GLAND SURGERY

# EXPRESSION OF KI-67 AND ITS CORRELATION WITH ESTROGEN RECEPTOR, PROGESTERONE RECEPTOR, AND HER2/NEU STATUS IN BREAST CARCINOMA: A CROSS-SECTIONAL IMMUNOHISTOCHEMICAL STUDY

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## Abstract

### Background

Ki-67 is a well-established marker of cellular proliferation and has emerged as an important prognostic biomarker in breast carcinoma. Its relationship with hormone receptor status and HER2/neu expression remains variable across populations.

### Objective

To evaluate Ki-67 expression in breast carcinoma and determine its association with estrogen receptor (ER), progesterone receptor (PR), HER2/neu status, and clinicopathological parameters.

### Materials and Methods

This hospital-based cross-sectional study included 52 histopathologically confirmed breast carcinoma cases. Immunohistochemistry was performed for Ki-67, ER, PR, and HER2/neu. Associations between Ki-67 expression and clinicopathological variables were analyzed using Chi-square and logistic regression analyses.

### Results

Ki-67 positivity was observed in 29 of 52 cases (55.8%). Among Ki-67-positive tumors, high proliferative activity (>20%) was identified in 48.3% of cases. Ki-67 expression demonstrated a significant positive association with higher tumor grade (p=0.023) and significant inverse associations with ER expression (p=0.024) and PR expression (p=0.038). No significant correlations were observed with age, tumor size, lymphovascular invasion, lymph node status, combined ER/PR status, or HER2/neu expression. Univariate logistic regression revealed that Grade III tumors (OR=4.09, 95% CI: 1.25–13.36) and ER-negative tumors (OR=4.08, 95% CI: 1.27–13.13) were significantly associated with Ki-67 positivity.

### Conclusion

Ki-67 expression is significantly associated with higher histological grade and hormone receptor negativity in breast carcinoma. Routine assessment of Ki-67 alongside ER, PR, and HER2/neu may enhance prognostic stratification and facilitate individualized therapeutic decision-making.

**MeSH Keywords:** Breast Neoplasms, Ki-67 Antigen, Immunohistochemistry, Estrogen Receptors, Progesterone Receptors, Prognosis

## 1. Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and continues to be a major contributor to cancer-related morbidity and mortality. According to recent global cancer statistics, breast cancer accounts for more than 2.3 million newly diagnosed cases annually and has surpassed lung cancer as the most commonly diagnosed cancer worldwide.[1] It represents approximately one-quarter of all female cancer diagnoses and is responsible for an estimated 670,000–764,000 deaths each year globally. Despite significant advances in early detection, screening programs, diagnostic technologies, and targeted therapeutic strategies, breast cancer remains a substantial public health challenge. The disease exhibits considerable molecular and clinical heterogeneity, resulting in diverse treatment responses and variable patient outcomes. Furthermore, the global burden of breast cancer is expected to increase markedly, with annual incidence projected to exceed 3.5 million cases by 2050, underscoring the urgent need for improved prevention, diagnostic, and therapeutic approaches.[1-2]

Breast carcinoma is a biologically diverse disease characterized by distinct molecular subtypes, histopathological features, therapeutic responses, and prognostic profiles. The routine assessment of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2/neu) has revolutionized breast cancer classification and treatment selection. Hormone receptor-positive tumors generally demonstrate favorable outcomes and responsiveness to endocrine therapy, whereas HER2-positive tumors exhibit aggressive biological behavior but benefit from anti-HER2 targeted therapies.[3-4]

In addition to receptor profiling, proliferation markers have emerged as important determinants of tumor aggressiveness. Among these, Ki-67, a nuclear non-histone protein expressed during active phases of the cell cycle, is widely used to evaluate proliferative activity. Elevated Ki-67 expression has been associated with increased tumor growth, higher histological grade, lymph node metastasis, reduced survival, and resistance to certain therapeutic interventions. Consequently, Ki-67 has gained considerable attention as both a prognostic and predictive biomarker.[5]

International consensus guidelines increasingly recognize the clinical utility of Ki-67, particularly in differentiating luminal A from luminal B breast cancers and in guiding adjuvant treatment decisions. Nevertheless, variability in scoring systems, lack of universally accepted cut-off values, and inter-observer differences continue to challenge its routine implementation in clinical practice.[6]

Several studies have reported inverse associations between Ki-67 expression and hormone receptor positivity, while positive correlations have been observed with HER2 overexpression and high-grade tumors.[5,7] However, the strength and consistency of these relationships vary across populations and healthcare settings. Data from North Indian populations remain limited, particularly regarding the interaction between Ki-67 and established prognostic markers.

The present study was undertaken to evaluate Ki-67 expression in breast carcinoma and investigate its relationship with ER, PR, HER2/neu status, histological grade, tumor size, lymphovascular invasion, and nodal metastasis. Improved understanding of these associations may enhance prognostic stratification and support individualized treatment planning in breast cancer patients.

## 2. Materials And Methods

### Study Design and Setting

This hospital-based cross-sectional observational study was conducted in the Department of Pathology, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India, from July 2024 to December 2025.

### Ethical Considerations

Institutional Ethics Committee approval was obtained prior to study initiation (SGRD/IEC/2024-388). Patient confidentiality was maintained throughout the study, and all analyses were performed using



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anonymized data.

**Study Population**

Consecutive histopathologically confirmed cases of breast carcinoma received as mastectomy specimens during the study period were included.

**Eligibility Criteria**

**Inclusion criteria:** Histopathologically proven breast carcinoma, Availability of ER, PR, and HER2/neu immunohistochemical status, Adequate formalin-fixed paraffin-embedded tissue blocks.

**Exclusion criteria**: Patients who had received neoadjuvant chemotherapy, Lumpectomy specimens, Specimens showing significant autolytic changes.

**Sample Size**

A total of 52 eligible breast carcinoma cases were included in the final analysis.

**Histopathological Evaluation**

Representative tumor sections were stained with hematoxylin and eosin. Histological grading was performed according to the Nottingham modification of the Bloom–Richardson grading system based on tubule formation, nuclear pleomorphism, and mitotic activity.

**Immunohistochemistry**

Immunohistochemical staining for Ki-67 was performed on formalin-fixed paraffin-embedded sections using a rabbit monoclonal antibody. ER and PR expression were evaluated using the Allred scoring system. HER2/neu status was interpreted according to ASCO/CAP recommendations.

**Ki-67 Assessment**

Nuclear staining was considered positive. Tumors were categorized according to the percentage of positively stained tumor nuclei:
Low proliferation: 1–10%
Intermediate proliferation: 11–20%
High proliferation: >20%

**Outcome Measures**

Primary outcome:
Correlation of Ki-67 expression with ER, PR, and HER2/neu status.
Secondary outcomes:
Correlation of Ki-67 with histological grade, tumor size, lymphovascular invasion, and lymph node status.

**Statistical Analysis**

Statistical analyses were performed using Python version 3.10. Data management and descriptive statistics were conducted using Pandas (v1.5.3) and NumPy libraries. Continuous variables were summarized as mean ± standard deviation or median (IQR), while categorical variables were expressed as frequencies and percentages. Associations between categorical variables were assessed using Chi-square or Fisher's exact test. A p-value $<0.05$ was considered statistically significant.

## 3. Results



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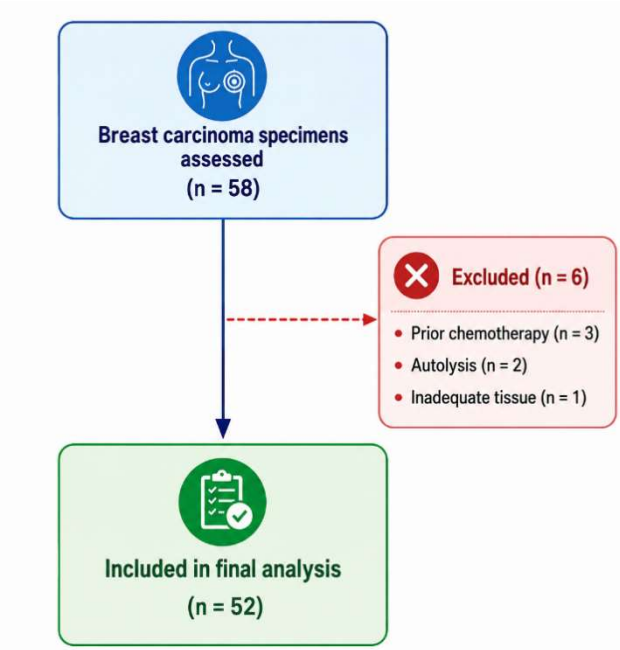


**FIGURE 1: FLOW DIAGRAM OF PATIENT SELECTION (STROBE FLOWCHART)**

**Results**

Of the 58 breast carcinoma specimens initially assessed, 6 were excluded due to prior chemotherapy (n = 3), autolysis (n = 2), or inadequate tissue samples (n = 1). Consequently, 52 eligible specimens were included in the final analysis (Figure 1). The study included 52 female patients with breast carcinoma, with a mean age of 54.4 ± 13.8 years and a median age of 54.5 years (IQR: 42–67), indicating that most patients were middle-aged to elderly. The age of participants ranged from 29 to 80 years. Histopathological grading revealed that Grade III tumors were more common, accounting for 61.5% of cases, while Grade II tumors comprised 38.5%. Regarding nodal involvement, 57.7% of patients had lymph node metastasis (N1–N3), whereas 42.3% were node-negative (N0). Among node-positive cases, N2 disease was the most frequent (26.9%), followed by N1 (21.2%) and N3 (9.6%), suggesting a substantial burden of advanced regional disease (Table 1).

**Table 1. Baseline Clinicopathological Characteristics of the Study Population (N = 52)**

| Variable | Value |
|---|---|
| Age, mean ± SD (years) | 54.44±13.8 |
| Median age (IQR) | 54.5 (42–67) |
| Age range (years) | 29–80 |
| Total Females | 52 (100%) |
| Right Breast involved | 31(59.6%) |
| Left breast involved | 21(40.4%) |
| Grade II tumors | 20 (38.5%) |
| Grade III tumors | 32 (61.5%) |
| Node-negative (N0) | 22 (42.3%) |
| Node-positive (N1–N3) | 30 (57.7%) |
| N1 disease | 11 (21.2%) |
| N2 disease | 14 (26.9%) |
| N3 disease | 5 (9.6%) |

**Data presented as n (%) unless otherwise specified.**



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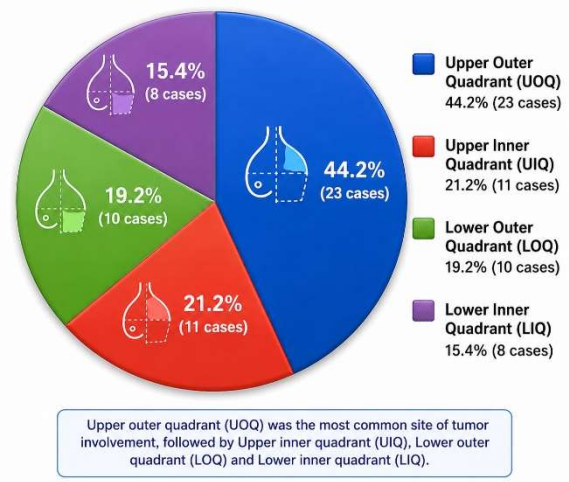


**Figure 2: Distribution of Tumor Location (n=52)**

The upper outer quadrant (UOQ) was the most common site of breast tumor involvement, accounting for 44.2% (23/52) of cases, followed by the upper inner quadrant (UIQ) at 21.2% (11/52). Lower outer quadrant (LOQ) and lower inner quadrant (LIQ) involvement were observed in 19.2% (10/52) and 15.4% (8/52) of cases, respectively (Figure 2).

Immunohistochemical analysis demonstrated variable expression of hormonal and growth factor receptors among the study population. Estrogen receptor (ER) positivity was observed in 42.3% of cases (Figure 4a), while progesterone receptor (PR) positivity was identified in 32.7%, indicating that a substantial proportion of tumors lacked hormone receptor expression (Figure 4b). HER2/neu overexpression was present in 26.9% of patients, whereas 73.1% were HER2-negative (Figure 4c). The combined receptor profile showed that 32.7% of tumors exhibited the ER+/PR+ phenotype, reflecting potential responsiveness to endocrine therapy. In contrast, 57.7% of cases were ER−/PR−, suggesting a predominance of hormone receptor–negative tumors, which are generally associated with more aggressive biological behavior and limited endocrine treatment options (Table 2).

**Table 2. Immunohistochemical Marker Expression Profile**

| Marker | Positive, n (%) | Negative, n (%) |
|---|---|---|
| Estrogen Receptor (ER) | 22 (42.3%) | 30 (57.7%) |
| Progesterone Receptor (PR) | 17 (32.7%) | 35 (67.3%) |
| HER2/neu | 14 (26.9%) | 38 (73.1%) |
| ER+/PR+ phenotype | 17 (32.7%) | — |
| ER+/PR− phenotype | 5 (9.6%) | — |
| ER−/PR− phenotype | 30 (57.7%) | — |

The Ki-67 proliferation index showed considerable variation among the studied tumors. The mean Ki-67 value was 16.5% ± 23.8%, while the median value was 5%, indicating that most tumors had relatively low proliferative activity, with a smaller number showing markedly elevated levels (Figure 5). The interquartile range (0–27.5%) suggests substantial variability in cellular proliferation across cases. Ki-67 values ranged from 0% to 75%, reflecting the presence of both low- and high-proliferative tumors within the study population. These findings highlight the heterogeneity of tumor growth potential among breast cancer patients (Table 3).

**Table 3. Proliferative Activity Assessed by Ki-67 Index**

| Parameter | Value |
|---|---|
| Mean Ki-67 (%) | 16.5 ± 23.8 |
| Median Ki-67 (%) | 5.0 |
| Interquartile range | 0–27.5 |



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| | |
|---|---|
| Range | 0–75 |
| **Ki-67 Status** | **n (%)** |
| Positive | 29 (55.8) |
| Negative | 23 (44.2) |
| **Ki-67 Category** | **n (%)** |
| Low (1–10%) | 13 (44.8) |
| Intermediate (11–20%) | 2 (6.9) |
| High (>20%) | 14 (48.3) |

Ki-67 expression was observed in 29 of 52 cases (55.8%), whereas 23 cases (44.2%) were negative for Ki-67 immunostaining. Among the Ki-67-positive tumors, high proliferative activity (>20% positive nuclei) was identified in 14 cases (48.3%), low proliferative activity (1–10%) in 13 cases (44.8%), and intermediate proliferative activity (11–20%) in 2 cases (6.9%). The percentage of positive tumor cells ranged from 3% to 70%, demonstrating substantial heterogeneity in proliferative behavior across breast carcinomas.

The association between tumor grade and receptor status revealed significant differences for hormonal markers. Estrogen receptor (ER) positivity was significantly more frequent in Grade II tumors compared with Grade III tumors (65.0% vs. 28.1%, p = 0.020). Similarly, progesterone receptor (PR) expression was higher in Grade II tumors than in Grade III tumors (55.0% vs. 18.8%, p = 0.016). These findings indicate that lower-grade tumors are more likely to retain hormone receptor expression. Although HER2/neu positivity was more common in Grade III tumors (34.4%) than Grade II tumors (15.0%), the difference was not statistically significant (p = 0.226). This suggests a relationship between higher tumor grade and loss of hormonal receptor expression (Table 4).

**Table 4. Association Between Tumor Grade and Hormone Receptor Status**

| Marker | Grade II Positive n (%) | Grade III Positive n (%) | p-value |
|---|---|---|---|
| ER | 13/20 (65.0%) | 9/32 (28.1%) | 0.020 |
| PR | 11/20 (55.0%) | 6/32 (18.8%) | 0.016 |
| HER2/neu | 3/20 (15.0%) | 11/32 (34.4%) | 0.226 |

**Statistical test:** Chi-square test.

The summary of key findings in table 5 indicates that Grade III was the predominant histological grade, accounting for 61.5% of all cases, suggesting a high proportion of poorly differentiated tumors in the study population. Hormone receptor positivity was observed in 42.3% of cases for ER and 32.7% for PR, while HER2 positivity was detected in 26.9% of patients. More than half of the patients (57.7%) had lymph node involvement, reflecting a considerable burden of advanced disease. The ER−/PR− phenotype was also present in 57.7% of cases. Furthermore, significant associations were identified between tumor grade and both ER status (p = 0.020) and PR status (p=0.016), indicating that hormone receptor expression decreases with increasing tumor grade.

Multivariate logistic regression analysis was performed to identify independent predictors of Ki-67 positivity. After adjustment for hormone receptor status and tumor grade, Grade III tumors showed approximately three-fold higher odds of Ki-67 positivity compared with Grade II tumors (AOR = 2.96, 95% CI: 0.83–10.58, p = 0.095). ER-negative tumors demonstrated 3.13-fold increased odds of Ki-67 positivity (95% CI: 0.42–23.44, p = 0.267), whereas PR status was not independently associated with Ki-67 expression (AOR = 0.94, 95% CI: 0.11–7.94, p = 0.952). Although none of the variables remained independently significant after adjustment, the overall regression model was statistically significant (Likelihood Ratio Test p = 0.033), suggesting that tumor grade and hormone receptor status collectively contribute to Ki-67 expression. Univariate logistic regression analysis identified higher histological grade and ER negativity as significant predictors of Ki-67 positivity. Grade III tumors showed



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approximately four-fold increased odds of Ki-67 expression compared with Grade II tumors (OR = 4.09, p = 0.020), while ER-negative tumors demonstrated a similar four-fold increase in the likelihood of Ki-67 positivity (OR = 4.08, p = 0.018). These findings suggest that increased proliferative activity is strongly associated with poorly differentiated and hormone receptor-negative breast carcinomas (Table 5).

**Table 5. Multivariate and Univariate Logistic Regression Analysis for Predictors of Ki-67 Positivity (n= 52)**

| Variable | Adjusted Odds Ratio (AOR) | 95% CI | p-value |
|---|---|---|---|
| **Multivariate Logistic Regression Analysis** | | | |
| Grade III vs Grade II | 2.96 | 0.83 – 10.58 | 0.095 |
| ER Negative vs ER Positive | 3.13 | 0.42 – 23.44 | 0.267 |
| PR Negative vs PR Positive | 0.94 | 0.11 – 7.94 | 0.952 |
| Model statistics: Pseudo $R^2$ = 0.123; Likelihood Ratio Test p = 0.033. | | | |
| **Univariate Logistic Regression Analysis** | | | |
| Grade III vs Grade II | 4.09 | 1.25–13.36 | 0.020 |
| ER Negative vs ER Positive | 4.08 | 1.27–13.13 | 0.018 |

**Table 6. Summary of Ki-67 Correlations with Clinicopathological Parameters**

| Variable | p-value | Interpretation |
|---|---|---|
| Age | 0.368 | NS |
| Tumor Size | 0.905 | NS |
| Tumor Grade | 0.023 | Significant |
| Lymphovascular Invasion | 0.327 | NS |
| Lymph Node Status | 0.344 | NS |
| ER Expression | 0.024 | Significant |
| PR Expression | 0.038 | Significant |
| Combined ER/PR | 0.056 | NS |
| HER2/neu | 0.348 | NS |

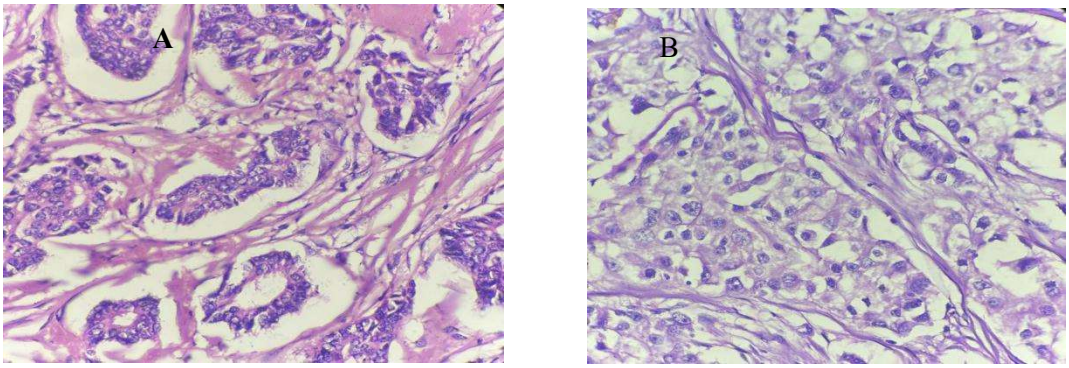


**Figure 3. Representative photomicrographs of invasive ductal carcinoma, no special type (NST), showing histological grades II and III (Hematoxylin & Eosin stain, ×400).**
(A) Grade II invasive ductal carcinoma demonstrating moderate tubule formation, moderate nuclear




B C A

pleomorphism, and intermediate mitotic activity.
(B) Grade III invasive ductal carcinoma showing marked nuclear pleomorphism, minimal tubule formation, and increased mitotic figures, consistent with a poorly differentiated tumor.

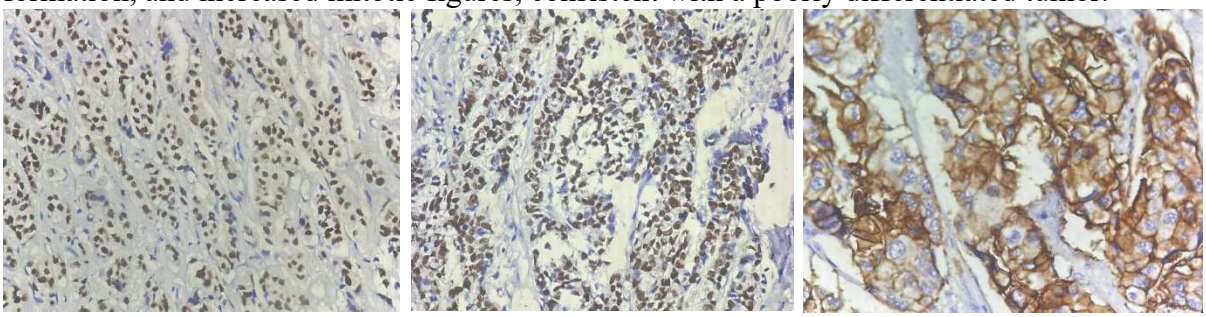

**Figure 4. Immunohistochemical photomicrographs demonstrating strong receptor expression in breast carcinoma (×400).**
(A) Strong nuclear positivity for estrogen receptor (ER).
(B) Strong nuclear positivity for progesterone receptor (PR).
(C) Strong complete circumferential membranous staining (3+) for HER2/neu.

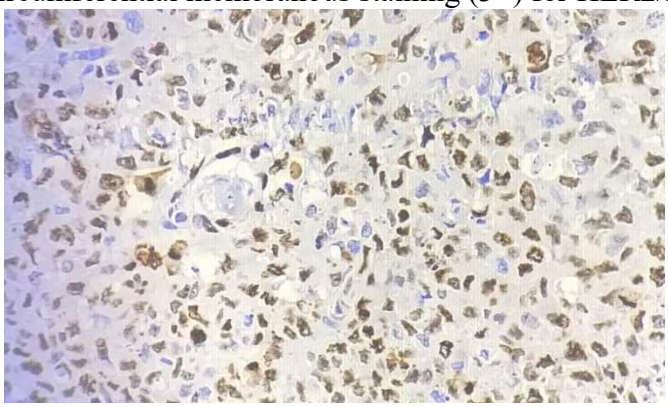

**Figure 5. Immunohistochemical photomicrograph showing high Ki-67 proliferative index in invasive ductal carcinoma (×400).**
Tumor cells exhibit strong nuclear immunoreactivity for Ki-67, indicating high proliferative activity and aggressive biological behavior.

## 4. Discussion

The present study evaluated the expression of Ki-67 and its association with established clinicopathological and immunohistochemical parameters in invasive breast carcinoma. Breast cancer remains the most common malignancy among women, and the identification of reliable prognostic biomarkers is essential for risk stratification and therapeutic decision-making.
The mean age of patients in the present study was 54.44 years, with the majority of cases occurring between 40 and 70 years. Similar age distributions have been reported by Sharma et al.[8] and Parshad et al.[9] who observed a predominance of breast carcinoma among postmenopausal women. The right breast was more frequently involved than the left, consistent with findings of Kakkar et al.[10] and Memon et al.[11] The upper outer quadrant represented the most common tumor location, which may be attributed to the greater volume of breast tissue present in this region and has been documented in several previous studies.
Most tumors measured between 2 and 5 cm, in agreement with reports by Mahdi et al.[12] and Kapoor et al.[13] Histologically, Grade III tumors predominated in our series, indicating a relatively aggressive disease profile. Similar observations have been reported by Mahdi et al.,[12]; Zhang et al.[14] and Hashmi et al.[15] who documented a high prevalence of poorly differentiated tumors. Lymphovascular



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invasion and lymph node metastasis were observed in more than half of the cases, reflecting the advanced pathological stage at presentation commonly encountered in developing countries.

Hormone receptor analysis revealed ER positivity in 42.3% and PR positivity in 32.7% of cases, findings comparable to those reported by Kanwar et al. [16] The predominance of ER−/PR− tumors in the present study is also consistent with observations from Indian populations, suggesting a relatively high burden of biologically aggressive, hormone-independent tumors. Furthermore, ER and PR expression showed a significant inverse association with histological grade, indicating progressive loss of hormone receptor expression with increasing tumor dedifferentiation. Similar findings have been documented by Roshed et al.[17] and Shrestha et al. [18] supporting the established relationship between receptor negativity and aggressive tumor behavior.

HER2/neu overexpression was identified in 26.9% of cases, a frequency comparable to that reported by Shokouh et al.[7] Although most HER2-positive tumors belonged to Grade III, the association between HER2 expression and tumor grade did not reach statistical significance. Similar observations have been reported by Dodiya et al. [19] and Shrestha et al.[18] although other investigators have demonstrated a positive relationship between HER2 overexpression and higher tumor grade.

Nearly half of the Ki-67-positive tumors (48.3%) demonstrated high proliferative activity (>20%), suggesting a substantial proportion of biologically aggressive tumors. Furthermore, Ki-67 expression showed a statistically significant positive association with higher histological grade and significant inverse associations with ER and PR expression. These findings support the concept that highly proliferative breast carcinomas tend to exhibit loss of hormone receptor expression and aggressive tumor biology. Ki-67 expression was observed in 55.8% of cases, which falls within the range reported in previous studies by Yan et al.[20] and Mahdi et al. [12]Variations in Ki-67 positivity across studies may be explained by differences in patient characteristics, tumor biology, and immunohistochemical cut-off values. No significant association was found between Ki-67 expression and patient age, tumor size, lymph node status, or lymphovascular invasion, findings that are in agreement with studies by Baban et al.[21]; Gogoi et al.[22]; Patil [23] and Sandilya & Mamatha.[24]

A significant positive correlation was observed between Ki-67 expression and histological grade, with Grade III tumors demonstrating the highest proliferative activity. Similar results have been reported by Abubakr et al.[25] and Jogie et al. [26] confirming the value of Ki-67 as a marker of tumor aggressiveness. Additionally, Ki-67 showed a significant inverse correlation with ER and PR expression, indicating that hormone receptor-negative tumors possess greater proliferative potential. These findings are supported by Baban et al.[21] Al-Nuaimi et al.[27] and Nigam et al. [28] Although Ki-67 positivity was more frequent in ER−/PR− tumors and HER2-negative cases, no significant association was observed with combined hormone receptor status or HER2 expression.

Overall, the findings of the present study emphasize the clinical utility of Ki-67 as a proliferation marker in breast carcinoma. Its significant association with higher tumor grade and hormone receptor negativity suggests that Ki-67 can serve as a practical adjunct to routine histopathological evaluation, particularly in resource-constrained settings where advanced molecular profiling may not be readily available.

**Limitations**

The study was conducted at a single tertiary care center, which may limit the generalizability of the findings. The sample size was relatively small (n=52), potentially reducing statistical power for detecting weaker associations. Molecular subtyping and genomic profiling were not performed. Survival outcomes and treatment response data were unavailable, precluding assessment of prognostic impact. Variability in Ki-67 scoring remains a recognized limitation despite standardized assessment criteria.

## 5. Conclusion

Ki-67 expression was detected in more than half of breast carcinoma cases and demonstrated significant



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associations with higher histological grade and hormone receptor negativity. The inverse relationship between Ki-67 and ER/PR expression highlights the aggressive biological behavior of highly proliferative tumors. Although no significant associations were observed with age, tumor size, lymphovascular invasion, lymph node status, or HER2/neu expression, Ki-67 proved to be a valuable adjunct prognostic marker. Routine assessment of Ki-67 alongside ER, PR, and HER2/neu may improve risk stratification and aid therapeutic decision-making in breast carcinoma patients.

**Future Directions**

Larger multicenter prospective studies are needed to validate these findings. Integration of Ki-67 with molecular subtypes may improve prognostic stratification. Longitudinal studies evaluating disease-free and overall survival are warranted. Standardization of Ki-67 scoring and cut-off values should be emphasized to improve reproducibility. Future studies should explore the predictive value of Ki-67 in guiding targeted and personalized therapies.

**Conflict of Interest**

The authors declare no conflict of interest.

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