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Original Article

ASSOCIATION BETWEEN HISTOLOGIC GRADES AND Ki67 IN BREAST CANCER

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ABSTRACT:

Ki 67 is a key proliferative marker in breast cancer, often associated with tumor aggressiveness and grade. Despite its established role, the correlation between Ki 67 and histological grade remains inconsistent across studies. This study aimed to explore the association between Ki 67 expression and tumor grades in breast cancer patients. This was a cross-sectional study conducted at the Department of Medical Oncology, Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan over six months period (January 2024- June 2024). A sample of 78 breast cancer patients was included, divided into groups based on Ki 67 protein expression (Positive defined as >21% of positive cells). Histological grading was assessed by using the Elston-Ellis modification of Scarff-Bloom-Richardson grading system, while demographic and clinical data, including age, marital status, and BMI, were collected. High Ki-67 expression was observed predominantly in Grade 3 tumors (n=33, 91.7%) compared to Grade 2 (n=52, 66.7%) and Grade 1 (n=3, 50%) (p-value =0.008). No significant associations were found between Ki 67 and other variables, including tumor size, axillary lymph node involvement, and TNM stage. This study demonstrates a strong association between higher Ki 67 and advanced histological grades in breast cancer, suggesting that Ki 67 may serve as a valuable prognostic indicator. However, further research is needed to clarify its role in predicting clinical outcomes across diverse patient populations.

Keywords: Ki-67, breast cancer, tumor grade, histological grade, prognosis, proliferation marker

INTRODUCTION

Breast cancer is the most common cancer in females, accounts for one-third of all malignancies affecting women, this cancer has high metastatic potential leading to high mortality in Pakistan. Early detection of this disease leads to improved outcomes and increased survival rate (1). In Asian countries, breast cancer is the most common with a peak age between 50 and 64 years (2). Urban females are more likely to develop breast carcinoma than rural women (3). There are vast clinical presentations and behaviors in different patients and racial populations due to genetic heterogeneity (4). Various clinicopathological factors help evaluate the prognosis and determine the appropriate management strategy in breast cancer patients (3-5). Factors include patient age, tumor size, lymph node status, histological type, grade, lymphovascular invasion, hormonal receptor status, human epidermal growth factor receptor 2 (HER2-neu) expression, and Ki-67 labeling index (3-5). Various molecular techniques are used to ascertain the molecular classification of breast carcinoma. The different molecular classification helps determine suitable, specific, and personalized targeted breast cancer treatments (6).

The Ki 67 antigen is a labile, non-histone nuclear protein identified in the early 1980's. Ki 67 regulates the cell cycle, associated with cellular proliferation, and is the most widely used proliferation marker (7). Previous studies have demonstrated that Ki-67 is expressed in all the active cell cycle phases, and not the resting G0 phase. Furthermore, Ki 67 has been used as a biomarker to assess the growth fraction of a given cell population (8, 9). Biology of breast cancer with high Ki 67 and grade looks similar but whether there is a definite and clear correlation between high grade and high Ki 67 and vice versa is not yet clear. Therefore, we wanted to clear this dilemma in this study. Immunostaining techniques that use monoclonal Ki 67 antibodies can assess the growth fraction of neoplastic cell populations (10). Although Ki 67 is an accepted prognostic marker, the role of the protein in the management of BC is unclear. At present, a standard operating procedure, or generally accepted cut-off definition, is not defined for Ki 67 (11).

Despite the observation that high Ki 67 levels are associated with worse prognosis and survival rates in patients with early breast cancer (12), the marker has not yet been implemented for routine clinical use. Due to insufficient quality assurance and existing data, The College of American Pathologists (CAP) has not advised the routine use of Ki 67 screening for the prognosis of patients with breast cancer (13). However, at the 2011 and 2013 St. Gallen Consensus Conferences, the use of Ki 67 screening was recommended for the analysis of cellular proliferation, and for identifying the differentiation status of luminal A and B tumors (14,15). A study by Nigam JS et al (16) reported the positive vs negative expression rate of Ki 67 in 39.13% vs 10.87% among patients for grade 2 breast cancer, respectively. Although there is still no consensus over an optimal cutoff value used to decide chemotherapy, several studies found that a high ki67 index is associated with a higher rate of relapse and worse breast cancer survival (17).

We anticipated that a high Ki 67 would correspond to a higher grade of breast cancer, and vice versa; however, some studies did not demonstrate a clear association between these parameters. Therefore, this study was conducted to examine the correlation between Ki 67 and breast cancer grade and to determine if any significant association exists between them.

METHODS

The study was designed as a cross-sectional analysis and conducted in the Department of Medical Oncology at Jinnah Postgraduate Medical Centre (JPMC) Hospital, Karachi, Pakistan, over a six-month period following approval from Ethical Review Committee. A sample size of 39 participants per group was estimated using the World Health Organization (WHO) sample size calculator, based on a frequency of grade 2 breast cancer among women with positive versus negative Ki 67 (39.13% vs. 10.87%) with a test power (1-β) of 90% and a 95% confidence Interval and Probability level of 5%. Non-probability consecutive sampling was employed to select participants.

Inclusion criteria consisted of female patients aged 18-75 with histologically confirmed breast cancer samples that included both grade and Ki 67 assessment. The study included all stages of breast cancer. The eligible women with breast cancer were recruited from the outpatient department. Study details were thoroughly explained to participants, and written informed consent was obtained. Baseline demographic and clinical data, including age, residence, education, ethnicity, marital status, height (measured using a wall-mounted scale in cm), weight (measured with a digital scale in light clothing), and Basal Metabolic Rate (BMI) (calculated as weight in kg divided by height in m^2), were recorded in a predesigned proforma. Each participant underwent breast cancer staging, immunohistochemical staining, and histological grading based on their histopathology report.

For immunohistochemical analysis, breast tissue samples were fixed in 10% formaldehyde for 24 hours, dehydrated, cleared, embedded in paraffin, and sectioned into 5 μm slices. The slices were baked at 65°C, dewaxed with xylene, hydrated with graded ethanol, treated with 3% hydrogen peroxide, and incubated at 37°C for 10 minutes to inactivate endogenous peroxidase. After antigen retrieval through microwave heating and blocking with normal goat serum, the slices were incubated at 4°C overnight with a primary Ki 67 antibody. The following day, biotin-labeled secondary antibody incubation was performed at room temperature for 30 minutes, followed by development with di-amino-benzidine, counterstaining with hematoxylin, differentiation with hydrochloric acid ethanol, dehydration with graded ethanol, clearing with xylene, and mounting with neutral gum for microscopic examination. Phosphate-buffered saline was used in place of the primary antibody as a negative control. The Ki 67 marker index was considered positive if 20% or more of the tumor cells exhibited nuclear staining, categorizing participants into Group A (Ki 67 positive) and Group B (Ki 67 negative). Histological grading of breast cancer was performed according to the Elston Ellis modification of Scarff-Bloom-Richardson grading system.

Statistical analyses

Data were entered and analyzed using Statistical Package for Social Sciences (SPSS version 24.0). Continuous variables such as age, age at menarche, tumor size, weight, height, BMI, and parity were summarized as mean ± Standard Deviation (SD) or median and Interquartile range (IQR), while categorical variables, including residential

status, marital status, educational status, ethnicity, tumor sidedness, histological type and grade, multifocal/multicentric status, axillary lymph node involvement, TNM stages, nuclear grade, hormone replacement therapy, use of oral contraceptives, family history of cancers, family history of breast cancer, menopausal status, and lactation, were presented as frequencies and percentages. The association between breast cancer grades and Ki 67 was assessed using the Chi-square or Fisher's Exact test, with an odds ratio greater than 1 considered significant. Potential confounders (age groups, BMI, age at menarche, tumor size, residential status, marital status, educational status, ethnicity, tumor sidedness, histological type, multifocal/multicentric status, axillary lymph node involvement, TNM stages, nuclear grade, hormone replacement therapy, use of oral contraceptives, family history of cancers, family history of breast cancer, and menopausal status) were controlled through stratification, and post-stratification analyses were conducted using the Chi-square or Fisher's Exact test. A p-value ≤ 0.05 and an OR >1 were considered statistically significant. Data visualization was performed using bar graphs and pie charts where appropriate.

RESULTS:

The mean age at the time of presentation for the participants was 47.3 years (±SD= 12.63). The mean age at menarche was 12.72 years (±SD=1.64). The age distribution of participants was as follows: <30 years, 9 (7.5%); 30-50 years, 75 (62.5%); 51-70 years, 34 (28.3%); and >70 years, 2 (1.7%). Ethnic distribution included Urdu, 54 (45%); Sindhi, 32 (26.7%); Punjabi, 22 (18.3%); Pashto, 5 (4.2%); Balochi, 3 (2.5%); and Other, 4 (3.3%) (Figure 1a-i).

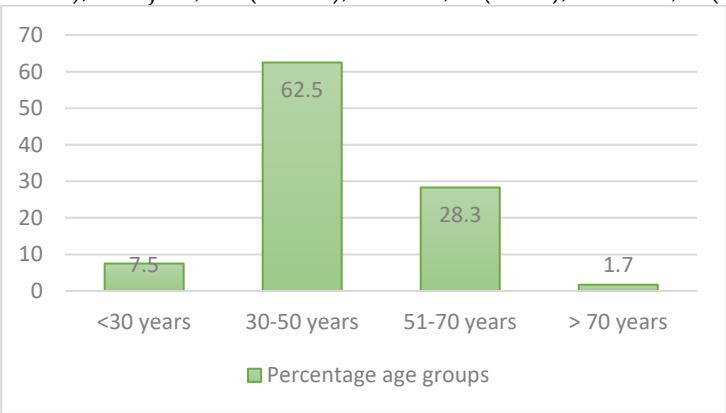

Figure 1-a. Distribution of age groups in the study population

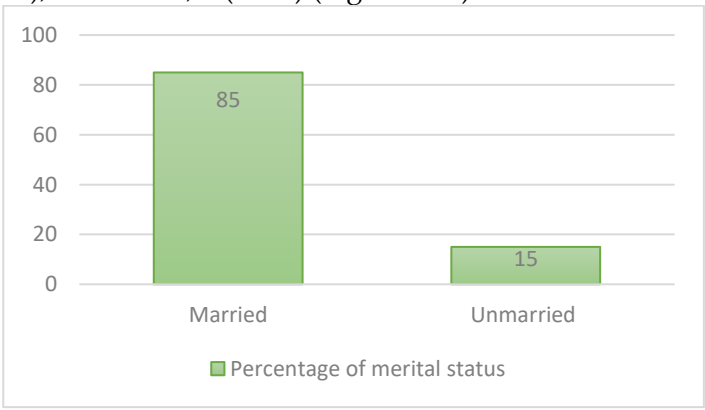

Figure 1-b. Pattern of marital status of the study population

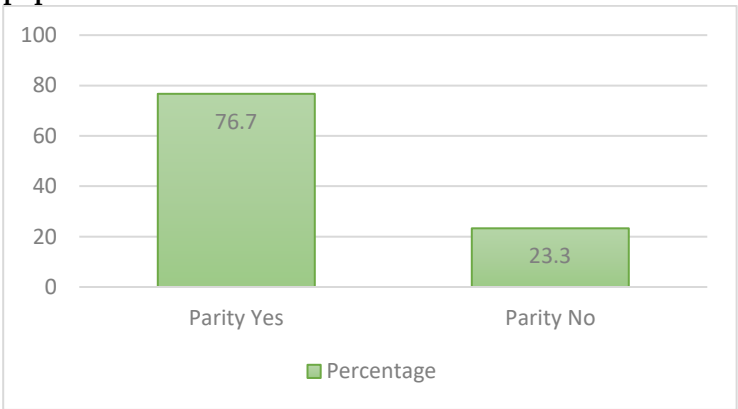

Figure 1-c. Pattern of parity of the study population

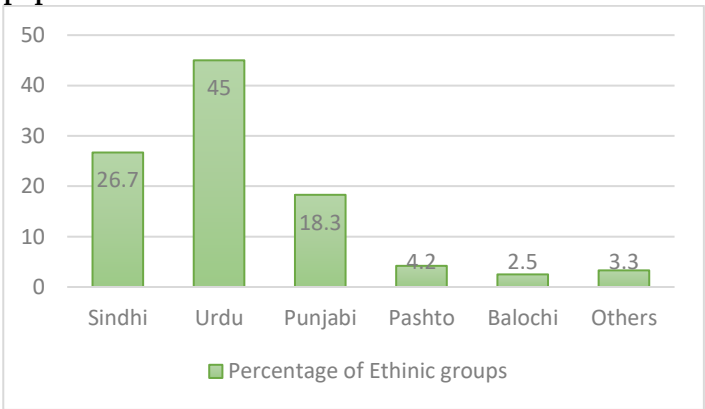

Figure 1-d. Pattern of Ethnic groups in study population

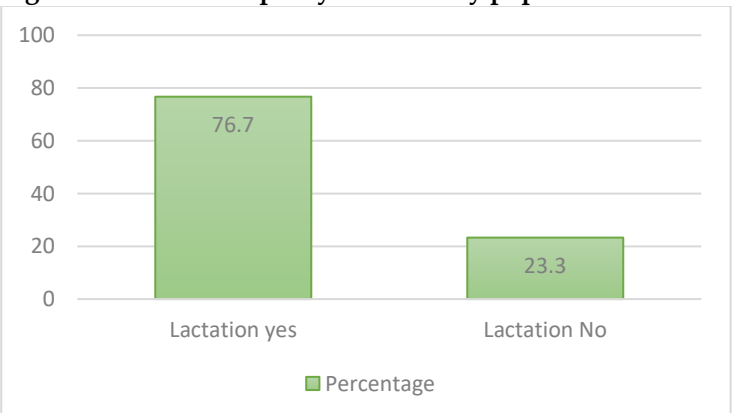

Figure 1-e. Pattern of Lactation of study population

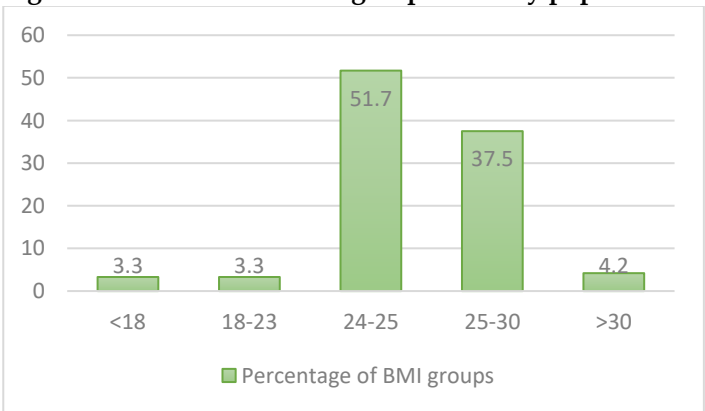

Figure 1-f. Pattern of Basal Metabolic Index (BMI) groups

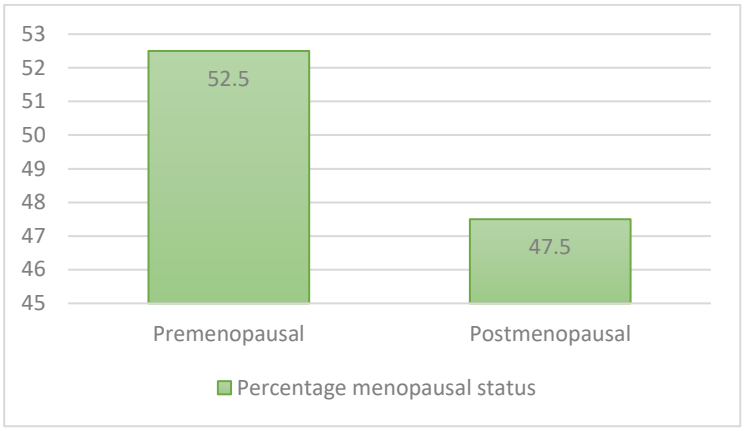

Figure 1-g. Pattern of menopausal status of study population

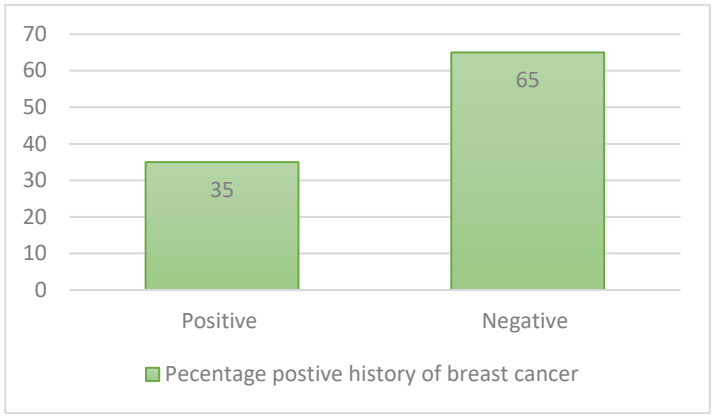

Figure 1-h. Pattern of positive history of breast cancer

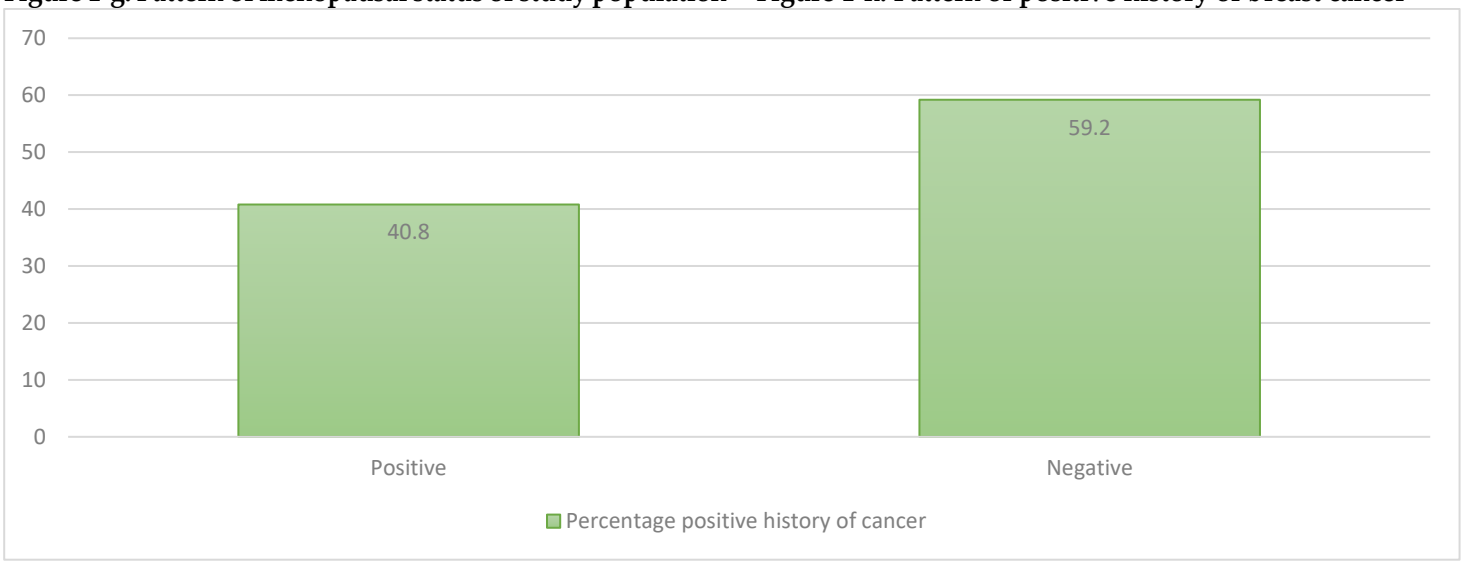

Figure 1-i. Pattern of positive history of cancer in study population

The clinical characteristics of patients were as follows: cancer was located on the left side in 43 (35.8%), right side in 71 (59.2%), and bilateral in 6 (5%) patients. Histologically, 101 (84.2%) had infiltrating ductal carcinoma, 17 (14.2%) had lobular carcinoma, and 2 (1.7%) had other types. There were 6 (5%) Grade I, 78 (65%) Grade II, and 36 (30%) Grade III cancers. The Ki 67 index was <15% in 14 (11.7%), 15-60% in 85 (70.8%) patients, and >60% in 21 (17.5%) patients. Tumor size was <2 cm in 6 (5%), 2-5 cm in 58 (48.3%), and >5 cm in 55 (45.8%) patients, with 1 (0.8%) unknown. Multifocal/multicentric tumors were present in 29 (24.2%) patients. Axillary lymph nodes involvement were observed in 90 (75%) patients. TNM staging showed 7 (5.8%) in stage I, 46 (38.3%) in stage II, 54 (45%) in stage III, and 13 (10.8%) in stage IV. Nuclear grading was Grade 1 in 9 (7.5%), Grade 2 in 75 (62.5%), and Grade 3 in 36 (30%). HER2 status was positive in 45 (37.5%), negative in 67 (55.8%), borderline in 5 (4.2%), and unknown in 3 (2.5%). Estrogen receptor status was positive in 75 (62.5%) and negative in 45 (37.5%), while progesterone receptor status was positive in 57 (47.5%) and negative in 63 (52.5%).

The association between Ki-67% and clinical variables in breast cancer patients showed significant differences in certain categories. For histological grade, higher Ki-67 levels (>60%) are more frequent in Grade 3 tumors (36.1%) compared to Grade 1 (0%) and Grade 2 (10.3%), with a significant p-value of 0.005. Regarding histological type, the infiltrating duct type shows the highest proportion of patients with Ki-67 >60% (21.0%), though the association is not statistically significant (p-value =0.144). Tumor size does not exhibit a significant trend (p=0.223), but larger tumors (>5 cm) tend to have a higher proportion of Ki 67 >60% (25.0%). Multifocal or multicentric lesions show no significant difference in Ki 67 levels compared to unifocal lesions (p-value =0.437). Similarly, axillary lymph node status (p-value =0.337) and TNM stage (p-value =0.386) did not show a statistically significant relationship with Ki 67%. However, the nuclear stage shows a significant association (p-value =0.005), with Grade III nuclear tumors exhibiting the highest proportion of Ki 67 >60% (36.1%). HER2-positive tumors showed a relatively higher percentage of Ki 67 >60% (24.4%) compared to HER2-negative tumors (11.9%), but it was not statistically significant (p-value =0.217). (Table 1).

Variables	Ki 67%			Total	p-value
	<15%	15-60%	>60%		
Histological grade					
Grade 1	2 (33.3%)	4 (66.7%)	-	6 (100%)	0.005
Grade 2	9 (11.5%)	61 (78.2%)	8 (10.3%)	78 (100.0%)	
Grade 3	3 (8.3%)	20 (55.6%)	13 (36.1%)	36 (100.0%)	
Histological Type					
Infiltrating duct	10 (10.0%)	69 (69.0%)	21 (21.0%)	101 (100.0%)	0.144
Lobular	4 (23.5%)	13 (76.5%)	-	17 (100.0%)	
Others	-	2 (100.0%)	-	2 (100.0%)	
Tumor size					
<2 cm	-	5 (83.3%)	1 (16.7%)	6 (100.0%)	0.223
2-5 cm	9 (15.5%)	43 (74.1%)	6 (10.3%)	58 (100.0%)	
>5 cm	5 (8.9%)	37 (66.1%)	14 (25.0%)	56 (100.0%)	
Multifocal/Multicentric lesion					
Yes	5 (17.2%)	18 (62.1%)	6 (20.7%)	29 (100.0%)	0.437
No	9 (9.9%)	67 (73.6%)	15 (16.5%)	91 (100%)	
Axillary lymph node					
Yes	9 (10%)	63 (70.0%)	18 (20.0%)	90 (100.0%)	0.337
No	5 (16.7%)	22 (73.3%)	3 (10.0%)	30 (100.0%)	
TNM Stage					
I	1 (14.3%)	4 (57.1%)	2 (28.6%)	7 (100.0%)	0.386
II	7 (15.2%)	33 (71.7%)	6 (13.0%)	46 (100.0%)	
III	3 (5.6%)	39 (72.2%)	12 (22.2%)	54 (100.0%)	
IV	3 (23.1%)	9 (69.2%)	1 (7.7%)	13 (100.0%)	
Nuclear Stage					
I	2 (33.3%)	4 (66.7%)	-	9 (100.0%)	0.005
II	8 (10.7%)	59 (78.7%)	8 (10.7%)	75 (100.0%)	
III	3 (8.3%)	20 (55.6%)	13 (36.1%)	36 (100.0%)	
HER2 status					
Positive	7 (15.6%)	27 (60.0%)	11 (24.4%)	45 (100.0%)	0.217
Negative	5 (7.5%)	54 (80.6%)	8 (11.9%)	67 (100.0%)	
Borderline	1 (20.0%)	3 (60.0%)	1 (20.0%)	5 (100.0%)	
Unknown	1 (33.3%)	1 (33.3%)	1 (33.3%)	3 (100.0%)	

DISCUSSION

Our study confirms a significant association between Ki 67% and the histological grade of breast cancer, suggesting that higher Ki 67 levels are predominantly observed in higher-grade tumors. This finding aligns with prior studies, such as Trihia et al., where high Ki 67 expression was also correlated with increased tumor grade, specifically in Grades 2 and 3 (18). Similarly, Kanyılmaz et al. identified a clear link between high Ki 67 and more aggressive tumor grades, reinforcing the role of Ki 67 as an indicator of tumor proliferation and aggressiveness (6).

The relationship between Ki 67 and cancer grade in our findings are consistent with other international studies, which have reported a trend of higher Ki 67 expression in tumors of higher histological grade. One such study reported by Brown et al. demonstrated that in early hormone receptor-positive breast cancers, patients with Grade-3 tumors had significantly higher Ki 67 levels (over 20%), supporting its utility as a prognostic marker for aggressive disease (19). Moreover, in a retrospective cohort by Stathopoulos et al., patients classified under the basal-like subtype, typically associated with higher grade, frequently exhibited elevated Ki 67 levels (20).

The significance of Ki 67 as a proliferation marker is further underscored in studies focusing on molecular subtypes of breast cancer. Yip et al. and Pai et al. reported that in luminal subtypes, particularly in luminal B, Ki 67 was frequently elevated, contrasting with lower levels in luminal A cases, which tend to have a better prognosis (21, 22). This aligns with our study, where high-grade tumors with elevated Ki 67 likely represent more aggressive molecular subtypes such as luminal B or HER2-enriched types. Additionally, Stathopoulos et al. highlighted that the triple-negative subtype also presented with consistently high Ki-67, further linking it with poor prognosis (20).

Beyond histological grading, our study found no statistically significant association between Ki 67 and histological type, tumor size, axillary lymph node involvement, or TNM staging. This finding, while consistent with some studies, contrasts with those indicating a correlation between tumor size and Ki-67 levels, as noted by Kanyılmaz et al. (6). These discrepancies may stem from population heterogeneity, sample size variations, or differences in assessment methods for Ki 67. The diversity in findings reinforces the need for standardized assessment protocols in Ki 67 testing, as advocated by Brown et al. (19).

Other studies have also illustrated the variability in Ki 67 association with TNM stage and nodal involvement. For example, Fasching et al. demonstrated that while Ki 67 could predict five-year disease-free survival in specific subgroups, it had limited prognostic value in isolation (23). This underscores the importance of combining Ki 67 with other biomarkers to enhance prognostic accuracy, particularly for cases with intermediate risk.

Finally, HER2 status did not exhibit a significant association with Ki 67 in our study, a finding consistent with Yip et al., who noted that HER2 overexpression does not necessarily correspond to higher Ki 67 levels (21). However, this is somewhat contradictory to studies like Trihia et al., which showed a positive relationship between HER2 positivity and elevated Ki-67, emphasizing that HER2's influence on proliferation may vary based on additional tumor characteristics (18).

CONCLUSION

In conclusion, our study highlighted the strong association between Ki 67 and histological grade in breast cancer, supporting its role as a marker of tumor proliferation and aggressiveness. While Ki 67's relationship with other clinical parameters remains less definitive, this study reinforces its utility as a complementary biomarker in evaluating breast cancer prognosis, particularly when used alongside other established indicators.

Conflict of Interest

Authors declare no conflict of interest.

Ethical consideration

The local Ethical Review Committee approved the study, informed consent was taken from all the participants and their identity was anonymized.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
2. Eliyatkın N, Yalçın E, Zengel B, Aktaş S, Vardar E. Molecular classification of breast carcinoma: from traditional, old-fashioned way to a new age, and a new way. J Breast Health. 2015;11:59-66.
3. Joensuu K, Leidenius M, Kero M, Andersson LC, Horwitz KB, Heikkilä P. ER, PR, HER2, Ki-67 and CK5 in early and late relapsing breast cancer—Reduced CK5 expression in metastases. Breast cancer: basic and clinical research. 2013;7:23-34.

4. Kamranzadeh H, Ardekani RM, Kasaeian A, Sadighi S, Maghsudi S, Jahanzad I, Maleki N. Association between Ki-67 expression and clinicopathological features in prognosis of breast cancer: a retrospective cohort study. J Res Med Sci. 2019;24:30.
5. Marwah N, Batra A, Marwah S, Gupta V, Shakya S, Sen R. Correlation of proliferative index with various clinicopathologic prognostic parameters in primary breast carcinoma: a study from North India. J Cancer Res Ther. 2018;14:537-42.
6. Kanyılmaz G, Yavuz BB, Aktan M, Karaağaç M, Uyar M, Fındık S. Prognostic importance of Ki-67 in breast cancer and its relationship with other prognostic factors. Eur J Breast Health. 2019;15:256-61.
7. Patani N, Martin LA, Dowsett M. Biomarkers for the clinical management of breast cancer: international perspective. Int J cancer. 2013;133(1):1-3.
8. Gerdes J, Schwab U, Lemke H, Stein H. Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. Int J cancer. 198315;31(1):13-20.
9. Andrés-Sánchez N, Fisher D, Krasinska L. Physiological functions and roles in cancer of the proliferation marker Ki-67. J Cell Sci. 2022;135(11):JCS258932.
10. Davey MG, Hynes SO, Kerin MJ, Miller N, Lowery AJ. Ki-67 as a prognostic biomarker in invasive breast cancer. Cancers. 2021;13(17):4455.
11. Miya MA, Kunchy AK, Sunethri P, Reddy S. Assessing the relationship between tumor proliferation and prognosis in breast cancer patients: A pathological analysis. Asian J Med Sci. 2023;14(11):249-55.
12. Nielsen TO, Leung SC, Rimm DL, Dodson A, Acs B, Badve S, et al. Assessment of Ki67 in breast cancer: updated recommendations from the international Ki67 in breast cancer working group. JNCI: J Nati Cancer Inst. 202;113(7):808-19.
13. Luporsi E, Andre F, Spyratos F, Martin PM, Jacquemier J, Penault-Llorca F, et al. Ki-67: level of evidence and methodological considerations for its role in the clinical management of breast cancer: analytical and critical review. Breast Cancer Res Treat. 2012;132:895-15.
14. Harbeck N, Rastogi P, Martin M, Tolaney SM, Shao ZM, Fasching PA, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021;32(12):1571-81.
15. Lester SC, Bose S, Chen YY, Connolly JL, de Baca ME, Fitzgibbons PL, et al. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. Arch Pathol Lab Med. 2009;133(10):1515-38.
16. Nigam JS, Kumar T, Bharti S, Sinha R, Bhadani PP, Bhadani P. Association of ki-67 with clinicopathological factors in breast cancer. Cureus. 2021 Jun 13;13(6).
17. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013;24(9):2206-23.
18. Trihia H, Murray S, Price K, Gelber RD, Golouh R, Goldhirsch A, Coates AS, Collins J, Castiglione-Gertsch M, Gusterson BA. Ki-67 expression in breast carcinoma: Its association with grading systems, clinical parameters, and other prognostic factors—A surrogate marker?. Cancer: Interdisciplinary International Journal of the American Cancer Society. 2003 Mar 1;97(5):1321-31.
19. Brown J, Scardo S, Method M, Schlauch D, Misch A, Picard S, Hamilton E, Jones S, Burris H, Spigel D. A real-world retrospective study of the use of Ki-67 testing and treatment patterns in patients with HR+, HER2− early breast cancer in the United States. BMC cancer. 2022 May 6;22(1):502.
20. Stathopoulos GP, Malamos NA, Markopoulos C, Polychronis A, Armakolas A, Rigatos S, Yannopoulou A, Kaparelou M, Antoniou P. The role of Ki-67 in the proliferation and prognosis of breast cancer molecular classification subtypes. Anti-cancer drugs. 2014 Sep 1;25(8):950-7.

21. Yip CH, Bhoo-Pathy N, Daniel JM, Foo YC, Mohamed AK, Abdullah MM, Ng YS, Yap BK, Pathmanathan R. Roles of Ki67 in Breast cancer-important for management?. Asian Pacific Journal of Cancer Prevention. 2016 Mar 1;17(3):1077-82.
22. Pai S, Murthy SV. Molecular Subtypes and Ki-67 index in Breast Carcinoma with Special Emphasis on Triple Negative Breast Cancer. A 3-year Study in a Tertiary Care Center. Indian Journal of Surgical Oncology. 2023 May 30:1-3.
23. Fasching PA, Gass P, Häberle L, Volz B, Hein A, Hack CC, Lux MP, Jud SM, Hartmann A, Beckmann MW, Slamon DJ. Prognostic effect of Ki-67 in common clinical subgroups of patients with HER2-negative, hormone receptor-positive early breast cancer. Breast cancer research and treatment. 2019 Jun 30;175:617-25.