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Original Article

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A Study on Association of Her2/neu and Ki - 67 Positivity with Extent of Disease in Breast Carcinoma

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ABSTRACT

Background: Breast carcinoma has become a serious threat worldwide, owing to the increasing incidence of the disease in both developing and developed countries.
Aims and objectives: To study the association between Her2/neu and Ki-67 values and the extent of disease in breast carcinoma.
Methods: This was a hospital based cross-sectional study conducted over the duration of 18 months. All the females admitted with breast cancer reporting the health facility were included in the study. Their detailed medical history, clinical information, and laboratory investigations were recorded in excel and analysed.
Results: Mean age of participants was found to be 49.12±10.64 years. 91.2% females were multiparous. History of breast feeding was reported in 88.2% females, 38.2% females had history of HRT/OCP intake and 32.4% females had positive history of chemoradiation for breast cancer. On histopathology. Majority (85.3%) of cancer were ductal carcinoma. PR, ER, Her2neu and Ki67 >14 expression was reported in 41.2%, 55.9%, 8.8% and 94.1% of findings respectively. 96.2%, 91.2% and 85.3 of grade 3 tumours reported Ki67 >14, Her2neu and Her2neu/Ki67 expressions respectively.
Conclusion: This study explored the association of Her2/neu and Ki-67 positivity with the extent of disease in breast carcinoma. Understanding various factors is essential for tailored management strategies and highlights the need for early detection and comprehensive screening programs to improve patient prognosis. Therefore, it is recommended that all individuals diagnosed with breast cancer should undergo testing for four specific markers.

Key Words: breast cancer, Her2neu expression, Ki67 expression, ductal carcinoma, management strategies.

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INTRODUCTION:

Breast carcinoma (BC) stands as the most prevalent malignancy in the female population, globally.[1] According to the WHO report from 2021, there were 2.3 million women diagnosed with breast cancer and 685,000 deaths attributed to it in 2020. This has led to a staggering count of 7.8 million women who were diagnosed with breast cancer in the past 5 years by the end of 2020, solidifying its position as the world's most widespread cancer.[2] The escalating incidence of breast cancer poses a grave threat across the globe, impacting both developed and developing nations.[1] This rise can be attributed, in part, to factors like aging and population expansion.[3] In Asia, breast cancer reigns as the most prevalent cancer and the second leading cause of cancer-related deaths in women. The Asian region accounts for a substantial 39% of all breast cancer incidents reported worldwide.[3] In India with breast carcinoma surpassing cervix carcinoma to claim the position of the most prevalent carcinoma among Indian women. This shift is attributed to the gradual evolution of Indian women's lifestyles.[1]

The identification and addressing of several modifiable risk factors, such as lifestyle choices, obesity, alcohol consumption, smoking, physical activity levels, and diet quality, could potentially contribute to the control and prevention of cancer.[4] Furthermore, the adoption of Westernized lifestyles and infection-related etiological factors has also played a role in the increased incidence and mortality of breast cancer in developing and underdeveloped countries.[3] The outcome of breast carcinoma displays significant variation, and the stratification of patients using diverse prognostic parameters has assumed paramount therapeutic importance.[1] The College of American Pathologists has delineated numerous prognostic and predictive factors that guide the clinical management of afflicted women. Established parameters such as tumour size, histological grade, histological subtype, lymph node status, over expression of HER2/neu, estrogen receptor (ER), and progesterone receptor (PR) status play a pivotal role in prognosis and treatment decisions.[1]

In current breast carcinoma management guidelines, the assessment of estrogen receptors (ER), progesterone receptor (PR), and HER2/neu expression proves to be highly valuable for predicting response to specific therapeutic interventions.[1] The human epidermal growth factor receptor 2 (HER2, also known as neu, ErbB-2, and p185Her2) emerges as a transmembrane glycoprotein possessing intracellular tyrosine kinase activity and an extracellular domain akin to the epidermal growth factor receptor's epidermal growth factor-binding domain. Approximately 20 to 25% of invasive breast cancers exhibit amplified and/or over expressed HER2/neu proto-oncogene.[3] This overexpression correlates with lower survival rates and serves as a significant predictor of response to drugs targeting this transmembrane protein, such as Herceptin.[1]

Cancer cells' unchecked proliferation stands as a hallmark trait, albeit tumours manifest diverse growth rates, spanning from slow to aggressive. Among the methodologies employed for assessing cancer cell proliferation, Ki-67 evaluation is arguably the most recognized.[3] Ki-67, a cell cycle protein, enables the measurement of the proliferative rate of tumour cells.[1] Tumours can be categorized based on a predetermined threshold into those with a high or low Ki-67 index. Tumours exhibiting a high Ki-67 index feature a greater number of proliferating cells, implying a faster growth and dissemination rate.[3] Malignancies characterized by a high proliferative index tend to have a poorer prognosis but may respond favourably to chemotherapy.[1,5]

Histopathological analysis of the aforementioned markers can have prognostic implications and also aid in the selection of patients for systemic therapy. Against this backdrop, the present study was undertaken to examine the association between HER2/neu and Ki-67 values and the extent of disease in breast carcinoma.

Materials and methods:

Study area: Department of General Surgery Gandhi Medical College and associated Hamidia Hospital, Bhopal M.P.
Study Design: Hospital based cross sectional study
Study Period: Over the duration of 18 months
Study population: All females admitted with Breast Cancer at Gandhi Medical College and associated Hospital Bhopal and Kamla Nehru Hospital during the period of study.

Consent: Written and informed consent were obtained from patients. Information was provided in a language that they could understand about the aim and objective of the study before their voluntary participation in the study.

Inclusion Criteria: All histologically diagnosed females of breast cancer with evidence of metastasis were included in the study.
Exclusion Criteria: a) histologically undiagnosed cases; b) Participation in another intervention-trial with interference of intervention on outcome of this study; c) Multiple malignancies; d) Expected lack of compliance; e) Male patients with breast cancer; f) Patients who have received prior chemoradiation for cancers other than breast.
Study tool: a) Pretested semi-structured proforma; b) Radiological investigations; c) Histological investigations ; d) Immunohistochemistry

Methodology: Permission to conduct the study was obtained by institutional ethical committee (27342/MC/IEC/2021). Patient recruitment adhered to the defined inclusion and exclusion criteria. Data collection was using semi-structured proforma. All interviews were conducted by face-to-face by the investigator. Detailed medical histories, clinical information, and laboratory investigations were collected for each patient and recorded in Microsoft Excel. Patients underwent procedures such as wedge/excisional biopsy, trucut biopsy, or mastectomy. Samples of breast carcinoma were sent to the Department of Pathology for immunohistochemical analysis.

A comprehensive range of investigations was conducted, including complete blood counts (CBP), liver function tests (LFT), ultrasound of the breast (USG Breast), fine-needle aspiration cytology (FNAC) diagnosis, histological diagnosis, and immunohistochemical analysis for estrogen receptor (ER) and progesterone receptor (PR). Additional tests included the assessment of Her2neu, Ki67 levels, chest X-rays, skull X-rays, dorso-lumbar spine X-rays, and ultrasound of the abdomen and pelvis or CT scan of the abdomen.

Statistical analysis: Resultant data were documented using a predefined Proforma and compiled in a Microsoft Excel sheet. Statistical analysis was performed using SPSS version 20 and Mecalc 19.5 software. Mean, standard deviation (SD), and percentage were used to analyze the collected data. Student's t-test was employed for measuring intergroup variance of metric data, while Fisher's exact test was utilized for non-metric data analysis. A significance level of $p < 0.05$ was established for statistical significance.

Results:

Table/ figure 1 depicts distribution of study participants on the basis of their age. Mean age of study participants was 49.12±10.64 years. Majority (35.3%) of the patients were aged between 41-50 years followed by 51-60 years (32.4%) of age.

Table/ figure 2 displays baseline details of study participants. 91.2% of females were nulliparous. Breast feeding was reported in majority of the females. History of HRT/OCP and Chemoradiation for Carcinoma breast was observed in 38.2% and 32.4% of females respectively.

Distribution of study participants on the basis of their histopathological diagnosis have been demonstrated in table/ figure 3. Ductal carcinoma was found to be the most common diagnosis among study participants.

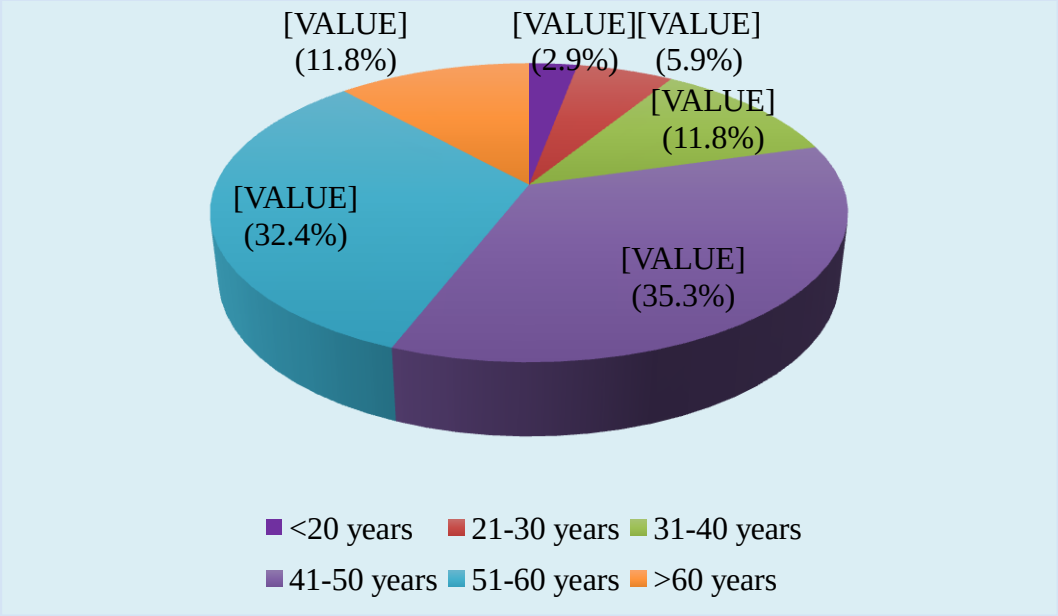
The TNM staging of tumour have been observed in table/ figure 4. Most common tumour grade was found to be T3 followed by T2. N1 and N2 were found to be commoner grades in Nodal involvement.

Table/ figure 5 describes the distribution of tumor characteristics of study participants. Grossly, around 97% of tumors reported size more than 3 cm with Grade 3 being the commoner grade on histopathology. Expression of PR, ER and Her2/neu was positive in 41.2%, 55.9% and 8.8% of cases respectively. Expression of high Ki - 67 value was in 94.1% of cases.

Association of prognostic parameters with tumor grade have been displayed in table/ figure 6. On comparison of tumor grade with Ki-67 index, Her2neu index and Her2neu/Ki67 no significant association was observed (p>0.05).

Tables and Figures:

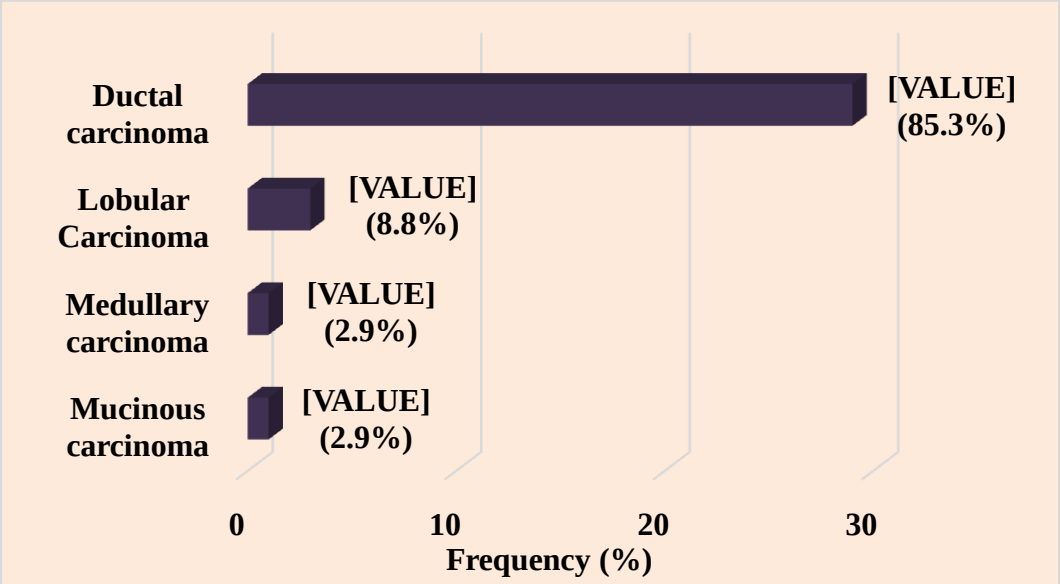
Table/ figure 1: Age-wise distribution of study participants



Table/ figure 2: Baseline characteristics of study participants

Variable	Frequency (%)
Nulliparity	3 (8.8)
Multiparity	31 (91.2)
History of Breast Feeding (Present)	30 (88.2)
History of HRT/OCP (Present)	13 (38.2)
History of Chemoradiation for Ca Breast (Present)	11 (32.4)

Table/ figure 3: Distribution of study participants on the basis of their histopathological diagnosis



Table/ figure 4: Distribution of patients according to TNM Staging

T	Frequency (%)	N	Frequency (%)	M	Frequency (%)
T1	1 (2.9)	N0	3 (8.8)	M1	34 (100)
T2	8 (23.5)	N1	14 (41.2)	-	-
T3	16 (47.1)	N2	16 (47.1)	-	-
T4a	3 (8.8)	N3a	1 (2.9)	-	-
T4b	6 (17.6)	-	-	-	-
Total	34 (100)	Total	34 (100)	Total	34 (100)

Table/ figure 5: Distribution of tumor characteristics of study participants.

Variable	Frequency (%)
Tumor Size (cm)	
<3	1 (2.9)
>3	33 (97.1)
Tumor Grade	
Grade-2	8 (23.5)
Grade-3	26 (76.5)
PR Expression	
Positive	14 (41.2)
Negative	20 (58.8)
ER Expression	
Positive	19 (55.9)
Negative	15 (44.1)
Her2neu Expression	
Positive	3 (8.8)
Negative	31 (91.2)
Ki 67 Expression	
>14	32 (94.1)
<14	2 (5.9)

Table/ figure 6: Association of prognostic parameters with tumor grade.

	Tumor grade		Total	P value
	Grade 2	Grade 3		
Ki67				

> 14%	7 (87.5)	25 (96.2)	32 (94.1)	0.307
< 14%	1 (12.5)	1 (3.8)	2 (5.9)	
Her2neu				
Negative	1 (12.5)	2 (7.7)	3 (8.8)	0.6796
Positive	7 (87.5)	24 (92.3)	31 (91.2)	
Her2neu/ Ki67+				
Negative	2 (25.0)	3 (11.5)	5 (14.7)	0.3543
Positive	6 (75.0)	23 (88.5)	29 (85.3)	
Total	8 (100.0)	26 (100.0)	34 (100.0)	

Discussion:

Breast cancer remains a significant global health concern, accounting for 20% of all cancers in women worldwide.[6] In India, breast cancer is a growing public health challenge, with over 100,000 new cases being diagnosed annually.[6] The disease has undergone a transition, becoming the most common carcinoma among urban Indian women, comprising more than 30% of all female cancers in this demographic.[6] The epidemiological landscape of breast cancer has evolved, and understanding its risk factors and prognostic markers is crucial for better management and prevention strategies.[3]
The age distribution of breast cancer patients in our study revealed interesting patterns. The mean age of patients was 49.12±10.64 years, with the majority falling between 41-50 years (35.3%) and 51-60 years (32.4%).[7] This distribution contrasts with findings from Western populations, where breast cancer often exhibits age peaks around 50-59 and 65-70 years[85]. This discrepancy may suggest that breast cancer presents at a younger age among Asian populations, including India, as compared to European countries.[8] The prevalence of carcinoma in situ in our study (24%) aligned with previous reports.[9,10]

The impact of parity on breast cancer development is complex and varies based on hormone receptor and HER2 expression.[11] In our study, nulliparous women accounted for 8.8%, while parous women constituted the majority (91.2%).[7] This contrasts with findings from Chinese and Polish populations, where increasing parity was associated with higher Nottingham Prognostic Index (NPI).[12] However, it's important to note that differences in these results might be attributed to variations in time since last childbirth. Furthermore, our study indicated a history of breastfeeding in 88.2% of cases, highlighting a potential protective factor.[7] However, the relationship between breastfeeding, hormone replacement therapy (HRT), oral contraceptive pill (OCP) use, and breast cancer outcomes remains inconsistent in the literature.[11]

Family history of breast cancer (FHBC) emerged as a significant factor in disease presentation. Women with a positive FHBC were less likely to have clinically advanced disease, potentially due to increased surveillance and early detection.[11] However, further research is needed to establish definitive relationships between FHBC, prognostic biomarkers, and clinical outcomes. A study by Gajalakshmi et al. found that less duration of breastfeeding is associated with increased breast cancer risk, and lifetime breastfeeding duration is inversely associated with risk among premenopausal women.[13]

In our study, 32.45% of women had undergone chemoradiation for breast cancer, emphasizing the role of chemotherapy in treating advanced breast carcinoma and hormone receptor-negative disease. However, a clear consensus on when to administer chemotherapy remains elusive. Certain clinicopathological factors suggest poor prognosis and potential indicators for chemotherapy, such as age under 40, lymph node status, tumor size, lymphovascular invasion, histological grade, high Ki-67 index, luminal B-Her2 neu positive tumors, hormone treatment resistance, distant metastasis, and serious disease.[14]

Our findings on histological variants align closely with Dixon et al.'s research.[15] We observed that 85.3% had ductal carcinoma, 8.8% had lobular carcinoma, and medullary and mucinous carcinoma each constituted 2.9%.[16] Examining TNM staging, most cases were categorized as T3 (47.1%) and N1 (47.2%), with all cases at M1 stage.[16] Our results somewhat match Wani et al.'s study on stage distribution.[17] Limited awareness, funding, infrastructure, and public health prioritization contribute to advanced breast cancer stages in developing countries.[18]Tumor size analysis showed that 99.1% had sizes exceeding 3 cm. Grade-3 tumors dominated (76.5%), unlike Mehta and Yadav's study.[19] Developing Asian nations exhibit lower breast cancer incidence but higher mortality rates, diagnosing patients a decade earlier with more adverse prognostic factors.[18,19]

Our study extensively examined the role of ER/PR and Her2 neu in breast cancer analysis. We observed positive PR expression in 41.2% of cases, ER positivity in 55.9%, and HER2/neu positivity in 91.2%.[20,21] ERs and PRs are crucial nuclear transcription factors involved in breast development, growth, and tumorigenesis. ER also regulates genes like progesterone and bcl2. ER alpha and ER beta, encoded by 6p25.1 and 14q, respectively, exhibit different tissue distributions.[20,] ER and PR-positive tumors tend to have better disease-free survival.[22] Conversely, Her2 neu, situated in 17q 11.2 –q12.13, indicates poorer prognosis.[21] Earlier studies demonstrated higher receptor expression, whereas our

Indian results may stem from racial, geographic, age, and grade differences.[23,24] HER2/neu positivity in our study was 91.2%, although not statistically significant, it was higher compared to a reported range of 10–34%.[24] This hints at the influence of HER2/neu positivity on the aggressive nature of breast carcinomas.

Our classification identified cases as: Luminal A (Ki-67 > 20) - 2.9%, Luminal B - 29.2%, Triple negative - 2.9%, Her-2/neu enriched - 64.4%. ER, PR, and Ki67 correlate with progression risk, while absence of PR in ER+ tumors suggests aggressiveness.[26,27] We explored tumor grade and Ki-67 index, finding comparable data among grade-3 and grade-2 tumors, although without statistical significance with similar studies.[28] High Ki67 is considered an unfavorable prognostic factor, influencing tumor progression.[28] Our contrary findings could be due to study size limitations. PR levels were unrelated to various factors, while ER+/PR- tumors exhibited greater aggressiveness.[29] HER2 over expression signifies aggressive tumor behavior.[29] Examining tumor grade and Her2/neu positivity, we noted correlations, with grade 3 tumors displaying higher Her2neu-Ki67 positivity.[29]

In summary, our study aligns with prior research on ER, PR, Her2 neu, and Ki67 correlations, shedding light on their significance in breast cancer prognosis.[20,21,25-29]

Conclusion:

This study explored the association of Her2/neu and Ki-67 positivity with the extent of disease in breast carcinoma. The findings provide insights into the demographic, histological, and molecular characteristics of breast cancer in the studied population. Age, parity, hormone receptor expression, and histological variants play complex roles in breast cancer presentation and outcomes. Understanding these factors is essential for tailored management strategies and highlights the need for early detection and comprehensive screening programs to improve patient prognosis.

Therefore, it is recommended that all individuals diagnosed with breast cancer should undergo testing for four specific markers: estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her2/neu), and Ki67. The expression levels of ER, PR, and Her2/neu are crucial in determining the appropriate treatment approach, while the expressions of Her2/neu and Ki67 play a significant role in predicting the prognosis, particularly when there is a high Ki67 expression in cases where ER and PR are absent, indicating a less favorable prognosis. Notably, breast cancer cases exhibiting elevated Ki67 expression have shown improved responsiveness to chemotherapy.

In our investigation, we observed a correlation between metastasis and high Ki67 values, as well as Her2/neu positivity; however, these associations did not achieve statistical significance. This contrasts with previously documented findings, possibly due to the limited size of our study's sample. Analyzing the expression of these immunohistochemical markers in early-stage breast cancer holds promise in anticipating disease progression and aiding in the formulation of more effective treatment strategies.

Limitations: The study's constraints encompass its exclusive reliance on a single center for patient data, an insufficiently small sample size to establish definitive outcomes, and the lack of a comparison group to corroborate the findings.

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