

## Correlation Between Ki67 And Novel Bioscore System (Seer Data Base Analysis) In Predicting The Prognosis Of Breast Cancer

Dr M. Banu<sup>1</sup>, Dr S. Karthikeyan<sup>2</sup>, Dr Chitra R<sup>3</sup>,  
Dr Rajesh S<sup>4</sup> & Dr Prem Kumar S<sup>5</sup>

<sup>1</sup>(MCh IIIrd Year Surgical Oncology Resident, Sri Ramachandra Medical College , Chennai )- previously MS General Surgery postgraduate in PSG Institute of Medical Sciences and Research, Coimbatore

<sup>2</sup>Professor, PSG Institute of Medical Sciences and Research, Coimbatore, India

<sup>3</sup>Professor, PSG Institute of Medical Sciences and Research, Coimbatore, India

<sup>4</sup>Professor & HOD, PSG Institute of Medical Sciences and Research, Coimbatore, India

<sup>5</sup>Professor, PSG Institute of Medical Sciences and Research, Coimbatore, India

Corresponding author email: [dr.mbanu2017@gmail.com](mailto:dr.mbanu2017@gmail.com)

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### ABSTRACT

*Breast cancer is the leading cause of death from cancer for women worldwide.*

*Proliferation of cells has a major impact on prediction of risk of recurrence, thereby assessment of proliferation is one of the major factors in determining the prognosis of breast cancer. Ki67 is a nuclear protein associated with cellular proliferation.*

*The SEER (Surveillance, Epidemiology and End Results) database includes the various potential risk factors for breast cancer that are significantly associated with the overall prognosis of breast cancer patients. The Demographic data included the age at the presentation of cancer and the pathological findings included tumour size, axillary lymph node status, tumor histological grade, hormone receptor status.*

*The purpose of the study is to find out if, just by doing Ki67 alone in a newly diagnosed breast cancer patient, whether we can predict the prognosis. Further prognostic significance of Ki67 pre and post neo adjuvant therapy is to be evaluated in the various types of breast cancer.*

**Keywords:** Breast Cancer, Ki 67, SEER database

### INTRODUCTION

Breast cancer is the leading cause of death from cancer for women worldwide. In India, the age adjusted incidence rate of carcinoma breast is as high as 41 per 1 Lakh women in Delhi followed by Chennai (37.9) and Bangalore (34.4). Mortality to incidence ratio was found to be as high as 66 in rural registries compared to urban registries where it was found to be as low as 8.<sup>(1)</sup>

Breast cancer is a heterogenous disease. Different subtypes exist which can be defined either by means of gene testing or based on IHC analysis.

Proliferation of cells has a major impact on prediction of risk of recurrence, thereby assessment of proliferation is one of the major factors in determining the prognosis of breast cancer. Ki67 is a nuclear protein associated with cellular proliferation.

Recently the “International Ki67 in Breast Cancer Working Group” published their recommendations concerning the evaluation and interpretation of Ki67 as one of the most robust biomarkers measured by

IHC. They emphasized the potential of Ki67 in predicting the prognosis of breast cancer and as a biomarker for treatment effectiveness.<sup>(2)</sup>

The SEER (Surveillance, Epidemiology and End Results) database includes the various potential risk factors for breast cancer that are significantly associated with the overall prognosis of breast cancer patients. The Demographic data included the age at the presentation of cancer and the pathological findings included tumour size, axillary lymph node status, tumor histological grade, hormone receptor status.

### AIMS AND OBJECTIVES

To correlate Ki67 and the Bioscore system as used by the SEER database in predicting the prognosis of breast cancer.

To assess the prognostic significance of Ki67 before and after neoadjuvant therapy in various types of breast cancer.

### MATERIALS AND METHODOLOGY

30 Breast cancer patients who have been detected and treated on an inpatient basis and followed up on an outpatient basis in the Department of General Surgery and Department of Medical Oncology at PSGIMSR from January 2016 to December 2018 were included in the study.

Retrospective and prospective analysis of the case reports regarding the age at presentation, stage of breast cancer and metastasis was analysed. Tissue biopsy reports were assessed for hormone receptor status of the tumor prior to neo adjuvant chemotherapy.

Details of the type of treatment undergone by the patients was noted. Histopathological analysis of the tissue specimen post surgery for tumor size, lymph node status, grade of tumor and hormone receptor status was done.

Data collected was entered into a Excel Spread Sheet and analysed using STATA statistical software package release 11. Simple calculations like percentages, proportions, mean values were derived. A type 1 error of 0.05 was considered in all analysis.

**RESULTS**  
The majority of patients were Greater than 50years (56.7%). 33.3% of patients were between 40-50 years and 10% of patients were Less than 40 years. The mean and standard deviation of Age in years is 52.433 ± 11.374. The median Age in years is 52 and the range is 52 (32-84). The inter-quartile range is 11.75 which we get from Q1 (45.5) and Q3 (57.25). (Table 1 )

**Table 1- Age in years**

Age in years	No. of Cases	Percentage
Lessthan40years	3	10%
40-50years	10	33.3%
Greaterthan50years	17	56.7%
<b>Total</b>	<b>30</b>	<b>100%</b>

The maximum number of patients were in grade 3 (66.7%). 33.3% of patients were in grade 2. **(Table 2)**

**Table 2- Grade of Tumor**

Grade	No.ofCases	Percentage
2	10	33.3%
3	20	66.7%
<b>Total</b>	30	100%

Out of 30 patients majority of them had tumor size of T3 (46.7%). 30% of patients had tumor size of T2 and 23.3% of patients had T4B tumor size. **(Table 3)**

**Table 3 - Tumor Size**

TumorSize	No.ofCases	Percentage
T2	9	30%
T3	14	46.7%
T4B	7	23.3%
<b>Total</b>	30	100%

In our study, most of the patients had N1 lymph node (56.7%). 23.3% of patients had N0 lymph node and 13.3% of patients had N2 lymph node. Similarly 6.7% of patients had N3 lymph node status. **(Table 4)**

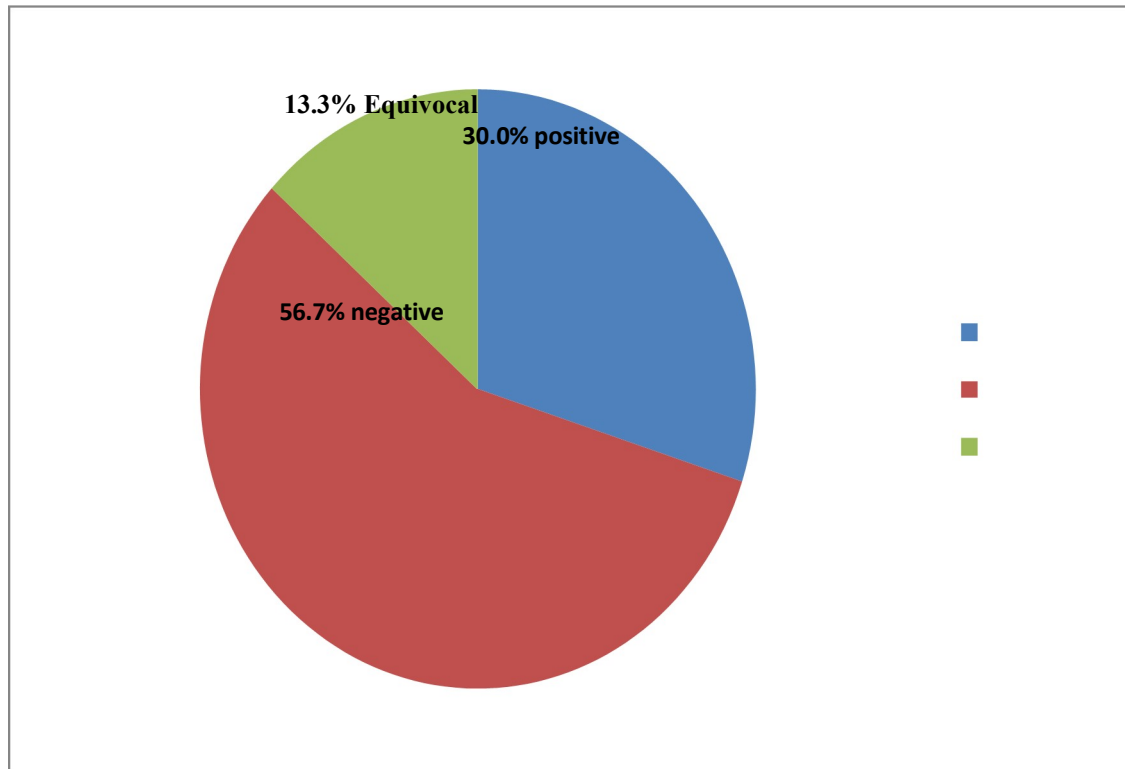
**Table 4 – Lymph Node Status**

LymphNode	No.ofCases	Percentage
N0	7	23.3%
N1	17	56.7%

N2	4	13.3%
N3	2	6.7%
<b>Total</b>	<b>30</b>	<b>100%</b>

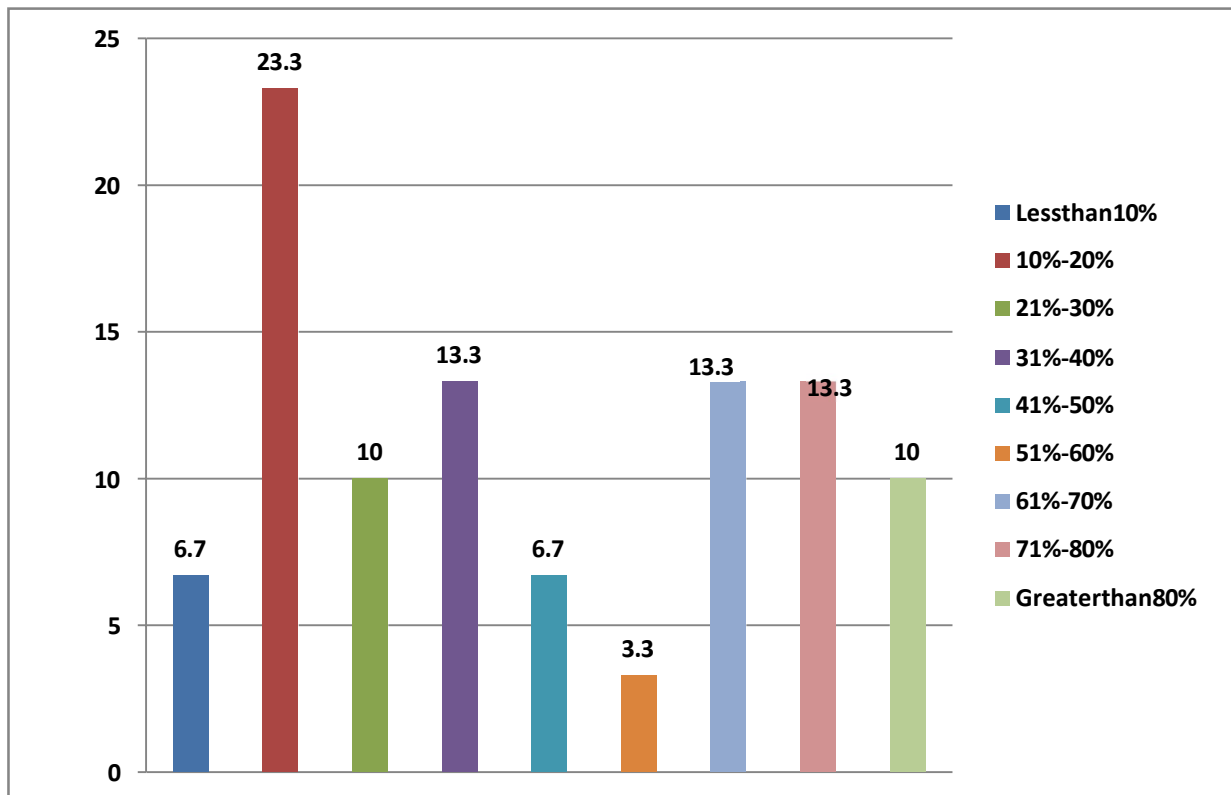
19(63.3%) of patients had ER positive receptor status. 14(46.7%) of patients had PR receptor positive status. 9(30%) of patients had Her2Neu positive receptor status. **(Fig 1)**

**Figure1 -Her2Neu Receptor status**



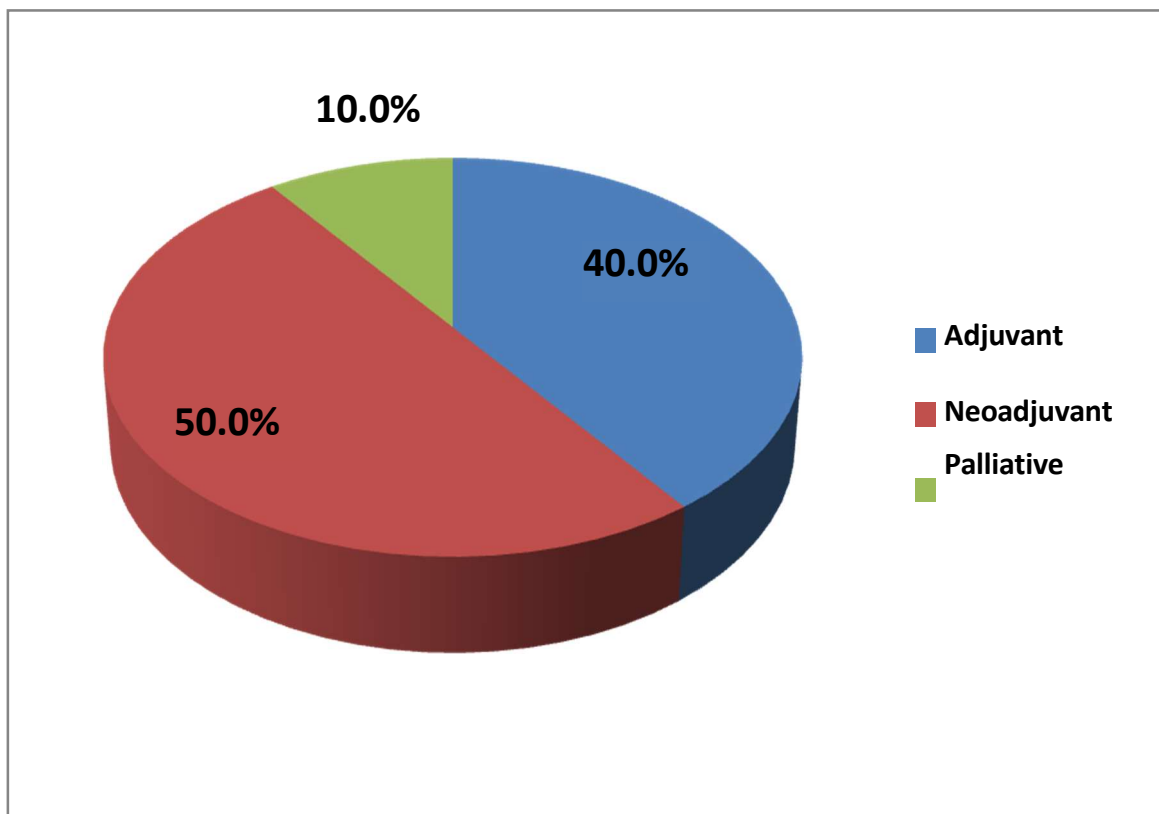
The result shows that majority of patients had Ki67 score between 10%-20% (23.3%). The mean and standard deviation of Hormone Receptor (Ki67) is  $0.445 \pm 0.281$ . The median Hormone Receptor (Ki67) is 0.38 and the range is 0.79 (0.06-0.85). The inter- quartile range is 0.5125 which we get from Q1 (0.2) and Q3 (0.71). **(Fig 2 )**

Figure 2 - Ki67 levels



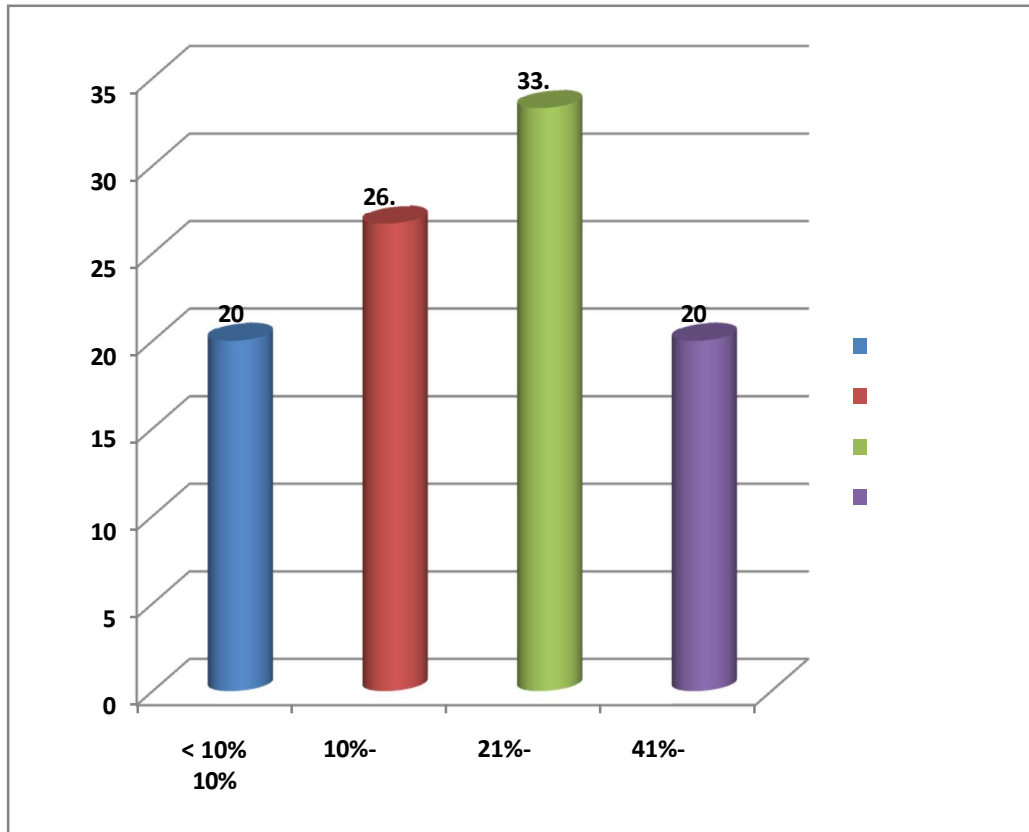
The majority of patients were treated with Neoadjuvant chemotherapy (50%). 40% of patients were treated with Adjuvant chemotherapy and 10% of patients were treated with Palliative chemotherapy. (Fig 3)

**Figure 3 - Chemotherapy**



The result shows that majority of patients had post chemotherapy Ki67 score between 21% - 30% (33.3%). The mean and standard deviation of Post Chemotherapy (Ki67) is  $0.231 \pm 0.171$ . The median Post Chemotherapy (Ki67) is 0.23 and the range is 0.47 (0.03-0.5). The inter- quartile range is 0.2 which we get from Q1 (0.1) and Q3 (0.3). (Fig 4)

**Figure 4- Post Chemotherapy Ki67 levels**



In our study, most of the patients had Infiltrating Ductal Carcinoma (96.7%) and 3.3% of patients had Mixed Mucinous Carcinoma.

The mean and standard deviation of Bioscore by SEER Model is  $0.283 \pm 0.16$ . The median Bioscore by SEER Model is 0.28 and the range is 0.69 (0.06-0.75). The inter- quartile range is 0.19 which we get from Q1 (0.16) and Q3 (0.35).

The following formula was used to calculate the SEER model score:

$$PI = -6.115 + 0.031 * \text{Age} + 0.549 * \text{Grade (II vs I)} + 1.162 * \text{Grade (III vs I)} + 1.023 * \text{Grade (IV vs I)} + 0.765 * \text{Tumor (2 vs 0-1)} + 1.491 * \text{Tumor (3-4 vs 0-1)} + 0.882 * \text{Node (1 vs 0)} + 1.484 * \text{Node (2 vs 0)} + 2.161 * \text{Node (3 vs 0)} + 1.054 * \text{Hormone Receptor (- vs +)}$$

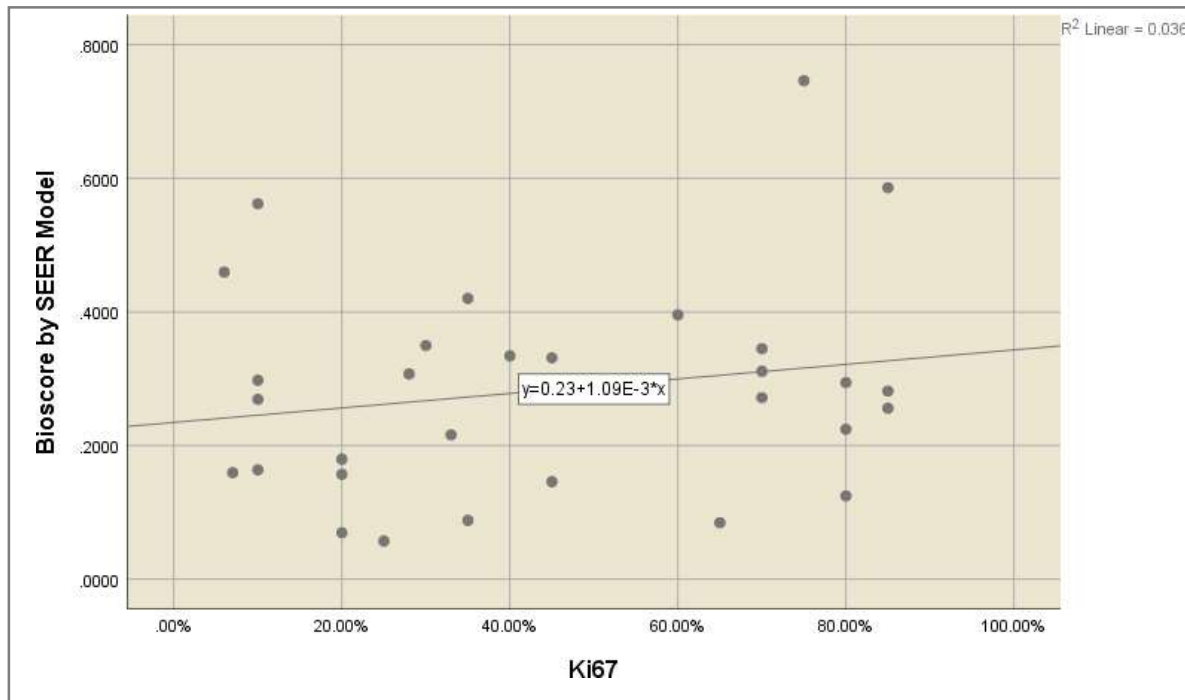
$$\text{Bioscore } (\hat{P}) = \frac{e^{PI}}{1 + e^{PI}}$$

The mean and SD of Bioscore by SEER Model is 0.283 and 0.1602 respectively. Also the mean and SD of Ki67 is 0.445 and 0.2809 respectively. The Pearson's correlation coefficient is 0.19. (Table 5, Fig 5)

**Table 5- Correlation between Bioscore by SEER Model and Ki67**

Parameters	Mean	SD	Pearson's Coefficient	Correlation	P Value
Bioscore by SEER Model	0.283	0.1602	0.19		0.157
Ki67	0.445	0.2809			

**Figure 5- Correlation between Bioscore by SEER Model and Ki67**



It shows there that there is a weak positive correlation between Ki67 value and Bioscore by SEER model. The result is not significant since the p value is greater than the significance level ( $\leq 0.05$ ). The R squared value is 0.036. It shows that the regression model accounts for 3.6% of variance. The F value is 1.052.

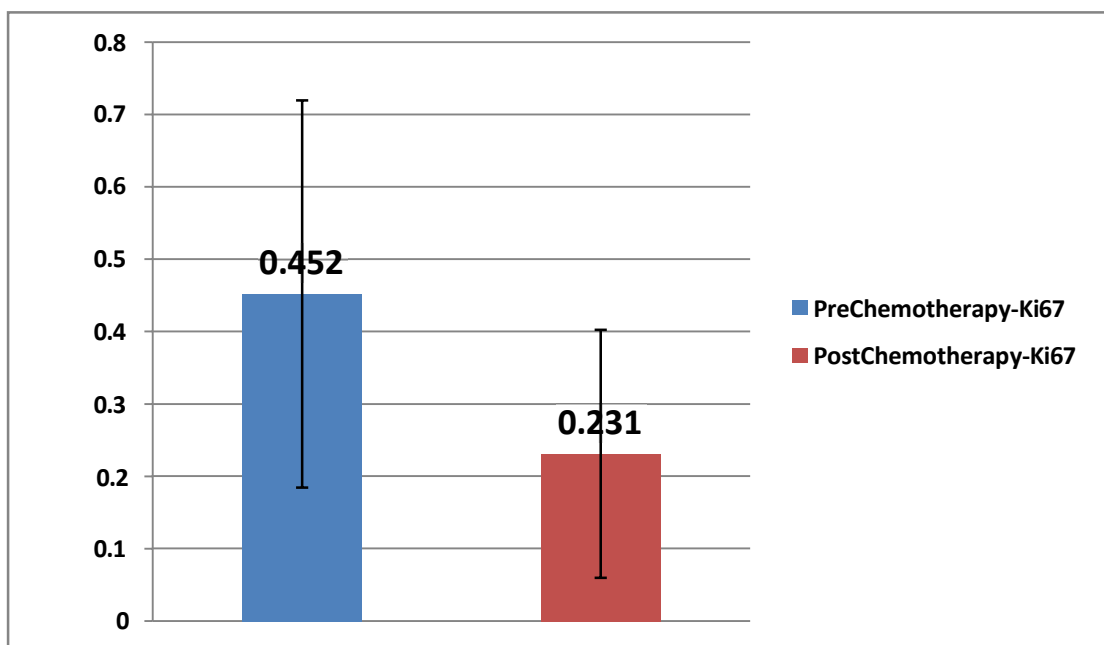
Since the p value is greater than the significance level ( $\leq 0.05$ ), we concluded that our regression model cannot significantly predict the Bioscore by SEER Model.

**Regression Equation is Bioscore by SEER Model =  $0.235+0.001*(Ki67)$**

It shows that for every unit increase of Ki67, Bioscore by SEER Model is increased an average unit of 0.001 times.

The paired sample T test results shows that there is a significant difference between the mean of Pre Chemotherapy- Ki67 value and Post Chemotherapy- Ki67 value (t value=5.632, P=< 0.001\*). (Fig 6)

**Figure 6 – Mean comparison of PreChemotherapy-Ki67 with Post Chemotherapy Ki67**



## DISCUSSION

Invasive breast carcinoma is the most common malignant tumor in women worldwide and is a heterogeneous disease with distinct pathological and histological features and can be classified into several subtypes based on the expression of 3 receptors: ER, PR, and HER2. Ki-67 is an immunohistochemical proliferation marker in many types of cancer and has been widely studied among Breast cancer patients mostly through retrospective studies.

We analysed 30 patients with breast cancer treated at our institute with the intention of correlating Ki67 and the SEER database prognostic variables in breast cancer (**Demographic data** included the age at the presentation of cancer and the **Pathological findings** included tumor size, axillary lymph node status, tumor histological grade, hormone receptor status )

The majority of patients included in the study were greater than 50 years (56.7%).The mean and standard deviation of **Age** in years is  $52.433 \pm 11.374$ .

The maximum numbers of patients had **grade 3** (66.7%) tumors. Out of 30 patients majority of them had **tumor size** of T3 (46.7%). In our study, most of the patients had N1 **lymph node status** (56.7%). 19 (63.3%) - patients were **ER** positive, 14 (46.7%) - patients were **PR** positive, 9 (30%) - patients were **Her2Neu** positive.

The result shows that majority of patients had **Ki67** score between 10%-20% (23.3%). The mean and standard deviation of Hormone Receptor (Ki67) is  $0.445 \pm 0.281$ .

15 patients underwent Neoadjuvant chemotherapy (50%). The result shows that majority of patients had post chemotherapy Ki67 score between 21%-30% (33.3%). 26.7% of patients had post chemotherapy Ki67 score between 10%-20% and 20% of patients had post chemotherapy Ki67 score Less than 10%.

Similarly 20% of patients had post chemotherapy Ki67 score between 41%-50%. The mean and standard deviation of Post Chemotherapy (Ki67) is  $0.231 \pm 0.171$ . The median Post Chemotherapy (Ki67) is 0.23 and the range is 0.47 (0.03-0.5).

In our study, most of the patients had Infiltrating Ductal CA (96.7%) and 3.3% of patients had Mixed Mucinous CA.

The study shows there that there is a weak positive correlation between Ki67 value and Bioscore by SEER model, thereby proving that , just by doing Ki67 alone in a newly diagnosed breast cancer patient, we cannot predict the prognosis in breast cancer patients . Several other demographic and pathological factors as included in the SEER bioscore contribute to determining the prognosis in breast cancer . Ki 67 is one of the many factors that determines the aggressiveness of tumor, but it is not an independent prognostic factor as determined in this study.

## CONCLUSION

Ki67 levels do not correlate with the Bioscore model (SEERDatabase) in predicting the prognosis of breast cancer, thereby indicating that Ki67 alone cannot be used in predicting the prognosis of breast cancer.

It is a combination of the age of the patient, grade of the tumor, tumor size, lymph nodal status and hormone receptor status that predicts the prognosis of breast cancer.

Also, there is a statistically significant reduction in Ki67 levels before and after neoadjuvant chemotherapy, thereby signifying that there is a reduction in the division of cancer cells post chemotherapy.

Further, whether Ki67 combined with SEER database scoring system proves to be a better predictor of prognosis compared to the Bioscore alone, needs to be further studied.

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