most prevalent cancer in women.(1) Its incidence is steadily increasing, particularly in low- and middle-income countries, although mortality rates have declined due to advances

in early detection and treatment. In Iran, breast cancer accounts for approximately 16% of all cancer cases, with women often being diagnosed nearly a decade earlier than those in developed countries.(2) This underscores the need for urgent attention to breast cancer in Iran, as its prevalence continues to rise. Iranian women frequently develop breast cancer at younger ages, further highlighting the importance of generating region-specific data to improve treatment outcomes.

Molecular biomarkers play a critical role in the diagnosis, prognosis, and management of breast cancer. Biomarkers such as estrogen receptors (ER), progesterone receptors (PR), HER2, and Ki-67 are fundamental for classifying breast cancer subtypes and determining the most appropriate therapeutic strategies.(3) These biomarkers are essential for guiding decisions regarding hormone therapy, chemotherapy, and targeted treatments. Estrogen receptors (ER) and progesterone receptors (PR) are proteins expressed on the surface of some breast cancer cells, and tumors that are ER- and PR-positive are more likely to respond to hormone therapies that inhibit estrogen and progesterone activity.(4) HER2 is a protein that promotes cancer cell growth, and HER2-positive breast cancers are typically more aggressive.

However, targeted therapies such as trastuzumab (Herceptin) have been shown to be highly effective in the treatment of HER2-positive breast cancers.(5) Ki-67 is a marker used to assess the proliferative activity of cancer cells, with elevated Ki-67 levels indicating rapidly growing tumours. This marker can influence chemotherapy decision-making, as cancers with high Ki-67 expression often require more aggressive treatment strategies.(6)

Although these biomarkers are routinely used in clinical practice in developed countries, their distribution and impact on treatment outcomes in regions such as northern Iran, where breast cancer frequently presents at a younger age, remain underexplored. Understanding the prevalence and clinical significance of these biomarkers in the Iranian population is essential for the development of more tailored and effective treatment strategies. Accordingly, this study aims to investigate the prevalence of key molecular biomarkers in breast cancer patients in Babol, northern Iran, providing region-specific data to enhance prognostic assessment and support more personalized treatment approaches for Iranian women.

Materials and methods

Study Design

This descriptive cross-sectional study was conducted to assess the prevalence of molecular biomarkers among breast cancer patients in Babol, northern Iran, between 2019 and 2023. The study aimed to evaluate the expression of estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67, and to examine their associations with demographic and clinical variables.

Study Population

The study included 117 female patients diagnosed with breast cancer who were referred to healthcare centers in Babol, Iran, between 2019 and 2023. Inclusion criteria were a confirmed diagnosis of breast cancer, availability of complete medical records, and absence of major comorbid conditions. Patients with incomplete medical records or non-invasive breast cancers, such as ductal carcinoma in situ, were excluded from the study.

Sampling Method

A census sampling method was employed, whereby all eligible patients who met the inclusion criteria were included. This approach ensured comprehensive representation of breast cancer patients attending the selected healthcare centers during the study period.

Data Collection:

Data were collected from medical records and a researcher-developed questionnaire. The questionnaire included demographic characteristics (such as age and marital status), tumour features (including TNM stage and histological grade), and the status of key molecular biomarkers (ER, PR, HER2, and Ki-67). ER, PR, and HER2 expression was assessed using immunohistochemistry (IHC) on formalin-fixed, paraffin-embedded tumour tissue samples. Ki-67 expression was also evaluated by IHC staining. Results were classified as positive or negative in accordance with

standard diagnostic criteria.

Tumor Staging

Tumor staging was conducted using the TNM system, which classifies cancers based on tumor size (T), lymph node involvement (N), and the presence of distant metastasis (M). This classification was applied to evaluate the stage, severity, and progression of cancer in each patient.

Statistical Analysis

Descriptive statistical methods were used to analyze the collected data. Frequencies and percentages were calculated for positive and negative expression of the molecular biomarkers (ER, PR, HER2, and Ki-67).

The chi-square test was applied to evaluate associations between biomarker expression and variables such as age, tumor stage, and lymph node status. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA).

Ethical Considerations

The study was approved by the Research Ethics Committee of the Islamic Azad University, Sari Branch (ethical code: IR.IAU.SARI.REC.1402.332). Patient confidentiality was strictly maintained, and only aggregated data were used for analysis. Informed consent was obtained from all participants, who were assured that the study findings would be shared with the healthcare center upon request.

Results

A total of 117 breast cancer patients participated in the study. The mean age of the patients was 56.23 years (SD = 10.88), with ages ranging from 40 to 81 years. The patients were categorized into three age groups: 39 patients were aged 40-49 years, 42 patients were aged 50-59 years, and 36 patients were aged 60 years and older.

The age distribution was relatively balanced across the groups. Regarding the expression of biomarkers, 66.7% of the patients were ER-positive, while 33.3% were ER-negative. For PR, 59% of patients were PR-positive, and 41% were PR-negative. HER2 expression was present in 23.1% of patients, while 76.9% were HER2-negative. The Ki-67 marker, indicating cell proliferation, was positive in 66.7% of the patients. No cases of distant metastasis (M1) were reported, with 100% of the patients in the M0 stage, indicating no distant spread of the disease. When biomarkers were analyzed by age group, it was observed that both ER and PR positivity increased with age.

In the 40-49 years group, 61% were ER-positive, compared to 83% in the 60+ years group. Similarly, PR positivity increased from 54.3% in the 40-49 years group to 83% in the 60+ years group. Ki-67 positivity, on the other hand, was higher in younger patients, with 84% of the 40-49 years group showing positive Ki-67, while only 50% of the 60+ years group had a positive result. No significant differences in HER2 expression were observed across age groups. (**Table 1**) When analyzed by tumor stage, ER and PR positivity decreased as the tumor stage advanced. For example, in stage T1, 76.9% of patients were ER-positive, but this dropped to 40% in stage T2

Similarly, PR positivity decreased from 69.2% in T1 to 30% in T2. On the other hand, Ki-67 positivity significantly increased with tumor stage. In stage T1, 53.8% of patients were Ki-67 positive, while in stage T2, 90% of patients had a positive Ki-67 result. No significant differences in HER2 expression were found across tumor stages. (**Table 2**)

Table 1. Distribution of Biomarkers Based on Age Group in Breast Cancer

Age Group	ER Negative (n, %)	ER Positive (n, %)	PR Negative (n, %)	PR Positive (n, %)	Ki-67 Negative (n, %)	Ki-67 Positive (n, %)	p-value
40-49 years	38 (15%)	61 (24%)	61 (24%)	38 (15%)	15 (6%)	84 (33%)	0.0355
50-59 years	42 (18%)	57 (24%)	42 (18%)	57 (24%)	35 (15%)	64 (27%)	0.0004
60+ years	16 (6%)	83 (30%)	16 (6%)	83 (30%)	50 (18%)	50 (18%)	0.0059

Table 2. Relationship Between Biomarker Status and Tumor Stage

Tumor Stage	ER Negative (n, %)	ER Positive (n, %)	PR Negative (n, %)	PR Positive (n, %)	Ki-67 Negative (n, %)	Ki-67 Positive (n, %)	p-value
T1	18 (23.1%)	60 (76.9%)	24 (30.8%)	54 (69.2%)	36 (46.2%)	42 (53.8%)	0.013
T2	18 (60.0%)	12 (40.0%)	21 (70.0%)	9 (30.0%)	3 (10.0%)	27 (90.0%)	0.009
T3	3 (33.3%)	6 (66.7%)	3 (33.3%)	6 (66.7%)	0 (0.0%)	9 (100%)	0.001

Biomarker expression was also analyzed in relation to lymph node involvement. Ki-67 expression was significantly higher in patients with lymph node involvement. Among patients with N1 lymph node status, 80% were Ki-67 positive, compared to 55% in those with no lymph node involvement (N0). ER positivity was mildly reduced in patients with lymph node involvement (66.7% in N0 vs. 62.3% in N1-N3), but no significant differences were found for PR or HER2 expression across lymph node status. (**Table 3**) Lastly, the analysis of biomarkers by histology type showed that invasive lobular carcinoma (ILC) cases were predominantly ER and PR-positive, with 100% of ILC cases being ER and PR-positive. In contrast, invasive ductal carcinoma (IDC) showed a lower rate of ER and PR positivity, but a higher rate of HER2 positivity. Ki-67 positivity was observed in 75% of ILC cases, compared to 65.7% in IDC cases. (**Table 4**).

Table 3. Association of Biomarker Status with Lymph Node Involvement

Lymph Node Status	ER Negative (n, %)	ER Positive (n, %)	PR Negative (n, %)	PR Positive (n, %)	Ki-67 Negative (n, %)	Ki-67 Positive (n, %)	p-value
N0	21 (35%)	39 (65%)	21 (35%)	39 (65%)	27 (45%)	33 (55%)	0.143
N1	15 (33.3%)	30 (66.7%)	21 (46.7%)	24 (53.3%)	9 (20%)	36 (80%)	0.1104
N2	0 (0%)	9 (100%)	3 (33.3%)	6 (66.7%)	0 (0%)	9 (100%)	0.0005
N3	3 (100%)	0 (0%)	3 (100%)	0 (0%)	3 (100%)	0 (0%)	N/A

Table 4. Biomarker Expression by Histological Subtype of Breast Cancer

Histology Type	ER Negative (n, %)	ER Positive (n, %)	PR Negative (n, %)	PR Positive (n, %)	HER2 Negative (n, %)	HER2 Positive (n, %)	Ki-67 Negative (n, %)	Ki-67 Positive (n, %)	p-value
IDC	39(37.1%)	66(62.9%)	48(45.7%)	57(54.3%)	78(74.3%)	27(25.7%)	36(34.3%)	69(65.7%)	0.0097
ILC	0 (0%)	12(100%)	0 (0%)	12(100%)	12(100%)	0(0%)	3(25%)	9(75%)	0.0023

IDC :Invasive ductal carcinoma
ILC: Invasive lobular carcinoma

Discussion

Breast cancer remains one of the most common and significant health challenges faced by women worldwide. Despite advances in early detection and treatment, the clinical management of breast cancer is complicated by the heterogeneity of the disease, which is influenced by various biological and molecular factors.(7) The identification of reliable biomarkers plays a crucial role in the prognosis, treatment selection, and monitoring of breast cancer patients.(8) In this study, we aimed to investigate the prevalence of molecular biomarkers-ER, PR, HER2, and Ki-67-in breast cancer patients in Babol, Northern Iran, and assess their correlation with key clinical factors. One of the key findings of our study was the significant association between age and the expression of ER and

PR. Older patients exhibited a higher rate of hormone receptor positivity, with 83% of those aged 60 years and above being ER-positive. This is consistent with previous studies that have shown that hormone receptor positivity tends to increase with age.(9, 10)

Tumors in older patients are often more hormone-sensitive, which makes them more likely to respond to endocrine therapies such as tamoxifen or aromatase inhibitors. In contrast, younger patients (40-49 years) in our study had a higher expression of Ki-67, which suggests a higher rate of tumor proliferation. This finding is in line with the well-established notion that younger patients often have more aggressive, less differentiated tumors that are more proliferative and less responsive to hormonal therapies.(11) Our study also revealed a significant relationship between tumor stage and Ki-67 expression. As tumor stage advanced, the rate of Ki-67 positivity increased, indicating a higher proliferative activity in advanced stages of breast cancer.

This is consistent with the current literature, which suggests that Ki-67 is a reliable marker of tumor aggressiveness and proliferation. Higher Ki-67 levels are typically associated with poorer prognosis, indicating the presence of rapidly dividing tumor cells that may lead to faster disease progression and metastasis.(12, 13) Additionally, in the more advanced tumor stages (T2 and beyond), ER and PR positivity decreased, highlighting the shift towards more aggressive tumor behavior in later stages of cancer.(14) Another significant finding in our study was the association between lymph node involvement and Ki-67 expression.

Patients with lymph node involvement (N1-N3) had significantly higher Ki-67 positivity compared to those with no lymph node involvement (N0). This observation aligns with the current understanding that lymph node involvement is a critical factor in breast cancer prognosis, as it often signifies tumor spread and increased biological aggression. However, no significant correlation was found between lymph node status and ER, PR, or HER2 expression, suggesting that these biomarkers alone may not fully capture the prognostic significance of lymph node involvement in our cohort. While HER2 is known to be an important biomarker for breast cancer aggressiveness, our study found that HER2 expression was present in only 23.1% of patients. This is lower than the global average of 25-30% for HER2-positive breast cancer.(15) Interestingly, we did not find a significant relationship between HER2 expression and tumor stage, age, or lymph node involvement.

Previous studies have shown that HER2-positive tumors are typically associated with more aggressive disease and poorer prognosis.(16) However, the lack of a significant relationship in our study may be due to the relatively low frequency of HER2-positive cases, as well as the small sample size in our study. It is also possible that other molecular alterations may play a role in the aggressiveness of breast cancer in this population. The histological analysis in our study revealed that invasive lobular carcinoma (ILC) cases were predominantly ER-positive and PR-positive, with 100% of ILC cases showing positivity for both markers. This is in line with existing literature, which reports that ILC is typically more hormone-sensitive compared to invasive ductal carcinoma (IDC).(17) IDC, on the other hand, exhibited a lower rate of ER and PR positivity but a higher rate of HER2 positivity.(18) The findings of our study support the notion that IDC and ILC are biologically distinct subtypes of breast cancer with different molecular characteristics. ILC tends to have a more favorable prognosis due to its hormone sensitivity, whereas IDC may be more aggressive and less responsive to hormonal therapies.

Conclusion

In conclusion, our study highlights the significant role of molecular biomarkers in assessing breast cancer prognosis and treatment decisions. The findings suggest that older patients tend to have more hormone-sensitive tumors, while younger patients exhibit higher tumor proliferative activity. Additionally, advanced tumor stages and lymph node involvement were associated with higher Ki-67 expression, reflecting increased tumor proliferation. These results emphasize the importance of incorporating molecular biomarkers into clinical practice for personalized treatment strategies, ultimately improving patient outcomes and

survival rates.

Limitations and Future Directions:

Although this study provides valuable insights into the biomarker expression patterns in breast cancer patients in Babol, several limitations should be acknowledged. The sample size was relatively small, which may limit the generalizability of the findings. Additionally, we only assessed four biomarkers (ER, PR, HER2, and Ki-67), and there are many other biomarkers that may play an important role in breast cancer prognosis, such as p53, EGFR, and BRCA1/2 mutations.

Future studies with larger sample sizes and a broader range of biomarkers are needed to provide a more comprehensive understanding of breast cancer in this population. Moreover, further research into the molecular mechanisms underlying the association between biomarkers and clinical outcomes is crucial for improving personalized treatment strategies.

Declaration

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Author Contributions

Conception and design: SM, AT. Analysis and nterpretation: AFT. Data collection: SM, AT, AFT. Writing the article: SM, AT, AFT. Critical revision of the article: SM, AT. Final approval of the article: SM Statistical analysis: AFT. Obtained funding: SM. Overall responsibility: SM.

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