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ORIGINALRESEARCH ARTICLE

Ki-67 Expression in Breast Cancer: Association with Molecular Classification and Prognostic Indicators

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ABSTRACT

Introduction: Breast cancer is the most common malignancy in female and the second most common cause of death in women. Prognostic factors are essential in identifying high-risk patients, where adjuvant therapy can improve outcomes. Ki-67, a potential marker of breast cancer, has gained importance recently for predicting the responsiveness to chemotherapy. Different Molecular subtypes (Luminal A, Luminal B, HER2-enriched, Triple-negative/Basal-like) exhibit diverse proliferative activities, influencing therapeutic strategies and prognostic assessments. Histopathological grading further underscored tumour aggressiveness, particularly in HER2-enriched and Triple-negative/Basal-like subtypes with elevated Ki67 levels. Aims/Objectives: To evaluate the association of Ki-67 proliferative index with molecular subtypes & clinicopathological prognostic parameters in breast carcinoma.

Materials and Methods: This is a retrospective study conducted between January 2024 and December 2025 .Ki-67 expression was assessed in 45 cases of biopsy-proven primary breast carcinoma in patients , who underwent radical or modified radical mastectomy . Association with other prognostic parameters (tumour histological type, grade, and lymph node metastasis,ER PR,HER2 ,P53 & molecular subtypes), was evaluated .Statistical analysis was done by Chi square test and a p value of <0.05 was taken as significant.

Results: Increased Ki-67 expression is seen with high tumour grade, lymph node metastasis, HER2 positivity, and P53 mutations. Conversely, it has a strong inverse relationship with ER/PR receptors .Ki-67 expression was not significantly related to age, tumour size, or specific histological subtype.

Conclusions: By incorporating proliferative index into routine histology reporting can guide clinicians for prediction of disease progression and management, therefore can determine survival rate and overall patient outcomes.

Keywords: Breast carcinoma, Ki-67, Proliferative index.

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INTRODUCTION

GLOBOCAN 2022 data show that breast cancer is the second most common cancer worldwide, accounting for approximately one quarter of all cancers diagnosed in women. In India, breast cancer is the leading malignancy among women, constituting about 27% of all female cancers and posing a major public health concern. Although India ranks third worldwide in terms of breast cancer incidence (192,020 cases), it records one of the highest mortality burdens, with 98,337 deaths reported in 2022. The incidence and mortality rates among younger females (≤29 years) are considerably high in India, further aggravating health care concerns. [1]

Various predictive and prognostic factors affect tumour progression.[2–4] Predictive factors are distinguished from prognostic factors in that the latter can be measured and are associated with the nature of the disease, whereas the former

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determine the response to treatments.[2] Some factors are both prognostic and predictive, including oestrogen receptor (ER) and progesterone receptor (PR) status, p53 mutation status, and human epidermal growth factor receptor (HER2/ neu) overexpression. Prognostic factors include the type of tumour, number of involved lymph nodes at the time of tumour diagnosis, size of the tumour, tumour grade, Ki67 status (cellular marker for proliferation), and the patient's age.[3–5]

The presumed correlates of a favourable prognosis, about morphological markers, include smaller tumour size,.[6]special histological types in comparison to the commonest type i.e. infiltrating duct carcinoma-No special type (IDC-NST) [7, 8]; low tumour grade based on the modified Scarf Bloom Richardson (SBR) system [8]; [9]. The status of axillary lymph node serves as an independent predictor of both disease-free survival and overall survival in patients with breast cancer. [9–12]

High Ki-67 is a sign of poor prognosis associated with a good chance of clinical response to chemotherapy.[14] Studies show that p53 mutations are present in up to 50% of invasive breast carcinomas with poor clinical outcomes.[14]

The present study was conducted to analyse the correlation of proliferative index with various pathologic prognostic parameters like molecular subtypes, histopathological grades and types in breast cancer.

MATERIALS AND METHODS

The was a retrospective study in a tertiary care hospital from January 2024 to January 2025 on 45 histologically confirmed cases of primary breast carcinoma in Trucut biopsy, mastectomy, or modified radical mastectomy. Exclusion criteria include Patients who are treated with neoadjuvant chemotherapy. Male breast carcinoma, recurrent breast carcinoma & metastatic breast carcinoma. College of American Pathologists (CAP) protocol was used for histopathological examination.[16] Clinical & pathological data were extracted from medical records including age, sex, family history histologic type , histopathological grade (I-III),tumour stage(I-IV),oestrogen receptor (ER),Progesterone receptor(PR),HER2 status,ki67 proliferation index and p53 expression. Tumour size (T) and lymph node(N) status were also documented. All the data were compiled & analysed for Ki-67 expression in molecular subtypes & other prognostic indicators.

Table Fig 1 : Baseline characteristics of the study population

Variables	*Characteristics*	*Number*	*percentage*
Age group (in years)	Mean	47.0	
	Standard deviation	10.05	
	Range	30-70	
Side of breast affected	Left	19	42.22%
	Right	26	57.77%
Tumour size	<2cm	5	11.11%
	2-5 cm	27	60%
	>5 cm	13	28.88%
Histopathological type	Invasive ductal carcinoma	42	93.33%
	Invasive Lobular carcinoma	3	6.66%
Lymph node status	negative	8	17.77%
	1-4	24	53.33%
	>4	13	28.88%
Histological Grade	Grade I	8	17.77%
	Grade II	30	66.66%
	Grade III	7	15.55%
ER status	positive	24	53.33%
	Negative	21	63.63%
PR status	positive	18	40%
	Negative	27	60%
HER2 status	positive	20	44.44%
	Negative	25	55.55%
P53 expression	positive	28	62.22%
	Negative	17	37.77%
Ki-67	<20%	20	44.44%
	>20%	25	55.55%

Immunohistochemical scoring and interpretation as per the following protocol

ER/PR Reporting

Nuclear positivity was assessed in tumour cells. The percentage of tumour cells showing positivity was noted, and staining intensity was graded (1 + for weak, 2 + for moderate, and 3 + for intense staining).[17, 18]

HER2neu Reporting

Scored as negative, 1+, 2+, or 3 + according to the Hercep

Table/Fig 2 : Ki-67 expression in breast cancer and association with clinic-pathological parameters

Variables	*Subtypes*	*Ki-67 <15%*		*Ki-67>15%*		χ^2, *p-Value*
		No.	***%***	***No.***	***%***	
Age	<50 years	14	39%	22	61%	$\chi^2 = 0.0926$, df = 1, p = 0.761 (Not Sig.)
	>50 years	4	44%	5	56%	
Tumour Size	<2 cm	2	40%	3	60%	$\chi^2 = 0.019$, df = 2, p = 0.991 (Not Sig.)
	2–5 cm	11	40%	16	60%	
	>5 cm	5	39%	8	61%	
Lymph Node Status	Negative	6	75%	2	25%	$\chi^2 = 9.108$, df = 2, p = 0.011 (Sig.)
	1–4	6	25%	18	75%	
	>4	2	15%	11	85%	
Histological Grading	I	7	88%	1	12%	$\chi^2 = 8.825$, df = 2, p = 0.012 (Sig.)
	II	12	40%	18	60%	
	III	1	14%	6	86%	
Histopathology Types	IDC	28	62%	14	31%	$\chi^2 = 1.3578$, df = 1, p = 0.244 (Not Sig.)
	ILC	1	33%	2	67%	
ER Status	Positive	17	71%	7	29%	$\chi^2 = 14.504$, df = 1, p = <0.001 (Highly Sig.)
	Negative	3	14%	18	86%	
PR Status	Positive	13	72%	5	28%	$\chi^2 = 12.978$, df = 1, p = <0.001 (Highly Sig.)
	Negative	5	19%	22	81%	
HER2 Status	Positive	4	19%	16	81%	$\chi^2 = 6.000$, df = 1, p = 0.014 (Sig.)
	Negative	14	55%	11	45%	
p53 Expression	Positive	19	68%	9	32%	$\chi^2 = 13.372$, df = 1, p = <0.001 (Highly Sig.)
	Negative	2	12%	15	88%	

Table Fig 3 : Molecular subtypes in breast cancer patients

Molecular subtypes	*Frequency (%)*
Luminal A (ER+, PR+, Ki-67<15%)	17 (37.77%)
Luminal B (ER+, PR+, Ki-67>15%)	7(15.55%)
HER2 enriched (HER2+, ER-, PR-, Ki-67>15%)	16(35.55%)
Basal like (Triple negative)	5(11.11%)

Table Fig 4 : Association of Ki-67 with molecular subtypes of breast cancer patients

	Ki-67<20%	*Ki-67>20%*	*p-Value*
Luminal A	15(88.2%)	2(13.33%)	χ^2 = 33.558, df = 3, p < 0.001 (FFH exact)
Luminal B	1(14.3%)	6(85.7%)	
HER-2 NEU	0(0%)	16(100%)	
Basal like	0(0%)	5(100%)	

test guidelines. Scores of 0 or 1 + were considered Negative (no staining/faint incomplete staining), 2 + equivocal, and 3 + positive (strong complete membranous staining).[19, 20]

Ki67 Labelling Index

The percentage of positive nuclei was expressed as the Ki67 index. Tumours with <15%: Low proliferation,15-30%: Intermediate,> 30% positivity were classified as having a high Ki67 index.[21]

P53 Immunohistochemistry

P53 interpretation correlates with TP53 mutation status. Wild-type pattern: heterogeneous weak staining. *Mutant pattern*: strong diffuse (>60%) or complete absence.[22]
Molecular classification [23]

Luminal A

ER + and/or PR +, HER2- with low Ki67 (<15%)

Luminal B

ER + and/or PR +, HER2+ with high Ki67 (> 15%).

HER2-enriched

HER2 + and ER/PR-.with high Ki67(>15%)

Basal-like

Triple-negative (ER-, PR-, HER2-) with EGFR/CK5/6 positivity.

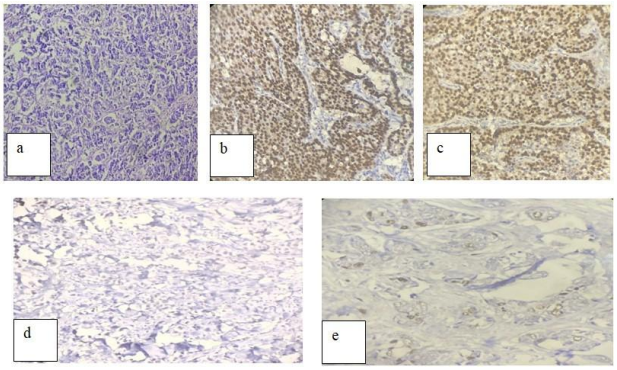

Table Fig- 1 : Molecular subtype Luminal A (a)IDC-NST- Gr 1 (H&E,100x) (b)ER +ve (IHC,400x) (c)PR +ve (IHC,400X) (d) HER2 -ve (IHC,400x) (e)Ki-67 : 10 % (IHC,400x)

Unclassified

Tumours with characteristics not fitting into any of the above categories

Statistical analysis was performed using R.**The chi-square test** was used to determine the associations between ki-67 with molecular subtypes and histopathological characteristics, with p-values ≤ 0.05 considered statistically significant. For contingency tables with expected cell frequencies <5 ,Fisher's exact or Fisher-Freeman -Halton exact test was used, as applicable.

RESULT

A total of 45 histopathologically confirmed cases of primary breast carcinoma were included in the present study. The clinicopathological parameters along with immunohistochemical findings were systematically analysed and correlated with the Ki-67 proliferative index. The age of patients ranged from 30 to 70 years, with a mean

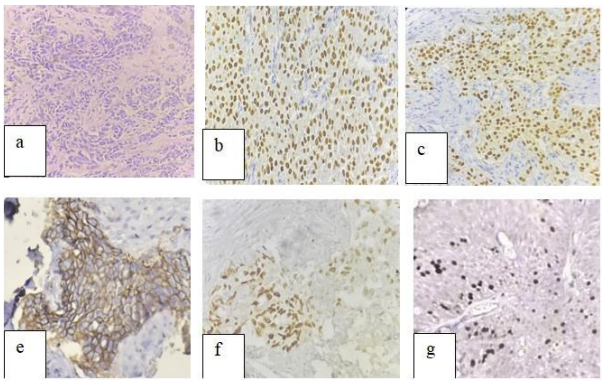

Table Fig- 2 : Molecular subtype : Luminal B ; (a)IDC-NST-gr 3 (H& E,400x),(b)ER +ve (IHC,100x),(c)PR +ve (IHC,100x),(d)HER2 +ve (IHC,100x),(e)p53 +ve ,100x,(f)Ki-67 appx.45%(IHC,100x)

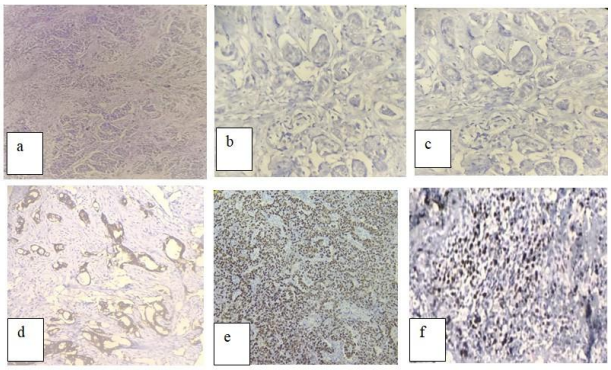

Table Fig 3: Molecular Subtype : HER2 Enriched ; (a) IDC-NST-gr 2(H&E,400X) (b)ER -ve (IHC,400x); (c)PR -ve (IHC,400x);(d) Her2 score 4+(IHC,100x)(e)P53 +ve,100x;(f)Ki-67 high appx.80%

age of 47.0 ± 10.05 years. The majority of patients were in the younger age group (<50 years).Laterality analysis revealed a predominance of right breast involvement (57.77%) compared to the left side (42.22%).Invasive ductal carcinoma (IDC) was the most common histological subtype, accounting for 93.33% (n=42) of cases. Invasive lobular carcinoma (ILC) constituted 6.66% (n=3).Tumour size distribution showed:<2 cm: 11.11% , 2–5 cm: 60% (most common) ,>5cm: 28.88%.Histological Grade shows Grade II tumours predominated (66.66%), followed by Grade I: 17.77% & Grade III: 15.55%.Lymph Node Status revealed 53.33% cases showed involvement of 1–4 lymph nodes,28.88% had >4 nodes involved, Only 17.77% cases were node-negative This indicates a high proportion of cases presenting with nodal metastasis.The immunohistochemical profile shows ER positivity in 53.33% cases, PR positivity in 40% cases, HER2 positivity in 44.44% cases, and p53 positivity in 62.22% cases. Ki-67 Proliferation Index data shows High Ki-67 (>15%) in 55.55% cases and Low Ki-67 (<15%) in 44.44% of cases. This indicates that more than half of the tumours exhibited high proliferative activity. Table Fig- 1

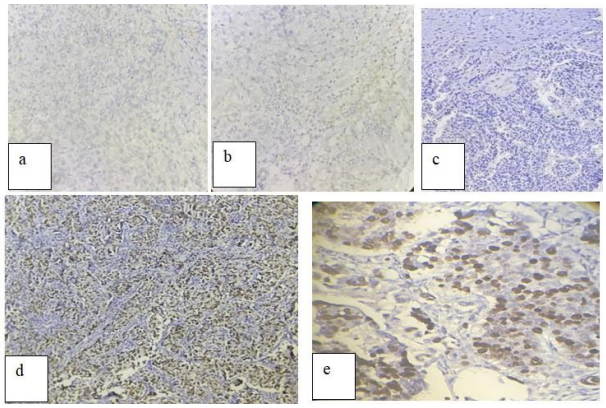

Table Fig- 4 : Molecular Subtype :Basal-Like;(a) ER -ve (IHC,400x);(b)PR -ve (IHC,400X);(c)Her2 -ve(IHC,400X)(IHC,400x)(d)P53 +ve, (IHC,100x)(e) Ki-67 high(>90%),(IHC,400x)

A significant positive correlation was observed between high Ki-67 index and Lymph node involvement($p = 0.011$) , Histological grade ($p = 0.012$) (Higher grades showed increased Ki-67 expression) ,HER2 positivity ($p = 0.014$) ,p53 expression ($p < 0.001$). Additionally, a strong inverse relationship was observed between Ki-67 and ER status ($p < 0.001$) , PR status ($p < 0.001$).ER/PR-negative tumours showed significantly higher proliferation.

No statistically significant correlation was found between Ki-67 and Age ($p = 0.761$; Fisher's exact $p = 1.000$), Tumour size ($p = 0.991$) & Histological type ($p = 0.244$; Fisher's exact $p = 0.285$). This indicates that Ki-67 acts as an independent proliferative marker, not influenced by these variables.Table/Fig- 2

The distribution of molecular subtypes was as follows: Luminal A: 17 cases, Luminal B: 7 cases, HER2-enriched: 16 cases, Basal-like (Triple-negative): 5 cases. Table Fig- 3

A highly significant association was observed between Ki-67 expression and molecular subtypes ($p < 0.001$; Fisher-Freeman-Halton exact test).

The below table Table Fig- 4 shows Luminal A tumours showing Predominantly low Ki-67 (88.2%) ; Luminal B tumours showing Majority high Ki-67 (85.7%) .In HER2-enriched subtype,100% cases showing high Ki-67 & in Basal-like subtype ,100% cases showing high Ki-67.The association is clinically coherent: Ki-67 >20% (high proliferative index) was present in 100% of HER-2 NEU and Basal-like subtypes, compared to only 13.3% of Luminal A — fully consistent with established breast cancer biology.

To summarize, Ki-67 expression increases with tumour aggressiveness, as reflected by higher histological grade, greater lymph node involvement, HER2 positivity & p53 expression. Ki-67 shows a negative association with hormone receptor positivity, indicating; ER/PR-positive tumours are less proliferative whereas ER/PR-negative tumours are more aggressive. The marker is independent of age, tumour size, and histological subtype, reinforcing its reliability. A clear gradation of proliferation across molecular subtypes was observed: Lowest: Luminal

A; Table Fig- 5 Intermediate: Luminal B; TableFig- 6 Highest: HER2-enriched Table Fig- 7 & Basal-like. Table Fig- 8

DISCUSSION

Ki-67 is a well-established nuclear antigen associated with cellular proliferation and is widely used as a prognostic and predictive biomarker in breast carcinoma. It acts as a marker of tumour aggressiveness ,therefore help the clinicians in classify patients into various molecular subtypes that aids in therapeutic decision making, particularly chemotherapy. [14, 24]

Our study demonstrated a statistically significant association between Ki-67 and histological grade .Higher-grade tumours show increased ki-67 index.Similar findings finding are reported in previous studies by Urruticoechea A et al.[14] and Dowsett M et al. [25]. .

Ki-67 expression is also significantly associated with lymph node metastasis in our studyIt indicates that tumours with increased proliferative activity has a greater tendency to metastasize. This type of association was also found in other studies by Inwald EC et al.[26]

Our study also highlights a significant inverse association between Ki-67 and hormone receptor status (ER and PR). ER/PR negative tumors shows increased Ki-67 indices. Similar observation was found by Cheang MC et al.[27] Decreased Ki-67 in hormone receptor positive tumors (luminal types) may be attributed to their slower growth rate and favourable prognosis.

On the other side, HER2-positive tumours show increased Ki-67 expression in this study similar to Slamon DJ et al [28] .Her 2 overexpression promotes tumour proliferation through activation of different growth signalling pathway . The association between ki-67 and Her 2 further highlights its role in aggressive behaviour.

An important finding in the present study was the significant association between Ki-67 and p53 expression. Tumours with p53 positivity exhibited higher proliferative indices, indicating genomic instability and aggressive tumour behaviour. This is in agreement with studies by Petitjean A et al., who demonstrated that p53 mutations are frequently associated with high-grade tumours, increased proliferation, and poor clinical outcomes.[29]

Our study further shows strong association between Ki-67 and molecular subtypes that further validates its biological significance. Luminal A tumours mostly possess low Ki-67 indices, whereas Luminal B, HER2-enriched, and triple-negative subtypes showed higher proliferative activity. 100% of HER2-enriched and basal-like tumours demonstrated high Ki-67 expression, which is consistent with established molecular classifications of breast cancer. These findings are supported by other studies like Perou CM et al., who first described the intrinsic subtypes of breast cancer, specific to their biological behaviours [30], and Goldhirsch A et al. emphasised the role of Ki-67 in distinguishing Luminal A from Luminal B tumours for therapeutic decision-making [31]

Interestingly, no significant association was found between Ki-67 and age, tumour size, or histological subtype in the present study. Similar observations have been reported in several studies, suggesting that Ki-67 is an independent marker of proliferation and is not directly influenced by demographic or tumour size variables [24, 32]. This independence enhances its value as a robust biomarker in clinical practice.

CONCLUSION

Our study conclude that Ki-67 is a reliable marker in breast cancer, as it shows significant association with tumour grade, lymph node involvement, molecular subtypes and p53 expression. Increased Ki-67 levels were mostly observed in aggressive molecular subtypes like HER2-enriched and basal-like .On the other side, luminal A tumours showed decreased proliferative activity. So,incorporation of Ki-67 into routine breast cancer reporting along with histological & immunohistochemical marker can can guide clinicians for better risk stratification & patient management.

LIMITATIONS

As this study was undertaken in a newly established Medical college ,sample collections are fewer ,and limited histological subtypes were found.

AUTHOR DECLARATION

Conflict of Interests

None

Was informed consent obtained from the subjects involved in the study?

Yes

For any images presented, appropriate consent has been obtained from the subjects

Yes

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