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Ki-67 expression in breast cancer and its correlation with other prognostic factors

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Abstract

Objectives: The degree of neoplastic cells proliferation is positively connected with the aggressiveness of breast malignant tumors; this can be observed by analyzing the proliferative index (Ki-67) using immunohistochemistry. The current study's objective is to identify Ki-67 expression in breast cancer patients in Erbil Province, Iraq, and to correlate that expression with progesterone and estrogen receptors expression as well as other prognostic variables.

Methods: This is a retrospective-case series study that was conducted between January 2022 and January 2024, in collaboration with the pathology departments at Rizgary and Erbil Teaching General Hospitals Tissue sections coated in paraffin wax underwent immunohistochemistry for Ki-67, Estrogen Receptor (ER), and Progesterone Receptor (PR). To analyze Ki-67, sections in the specimen with the most proliferation was selected, and cases with ≥20% positive nuclei were deemed to have high Ki-67 expression, while those with <20% positive nuclei were deemed to have low Ki-67 expression. The results of Ki-67 were tested in relation to the patient's age, the histological type, the tumor's grade, and the estrogen and progesterone receptors.

Results: Among a total of 163 patients, (54%) were younger than 50 years (age range 23-78 years). With regards to tumor histopathology: Invasive Ductal Carcinoma (IDC-NOS) was detected in 80.4% of cases and 51.1% were of grade lll. The Ki-67 immunoreactivity was highly expressed in (44.2%) of all cases. Expression of Estrogen, progesterone, and HER2 overexpression was observed in (58.4%), (62.6%), (54%) cases respectively. Higher level of Ki-67 expression was significantly associated with grade III tumor, negative expression of estrogen receptor, and progesterone receptor with a P value of 0.0052, 0.0014, and 0.0011

respectively. The association of Ki-67 expression was not statistically significant in relation to patient's age, histological types of tumor or size, lymph node status, and HER2 overexpression; P value = 0.967, 0.733, 0.514, 0.348, 0.9675 respectively.

Conclusion: This study showed a significant inverse correlation between Ki-67 expression and well-known predictive factor (estrogen and progesterone receptors) and no association with HER2 overexpression but there was an over expression of Ki-67 in breast cancer grade III.

Keywords: Erbil; Breast cancer; Ki-67; Estrogen receptor; Progesterone receptor; HER2 overexpression; Immunohistochemistry.

Background

Breast Cancer (BC) is the most common cancer in woman worldwide with an incidence of 25% and ranks fifth globally in terms of cancer death as per the GLOBOCAN 2020 study [1]. One in fourteen women worldwide will get breast cancer below the age of 79, in industrialized nations, this percentage will grow to one in nine women [2]. For the past thirty years in Iraq, BC has been the most common cancer among Iraqis. In women, BC accounts for up to 29% of all newly diagnosed cases and 14% of cancer-related fatalities [3]. Breast cancer molecular biology is based on immunohistochemistry assessment and expression of biomarkers such as the Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2), and cell proliferation index (Ki-67) [3,4]. These biomarkers help to identify the tumor phenotype and prediction of response to certain therapy therefore, aid in determining the best treatment strategy. In addition, identification of molecular subtypes would influence disease recurrence, survival, and treatment outcomes [5]. Accurate profiling of hormone receptors expressed in breast cancer provides evidence-based guidance for tailored endocrine therapy, which is one of the foundations of customized breast cancer care [6]. Estrogen Receptors (ER) and Progesterone Receptors (PR) have been identified as important predictive and prognostic markers for breast cancer [3]. They operate as DNA binding transcription factors, regulating the activity of many genes involved in breast cell proliferation and DNA replication, which leads to mutation [6]. Patients with hormone-sensitive malignancies have the best survival rates and responses to hormonal therapy [3].

Ki67, as a biomarker of cellular proliferation, has been shown to be prognostic of clinical outcomes in early-stage luminal BC and a predictor of response to neoadjuvant chemotherapy [7].

Core staining is the most often used criterion of the proliferation index, and it is typically used to forecast Ki-67 expression as a positive percentage of tumor cells in antibody staining. With the exception of the G0 phase of the cell cycle, the Ki-67 Index will express cells that proliferate in phases G1, S, G2, and M. During the G1 and S phases, low quantities of Ki-67 are present, and during mitosis, these levels surge [4].

Ki67 proliferation index is a molecular marker used to quantify the activity of cell proliferation, which is frequently employed in detecting breast cancer as well as a predictive factor [5-26]. When using antisense nucleotide downregulation of Ki-67 occurs and lead to inhibition of proliferation, hence, Ki-67

plays a crucial function in cell proliferation, as evidenced by its stringent control and regulation [11].

This study was performed to assess Ki-67 expression and to correlate the Ki-67 findings with patients' age, histological types, grade of tumors, and ER and PR receptor expression.

Materials and Methods

Patients and specimens

This retrospective case series investigation was conducted in the Pathology Departments at Rizgary and Erbil Teaching General Hospitals from January 2022 to January 2024. Non-residents of Erbil governorate, cases diagnosed outside the research period, breast cancer with known distant metastases (liver, bones, lung), and known recurrent breast cancer were excluded from this study. Formalin-fixed paraffin-embedded tissue blocks from hundred sixty-three (163) female patients with primary breast cancer were examined in this study. Sections from paraffin-embedded tissue were H&E stained and re-reviewed under a light microscope to examine the primary tumor. The histological types were established by the WHO categorization of breast tumors and rated using the Modified Bloom-Richardson grading method [8]. The age of the patients was retrieved from the medical reports. One section from each case was selected for immune-histochemical study. This study was approved by the Ethics Committee of Hawler Medical University, College of Medicine, Erbil, Iraq.

Immunohistochemistry

Each case was studied for ER, PR, HER 2, and Ki-67 expression. Antibodies, buffers, glass slides, and linking systems were purchased from DAKO TM (Dako/Denmark). Sections of 4-millimeter thickness were deparaffinized in xylene and dehydrated, and the immunohistochemical study was performed according to manufacturer's instructions. Primary antibodies used for ER were (1D5 Dako Cytomation, dilution 1:100), PR (PgR636 Dako Cytomation, dilution 1:100), HER2 (DAKO, clone 124, 1:100) and for Ki-67 was (MIB-1 (M7240; Dako Cytomation, dilution 1:100).

Immunohistochemical evaluation

The immunostaining of ER, PR, and Ki-67 produces a brown nuclear stain. All slides were examined for immunological staining under light microscopy using a Leitz dialux microscope. Positive cases for ER and PR expression were defined as ≥10% of neoplastic cells showing positive nuclear staining. ER, and PR were scored using the Allred scoring system. This approach considers both the percentage of tagged cells and the medium intensity of nuclear labeling. The Allred score is calculated by adding the percentage score (% of labeled cells) and the intensity score (labeling intensity).

HER2 was scored on a scale from 0 to 3 according to the Dako criteria. The staining was scored as negative (0) when no membrane staining was observed, or when membrane staining was observed in less than 10% of the tumor cells, weak positive (+1) if weak focal membrane staining was seen in more than 10% of the tumor cells, intermediate (+2) if weak to moderate, complete membrane staining was seen in

more than 10% of the tumor cells, and strongly positive (+3) if intense and complete membrane staining with weak to moderate cytoplasmic reactivity was seen in more than 30% of the tumor cells. In the final analysis, only scores (+3) were considered as HER2 overexpression cases. Total score = proportion score + intensity score. Tumors with an Allred score ≤2 were considered negative and tumors with a score >2 were considered positive for ER and PR [9].

Ki-67 was expressed as a percentage of positively stained cells per 100 epithelial cells after counting at least 1000 cells at high magnification (400X). Ki-67 expression was evaluated in a region with the highest proliferation, with ≥20% positive nuclei indicating high expression and <20% positive nuclei indicating low expression [10].

Statistical analysis

The association between Ki-67 and variable categories was assessed using the Chi-square test and Fisher Exact test when indicated. Regarding statistical analyses, P value of <0.05 is considered statistically significant.

Results

Table 1 shows the age, pathological characters, ER, PR, HER2 overexpression, and Ki-67 expression among the studied group.

In the present study, the patient's ages ranged from 23-78 years (mean = 51.63) with 88 cases (54%) were younger than 50 years. Regarding the histological types of the cases included in the study; the majority of cases (131 out of 163) were of IDC-NOS, which form 80.4% of all the cases and their grades were; 23 cases (17.6%) grade I, 41 cases (31.3%) grade II and 67 cases (51.1%) grade III. The remaining pathological cases were: invasive lobular carcinoma (ILC), 17 cases (10.4%) and 15 cases were Ductal Carcinoma In Situ (DCIS) which form 9.2 % of all cases. The ER positivity, PR positivity, and HER2 over-expression were evident in 58.4%, 62.6%, and 54% of cases respectively. Immunohistochemical study of Ki-67 showed high expression (≥20% of nuclei were positive) in 72 (44.2%) of patients and low expression was observed in 91 cases (55.8%). Table 2 illustrates the correlation of Ki-67 expression with the age of the patients and other pathological parameters. The correlation of Ki-67 expression with the age of the patients, histological types, tumor size, and lymph node status was not statistically significant (P value 0.967, 0.733, 0.514,0.348 respectively). However, a significant direct association of Ki67 expression with the cancer grades (ll & lll) was noted (P=0.0052). Table 3 delineates relationship of Ki-67 with ER, PR, and HER2 overexpression. A higher expression of Ki-7 was found in ER negative cases BC, in which the association was statistically highly significant (p=0.00144). In addition, Ki-7 was detected more in PR negative cases in comparison to PR positive cases (p=0.0011). The association between high expression of Ki-67 and HER2 overexpression was not significant.

Table 1: Age, pathological characteristics, PR, ER, Ki-67 expression status of 163 patients.

Parameter		No.	%
Age	≥50	75	46
	<50	88	54
Histology	IDC-NOS	131	80.4
	ILC	17	10.4
	DCIS	15	9.2
Grade IDC-NOS	l	23	17.6
	ll	41	31.3
	lll	67	51.1
Estrogen receptor	Positive	95	58.3
	Negative	68	41.7
Progesterone receptor	Positive	102	62.6
	Negative	61	37.4
HER2 expression	Score +3	88	54
	Score 0,+1,+2	75	46
Ki-67 expression	High	72	44.2
	Low	91	55.8

Table 2: Relation of Ki-67 expression with age & pathological parameters.

	Ki 67			Total	p-value
Parameter		**High expression**	**Low expression**		
Age	≥50	33	42	75	0.967
	<50	39	49	88	
	Total	72	91	163	
Histological types	IDC-NOS	59	72	131	0.733
	ILC	6	11	17	
	DCIS	7	8	15	
	Total	72	91	163	
Tumor size (cm)	≤ 2	27	28	55	0.514
	2-5	21	25	46	
	>5	24	38	62	
	Total	72	91	163	
Lymph node Status	Positive	40	45	85	0.438
	Negetive	32	46	78	
	Total	72	91	163	
Tumor grade (IDC-NOS)	I	9	14	23	0.0052
	II	11	30	41	
	III	39	28	67	
	Total	59	72	131	

Table 3: Relation of Ki-67 expression with ER, PR & HER2 expression.

Parameter	Ki 67			Total	p-value
		High	Low		
ER	Positive	33	63	95	0.00144
	Negetive	39	28	68	
	Total	72	91	163	
PR	Positive	35	67	102	0.0011
	Negetive	37	24	61	
	Total	72	91	163	
HER2 expression	Positive	39	49	88	0.9675
	Negetive	33	42	75	
	Total	72	91	163	

Discussion

When a patient is diagnosed with breast cancer it is vital to perform a thorough assessment of as many clinical, pathological, and anatomical criteria as feasible to determine their specific prognosis [8]. Identifications of variable biomarkers that represent the unique features of the tumor will guide patient's prognosis with breast cancer [11]. Analyzing and assessing these variables is essential to choose the cancer-specific therapy that will be effective and have the fewest harmful side effects from otherwise insufficient treatment plans [12]. Age is an important risk factor for breast cancer, and women aged 45 to 54 have the highest risk of developing the disease when compared to other age groups. One reason is they are at the perimenopausal era, which increases the risk of breast cancer due to aberrant estrogen levels [17]. In the current study, 88 (54%) patients were younger than 50 years old, such findings were remarkably similar to that of another Iraqi survey conducted in nearby Nineveh Province in 2020 by Al-Nuaimi [3], in which the average age was 51 years old. Many studies in Iraq have found that the greatest incidence of breast cancer occurs in older females over the age of 70, who are at high risk of getting breast cancer [13]. Another Iraqi study found that female patients diagnosed with BC had a mean age of 46.4±9.5 years [18]. In 2023, Egypt completed a big comprehensive study that described the clinical and pathologic profile of BC in Egypt over a period of two decades, with a sample size of more than 31,000 Egyptian BC patients. The Egyptian BC population was substantially younger than their Western counterparts, with an average age of 50.4 years at diagnosis [14]. In comparison to the current findings, a study conducted in Ethiopia found that the average age of BC patients at diagnosis was even lower than our current findings with an age of 43.9 years, and the majority of patients were premenopausal [15]. In the last decade (2012-2019), a notable increase in incidence of BC was observed and the rise was steeper among women under 50 years of age (1.1% each year) than in those over 50 years.

Our study showed that IDC-NOS was the most common histological type, accounting for 80.4% of cases. This outcome is comparable to what was attained in Iraq's Nineveh and Erbil provinces (86.25%) and (84.4%) respectively [3,18]. A study in India indicated that IDC-NOC was the most common form (88%), which was consistent with reports from other parts of India [19]. In a survey that was conducted

among 15,171 Egyptian patients with BC and described in 12 published papers; the estimated prevalence of invasive duct carcinoma was 87% [14]. Concurrent with the current findings, research conducted in two public hospitals in Belém, the Brazilian Amazon Region, that offer high-complexity oncology care for BC, revealed that the most common histological subtype, accounting for 94.7% of cases, is Invasive Ductal Carcinoma (IDC) [20].

In the current study, 51.1% were of grade lll while grade ll was detected in 31.3% of cases. Previous studies in Iraq had mentioned that the percentage of grade lll was 46.4%, 30.7%, and 23.7% respectively [3,9,18]. Detection rates of grade lll BC had been declared as: 44.5% by Demir H [21]. and 30.4% by Nigam et al. [22].

These variations in the data may be attributable to the difference in demographic traits, and racial backgrounds, or most likely to reflect tumor cell heterogeneity [3].

In the current study, a positive immunohistochemical ER and PR were observed in 58.3% and 62.6% respectively, while HER2 expression was positive in 54% of cases (score 3). Different rates of positive ER, PR, and HER2 expression had been mentioned worldwide by several studies such as (48.4%, 42.8%, 19.4%) by Ayandipo et al. [6], (58.8%, 49.1%, 29.8%) by Al-Khayat et al. [9], (87.4%, 85.3%, 33.7%) by Khoshnaw et al. [18], (78.4%, 62.3%, 14.8%) by Demir H et al. [21], (38.7%, 37.2%, 48.8%) by Nigam et al. [22], (68%, 58%, 58%) by Abdulrazzaq & Ahmed [23]. It is proven that different ethnic groups have varied hormonal statuses [6]. Different racial groups' hormonal statuses among breast cancer patients may be related to genetic differences as well as socioeconomic factors such as lifestyle choices, nutritional status, and exposure to the environment [4]. Breast cancer that can have unfavorable outcomes are those with, HR negative status, HER2 overexpression, or high-grade tumors, and are more commonly encountered in particular races [4]. In terms of socioeconomic variables, pervious researches has suggested a possible link between HER2 breast cancer and poor socioeconomic condition [25]. However, the discrepancy in these results may be linked also to pre-analytic variables, which can produce inaccurate results. For example, using a fixative other than 10% neutral buffered formalin (unless the laboratory has validated it before offering the assay) or fixing biopsies for intervals shorter than or longer than 72 hours can also lead to an incorrect results [9].

Ki-67 expression

In our study Ki-67 was expressed in 72 patients (44.2%). There was no statistically significant association between Ki-67 expression and patient age, histological type, tumor size, or lymph node status. These results were consistent with previously published results in the literatures [3,18,21,22]. There was a substantial correlation found between the grade of tumor and Ki-67 expression. Furthermore, it was observed in this group that PR-positive and ER-negative had increased Ki-7 expression. However, there was no significant correlation seen between HER2 overexpression and high Ki-67 expression. Different levels of Ki-67 were announced by numerous published studies. Al-Zawi A et al. [2] and Al-Nuaimi et al. [3] both reported and expression of (45%) in there BC case, others studies results were as following: (29.2%) declared by Hu X et al. [4], (68.5%) was noted by Ayandipo O et al. [6], (59.05%) in Mighri N et al. [2] study,

(43%) reported in Belachew EB et al. [15] and (46.9%) in Demir H [21] published data.

A significant correlation between Ki-67 expression and the tumor grade ll & grade lll had been observed in previous studies that did not showed a specific consistency between them among these are: (57%, 79%) Al-Zawi A et al. [2], (26.1%, 23.2%) Al-Nuaimi et al. [3], (67.1%, 14.1%) Ayandipo O et al. [6], (57.6%, 24.2%) Brown J et al. [10], (ll&lll :94.4%) Mighri N et al. [6], (34.2%, 64.5%) Demir H et al. [21]. Several investigations have reported significant expression of Ki-67 in ER-negative subjects [3-6].

Ki-67 plays a crucial function in cell proliferation, as evidenced by its stringent control and regulation [4]. Ki67 proliferation index is a molecular marker used to quantify the activity of cell proliferation, that is regularly employed in detecting breast cancer [26] in addition, Ki-67 works as a predictive factor. In order to select the best course of treatment for patients with breast cancer, the histological grade is a crucial determinant of breast cancer prognostic tools. It is included in the staging assessment, such as in the Nottingham Prognostic Index (NPI) algorithms [2]. The tumor's histological grade is determined by assessing morphological markers such as mitotic count, tubule development, and nuclear pleomorphism [8]. This may emphasize the concept that the histological grade is indirectly related to Ki-67 based on the mitotic count [22].

It had been determined that patients with low expression of Ki-67 in both primary and metastatic foci had the best prognosis and the longest Disease-Free Survival (DFS), while patients with high expression of Ki-67 in both primary and metastatic foci had the poorest prognosis and the shortest DFS [27]. This may be due to the fact that the DNA-binding protein Ki-67, which is strongly correlated with the growth, metastasis, and prognosis of malignant tumors, is overexpressed in a number of disorders associated with malignant tumors, indicating tumor cell activity [28]. There was a noteworthy negative correlation found between Ki-67 and ER, as well as between Ki-67 and PR. It has been shown that high Ki-67 readings are associated with negative ER, negative PR, and positive HER2 expression [3,21,29]. However, the present study couldn't find a correlation of Ki-67 score with HER2. A portion of the underlying disease's heterogeneity factors could be the source of this discrepancy in the results. For example, the population of tumor cells would exhibit heterogeneity in gene expression due to the consequences of genomic instability and the accumulation of different mutations and other genetic abnormalities, for example ER-ve tumors are more frequent in some hereditary breast cancers that bear BRCA1 mutation [2,4,7]. Most researches have established the predictive importance of the Ki-67 proliferation index in breast cancer [21]. Nowadays, as part of breast cancer biological assessment, the Ki-67 index is utilized to predict how well neoadjuvant chemotherapy would work [2]. Additionally, it is employed as a distinction between invasive breast cancers' Luminal A and Luminal B molecular subtypes [12].

It has been demonstrated that the cellular proliferation biomarker Ki67 can predict response to neoadjuvant chemotherapy and predict clinical outcomes in early-stage luminal BC [11,22]. While there is universal agreement that Ki-67 is a prognostic biomarker in BC, there are still differences in the global guidelines for its application in the prognostic and predictive assessment of BC [30]. The Italian Association of Medical Oncology, the European Group on Tumor Markers, the European Society for Medical Oncology

(ESMO), and the National Institute for Health and Care Excellence all advocate or propose using Ki67 in the prognostic evaluation of BC patients [28,30,31].

However, because Ki67 rating is subjectively determined and lacks standardization, it exhibits inconsistent reproducibility [30].

According to the National Swedish recommendations, 200 tumor cells should be counted in a location that has been identified as a Ki67 hotspot, and the percentage of Ki67-positive tumor cells should be noted [28]. On the other hand, the International Ki67 Breast Cancer Working Group suggested counting a minimum of 1,000 cells, with 500 cells permitted in typical fields [7].

Another issue with using Ki-67 in clinical practice is the disagreement over the ideal cutoff value for clinical relevance. At the 2009 St. Gallen consensus meeting, the use of Ki-67 was originally proposed as a mean of identifying highly growing tumors within Luminal breast malignancies. The consensus meeting in 2011 recommended a cutoff number of 14%; however, in 2013, that recommendation was modified to 20% [3-11]. The best cut points for Ki67 to distinguish between high- and low-risk patients while making treatment decisions are still up for debate. The widely used Predict online breast cancer decision aid (http://www.predict.nhs.uk) uses a 10% cutoff and, for adjuvant abemaciclib treatment, a 20% cutoff has determined eligibility. In contrast, Ki67 scores of 5% or less and 30% or more (but not 6%-29%) can be used for clinical decision-making [28,29,31]. The prognostic utility of Ki67 in the neoadjuvant context and the extent to which Ki67 scores add value beyond well-established prognostic factors like stage, grade, and the presence of the Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epidermal Growth Factor Receptor 2 (HER2) are also unknown. Concerns have also been raised regarding the inconsistency of Ki67 measurements amongst various pathology labs [5,7,10]. Ki67 expression exhibits significant heterogeneity, which affects tumor behavior and patient fate. This heterogeneity can be spatially recorded with precise cell detection and classification [2,4,5,7]. Recently, the significance of Ki67's spatial distribution has been studied in an effort to develop a measurement method that is less subjective and more repeatable. Digital Image Analysis (DIA) is one of the automated Ki67 scoring techniques that has been suggested to increase the reproducibility of Ki67 scoring. Nevertheless, there is still room for improvement in the prognostic relevance of these automated Ki67 scoring techniques, and strategies that combine current Ki67 scoring with novel features should be investigated. For instance, it was discovered that the DIA of Ki67 in hotspots was better than both manual Ki67 and mitotic counts [32,33].

The present study's limitations include limited sample size, which limits the generalizability of the data, a lack of comparison analysis of the intermediate Ki67 range with other prognostic tests such as multigene tests, and the retrospective nature of the study. Ki-67 indices from relevant biopsies should be interpreted with caution due to their limited inter-laboratory consistency due to the lack of standardized staining, scoring procedures, and consistent cut-offs. Many elements may be overlooked in the study, such as economic income, body mass index, and other major risk factors, which may have an impact on the final findings.

Conclusion & Recommendation

In the current study a high Ki-67 expression was found in (44.2%) of a female with BC in Erbil Province /Iraq. No significant relation was found between Ki-67 with the age of patients and histological types of BC. A direct significant relation was observed between the Ki-67 expression and the grade of tumor while Ki-67 was inversely associated with a well-known predictive factor (ER and PR). Further research including follow-up of patients with breast cancer with varying Ki-67 expression, ER/PR cancer phenotypes, and metastatic cases is required to determine the predictive and prognostic effect of this marker.

Declarations

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Authors contributions: Ahmed A Baban: Design of the study, data collection and written the bulk of the paper. Azhy Muhammed Dewana: Review of pathology slides, lab analysis and production of datas. Baderkhan Saeed Ahmed: Data collection, written method section, and review paper. Sarhang Hussein Muhammed: statistical analysis, written result section and review of paper. Kawan Shalli: Overall review of the study and final corrections of the paper.

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