ORIGINAL ARTICLES

ASSESSMENT OF KI-67 AS A PROGNOSTIC MARKER IN BREAST CANCER PATIENTS TREATED AT THE UNIVERSITY HOSPITAL CENTER" MOTHER TERESA", ALBANIA

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ABSTRACT

Introduction: Breast cancer is a very coherent disease as well as one of the most common tumor diseases in women. Although awareness has increased nowadays, it is often not detected in its early stages. Ki-67, also called the proliferative index, is a marker that is now used in breast cancer as an evaluative indicator for tumor growth, prognosis, risk of recurrence, and progress towards medical treatment. This study aims to evaluate the expression of this marker in breast cancer as well as its correlation with other prognostic factors of this disease.
Materials and Methods: This is a retrospective study that includes 252 subjects with breast cancer, from the oncology department of the "Mother Teresa" University Hospital. Statistical data analysis was conducted using the SPSS software package.
Results: According to the study's results, 50.38% of the subjects exhibited high Ki-67 values. A significant correlation of Ki-67 with disease stage and age was found ($p<0.001$; $p=0.008$). A strong correlation was also found between ER/PR receptor expression and Ki67 ($p=0.00$; $p=0.03$) and a positive but non-significant correlation with HER-2 ($p=0.09$).
Conclusions: Ki67 proliferative index is an important biomarker for the general evaluation of breast cancer.

Keywords: Breast cancer, Albanian population, Ki67 proliferative index, biomarkers.

INTRODUCTION

Breast cancer is the most common cancer diagnosed in women worldwide[1]. Distinct molecular subtypes, varied clinical manifestations, and diverse therapeutic responses characterize this heterogeneous disease. It arises from a complex interplay of multiple factors, including genetics, environmental influences, and lifestyle choices. Breast cancer is most prevalent among postmenopausal women, with its incidence increasing with age. Genetics and heritable factors play a significant role in the development of breast cancer, and a first-degree family history substantially raises the risk. Factors such as women's reproductive activity, obesity, alcohol consumption, smoking, physical inactivity, and hormone replacement therapy have all been linked to an increased risk of breast cancer [2].

Being aware of its etiology aids in understanding its pathophysiology and highlights essential preventive measures to reduce risk. Screening methods, treatment options, and patient counseling and education can all improve through insights into the etiology of breast cancer.

Various factors, including age, histological diagnosis, stage, tumor size, and prognostic biomarkers, influence the prognosis of breast cancer.

Nowadays, prognostic and predictive biomarkers are essential for optimizing patient outcomes and personalizing treatment. These biomarkers consist of four subtypes: estrogen (ER), progesterone (PR), human epidermal growth factor receptor 2 (HER2), and the proliferative index (Ki-67). However, it is important to emphasize that these are the most commonly used, as the range of biomarkers available in different countries is even broader, including the BRCA1 and BRCA2 genomic biomarkers.

Ki-67, known as the proliferative index, is a nuclear protein expressed as the percentage of cells in the cell cycle[3] [4]. It is considered a reliable indicator of breast cancer proliferative activity, indicating how quickly cells are dividing [5] [6]. A higher Ki-67 score suggests that more cancer cells are actively dividing and growing, potentially leading to a more aggressive tumor. This biomarker plays a crucial role in assessing prognosis, guiding treatment, and predicting disease outcomes.

According to current estimates from Globocan, it is thought that by 2030, there will be an increase in breast cancer cases. In low- and middle-income countries, the incidence of breast cancer is expected to increase due to the Western lifestyle (late pregnancy, reduced breastfeeding, early menstruation, lack of physical activity)[7].

MATERIALS AND METHODS

A total of 252 participants took part in this study. Medical records of patients diagnosed with breast cancer at the oncology unit of Mother Teresa University Hospital Center from 2021 to 2024 provided our data.

Variables directly related to breast cancer assessed in each patient's records included age, clinical symptoms, stage, histopathological diagnosis, prognostic biomarkers, and family history of cancer.

The receptors included in the study were immunohistochemically evaluated using the Ventana BenchMark Ultra system. The following scoring system was used to interpret Ki-67:

- Score less than or equal to 14%: low proliferative index.
- Score 14-25%: moderate proliferative index.
- Score greater than 25%: high proliferative index.

The statistical analysis was carried out using the SPSS program. Both descriptive and analytical data were assessed. A p-value of less than or equal to 0.05 was considered statistically significant. Tables and charts represent the results.

RESULTS

252 breast cancer patients took part in our study. Compared to 7.5% in the under-45 age group, 92.5% of participants were over 45. The average age was 62.2 years, with a standard deviation of 11.73. 13.9% of cases had a family history of cancer.

The most common histological type was ductal carcinoma, present in 81.3% of cases. Lobular carcinoma accounted for 8.3%, while other types, such as medullary, mucinous, mixed, papillary, and Paget's disease, were less frequent. Most patients were diagnosed with stage II breast cancer (69.8%), followed by stage III (21.8%). The remaining cases were identified at stages I and IV, in smaller percentages. Among all subjects, 42.1% had involvement of the right breast, while a higher percentage (57.1%) involved the left breast. Bilateral cases were rare, comprising only 0.8% of the cases.

21.4% of cases had a low proliferative index Ki-67; 28.1% had a moderate index; 50.38% had a high index. Ki-67 showed a statistically significant correlation with age ($p=0.008$; $r= -.170$) and with disease stage ($p<0.001$; $r=0.232$). Regarding the other receptors measured in this study, Ki-67 showed a statistically significant inverse correlation with ER ($p=0.000$; $r=-.2248$) and PR ($p=0.034$; $r=- .138$), and a positive but not statistically significant correlation with HER-2/neu ($p=0.093$; $r=.110$).

Table 1: Correlative associations of Ki-67 with ER, PR, and HER-2/neu receptors.

Correlations							
			ER	PR	Ki67	HER-2	Receptor status
Spearman's rho	ER	Correlation Coefficient	1,000	.589**	-.248**	-.174**	.678**
		Sig. (2-tailed)	.	.000	.000	.006	.000
		N	252	250	238	245	252
	PR	Correlation Coefficient	.589**	1,000	-.138*	-.171**	.578**
		Sig. (2-tailed)	.000	.	.034	.008	.000
		N	250	250	236	243	250
	Ki67	Correlation Coefficient	-.248**	-.138*	1,000	.110	-.166*
		Sig. (2-tailed)	.000	.034	.	.093	.010
		N	238	236	238	233	238
	HER-2/neu	Correlation Coefficient	-.174**	.171**	.110	1,000	-.084
		Sig. (2-tailed)	.006	.008	.093	.	.191
		N	245	243	233	245	245
	Receptor status	Correlation Coefficient	.678**	.578**	-.166*	-.084	1,000
		Sig. (2-tailed)	.000	.000	.010	.191	.
		N	252	250	238	245	252

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

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

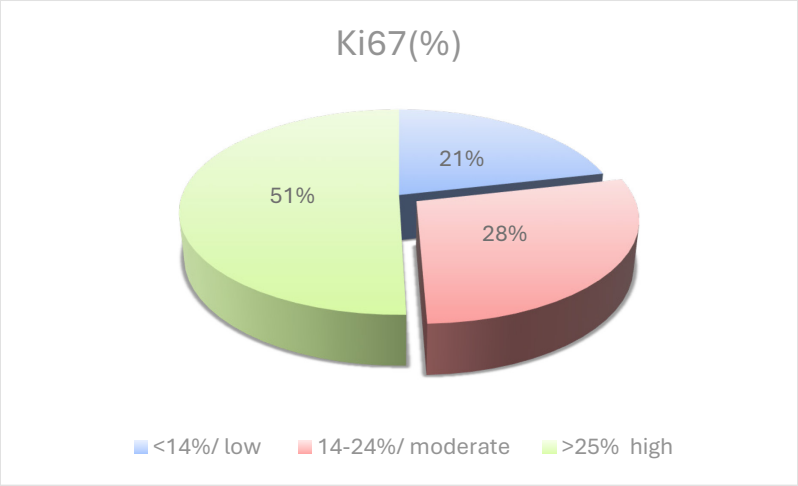
Table 3: Distribution of Ki-67 according to age groups.

		Age group		r, p
		<45 years old	≥45 years old	
		Count	Count	
Ki67	<14%/ low	4	47	r= -0.170; p=0.008
	14-24%/ moderate	2	65	
	25-50%/ high	10	91	
	>50%/ very high	3	16	
	Total	19	219	

Table 3: Distribution of Ki-67 according to disease stages.

<<		Disease stage				r, p
		Stage I	Stage II	Stage III	Stage IV	
		Count	Count	Count	Count	
Ki67	<14%/ low	7	36	7	1	r=0.232; p=<0.001
	14-24%/ moderate	5	48	12	0	
	25-50%/ high	3	74	23	1	
	>50%/ very high	0	8	11	0	
	Total	15	166	53	2	

Chart 1: Distribution of Ki67 receptor.



DISCUSSIONS

Currently, about 80% of breast cancer patients are individuals over the age of 50, while more than 40% are over the age of 65[8]. In our study, the average age of the subjects was 62.6 years. The age group over 45 years had the highest diagnostic rate (92.5%) compared to the group under 45 years (7.5%). Ductal carcinoma was the most common histological type of breast cancer (81.3%). The left breast presented the highest prevalence of localization (57.1%) and was most often classified as stage 2, consistent with other studies[9],[10],[11].

From the results of a study on the proliferative index Ki-67 in breast cancer patients, evaluating the relationship between Ki67 and prognostic factors of the disease, including age, tumor stage, ER and PR, HER-2/neu receptors and TNM classification, a statistically significant relationship was identified between Ki-67, age ($p<0.02$) and disease stage ($p<0.01$). A statistically significant relationship was also observed with HER-2/neu ($p<0.009$) and lymph node metastases ($p<0.001$). Although not statistically significant, an inverse relationship was found between Ki-67 and ER and PR ($p=0.377$; $p=0.149$)[12]. According to another study, a statistically significant inverse relationship was found between Ki-67 and ER/PR receptors. No relationship was found between Ki67 and the HER-2/neu receptor[13].

From the results of our study, a statistically significant relationship was also identified between Ki-67, age ($r=-0.170$; $p=0.008$), and disease stage ($r=0.232$; $p<0.001$). A statistically significant inverse correlation was observed with ER and PR ($r=-0.248$, $p=0.000$; $r=-0.138$, $p=0.034$), and a positive, but not statistically significant correlation was identified with HER-2/neu ($r=0.110$, $p=0.093$).

In another study, a statistically significant association was observed between Ki67 and disease stage and tumor size (T from the TNM classification). No significant association was observed between Ki-67 and ER, PR, HER-2/neu receptors, nor between Ki-67 and nodal metastases (N, from the TNM classification) and vascular invasion, with a p-value > 0.05 [14].

The results of another study evaluating the correlation of ER, PR, HER-2/neu and Ki-67 receptors with primary metastatic lesions of breast cancer, tumor size, lymph node metastases and TNM classification, showed that tumor size did not correlate with changes in ER, PR, HER2 and Ki-67 expression ($p=0.208$, 0.068, 0.823 and 0.781). Ki-67 ER, PR, HER2 had a significant association with lymphatic metastases ($p=0.046$, 0.036, 0.030, and 0.027)[15].

The results of our study showed that tumor size was not significantly associated with changes in ER, PR, HER2, and Ki-67 ($p=0.86$, 0.82, 0.26, and 0.57). Changes in PR and HER2 were not significantly associated with lymph node metastasis ($p=0.16$, 0.09). However, lymph node metastasis (N) showed significant associations with changes in ER and Ki-67 expression ($p=0.01$, 0.022).

CONCLUSIONS

Breast cancer prognosis is based on several clinical and pathological indicators. High Ki-67 expression is associated with a poor prognosis of the disease; therefore, immunohistochemical determination of the Ki-67 proliferation index should be performed in routine cases of breast cancer to obtain useful clinical information on tumor aggressiveness, as reflected by the proliferation rate.

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