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Correlation of prognostic biomarkers with histologic features in Albanian women with breast cancer

Albina Hasa,[1] Merita Xhetani,[2,3] Mirela Lika,[3] Floriana Marku,[4] Radomir Dishi,[5] Silvana Celiku[6]

[1]Department of Medical Laboratory Technician and Imaging, Faculty of Technical Medical Sciences, Aldent University, Tirana; [2]Center of Molecular Diagnostics and Genetic Research, Tirana; [3]Department of Biology, Faculty of Natural Sciences, University of Tirana, Tirana; [4]Department of Public Health, Faculty of Medicine, University of Medicine, Tirana; [5]Head of the Obstetrics and Gynecology Department, Regional Hospital of Dibër; [6]Head of the Oncology Department, Mother Teresa University Hospital, Tirana, Albania

Correspondence: Albina Hasa, Department of Medical Laboratory Technician and Imaging, Aldent University, Albania. University Obstetrics and Gynecology Hospital "Queen Geraldine", Tirana, Albania.
Tel.: +355682069165.
E-mail: albina.hasa@ual.edu.al

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Abstract

Breast cancer is the leading cause of cancer among women and remains one of the most prevalent contributors to cancer-related mortality worldwide. This study aims to evaluate biomarker expression in women with breast cancer and the correlations between them and other prognostic parameters. A retrospective analysis of 252 subjects was conducted at the Oncology Department of Mother Teresa University Hospital in Albania between 2021 and 2024. The highest rate of the disease was observed in the over-45 age group (92.5%). A family history of cancer was reported in 13.9% of patients. The most common histological type identified was ductal carcinoma (81.3%), which predominantly affected the left breast (57.1%) and was most frequently stage 2 (69.8%). A significant association ($p < 0.001$) was found between disease stage and expression of ER (Estrogen Receptors), PR (Progesterone Receptors), and HER2 (Human Epidermal Growth Factor Receptor 2), as well as between patient age and expression of ER, PR, and HER2 receptors ($p = 0.02$). HER2 and Ki-67 expression were inversely associated with ER and PR. Ki-67 was significantly correlated with age ($p = 0.008$) and stage ($p < 0.001$). Nodal metastasis correlated with Ki-67 ($p = 0.02$) and ER ($p = 0.01$).

Introduction

Globally, breast cancer is the most common type of cancer and the leading cause of cancer-related deaths among people under 70.[1] Research on breast cancer has led to significant advancements in our understanding of the condition and improved treatments over the past 20 years. However, it is often diagnosed at advanced stages because women neglect self-inspection and clinical examination of their breasts. Age, tumor size, tumor grade, histological type, lymph node status, and receptor status are all associated with the prognosis of breast carcinoma.[2] The literature shows that receptor status is consistently among the important predictors of five-year survival, mortality, and disease-free survival.[3,4]

In clinical practice, at least four distinct molecular subtypes of breast cancer, Luminal A, Luminal B, HER2 (Human Epidermal Growth Factor Receptor 2)-enriched, and Triple-negative, are recognized, based on the expression of hormone receptors and HER2 status. The identification of these subtypes, through diagnostic, prognostic, and therapeutic biomarkers, has greatly influenced clinical management and treatment strategies.[2,5] The main biomarkers used in assessing breast cancer are ER (Estrogen Receptor), PR (Progesterone Receptor), HER2, and Ki-67 (proliferative index).[6,7]

The hormone receptors, such as ER and PR, are present in breast tissue, among other tissues. They are essential for the growth, maturation, and regulation of hormone-responsive cells. ER and PR are highly expressed in breast cancer cells and are crucial as diagnostic and prognostic biomarkers for the disease. The overall survival and time to recurrence are positively correlated with increased expression of ER/PR. In contrast, a more aggressive course of the disease, as well as a worse prognosis and recurrence, is typically associated with low ER/PR levels.[8,9]

HER2-positive Breast cancer is defined as breast cancer that tests positive for the HER2 receptor. The HER2 receptor is encoded by the *c-erbB-2* (*ERBB2*) proto-oncogene, which is located on chromosome 17 and promotes the proliferation of breast cancer cells.[10]

Ki-67 is a nuclear protein that promotes tumor cell proliferation and is used as a prognostic factor in breast cancer.[11] A high Ki-67 index is an indicator associated with more aggressive tumors, while a low Ki-67 index indicates a less aggressive or slower-growing tumor.[5] The interaction of ER, PR, HER2, and Ki-67 has become crucial in the treatment of breast cancer.[12]

This study aims to evaluate the prognostic factors in breast cancer, with a particular emphasis on molecular receptor status and its association with patient-related factors, tumor-related factors, and other biological determinants. Within the broader study cohort, a target subgroup characterized by a family history of cancer has been delineated for subsequent analyses, specifically the assessment of *BRCA1* and *BRCA2* gene status and its potential correlation with receptor expression.

Several studies have shown that mutations in the *BRCA1* and *BRCA2* genes are major factors in hereditary breast cancer, mainly because of their crucial roles in maintaining genomic stability and facilitating DNA repair pathways.[13,14] In line with previous research on breast cancer and *BRCA* gene alterations,[15,16] our findings further highlight the importance of thoroughly exploring *BRCA* gene variants, especially among women with a hereditary risk of breast cancer.
Although the current manuscript is confined to biomarker evaluation, these forthcoming investigations are anticipated to yield further insights into the prognostic and predictive significance of biomarker status within the context of hereditary genetic predisposition.

Materials and Methods

Data collection and study design

This study was conducted in accordance with established ethical standards and by ensuring the confidentiality of patients' medical reports. The research included 252 Albanian women. Data were collected from patients diagnosed with breast cancer at the oncology department of Mother Teresa University Hospital between 2021 and 2024.

Patient data were collected retrospectively from medical records and contained the following information: personal information (origin, age, and family history of the disease), clinical data (clinical manifestations, tumor localization, histopathological classification, staging, biomarker status), and tumor staging according to the TNM (Tumor, Nodes, Metastases) system.

Histopathological examinations: immunohistochemical staining, and scoring

The immunohistochemical evaluation of hormone receptors and proliferative markers was performed in certified pathology laboratories in Tirana, Albania, using the Ventana BenchMark ULTRA automated staining system (Ventana Medical Systems, Inc., Tucson, Arizona, USA), following standardized clinical protocols for breast cancer receptor evaluation.

For the interpretation of ER and PR staining, the following scoring system (American Society of Clinical Oncology/College of American Pathology (ASCO/CAP)[17,18] was used: cases with no staining (score 0%) were considered negative, those with staining scores between 1-9% were classified as weakly positive, and those with staining scores of 10-100% were considered as strongly positive. HER2 immunohistochemical staining score was assessed according to the following criteria (ASCO/CAP guidelines for HER2 testing in breast cancer):[19] absence of membrane staining in less than 10% was considered score 0; barely perceptible membrane staining in more than 10% was scored as 1+; weak to moderate complete membrane staining in more than 10% was scored as 2+, considered weakly positive, equivocal cases need for further confirmation by Fluorescence In Situ Hybridization (FISH) analysis. Strong, complete membrane staining in more than 30% was scored as 3+, indicating a strongly positive result. The Ki-67 proliferative index was defined as follows: an index below 14% was classified as low, an index between 14 and 24% was classified as moderate, a score of 25-50% was classified as high, and a score over 50% was classified as very high. The assessment was done according to the laboratory protocol, based on the percentage of positive tumor cells. Although cut-off values vary across studies, our categorisation is approximately consistent with the St. Gallen Consensus 2013.[20]

Fewer subdivisions were used to generate more concise results in the correlations between variables. Overexpression of HER2 was defined as positive when 2+ or 3+ membranous staining was observed. ER and PR were considered positive when staining exceeded 1%, and Ki-67 was considered positive when membranous staining was greater than 25%.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA). Descriptive data were evaluated with various statistical tests, including frequency analysis, mean calculation, percentage determination, and Standard Deviation (SD). Analytical data were analyzed using statistical methods such as the Chi-square test, Spearman's rho, logistic regression analysis, and Fisher's test. A p-value of ≤ 0.05 was considered statistically significant. Results are presented in tables and graphs, using absolute values and percentages.

Results

The study included 252 women. The age group over 45 had the highest diagnostic rate (92.5%) compared to the under-45 age group (7.5%). The average age of the participants was 62.2 years, with a SD of 11.73. A family history of cancer was identified in 13.9% of the subjects.

Most breast cancer cases were diagnosed at stage II (69.8%), followed by stage III (21.8%), stage I (6.3%), and stage IV (0.8%). Data were unavailable for 1.3% of the subjects. Ductal Carcinoma (DC) was the most prevalent histological type, identified in 81.3% of cases. Lobular carcinoma accounted for 8.3%, with other morphological types representing smaller proportions. The left breast was more frequently affected (57.1%) than the right (42.1%), while bilateral involvement was reported in 0.8% of cases.

Regarding receptor status, ER positivity was observed in 85.3% of patients, PR positivity in 80.6%, and HER2 positivity in 9.4% of cases. ER was negative in 14.3% of cases, and PR was negative in 18.3%. HER2 status was equivocal (2+) in 4.9% and negative (0; 1+) in 85.7% of cases. The Ki-67 proliferation index was low in 21.4% of patients, moderate in 28.1%, and high in 50.4%.

As shown in Table 1, ER exhibited a strong, positive, and statistically significant correlation with PR ($r = 0.589$, $p < 0.01$). It showed a weak, negative, but statistically significant correlation with HER2 ($r = -0.174$, $p = 0.006$) and with the Ki-67 biomarker ($r = -0.248$, $p < 0.001$). PR was also strongly, positively, and significantly correlated with ER ($r = 0.589$, $p < 0.01$); it had a weak, negative, but significant correlation with HER2 ($r = -0.171$, $p = 0.008$), and with Ki-67 ($r = -0.138$, $p = 0.034$). HER2 displayed weak, negative, but significant

correlations with ER (r = -0.174, p = 0.006) and PR (r = -0.170, p = 0.008). Its correlation with the Ki-67 biomarker was weakly positive and not statistically significant (r = 0.110, p = 0.093).

The mean age of subjects with HER2, ER, and PR overexpression was 58, 63, and 63 years, respectively, compared to those lacking HER2, ER, and PR expression (63, 59, and 60 years, respectively). Our analysis of the association between receptor status and age group revealed a statistically significant association between the two variables (p = 0.02). As shown in Table 2, ER and PR expression exhibited a positive correlation with age (r = 0.129, 0.118; p = 0.04, 0.06). In contrast, HER2 expression and Ki-67 index were negatively correlated with age (r = -0.135, -0.170; p = 0.03, 0.008).

A statistically significant correlation was observed between receptor status and disease stage (p < 0.001). Associations between the two variables are detailed in Table 3. As demonstrated in the table, ER and PR expression exhibited a negative correlation with stage (r = -0.228, -0.129; p = <0.01, 0.04). HER2 expression and Ki-67 index were positively correlated with disease stage (r = 0.136, 0.232; p = 0.033, <0.001). There was a negative correlation between age and stage (r = -0.123), with a p value (0.052) suggesting a borderline significant relationship.

In the analysis of the distribution between receptor status and TNM classification, a significant association was found between estrogen receptor expression and node status, as well as between Ki-67 expression and lymph node status, highlighting the importance of these biomarkers in relation to nodal involvement, as presented in Tables 4 and 5.

Discussion

Currently, approximately 80% of patients with breast cancer are individuals aged over 50, while more than 40% are those over 65 years old.[8,21] In our study, the mean age of the subjects was 62.6 years. The over-45 age group had the highest diagnostic rate, compared to the under-45 age group.

DC was the most common histological type of breast cancer, with the left breast having the highest prevalence of disease localization and most frequently classified as stage 2, consistent with findings from other studies.[22,23]

Measurable amounts of ER and PR receptors are found in about 50–85% and 60-70% of patients with breast cancer.[24] In our study, the ER receptor was observed in 85.3% of the subjects, and PR positivity was observed in 80.6%. Other studies have reported varying levels of ER and PR expression in breast cancer.[8,25,26]
The *HER2* gene is overexpressed in 15-25% of breast cancer.[24,27] In our study, HER2 positivity was observed in 14.3% of cases.

Clinical observations and biomarker studies indicate that late-onset breast cancers grow more slowly. They are biologically less aggressive than early-onset breast cancers, even when controlled for hormone receptor (for example, ER) and growth factor receptor (for example, HER2) expression, supporting the conclusion that the biology of breast cancer is age-dependent.[28]

In our study, we used Spearman's rho correlation coefficient to assess the relationship between patient age and disease stage. The results demonstrated a weak negative correlation ($r = -0.123$, $p = 0.052$), indicating that older age may be associated with a lower disease stage at diagnosis. This finding aligns with previous evidence suggesting that breast cancer in older individuals may present less aggressively.

From a study similar to ours, it was emphasized that ER positivity increases, and HER2 positivity decreases with rising age. ER and PR expression were significantly lower in HER2-positive tumors compared to HER2-negative tumors (ER 83.8% vs 69.8%; PR 91.9% vs 77.8%). In HER2-positive tumors, ER and PR expression in high-grade tumors was significantly decreased compared with intermediate-grade tumors (ER 5.6% vs 10.5%; PR 0% vs 5.3%).[22] Another study highlighted a strong association between ER receptor and histological grade ($p=0.0003$).[29]

Our study revealed that advanced-stage tumors were more likely to have low ER/PR expression and high HER2/Ki-67 positivity, suggesting a more aggressive phenotype. We also observed age-related differences: ER and PR positivity increased with age, while HER2 and Ki-67 decreased, reflecting the tendency for older patients to develop less proliferative

tumors. These findings highlight the biological heterogeneity of breast cancer and its association with both disease stage and patient age.

A significant inverse relationship between HER2 overexpression and ER, PR expression was found in various studies.[22,30,31] Our study demonstrated an inverse association between HER2 and ER/PR biomarkers, with HER2 negatively correlated with ER and PR, while ER was positively correlated with PR. These findings reflect the biological heterogeneity of breast cancer and align with previous reports.[32]

In a study evaluating the proliferative index (Ki-67) in breast cancer patients and its relationship with prognostic factors, including age, tumor stage, ER and PR receptors, HER2 status, and TNM classification, a statistically significant association was found between Ki-67 and both age ($p < 0.02$) and disease stage ($p < 0.01$). Significant associations were also observed with HER2 ($p < 0.009$) and nodal metastases ($p < 0.001$). Although not statistically significant, an inverse association was identified between Ki-67 and ER ($p = 0.377$) as well as PR ($p = 0.149$).[33] Another study found a statistically significant inverse correlation between Ki-67 and ER/PR receptors. No statistically significant correlation was observed between Ki-67 and the HER2 receptor.[34]

In our study, Ki-67 expression showed a significant negative association with age and a positive association with disease stage, indicating its role as a marker of tumor aggressiveness. Furthermore, its inverse correlation with ER and PR supports its relationship with hormone receptor status. Although Ki-67 showed a positive association with HER2, this did not reach statistical significance, possibly due to biological variability.

The results of a study evaluating the correlation between ER, PR, HER2, and Ki-67 biomarkers with primary metastatic breast cancer lesions, tumor size, lymph node metastasis and Tumor Node Metastases (TNM classification) showed that tumor size did not correlate with the changes in the expression of ER, PR, in HER2, and Ki-67 ($p=0.208$, 0.068, 0.823, and 0.781, respectively). However, ER, PR, HER2, and Ki-67 expression were significantly correlated with primary lesions accompanied by lymphatic metastasis ($p=0.046$, 0.036, 0.030, and 0.027, respectively).[35] The correlation between ER receptors and nodal metastases was also underscored in another study ($p = 0.0003$).[36]

Our results indicated no correlation between tumor size and the expression of ER, PR, HER2, or Ki-67. Similarly, PR and HER2 expression did not show a significant association with

nodal metastases. In contrast, nodal metastases were significantly associated with ER and Ki-67 expression, suggesting a potential relationship between these biomarkers and metastatic spread.

Conclusions

The average age of breast cancer diagnosis is 62.6 years, with stage II DC being the most prevalent form. The left breast is the most commonly affected. A significant association exists between age and biomarker status, indicating that HER2 and Ki-67 positivity is higher in younger patients compared to older ones. In contrast, the positivity of ER and PR is higher in older patients. Low-stage cases exhibit higher ER and PR positivity compared to high-stage cases; conversely, HER2 and Ki-67 positivity increase with tumor stage. As a result, poor prognosis is associated with high levels of Ki-67 and HER2. An inverse correlation was observed between ER/PR and both HER2 and Ki-67 expression.

Our findings underscore the value of immunohistochemical analyses in breast cancer, highlighting their role in advancing biological insight and improving patient management.

In conclusion, ER, PR, HER2, and Ki-67 are crucial breast cancer biomarkers that aid in diagnosis, prognosis, and treatment decisions.

The only limitation of this study is the absence of histopathological staining images for the receptors. This is because the research was conducted using archived patient records, where only documented results were available rather than original tissue slides.

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Table 1. Correlative associations among molecular biomarkers.

Correlations

			ER	PR	Ki67	HER2
Spearman's rho	ER	Correlation Coefficient	1.000	.589**	-.248**	-.174**
		Significance (2-tailed)	.	0.000	0.000	0.006
		Number of cases	252	250	238	245
	PR	Correlation Coefficient	0.589**	1.000	-.138*	-.171**
		Significance (2-tailed)	0.000	.	0.034	0.008
		Number of cases	250	250	236	243
	Ki67	Correlation Coefficient	-.248**	-.138*	1.000	.110
		Significance (2-tailed)	0.000	0.034	.	0.093
		Number of cases	238	236	238	233
	HER2	Correlation Coefficient	-.174**	-.171**	.110	1.000
		Significance (2-tailed)	0.006	0.008	0.093	.
		Number of cases	245	243	233	245

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

ER, Estrogen Receptor, PR, Progesterone Receptor, HER2, Human Epidermal Growth Factor Receptor 2, Ki-67, Proliferative index.

Table 2. Distribution of biomarkers according to age groups.

		Age		r, p
		<45 years	≥45 years	
		Count	Count	
ER	0%/ negative	6	29	r = 0.129; p = 0.041
	1-9%/ low positive	1	5	
	10-100%/ positive	12	199	
	Total	19	233	
PR	0%/ negative	5	41	r = 0.118; p = 0.062
	1-9%/ low positive	1	3	
	10-100%/ positive	12	188	
	Total	18	232	
HER2	0-1+/ negative	15	195	r = -0.135, p = 0.035
	2+/ equivocal	1	11	
	3+/ positive	3	20	
	Total	19	226	
Ki67	<14%/ low	4	47	r = -0.170; p = 0.008
	14-24%/ moderated	2	65	
	25-50%/ high	10	91	
	>50%/ very high	3	16	
	Total	19	219	

ER, Estrogen Receptor, PR, Progesterone Receptor, HER2, Human Epidermal Growth Factor Receptor 2, Ki-67, Proliferative index.

Table 3, Distribution of biomarkers according to disease stage.

		Stage				r, p
		Stage I	Stage II	Stage III	Stage IV	
		Count	Count	Count	Count	
ER	0%/ negative	0	20	13	2	r = -0.228; p = <0.001
	1-9%/ low positive	1	2	3	0	
	10-100%/ positive	15	154	39	0	
	Total	16	176	55	2	
PR	0%/ negative	2	27	15	1	r = -0.129; p = 0.042
	1-9%/ low positive	0	4	0	0	
	10-100%/ positive	14	144	40	0	
	Total	16	175	55	1	
HER2	0-1+/ negative	14	152	42	1	r = 0.136; p = 0.033
	2+/ equivocal	0	10	2	0	
	3+/ positive	1	11	9	1	
	Total	15	173	53	2	
Ki67	<14%/ low	7	36	7	1	r = 0.232; p = <0.001
	14-24%/ moderated	5	48	12	0	
	25-50%/ high	3	74	23	1	
	>50%/ very high	0	8	11	0	
	Total	15	166	53	2	

ER, Estrogen Receptor, PR, Progesterone Receptor, HER2, Human Epidermal Growth Factor Receptor 2, Ki-67, Proliferative index.

Table 4. Biomarker distribution according to tumor size (T) and nodal metastases (N).

		ER		PR		HER2	
		Positive	Negative	Positive	Negative	Positive	Negative
		Count	Count	Count	Count	Count	Count
T	0	39	10	38	11	11	36
	≤2cm	78	9	70	15	10	77
	2-5cm	83	10	80	13	10	78
	>5cm	17	6	16	7	4	19
	p	0.865		0.827		0.266	
N	0	145	14	133	24	18	137
	1-3 lymph nodes	39	17	41	15	9	45
	>3 lymph nodes	33	4	30	7	8	28
	p	0.017		0.164		0.091	

ER, Estrogen Receptor, PR, Progesterone Receptor, HER2, Human Epidermal Growth Factor Receptor 2.

Table 5. Distribution of Ki-67 index according to tumor size (T) and nodal metastases (N).

		Ki-67		
		<14% low proliferative index	14-25% moderated proliferative index	>25% high proliferative index
		Count	Count	Count
T	0	9	14	22
	≤2cm	19	24	40

	2-5cm	19	26	43
	>5cm	4	3	15
	p	0.578		
N	0	37	46	66
	1-3 lymph nodes	9	16	29
	>3 lymph nodes	5	5	25
	p	0.022		