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CORRELATION OF ER AND PR WITH KI 67 LEVEL IN PATIENTS OF BREAST CANCER PRESENTING AT CMH RAWALPINDI

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Abstract

Background: *Prominent biomarker Ki-67 reflects breast cancer's tumor proliferation. Its relationship with histological grade, menopausal status and hormone receptor status offers important new perspectives on tumor biology that help to guide therapeutic decisions and prognosis.* ***Aims:*** *This study sought to assess, in breast cancer patients presenting at Combined Military Hospital, Rawalpindi, Ki-67 levels, estrogen receptor (ER), progesterone receptor (PR), menopausal state and histological grade.* ***Methods***: *180 histologically confirmed breast cancer patients participated in this cross-sectional observational research from October 2024 to March 2025. ER, PR, and Ki-67 expression were ascertained by immunohistochemical labeling. High proliferative tumors were those with ≥20% Ki-67-positive cells. Including multivariate regression, statistical analysis evaluated relationships with p-values <0.05 regarded as significant.* ***Results***: *Compared to ER-positive (23.4 ± 8.7) and PR-positive tumors (22.1 ± 7.9), mean Ki-67 levels were considerably higher in ER-negative (45.6 ± 12.3) and PR-negative tumors (44.3 ± 10.8) (p<0.01). With the p=0.03, pre-menopausal patients had greater Ki-67 levels (38.7 ± 9.8) than post-menopausal individuals (34.6 ± 8.4). Following Grade 2 (27.8 ± 8.1) and Grade 1 (12.3 ± 5.6), Grade 3 tumors exhibited the highest Ki-67 values (49.5 ± 11.2) (p<0.01). Strong predictors of elevated Ki-67 levels (p<0.01) were found by multivariate analysis as ER negativity (OR: 2.8), PR negativity (OR: 2.5), and tumor size >3 cm (OR: 2.1).* ***Conclusion***: *Ki-67 highlighted its importance in prognostic stratification since it is much linked with hormone receptor status, menopausal status and histological grade. These results confirmed how Ki-67 is included into standard breast cancer tests to maximize individualized treatment plans.*

INTRODUCTION

Among women worldwide, breast cancer is the most often diagnosed cancer and main cause of cancer-related death [1]. Its variation in clinical presentation and biological function emphasizes the need of

finding consistent prognostic and predictive indicators [2]. Considered frequently to guide treatment decisions, estrogen receptor (ER) and progesterone receptor (PR) are well-known biomarkers in breast cancer. The expression of these hormone receptors is highly correlated with tumor behavior and sensitivity to hormone-based treatments including aromatase inhibitors and tamoxifen [3-4]. Usually compared to receptor-negative subtypes, ER-positive and PR-positive cancers show a better prognosis. But not all patients with hormone receptor-positive cancers respond exactly, which emphasizes the need of extra prognostic indicators [5-6].

Rising as a useful prognostic and predictive biomarker in breast cancer is Ki-67, a nuclear protein linked with cellular proliferation. Measured as Ki-67 labeling index, its expression captures the fraction of actively dividing tumor cells [7]. Often suggestive of aggressive tumor characteristics, fast development and poor clinical outcomes are high Ki-67 values. By including Ki-67 testing into standard pathology, oncologists now have further tool to stratify the patients depending on their risk and adjust treatment plans. Still under active research, though, is the link between Ki-67 and hormone receptor status, especially ER and PR [8-10].

Combined Military Hospital (CMH) Rawalpindi is a key healthcare facility where patients with breast cancer arriving at this hospital offer a chance to investigate clinically the relationship between ER, PR and Ki-67 levels. Improving knowledge of tumor biology and honing predictive tools for individualized treatment approaches depend on such information. With an eye toward understanding how hormone receptor status shapes proliferative activity, this study seeks to assess the association between ER and PR expression and Ki-67 levels in breast cancer patients to maximize treatment interventions and enhance the clinical outcomes for breast cancer patients by means of pattern and association identification.

Materials and Methods

Study Design and Setting

Conducted at the Department of Medical Oncology, Combined Military Hospital, Rawalpindi, a tertiary care hospital with superior diagnostic and therapeutic capabilities, this cross-sectional observational study took place over 6 months, from October 2024 to March 2025.

Sample Size and Sampling Technique

The trial had 180 participants in all who had been diagnosed with breast cancer. Convenient sampling was used to choose participants, therefore guaranteeing feasibility within the allocated resources and timescale.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Patients, female, with histologically confirmed breast cancer.
- Patients having biopsies or surgical resections with enough tissue for immunohistochemistry study.
- Patients showing up at CMH Rawalpindi during the study period.

Exclusion Criteria:

- Patients having past neoadjuvant radiation or chemotherapy.
- Poor tissue samples unfit for immunohistochemical analysis.
- Patients missing hormone receptor status or with insufficient medical information.

Collection of Data

Structured proformas were used for data collecting; these covered clinical presentation, demographic information and histological results. The pathology department archives of the hospital yielded tissue samples from individuals suffering with breast cancer.

Immunohistochemistry

Using immunohistochemistry staining on tissue slices formalin-fixed, paraffin-embedded, ER, PR and Ki-67 expression was assessed. Standard procedures were used including deparaffinization, antigen retrieval and primary antibody application for ER, PR and Ki-67. Staining was seen with secondary antibodies and chromogen [11].

Interpretation of Results

1.ER and PR Status: Tumor cell proportion of positively stained determined scoring. Positive tumors were those having ≥1% nuclear staining.

2.Ki-67 Index: The fraction of tumor cells with nuclear staining computed the Ki-67 proliferation

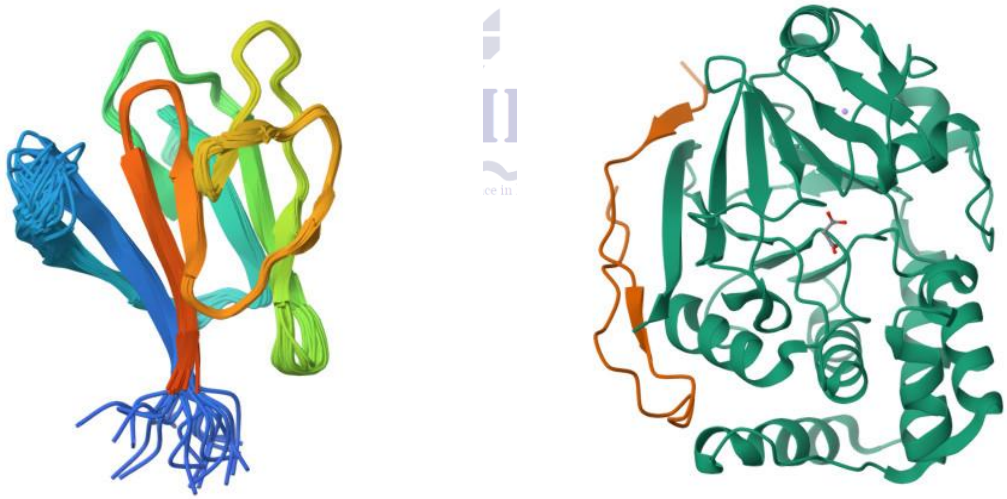
index. Differentiating between high and low proliferative activities was accomplished with a cut-off value of 20%.

Statistical Analysis

SPSS program version 25 was used to examine data. Clinically and demographic data were compiled using descriptive statistics. Depending on data normality, relationship between ER/PR status and Ki-67 levels was evaluated using ANOVA and multivariate regression analysis. We considered statistically significant values of $p < 0.05$.

Results

Expressed during all active phases of the cell cycle except G0, Ki-67 is a nuclear protein that marks cellular proliferation most importantly. In our study, evaluating tumor aggressiveness and predictive outcomes in breast cancer patients depends much on Ki-67. Immunohistochemistry helps one to understand the proliferative activity of tumor cells by means of expression. While low levels imply slower-growing malignancies and better results, high Ki-67 levels are linked with fast tumor development, poor prognosis, and the requirement of intensive therapy. The 3D molecular structures of the Ki-67 protein as found with two separate monoclonal antibodies, 5J28 and 1R21 is shown in Figure 1. By stressing the particular epitopes these antibodies target, the structural visualization helps one understand their binding specificities. These models underline in the framework of our research the molecular foundation for Ki-67 detection in breast cancer tissues, which is essential to evaluate tumor proliferative activity. By means of their compatibility with immunohistochemical techniques, these structures can assist validate the choice of antibody, therefore ensuring correct evaluation of Ki-67 expression as a prognostic and predictive marker in breast cancer patients (Figure 1).



a) b)

Figure 1: Ki-67 Protein Structures Visualized Using 5J28 and 1R21 Antibody Models

a: 3D Molecular Structure of Ki-67 Protein Using 1R21 Monoclonal Antibody

b: 3D Molecular Structure of Ki-67 Protein Using 5J28 Monoclonal Antibody

Comprising 180 breast cancer patients with the mean age of 48.3 ± 7.8 years, this study population had typical tumor size of 3.2 ± 1.4 cm; most tumors fell into Grade 3 (47.8%), followed by Grade 2 (36.1%) and Grade 1 (16.1%). Menopausal status was equal; 48.9% pre-menopausal and 51.1% post-menopausal patients made up the mix. Of all the malignancies, most were either PR positive (60.0%) or ER positive (63.3%). With the high Ki-67 proliferation index, more over half of the cases, 53.3% showed marked cellular proliferation and possible aggressive tumor activity. Important for knowledge of prognosis and treatment strategy modification, this demographic and clinical profile emphasized the varied tumor

biology and hormone receptor status of the investigated group (Table 1).

Table 1: Demographic and Clinical Characteristics

Characteristic	Mean ± SD / n (%)
Age (years)	48.3 ± 7.8
Tumor Size (cm)	3.2 ± 1.4
Histological Grade	
Grade 1	29 (16.1)
Grade 2	65 (36.1)
Grade 3	86 (47.8)
Menopausal Status	
Pre-menopausal	88 (48.9)
Post-menopausal	92 (51.1)
ER Positive	114 (63.3)
PR Positive	108 (60.0)
Ki-67 High	96 (53.3)

The Ki-67 index distribution among several statuses including ER, PR and menopausal categories indicated that with ER-negative and PR-negative groups showed notably higher Ki-67 High percentages (72.7 and 66.2%, respectively), the bar heights showed percentage values of "Ki-67 High" and "Ki-67 Low" values. On the other hand, ER-positive and PR-positive groups had rather lower Ki-67 High percentages, implying less aggressive tumor behavior. Overall the proliferative activity overlaid the high Ki-67 percentages. Including a secondary y-axis highlights this pattern, especially the higher proliferative index in post-menopausal patients relative to pre-menopausal ones. By clearly highlighting the relationships between hormone receptor status, menopausal status and proliferative activity, this complete depiction stratified the breast cancer prognosis and guide therapy (Figure 2).

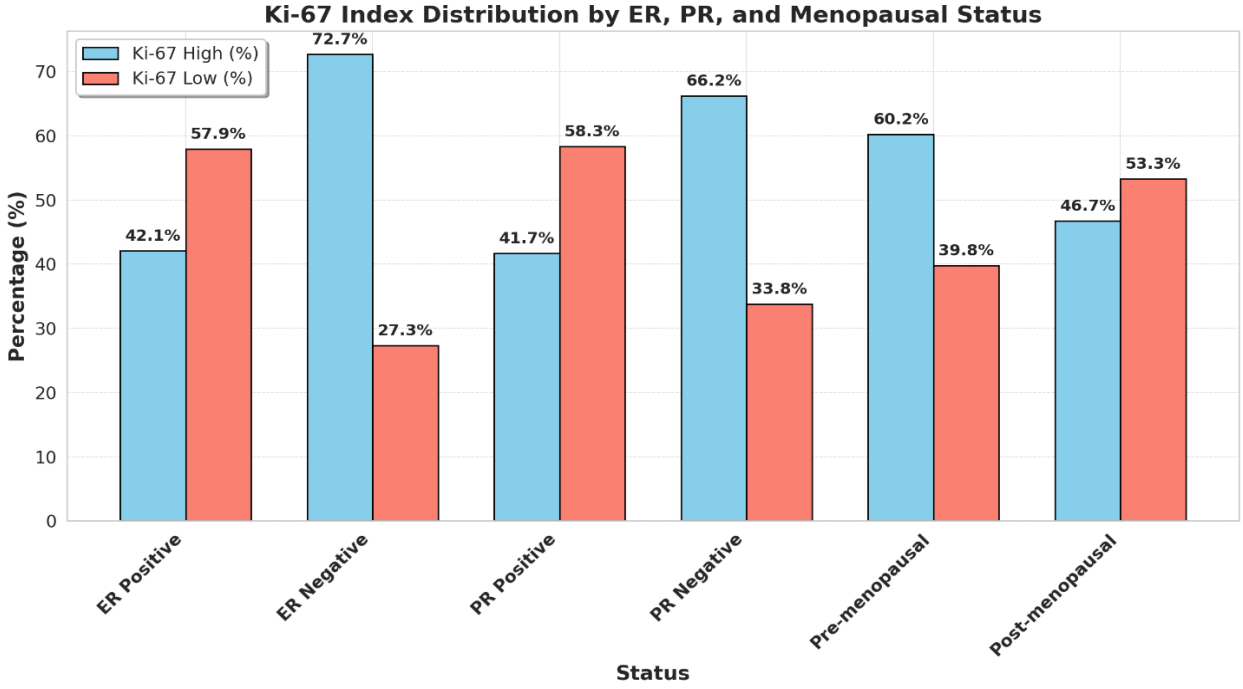


Figure 2: Ki-67 Index Distribution Based on ER, PR, and Menopausal Status

In breast cancer patients the notable variations in Ki-67 levels depending on hormone receptor status and menopausal state was recorded. Comparatively to ER-positive and PR-positive groups (23.4 ± 8.7 and 22.1 ± 7.9, respectively), ER-negative and PR-negative groups showed considerably higher mean Ki-67 percentages (45.6 ± 12.3 and 44.3 ± 10.8, respectively). With p-values 0.01 indicating statistical relevance, proportion of patients with elevated Ki-67 levels was also notably higher in ER-negative (72.7%) and PR-negative (66.2%) groups than in their positive counterparts (42.1%). Pre-menopausal patients had somewhat higher mean Ki-67 level (38.7 ± 9.8) and larger proportion of high Ki-67 cases (60.2%) than post-menopausal patients (34.6 ± 8.4, 46.7%), with p-values of 0.03. These results highlighted the link among hormone receptor status, menopausal status and tumor proliferative activity, therefore supporting the importance of these elements in prognosis and therapy planning (Table 2).

Table 2: Hormonal Receptor Status, Menopausal Status, and Ki-67 Levels with p-values

Category	Mean Ki-67 (%)	High Ki-67 n (%)	Low Ki-67 n (%)	p-value
ER Positive	23.4 ± 8.7	48 (42.1)	66 (57.9)	<0.01
ER Negative	45.6 ± 12.3	48 (72.7)	18 (27.3)	<0.01
PR Positive	22.1 ± 7.9	45 (41.7)	63 (58.3)	<0.01
PR Negative	44.3 ± 10.8	51 (66.2)	26 (33.8)	<0.01
Pre-menopausal	38.7 ± 9.8	53 (60.2)	35 (39.8)	0.03
Post-menopausal	34.6 ± 8.4	43 (46.7)	49 (53.3)	0.03

With notable variations across all grades, a strong correlation between histological grade and Ki-67 levels in breast cancer patients (p-value 0.01) was seen. Grade 3 tumors showed the greatest mean Ki-67 level (49.5 ± 11.2) and the highest proportion of patients with high Ki-67 levels (75.4%), indicating aggressive tumor behavior. Reflecting reduced proliferative activity, Grade 1 tumors had the lowest mean Ki-67 level (12.3 ± 5.6) and smaller proportion of patients with high Ki-67 levels (41.4%), with the mean Ki-67 score of 27.8 ± 8.1 and 58.5% of patients categorized as high Ki-67, grade 2 tumors displayed intermediate proliferative activity. These results underlined the link between higher histological grade and more tumor proliferation, supporting Ki-67's function as a predictive biomarker for tumor aggressiveness and treatment strategy (Table 3).

Table 3: Histological Grade and Ki-67 Levels with p-values

Histological Grade	Mean Ki-67 (%)	High Ki-67 n (%)	Low Ki-67 n (%)	p-value
Grade 1	12.3 ± 5.6	12 (41.4)	17 (58.6)	<0.01
Grade 2	27.8 ± 8.1	38 (58.5)	27 (41.5)	<0.01
Grade 3	49.5 ± 11.2	46 (75.4)	15 (24.6)	<0.01

Key determinants of high Ki-67 levels suggested increased tumor growth rates in breast cancer patients, as seen using multivariate regression analysis. With an odds ratio (OR) of 2.8 (95% CI: 1.9-3.7, p<0.01), ER-negative status showed the highest connection with high Ki-67, stressing a nearly threefold higher chance of high proliferative activity compared to ER-positive tumors. Likewise, high Ki-67 levels (OR: 2.5, 95% CI: 1.8-3.4, p<0.01) were powerfully correlated with negative PR-negative status. With an OR of 2.1 (95% CI: 1.5–2.9, p=0.01), higher tumor size (>3 cm) was also significant predictor showing that bigger tumors are more likely to show strong proliferation. Though statistically significant (OR: 1.6, 95% CI: 1.1-2.3, p=0.02), post-menopausal status displayed a lesser link between hormone receptor status and tumor size. These results highlighted the need of hormone receptor status and tumor properties in determining tumor aggressiveness, hence guiding the categorization of patients for directed treatments and prognosis evaluation (Table 4).

Table 4: Multivariate Regression Analysis of Predictors of High Ki-67

Variable	Odds Ratio (95% CI)	p-value
ER Negative	2.8 (1.9-3.7)	<0.01
PR Negative	2.5 (1.8-3.4)	<0.01
Post-menopausal Status	1.6 (1.1-2.3)	0.02
Larger Tumor Size (>3 cm)	2.1 (1.5-2.9)	<0.01

Discussion

In this study, we examined in breast cancer patients, the relationships between hormone receptor status (ER and PR), menopausal state and histological grade and Ki-67 levels. Our results showed that tumors with ER-negative and PR-negative Ki-67 values displayed far more aggressive proliferative activity. Likewise, elevated Ki-67 levels were highly correlated with tumors of higher histological grade (Grade 3) and greater size (>3 cm). These findings coincide with earlier research stressing the predictive value of Ki-67 in breast cancer [12].

Ki-67 Levels and Hormonal Receptor status, our study showed that ER-negative tumors had a mean Ki-67 level (45.6 ± 12.3) higher than ER-positive tumors (23.4 ± 8.7). This result is in line with the research of de Soliman and Yussif et al. (2016) [13], who noted that ER-negative breast tumors are more likely to show high Ki-67 indices, therefore indicating their aggressive character and poor prognosis. In our group, similarly, PR-negative tumors displayed higher Ki-67 levels than PR-positive tumors (44.3 ± 10.8 vs. 22.1 ± 7.9, p<0.01). These findings coincided with research by Cuzick et al. (2011), which underlined how lower hormone responsiveness and higher cell proliferation corresponded with PR negative [14].

Pre-menopausal patients in our study showed rather higher mean Ki-67 levels (38.7 ± 9.8) than post-menopausal patients (34.6 ± 8.4). Rajarajan et al. (2021) also observed similar results, hypothesizing that pre-menopausal women's hormonal oscillations would support more proliferative activity in breast cancers [15]. Some researched, like by Inwald et al. (2013), contend, however, that menopausal state may not independently predict Ki-67 levels and should be considered in concert with other tumor features [12].

In our investigation, higher Ki-67 levels and stronger histological grades showed a clear link. With their mean Ki-67 level of 49.5 ± 11.2 and highest proportion of high Ki-67 patients (75.4%, p<0.01), grade 3 tumors stood out. These findings are consistent with the Aman et al. (2019) study, which found that highly proliferative indices are more likely to show in poorly differentiated (Grade 3) tumors [16].

Tumor Size and Ki-67 Values Larger tumors (>3 cm) with an OR of 2.1 for high proliferation (p<0.01) emerged as a major predictor of high Ki-67 levels in our population. This outcome is consistent with the results of Soliman and Yussif et al. (2016) [13], who showed that bigger tumor size corresponds with higher Ki-67 expression, maybe due to advanced tumor growth and higher cellular turnover.

Our results highlighted the relevance of Ki-67 as a biomarker for prognostic classification and treatment planning in breast cancer. Given hormonal treatments are less effective in this subset, greater Ki-67 levels in ER-negative and PR-negative tumors imply these individuals would benefit from strong chemotherapy programs. Moreover, strong correlation between Ki-67 and histological grade helps to justify its use in improving treatment choices, especially in patients with high-grade malignancies. Kang et al. (2019) advises routine screening of Ki-67 alongside ER, PR and HER2 status to be considered standard practice in breast cancer management in view of these findings [17].

Our study has some limitations because we used single-center cohort that may restrict the generalizability of our results to more general groups. Furthermore, as noted by suggestions for standardization by different researchers, the semi-quantitative character of Ki-67 measurement in immunohistochemistry brings variability [18-20]. To confirm our findings and investigate other factors including molecular subtypes and genetic markers, more multicenter research using consistent procedures are required.

Our work creates opportunities for more investigation on the interaction among tumor biology, Ki-67, and hormone receptor state. Deeper understanding of Ki-67's clinical relevance would come from investigating its predictive value in more recent treatment

paradigms including immune checkpoint inhibitors or CDK4/6 inhibitors.

Conclusion

The important function of Ki-67 as a biomarker for tumor growth in breast cancer is underlined in this study together with its strong association with histological grade, menopausal status and hormone receptor Status. The greatly elevated Ki-67 levels seen in Grade 3 tumors, ER-negative and PR-negative cancers highlighted their aggressive biological behavior and poor prognosis. Further underlining its importance in risk stratification, pre-menopausal condition and greater tumor size were found to be major predictors of raised Ki-67. These results supported the regular use of Ki-67 measurement together with ER, PR and HER2 status in clinical practice to improve prognosis and advise individualized therapy regimens.

Conflict of Interest

None.

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