



(RESEARCH ARTICLE)



## An institutional analysis of the correlation between KI 67 index and other prognostic markers in invasive breast cancer in northern province, Sri Lanka

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### Abstract

**Introduction:** Breast cancer is the commonest cancer among females in Sri Lanka. The markers that define the treatment recommendations are Estrogen receptors (ER) status, Progesterone receptor (PR) status, HER-2 neu and Ki-67 proliferative index.

**Methodology:** This is a retrospective study performed on the pathological specimens of invasive ductal carcinoma at Teaching Hospital Jaffna from January 2020 to July 2022. Ki-67 index above 20 was considered high and below 20 as low. The correlation between Ki-67 and other prognostic markers was analyzed as categorical variables using chi-square test.

**Results:** 143 specimens were analyzed, of which 101 were core biopsies and 42 were mastectomy/ WLE specimens. ER, PR and HER2/neu positivity were noted in 100 (69.9%), 85 (59.4%) and 41(28.7%) cases, respectively. Nottingham tumour grade 1,2 and 3 was noted in 16 (11.2%), 74 (51.7%) and 38 (26.6%) cases, respectively. The mean Ki-67 index was 40.21 %. High Ki-67 index was noted in 107(74.8%) and low in 36(25.2%) cases. A significant correlation was noted between ER, PR positivity and Ki-67 index ( $p=0.02, 0.01$ ). The correlation between HER2/neu positivity and Ki-67 was insignificant ( $p=0.06$ ). A significant correlation was found between the Ki-67 index and tumour grade ( $p=0.01$ ).

**Conclusion:** This study showed that high Ki-67 expression is associated with high tumour grade, ER/PR positivity and HER2/neu negativity. Varying results with the published literature reveal geographical variations and warrant large-scale analysis with a bigger sample size.

**Keywords:** Invasive breast cancer; Prognostic markers; KI 67 index; Estrogen receptor; Progesterone receptor; HER2 neu

### 1. Introduction

Breast cancer is the commonest cancer among females in Sri Lanka. More than 3000 new cases are diagnosed every year [1]. Various prognostic markers are used to assess and manage breast malignancies.

The leading markers that define the treatment recommendations are Estrogen receptor (ER), Progesterone receptor (PR), Human Epidermal growth factor (HER-2) status and Ki-67 proliferative index. These markers are used to sub-classify the invasive carcinoma into Luminal A, luminal B, HER-2 overexpressing and basal-like breast cancers [2].

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Luminal A group tumours show high expression of luminal epithelial genes (ER) (ER+, PR $\geq$ 20%, HER2-, Ki67<20%), luminal B group tumours show a lower expression of luminal epithelium, but a higher level of proliferation and HER2-related genes than luminal A (ER+, PR<20% and/or HER2+ and/or Ki67 $\geq$ 20%), HER-2 overexpressing type shows high expression of HER-2 related genes, low expression of luminal genes (ER-, PR-, HER2+), and basal type shows high expression of basal epithelial and proliferation genes with low expression of HER2 and ER genes (ER-, PR-, HER2-) [2].

Ki-67 is recently getting more importance and getting included in the management guidelines. The Ki67 antigen is a non-histone protein identified by Gerdes and his colleagues and was named Ki for Kiel University, the researchers' institution [3].

It is considered to have a prognostic and predictive role in the management of breast cancer. The Nottingham grading system for breast cancer considers nuclear grade, tubular formation and mitotic rate to grade the tumour. Though Ki-67 proliferative index and mitotic index are cell proliferation markers, Ki-67 is expressed in all cell cycle phases except in the G0 phase. This makes Ki 67 superior to the mitotic rate as a better prognostic tool. Healthy breast tissue expresses very low levels of Ki-67 usually less than 3%. In ductal carcinoma in situ (DCIS), about 40% of tumours show high levels of Ki-67 and lobular carcinomas express low levels of Ki-67 index [4].

Other important prognostic markers of breast cancer include age, histopathologic subtypes, tumour size, tumour grade, lymph node metastasis, extracapsular extension and lymphovascular invasion [5].

American Society of clinical oncology recommends the use of Ki67 as a prognostic index in post-menopausal women with early-stage breast cancer to decide on adjuvant endocrine treatment and chemotherapy when other gene markers are not available [6].

A majority agreed at St. Gallen/Vienna 2021 consensus, on the use of the Ki-67 index in women with ER-positive, HER2-negative, node-negative early breast cancer to decide on adjuvant chemotherapy. Ki-67 proliferative index above 30 warrants adjuvant chemotherapy [7].

This study is to analyse the correlation of the Ki-67 index with other prognostic markers of invasive ductal breast cancers in a single institution.

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## 2. Material and method

This is a retrospective descriptive cross-sectional study performed at the Surgery and Histopathology departments of Teaching Hospital Jaffna from January 2020 to July 2022. This study includes 143 pathological specimens (Both biopsies and excision specimens) of invasive ductal cancer patients from surgical units which were processed at the Department of Histopathology of Teaching Hospital Jaffna. This includes mastectomies, wide local excisions and tru cut/core biopsies. Data was extracted from the histopathology reports of the patients documented at the Department of Histopathology. Ethical clearance was not obtained for the study as it doesn't involve any patient consent. Details regarding age, type of specimen, hormone receptor expression, Human epidermal growth factor receptor expression, Ki-67 proliferative index, Tumor size, Lymphovascular invasion and perineural invasion were collected.

Score of Ki-67 proliferative index above 20 was considered high and below 20 as low [8]. The correlation between Ki-67 and other prognostic markers such as age, tumour size, Nottingham grade, ER, PR, HER-2neu expression, Lymphovascular invasion and perineural invasion was analysed as categorical variables using chi square test. Data were expressed as mean and standard deviation. P value of less than 0.05 was considered as statistically significant.

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## 3. Results

A total of 143 histopathological specimens of invasive ductal carcinoma patients were analysed. Among them, 101 were tru cut/ core biopsy specimens and 42 were mastectomy/ wide local excision specimens. The mean age of the patients was 57.04  $\pm$  12.19 years (30-91).

ER, PR, HER-2 neu positivity was noted in 100 cases (69.9%), 85 cases (59.4%) and 41 cases (28.7%) respectively. Lymphovascular and perineural invasion was found in 19 (17.3%) and 4(3.6%) cases respectively. Nottingham tumour grade 1,2 and 3 was noted in 16(11.2%), 74(51.7%) and 38 (26.6%) cases respectively.

High Ki-67 proliferative index (>20) was noted in 107 (74.8%) cases and low (<20) in 36 (25.2%) cases.

Mean Ki-67 proliferative index was found to be 40.21 %. Statistically, significant correlation was noted between ER, PR positivity and Ki-67 proliferative index with p values of 0.020 and 0.010 respectively. The correlation between HER-2 positivity and Ki-67 was not statistically significant,  $p > 0.05$  (Table 1).

**Table 1** Correlation between Ki67 index and Hormone receptor/HER2 neo status

Receptor	Ki67		p value
	<20	>20	
ER			
Positive	31	69	0.020
Negative	5	38	
PR			
Positive	28	57	0.010
Negative	8	50	
HER 2 neu			
Positive	6	35	0.066
Negative	30	72	

Significant correlation was found between the Ki-67 proliferative index and the Nottingham tumour grade (Table 2). Correlation between Ki-67 proliferative index and ER+, PR+, HER2, ER+, PR - HER2+, Tripple negative and HER 2 + groups were noted to be statistically significant,  $P = 0.015$  (Table 3).

**Table 2** Correlation between Ki67 and sub groups of receptor status

Hormone receptors	Ki67type		P value
	<20	>20	
ER+, PR+, HER2-	28	51	0.015
ER+, PR +and HER2+	3	19	
Triple negative	2	23	
HER 2 +ve	2	14	

**Table 3** Correlation between Ki67 and Tumour grade

Ki 67	Tumour grade			P value
	1	2	3	
<20	9	17	4	0.001
>20	7	57	34	

#### 4. Discussion

The primary scope of the study is to analyse the correlation between Ki-67 and the other well-known prognostic markers of breast carcinoma. With the advent of gene studies and molecular analysis in medicine, various genetic tests and markers are being used and recommended in the management of breast carcinoma which includes BRCA, Oncotype DX, Endopredict, PAM 50, mamaprint, Ki-67 and etc. [9].

Although Ki-67 has been used as a predictive and prognostic marker in breast cancer management, the American Society of clinical oncology didn't recommend it as a routine biochemical marker. It might be due to inadequate data and evidence regarding the use of Ki-67 in breast cancer, variability in the cutoff values and lack of standardized procedure in the assessment of Ki-67 [10].

The 2009 St. Gallen consensus recommended the division of Ki-67 subgroups as low ( $\leq 15\%$ ), intermediate (16% to 30%), and high ( $\geq 30\%$ ), the 2011 St. Gallen consensus recommended a Ki-67 cut-off point of 14% for distinguishing between Luminal A-like and Luminal B-like tumours, the 2013 St. Gallen changed the cut-off point to 20%, the 2015 St. Gallen advised the Ki-67 values between 20% and 29% was used to distinguish luminal B-like disease and the 2021 St. Gallen consensus recommends that in patients with ER-positive HER2-negative, early breast cancer a low Ki-67  $\leq 5\%$  would not warrant chemotherapy, whereas a Ki-67  $\geq 30\%$  would justify chemotherapy [7,10].

But the latest guidelines of American Society of Oncology recommend the use of Ki-67 in postmenopausal women with early breast cancer to decide on adjuvant chemotherapy or endocrine therapy when other gene studies are not available [6]. These time-to-time variations and lack of guidelines make researchers dig further into the impact of Ki-67 in breast cancer prognosis.

#### 4.1. Correlation between Ki-67 and Hormone receptors

The correlation between Ki-67 and hormone receptors varies among published literature. The current study showed a significant correlation between Ki-67 with ER and PR positivity. One of the largest studies carried out in Germany with 1232 patients showed a significant correlation between Ki-67 and ER/PR negativity [11]. A similar study conducted among 194 Pakistani patients showed a significant association between Ki-67 and PR positivity but a negative correlation with ER positivity [12]. Another study on 258 post-radiotherapy breast cancer patients in Turkey showed high expression of Ki-67 was associated with ER/PR negativity [10]. Anyhow in the current study majority of the ER negative and PR negative patients had a high Ki-67 index. (Table 1)

Molecular classification of breast cancer is used in the breast cancer nomenclature and also predicts the prognosis. It is based on the hormone receptor status, Her 2 neu status and Ki-67 index [2]. Triple-negative and Her-2 positive subtypes have a significant correlation with Ki-67 proliferative index and the majority of those had a high Ki-67 proliferative index ( $p=0.010$ ) (Table 2). Correlation between Ki67 and Her 2 neu receptors

The current study showed a negative correlation between Her-2 positivity and Ki-67 proliferative index. There are controversies in the literature [10,12]. In this study majority of the HER2 negative patients had a high Ki-67 index though it is shown as statistically non-significant (Table 1)

#### 4.2. Correlation between Ki-67 and tumour grade

In the current study, tumour grade had a positive correlation with Ki-67 proliferative index with statistical significance ( $p=0.012$ ). It is also shown similarly in the published literature [10-12]. Majority of the patients with grades 2 and 3 had a high Ki-67 proliferative index (Table 3).

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### 5. Conclusion

This study showed that high Ki-67 expression is associated with high tumour grade, ER/PR positivity and HER2/neu negativity. Varying results with the published literature limit the scope of the study and warrant large-scale analysis with a larger sample size.

#### *Limitations*

This study included only 143 samples. The results would be better in case of large sample sizes. None of the studies has been done in this part of the world and the presence of regional variations should also be considered.

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### Compliance with ethical standards

#### *Disclosure of conflict of interest*

There is no conflict of interest between the authors as everybody is aware of the work and participated actively and equally.

*Statement of ethical approval*

Ethical approval was obtained in the Ethics Review Committee, Teaching Hospital, Jaffna, Sri Lanka.

*Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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