Aswan University Medical Journal, volume 5 / No.1/ March 2025 (76-85) Online ISSN: **2735-3117**

**ORIGINAL ARTICLE**

# Evaluation of the Prognostic Value of Ki-67 in Early-Stage Breast Cancer

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## ABSTRACT

**Keyword**: Breast Cancer, Early-Stage, Ki-67

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**Background:** The expression of Ki67 is linked to the proliferation and growth of tumor cells . There is a correlation between Ki67 index and patient survival. **Objectives**. : Assess the significance of Ki-67 as a prognostic indicator concerning DFS, OS, and various clinico-pathological factors in patients diagnosed with non-metastatic breast cancer. Methods: This retrospective study was carried out on 155 patients with BC, clinic-pathological data, along with prognostic information, were collected, and the optimal cutoff point for Ki-67 was established. This cut-off point facilitated the categorization of patients into two groups, allowing for an analysis of the differences in clinical-pathological characteristics and prognosis between these groups. **Results:** Ki-67 and tumour size were independent influencing factors of recurrence. Patients were categorized into two distinct groups according to determined KI-67 cut-off point, A notable correlation was observed between OS period and KI-67 . However, no significant correlation was found between DFS period and KI-67. Additionally, a significant correlation existed between DFS, tumor grade, and size. DFS was significantly lower in cases with grade III compared to cases with grade I/II. **Conclusions:** There was a significant correlation between Ki-67 and OS; also, there is a significant correlation between DFS, tumour size, and grade.

## INTRODUCTION

Breast cancer ranks as the most prevalent cancer among women globally, accounting for more than 10% of all new cancer diagnoses each year. It is the second leading cause of cancer-related mortality among women worldwide. (1).

Diagnosis of breast cancer involves physical examination, imaging, and tissue biopsy. Early detection through screening greatly improves survival rates. Breast cancer can spread through the lymphatic and hematological systems, resulting in distant metastases and unfavorable outcome. (2). BC consists of various subtypes. These subtypes are typically divided into four categories according to the presence or lack of hormone receptors, HER2 expression and ki-67. The presence of Estrogen receptor (ER) is essential in the diagnosis of breast cancer, as it is found in about 70-75% of invasive breast cancer. (3).

PR is typically found in over half of patients with ER-positive breast cancer, but is infrequently seen in those with ER-negative tumors. Both ER and PR are significantly present in breast cancer cells and act as important diagnostic and prognostic indicators. (4).

HER2 +ve BC represent about 15-25% of BC and is vital for determining treatment options. The overexpression of HER2 is linked to a more aggressive form of cancer. The amplification of HER2 results in the overactivation of cancer-promoting signaling pathways, leading to uncontrolled cell growth. (5)

The Ki67 antigen, a marker of cell proliferation, is useful in assessing the the cancer's aggressiveness. It is essential in identifying the best treatment strategy and possible monitoring for recurrence. Furthermore, Ki67 expression acts as a prognostic indicator and is linked to lower survival (6).

The aim of this study was to assess the significance of ki-67 as a prognostic indicator concerning DFS, OS, and other clinicopathological factors in Egyptian women with non metastatic breast cancer.

**PATIENTS AND METHODS:**

This retrospective study was carried out on 155 patients, with non metastatic BC, at clinical oncology department, Aswan university hospital, diagnosed from January 2017 to December 2019. Clinicopathological data and prognostic details of patients were collected , and the optimal cutoff value of Ki-67 was established through univariate and multivariate survival risk assessment. The cut-off value was utilized to categorize the patients, and the distinctions in the clinic-pathological characteristics and the prognosis were examined between the two groups.

The inclusion criteria were female patients, age of > 18 years, stage I,II,III, receiving radical treatment, availability of complete clinical and pathological information.

Exclusion criteria were metastatic disease, patient with double primary, pregnancy and treatment discontinuation..

All patients were subjected to: Age, menopausal status, comorbidities, family history, use of contraception, pathological type, grade, T N stage, ER, PR, and HER-2 status, proliferation index ki-67, type, and date of surgery, type of treatment (Neoadjuvant chemotherapy, adjuvant chemotherapy and Hormonal treatment) and ovarian ablation.

The patients' clinico-pathological information was gathered, and follow-up was carried out. .

The prognostic indicators were DFS, and OS.

DFS was defined as the duration from radical surgery until the occurrence of recurrence.

OS was described as the duration from radical surgery until death from any cause.(7)

The duration of the follow-up was 3 years. .

The research was conducted following approval from the Ethical Committee at Aswan University Hospitals. A knowledgeable written consent was acquired from the patients.

Statistical analysis

Statistical analysis was performed using SPSS v25 (IBM Inc., Armonk, NY: IBM Corp). Quantitative variables were expressed as mean and standard deviation (SD), along with range (minimum and maximum) and interquartile range (IQR), and comparisons were made using Student's t-test for the two groups examined. Qualitative variables were shown as frequency and percentage (%). The Shapiro-Wilk test was employed to assess the normality of distribution, while the Chi-square test was utilized for categorical variables to compare various groups. Survival analyses, both univariate and multivariate, were conducted utilizing a Cox regression model. A two-tailed P value less than 0.05 was viewed as significant.

**RESULTS:**

155 studied patients, 14 patients (9%) died by the end of the analysis. The mean age of the patients at the time of diagnosis was 49.4 ± 11.3 years, with a range of 23 to 70 years.

Patients were divided into two age groups, including less than 40 years (n = 33, 21.3%), and ≥40 years (n = 122, 78.7%). In all, 74 (47.7%) patients were on pre-menopausal status while more than half (52.3%) of them on post-menopausal status. Intraductal carcinoma (ICD) was the most common pathological type found in our studied patients repressing 91% of cases. Most cases (76.8%) had grade I or II and most of them had tumor size of ≤5 cm. Patients with positive ER accounted for 75.5% of cases, PR accounted for 78.1% of cases while positive HER-2 was found in 20% of cases. N0/N1 axillary L.Ns were reported in 81.9% of cases. Luminal B was the most frequent molecular subtypes (49%).

It was observed that 20 out of 155 (12.9%) cases reported recurrence/relapse. Regarding survival outcome, there were 141 (91%) cases alive while death was reported in 14 (9%) of cases.

The multivariate survival analysis included Ki-67, tumor size, axillary lymph node status, histological grade, and PR status. Ki-67 was a continuous variable, while the rest were categorical variables. The tumor size was categorized into groups of 5 cm or less and more than 5 cm; the axillary lymph node status was split into N0/N1 and N2/N3 categories; the histological grade was differentiated into grades 1&2 and grade 3; and the PR, ER, and HER-n status was organized into negative and positive classifications. Recurrence was selected as the prognostic marker in the multivariate survival analysis. The findings indicated that Ki-67 and tumor size were independent factors affecting recurrence. as shown in table (1).

**Table 1: Logistic regression analysis for factors associated with recurrence/relapse**

| **Parameters** | **B** | **S.E.** | **Wald** | **P-value** | **Odds ratio (OR)** | **95%CI** | |
|---|---|---|---|---|---|---|---|
| | | | | | | **Lower limit** | **Upper limit** |
| **KI-67** | .023 | .010 | 4.912 | **.027** | 1.023 | 1.003 | 1.044 |
| **Tumor size** | 1.050 | .488 | 4.620 | **.032** | 2.857 | 1.097 | 7.442 |
| **Axillary L.Ns** | .798 | .564 | 2.002 | .157 | 2.222 | .735 | 6.714 |
| **Grade** | .388 | .587 | .437 | .509 | 1.474 | .467 | 4.655 |
| **ER** | -1.454- | .905 | 2.579 | .108 | .234 | .040 | 1.378 |
| **PR** | .820 | .932 | .774 | .379 | 2.271 | .365 | 14.116 |
| **HER-2** | -1.328- | .847 | 2.457 | .117 | .265 | .050 | 1.395 |

B: Regression coefficient; S.E.: Standard error; CI: Confidence interval

Since Ki-67 was an independent factor affecting DFS, the subsequent step was to determine the optimal cut-off point for Ki-67. Univariate survival analysis was conducted using the Ki-67 cut-off within this range at 5% intervals. The findings indicated that when the Ki-67 cutoff levels were set at 20%, 25%, 30%, 35%, 40%, and 45%, the survival disparities between the two groups were statistically significant ($p<0.05$). A multivariate survival analysis was conducted utilizing the aforementioned cutoff points, revealing that the 35% cutoff point was an independent factor influencing recurrence as shown in table (2).

**Table 2: Univariate and Multivariate survival analysis for different Cutoff point of Ki-67.**

| Cutoff point of Ki-67 | P-value | Hazard ratio (HR) | 95%CI | |
|---|---|---|---|---|
| | | | Lower limit | Upper limit |
| **Univariate survival analysis** | | | | |
| **5%** | 0.770 | 1.349 | 0.181 | 10.078 |
| **10%** | 0.096 | 5.531 | 0.740 | 41.319 |
| **15%** | 0.103 | 2.774 | 0.813 | 9.465 |
| **20%** | **0.022** | 4.198 | 1.230 | 14.326 |
| **25%** | **0.007** | 5.399 | 1.582 | 18.427 |
| **30%** | **0.003** | 4.545 | 1.651 | 12.509 |
| **35%** | **0.001** | 5.428 | 1.972 | 14.940 |
| **40%** | **0.021** | 2.805 | 1.167 | 6.743 |
| **45%** | **0.017** | 1.011 | 1.002 | 1.020 |
| **50%** | 0.058 | 2.380 | 0.973 | 5.826 |
| **Multivariate survival analysis** | | | | |
| **20%** | 0.774 | 1.3 | 0.217 | 7.78 |
| **25%** | 0.252 | 2.843 | 0.475 | 17.017 |
| **30%** | 0.307 | 2.158 | 0.493 | 9.439 |
| **35%** | 0.035 | 5.849 | 1.134 | 30.159 |
| **40%** | 0.533 | 0.71 | 0.243 | 2.079 |
| **45%** | 0.941 | 1.085 | 0.122 | 9.656 |

CI: Confidence interval

Ki-67 had 75% sensitivity and 66.7% specificity at a cutoff of 35% with AUC = 0.686 and was highly significant (P= 0.002). (Table 3_ Figure 1)

**Table (3): Validity (AUC, sensitivity, specificity) for Ki-67 in prediction of recurrence/relapse.**

| | Best cut off | Sensitivity | Specificity | PPV | NPV | AUC | P-value |
|---|---|---|---|---|---|---|---|
| **Ki-67** | 35 | 75% | 66.7% | 69.3% | 72.7% | 0.686 | **0.002** |

AUC: Area Under a Curve, p value: Probability value , NPV: Negative predictive value, PPV: Positive predictive value, *: Statistically significant at $p \leq 0.05$

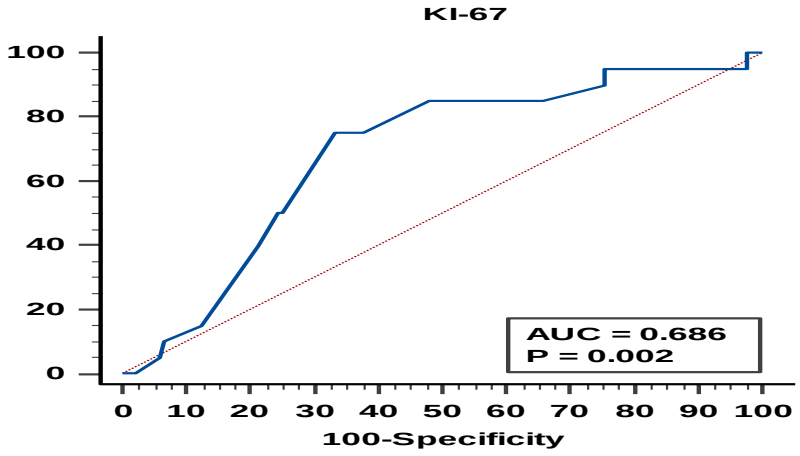


**Figure 1: ROC curve of KI-67 in prediction of recurrence/relapse.**

Using 35% as the cutoff point, patients were categorized into groups with Ki-67 levels of ≤35% and >35%, and the variations in age, menstrual status, pathological type, histological grade, ER, PR status, tumor size, and axillary lymph node status between the two cohorts were examined. Patients with a Ki-67 of ≤35% had a lower tumor grade compared to those with a Ki-67 of >35% (p<0.001). Patients with Ki-67 levels of ≤35% exhibited a greater proportion of ER-positive tumors compared to those with Ki-67 levels of >35% (p=0.005). as shown in table (4).

**Table 4: Relationship between Ki-67 at cutoff point 35% and clinicopathological features of breast cancer.**

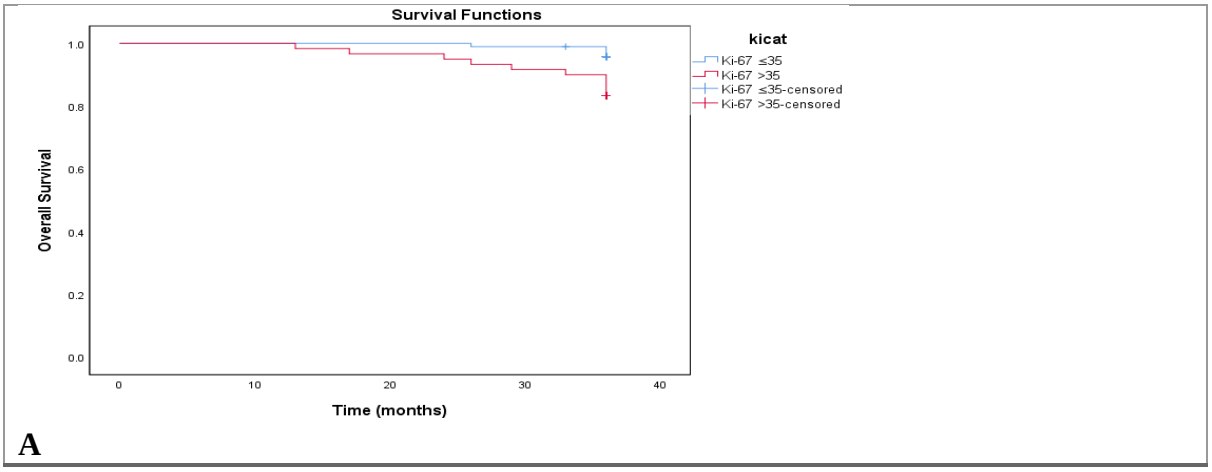
| | | **Ki-67 ≤35 (N= 95)** | | **Ki-67 >35 (N= 60)** | | **Test value** | **P-value** |
|---|---|---|---|---|---|---|---|
| | | **N** | **%** | **N** | **%** | | |
| **Age groups** | **<40 years** | 20 | 21.1% | 13 | 21.7% | $X^2$= 0.008 | 0.928 |
| | **≥40 years** | 75 | 78.9% | 47 | 78.3% | | |
| **Age (years)** | **Mean± SD** | 49.29± 11.37 | | 49.58± 11.20 | | T=0.155 | 0.877 |
| | **Range** | 23.0 – 70.0 | | 27.0 – 69.0 | | | |
| **Menopausal status** | **Pre-menopausal** | 42 | 44.2% | 32 | 53.3% | $X^2$= 1.227 | 0.268 |
| | **Post-menopausal** | 53 | 55.8% | 28 | 46.7% | | |
| **Pathological types** | **IDC** | 86 | 90.6% | 57 | 95% | $X^2$= 4.280 | 0.639 |
| | **ILC** | 5 | 5.3% | 2 | 3.3% | | |
| | **Other** | 4 | 4.2% | 1 | 1.7% | | |
| **Grade** | **Grade I/II** | 85 | 89.5% | 34 | 56.7% | $X^2$= 22.2 | **<0.001** |
| | **Grade III** | 10 | 10.5% | 26 | 43.3% | | |
| **Tumor size** | **≤5** | 72 | 75.8% | 38 | 63.3% | $X^2$= 2.769 | 0.096 |
| | **>5** | 23 | 24.2% | 22 | 36.7% | | |
| **ER** | **Negative** | 16 | 16.8% | 22 | 36.7% | $X^2$= 7.810 | **0.005** |
| | **Positive** | 79 | 83.2% | 38 | 63.3% | | |
| **PR** | **Negative** | 16 | 16.8% | 18 | 30.0% | $X^2$= 3.718 | 0.054 |
| | **Positive** | 79 | 83.2% | 42 | 70.0% | | |
| **HER-2** | **Negative** | 74 | 77.9% | 50 | 83.3% | $X^2$= 0.680 | 0.410 |
| | **Positive** | 21 | 22.1% | 10 | 16.7% | | |
| **L.Ns** | **Negative /N1** | 79 | 83.2% | 48 | 80.0% | $X^2$= 0.248 | 0.619 |
| | **N2/N3** | 16 | 16.8% | 12 | 20.0% | | |

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by X2: Chi-Square Test, T: Student T test

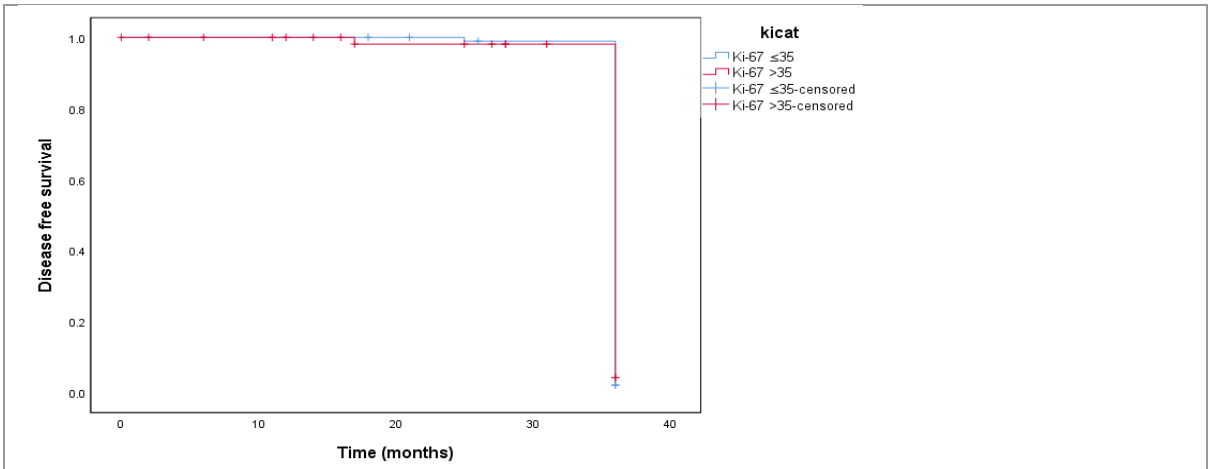
The mean OS of all patients examined was 35.5 months. OS was 35.9 months for patients with Ki-67 ≤35% and 34.8 months for those with Ki-67 >35%. A significant difference was found between the two groups in OS (P =0.007) as patients with Ki-67 ≤35% had higher overall survival rate. The mean DFS of all studied patients was 35.8 months. The mean DFS was 35.9 months for patients with Ki-67 ≤35% and 35.6 months for those with Ki-67 >35%. No significant difference was found between the two groups mean DFS (P=0.749) as shown in table (5) and figures (2).

**Table (5): Overall and Disease free survival analysis for among the studied breast cancer patients**

| **Overall survival** | | | | | |
|---|---|---|---|---|---|
| | Mean survival (months) | SE | 95% CI | | |
| **Ki-67 ≤35** | 35.9 | 0.121 | 35.658 | - | 36.132 |
| **Ki-67 >35** | 34.8 | 0.583 | 33.624 | - | 35.909 |
| **Overall** | 35.5 | 0.236 | 34.995 | - | 35.921 |
| | | | | | |
| **Comparison of survival curves (Log rank test)** | | | | | |
| **Chi-squared** | 7.157 | | | | |
| **DF** | 1 | | | | |
| **Significance** | **P=0.007** | | | | |
| **Disease free survival** | | | | | |
| **Ki-67 ≤35** | 35.9 | .118 | 35.650 | - | 36.114 |
| **Ki-67 >35** | 35.6 | .359 | 34.938 | - | 36.345 |
| **Overall** | 35.8 | .149 | 35.504 | - | 36.087 |
| | | | | | |
| **Comparison of survival curves (Log rank test)** | | | | | |
| **Chi-squared** | 0.102 | | | | |
| **DF** | 1 | | | | |
| **Significance** | p=0.749 | | | | |




**A**




**B**

**Figure 2: Kaplan-Meier survival curves showing (A) OS and (B) DFS in patients with Ki-67 ≤35% and patients with Ki-67 >35%.**

OS was weak significantly higher in cases with positive PR compared to cases with negative PR (p=0.05). Otherwise, no significant relation was observed between OS with age, menopausal status, Pathological types, grade, Tumor size, ER, HER-2 or axillary LNs (p>0.05) as shown in table (6).

**Table (6): Relationship between clinicopathological features of breast cancer and overall survival.**

| | | Overall survival | | Test value | P-value |
|---|---|---|---|---|---|
| | | Mean | SD | | |
| **Age groups** | **<40 years** | 35.8 | 1.22 | $Z_{MWU}$= 0.638 | 0.523 |
| | **≥40 years** | 35.3 | 3.15 | | |
| **Age (years)** | | | | r=0.013 | 0.870 |
| **Menopausal status** | **Pre-menopausal** | 35.4 | 3.09 | $Z_{MWU}$ = 0.561 | 0.575 |
| | **Post-menopausal** | 35.4 | 2.63 | | |
| **Pathological types** | **IDC** | 35.4 | 2.98 | Kw= 0.830 | 0.991 |
| | **ILC** | 36.0 | 0.0 | | |
| | **Other** | 36.0 | 0.0 | | |
| | **IDC&ILC** | 36.0 | - | | |
| | **IDC/Mucinous** | 36.0 | - | | |
| | **IDC/Paget's** | 36.0 | - | | |
| **Grade** | **Grade I/II** | 35.7 | 1.58 | $Z_{MWU}$ = 1.868 | 0.062 |
| | **Grade III** | 34.5 | 5.11 | | |
| **Tumor size** | **≤5** | 35.6 | 2.49 | $Z_{MWU}$ = 0.581 | 0.561 |
| | **>5** | 35.1 | 3.59 | | |
| **ER** | **Negative** | 34.7 | 4.79 | $Z_{MWU}$ = 1.714 | 0.086 |
| | **Positive** | 35.7 | 1.81 | | |
| **PR** | **Negative** | 34.6 | 5.05 | $Z_{MWU}$ = 1.862 | **0.050** |
| | **Positive** | 35.9 | 1.78 | | |
| **HER-2** | **Negative** | 35.5 | 2.70 | $Z_{MWU}$ = 0.356 | 0.722 |
| | **Positive** | 35.3 | 3.44 | | |
| **Molecular subtypes** | **Her-2 enriched** | 34.00 | 5.71 | Kw = 7.758 | 0.051 |
| | **Luminal A** | 36.00 | 0.00 | | |
| | **Luminal B** | 35.5 | 2.23 | | |

| | | | | | |
|---|---|---|---|---|---|
| | **Triple negative** | 34.6 | 5.43 | | |
| **L.Ns** | **Negative /N1** | 35.4 | 2.96 | $Z_{MWU}$ = 0.503 | 0.615 |
| | **N2/N3** | 35.5 | 2.32 | | |

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by ZMWU: Mann-Whitney U Test, r: Spearman correlation coefficient, Kw: Kruskal Wallis test

Disease free survival was significantly lower in cases with grade III compared to cases with grade I/II (p=0.004). DFS was significantly lower in cases with tumor size >5 cm compared to cases with tumor size ≤ 5 cm (p=0.032). Otherwise, no significant relation was observed between OS and age, menopausal status, pathological types, ER, PR, HER-2 or axillary L.Ns status (p>0.05) as shown in table (7).

**Table (7): Relationship between clinicopathological features of breast cancer and disease free survival.**

| | | **DFS** | | **Test value** | **P-value** |
|---|---|---|---|---|---|
| | | **Mean** | **SD** | | |
| **Age groups** | **<40 years** | 33.3 | 6.45 | $Z_{MWU}$= 1.245 | 0.213 |
| | **≥40 years** | 34.1 | 6.59 | | |
| **Age (years)** | | | | r=0.131 | 0.105 |
| **Menopausal status** | **Pre-menopausal** | 33.4 | 7.37 | $Z_{MWU}$ = 0.737 | 0.461 |
| | **Post-menopausal** | 34.4 | 5.72 | | |
| **Pathological types** | **IDC** | 33.8 | 6.81 | Kw= 8.288 | 0.218 |
| | **ILC** | 36.0 | 0.0 | | |
| | **Other** | 36.0 | - | | |
| | **IDC&ILC** | 36.0 | - | | |
| | **IDC/Mucinous** | 36.0 | - | | |
| | **IDC/Paget's** | 36.0 | - | | |
| **Grade** | **Grade I/II** | 34.8 | 4.98 | $Z_{MWU}$ = 2.913 | **0.004** |
| | **Grade III** | 31.1 | 9.73 | | |
| **Tumor size** | **≤5** | 34.7 | 5.28 | $Z_{MWU}$ = 2.151 | **0.032** |
| | **>5** | 32.0 | 8.71 | | |
| **ER** | **Negative** | 32.7 | 8.21 | $Z_{MWU}$ = 1.492 | 0.136 |
| | **Positive** | 34.3 | 5.90 | | |
| **PR** | **Negative** | 33.3 | 7.72 | $Z_{MWU}$ = 0.637 | 0.524 |
| | **Positive** | 34.1 | 6.21 | | |
| **HER-2** | **Negative** | 33.6 | 7.07 | $Z_{MWU}$ = 1.045 | 0.296 |
| | **Positive** | 35.1 | 3.66 | | |
| **Molecular subtypes** | **Her-2 enriched** | 34.3 | 5.73 | Kw= 5.438 | 0.142 |
| | **Luminal A** | 35.3 | 3.28 | | |
| | **Luminal B** | 33.4 | 7.30 | | |
| | **Triple negative** | 31.9 | 9.57 | | |
| **L.Ns** | **Negative /N1** | 34.2 | 6.39 | $Z_{MWU}$ = 1.739 | 0.082 |
| | **N2/N3** | 32.6 | 7.19 | | |

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant, SD: standard deviation, analysis done by ZMWU: Mann-Whitney U Test, r: Spearman correlation coefficient, Kw: Kruskal Wallis test

## DISCUSSION

Breast cancer is a disease that presents numerous significant characteristics with varying phenotypes. Treatment decisions in standard management primarily depend on the clinical and pathological features of the condition. Ki 67 is significant in this situation, particularly for patients lacking access to genetic profiles.
. The optimal cut-off point remains a topic of discussion among oncologists. [8] This research assessed the clinical importance of Ki-67 index as a prognostic indicator in non metastatic breast cancer among 155 cases at one institution. Additionally, the relationships between the Ki-67 index and clinic-pathological factors that indicate prognosis were studied.
Our results demonstrated that Ki-67 and was independent influencing factors of recurrence
p value =0.027, In ROC analysis Ki-67 had 75% sensitivity and 66.7% specificity at a cutoff point of 35% and was highly significant (P= 0.002). at cutoff point 35% there was significant difference was found between the two groups in OS ( p value =0.007) as patiets with ki-67 ≤ 35% had higher overall survival rate ,consistent with the findings presented by Bustreo et al concerning 1,577 patients, those with Ki-67 >20% exhibited a worse prognosis [9].
In this study, A high Ki-67 index (≥ 35%) showed a significant correlation with ER and the grade of the tumor. However, it did not have a correlation with PR status in our study. These findings were also consistent with those of Inwald et al.
in which there is correlation between ki-67, tumour grade, ER, and PR status. [10]
In this study, Ki-67 at cut-off point o 35% showed no correlation with tumor size or nodal status. This aligns with the findings presented by Inwald et al, which show no correlation between Ki-67 and T-stage, although there was a correlation with N-stage. [11]. Nevertheless, numerous studies showed the opposite; indicating a positive correlation between Ki-67 and both.[12]
The results in our study didn't show a significant relation between age, Ki67 index, and recurrence (P>0.05), which was consistent with the finding of Wei et al. as their study results suggested that although young patients had more aggressive pathological types, the clinical prognosis in different age groups were very similar [13].
Histological grade, and tumour size show significant difference in DFS as patients with grade III tumors have lower DFS compared to cases with grade I/II tumors (p=0.004). , DFS was significantly lower in cases with tumor size more than 5 cm compared to cases with tumor size less than or equal 5 cm (p=0.032). This finding is consistent with different studies conducted in an Asian countries [14].
The result of our study show no statistical significance, between LN status, negative and positive ER, and HER-2 on OS and DFS, but there is significance between PR status and OS.
Also there is no significant correlation between molecular subtypes,and LN status with DFS, and OS. In contrast to results were demonstrated by Engels et al**.,** [15]**.** This may be due to small sample size and short duration of follow up.
**Recommendations and limitations**: Simple, easily applied and economic prognostic markers such as Ki67 index and other clinic-pathological features must be taken into account within the context of clinical trials in patients with breast cacer, treatment of patients with BC should be individualized according to the patient phenotype and molecular profile. Future research involving a larger sample size and extended follow-up duration should be taken into account to give more conclusive results about the benefit of these markers and to better evaluate its prognostic and predictive value in breast cancer.

## CONCLUSIONS:

According to our study result the optimal cutoff point of KI-67 was 35%, and there was significant correlation between Ki-67, and overall survival, with cut off point 35%. Also there is a significant correlation between the disease free survival, the tumor size, and grade.

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