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Original Article

Her2/Neu Immunoexpression in Primary Breast Carcinoma and its Correlation with Er/Pr Status and Various Clinicopathological Features

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ABSTRACT

Background: Breast Carcinoma (BC) is a heterogeneous disease characterized by a wide range of morphological, molecular, and behavioural differences, contributing to variability in prognosis and treatment response. The human epidermal growth factor receptor 2 (HER2/NEU) is a transmembrane protein that plays a pivotal role in the pathogenesis of certain types of breast carcinoma. High HER2/NEU expression is associated with aggressive disease characteristics, including increased risk of recurrence and reduced overall survival. Despite this, HER2/NEU expression serves as an essential biomarker for predicting response to targeted therapies, such as trastuzumab, which significantly improves outcomes in HER2-positive patients.

Materials and methods: A total of 125 breast carcinoma cases were studied for the clinicopathological features followed by immunohistochemical study in the Department of Pathology. The lumpectomy or mastectomy specimens were fixed in 10% neutral buffered formalin immediately after surgery. Important clinical information from patients were collected in proforma. Finally routine hematoxylin and eosin sections were examined to confirm presence of invasive carcinoma, ascertain histological types, Histological Bloom Richardson grade (BRG) and axillary lymph node status. IHC of HER2/NEU, ER, PR protein was done using antibody following standard procedures.

Results: Hormone receptor analysis highlighted a high-risk profile: only 40.8% were ER-positive and 15.2% PR-positive, while the majority were receptor-negative, limiting endocrine therapy options. HER2/neu positivity was observed in 22.4% of cases, more common in pre-menopausal women and strongly associated with higher-grade tumors, particularly Grade 3, and inversely correlated with ER/PR expression. Overall, the findings underscore that breast carcinoma in this cohort predominantly affects older, post-menopausal women, often presenting late, with a substantial proportion lacking hormone receptor expression, emphasizing the urgent need for improved screening, awareness, and early detection strategies.

Conclusion: Breast carcinoma patients have good overall survival when treated with combination of surgery, chemotherapy, radiotherapy, targeted therapy, and hormonal therapy as per the indication. Estrogen receptor and progesterone receptor (ER and PR) and c-erb B-2 protein (HER2/neu) status remain one of the most important factors in determining response to treatment and prognosis of disease.

Keywords*: breast carcinoma, immunohistochemistry, Her2/neu, ER, PR, bloom Richardson grade.*

INTRODUCTION

Breast carcinoma is a heterogenous disease with variable biological and clinical characteristics because of its varied genetic make-up.[1] The death rate has been fundamentally decreased lately due to its early determination and the latest treatment modalities for treatment; but it is as yet a major reason of death from malignant growth in ladies in European and Western nations, just behind lung carcinoma.[2]

The incidence of breast carcinoma is increasing rapidly in India. Statistics reveal that it has overtaken carcinoma of the cervix[3] Certain factors increase the risk of breast carcinoma including increasing age, obesity, harmful use of alcohol, family history of breast carcinoma, history of radiation exposure, reproductive history (such as age that menopausal periods began and age at first pregnancy), tobacco use and postmenopausal hormone therapy. Approximately half of breast carcinomas develop in women who have no identifiable breast carcinoma risk factor other than gender (female) and age (over 40 years).[4]

An association has been found to exist between ER/PR status, Her-2/neu amplification or over expression and a wide variety of different clinical and pathological features including tumor size, tumor grade, stage, aggressiveness, proliferation, axillary lymph node status, age, sex, menopausal status, histological subtype etc.[5,6] ER/PR and Her-2/neu immunostaining are important prognostic markers and are important for from treatment point of view as well. Determination of ER/PR and Her-2/neu status in biopsy specimen prior to therapeutic intervention is now advocated as a standard practice.[7]

HER2/NEU (c-erb-B2) gene product is a 185 KD transmenbrane glycoprotein associated with tyrosine kinase activity. High levels of human epidermal growth receptor 2 (HER2/NEU) expression are associated with recurrence and death in breast carcinoma (BC) patients. Evaluation of HER2/NEU gene status is an important prognostic and predictive biomarker in breast carcinoma management. Over expression of this protein is seen in 15-30% cases. Though it is associated with poorer survival but its main importance is as predictors of response to agents that target this transmembrane protein (transtuzumab).[3]

AIM AND OBJECTIVES

The aim of the study was to evaluate the expression pattern of HER2/NEU in invasive component of breast carcinoma and correlate with Estrogen and Progesterone Receptor status and various clinic-pathological factor.

Objectives:

1. To determine the expression of HER-2/NEU in breast carcinoma
2. To determine the expression of ER/PR in breast carcinoma
3. To correlate the expression of HER-2/NEU with ER/ PR and various clinicopathological parameters like age, sex, menopausal status, grade of the tumor, stage of the tumor, and lymph node status.

MATERIALS AND METHODS

We analyzed the obtained biopsy specimens in 10% buffered formalin. A completely filled surgical pathology requisition form was verified, which included the patient's identification, age, sex, essential clinical information, provisional clinical diagnosis, and the submitted tissue.

Grossing was performed and processed according to standard protocol. Formalin-fixed and paraffin-embedded sections were subjected to routine Haematoxylin and Eosin staining. Immunohistochemistry for HER2/neu, ER, and PR was conducted in all cases.

For HER2/neu, we employed a rabbit monoclonal antibody (RMPD008) c-erb-2 oncoprotein (SP3). For ER, the rabbit monoclonal antibody (RMPD001), estrogen receptor (SP1), was utilized, and for PR, the rabbit monoclonal antibody (RMPD002), progesterone receptor (SP2), was used Interpretation of the IHC Scoring was carried as given below

Allred scoring framework was utilized for ER and PR (a negative outcome was characterized as a score of 0 or 2 and positive between 3 -8) (Table 1)

Table 1: Allred Scoring System

	Percentage of Positive Cells		**The Intensity of the Stain**
0	No positive cells	0	No positive stain
1	Positive cells <1%	1	Weak nuclear stain
2	2-10% positive cell	2	Moderate nuclear stain
3	11-33% positive cell	3	Strong nuclear stain
4	34-66% positive cell		
5	>66% positive cell		

The IHC score for Her2/neu ranges from **0 to 3+**:

0: No staining observed or barely perceptible membrane staining within ≤ 10% of invasive tumor cells.
1+: Incomplete faint membrane staining observed in > 10% of invasive tumor cells.
2+: Weak to moderate complete membrane staining seen in > 10% of invasive tumor cells.
3+: Strong complete reactivity observed in > 10% of tumor cells

Interpretation:

- **score of 3+** is categorized as **HER2 positive**.
- Score of 2+ is categorized as **equivocal**
- If the IHC result is **1+**, the cancer is considered **HER2-negative**.

Descriptive and Inferential statistical analysis has been carried out in the present study using computer software (IBM SPSS version 23). The qualitative data were expressed in number and percentages and the quantitative data expressed as mean and standard deviations. Association were analyzed by using chi-square test. Significance level for tests was determined as 95% (P< 0.05).

RESULTS

Out of 125 cases of breast carcinoma, 68 were modified redical mestectomy and the rest were lumpectomy or tru cut specimens. The mean age was 52.76 years with a standard deviation of 11.24 This result is statistically significant ($p < 0.05$). In the present study, the majority of breast carcinoma patients were above 40 years of age, with 89% falling into this category. This confirms the well-known trend that breast carcinoma incidence increases with age, particularly in peri- and post-menopausal women. Correspondingly, 62% of the patients in this study were post-menopausal, further supporting the established association between advancing age, hormonal changes, and breast carcinoma development.

This study showed a higher occurrence in the left breast compared to the right breast. Out of 125 cases, 75 cases (60%) involved the left breast, while 50 cases (40%) involved the right breast. This indicates a predominance of left-sided breast carcinoma .This result is statistically significant ($p < 0.05$).

Tumor size analysis revealed that most patients presented with lesions measuring 2–5 cm (73.6%), followed by tumors larger than 5 cm (10.4%). Only 16.2% had tumors smaller than 2 cm. This distribution suggests delayed detection and late clinical presentation, which is a common challenge in low-resource settings. Early-stage tumors (<2 cm) were comparatively fewer, reflecting possible gaps in screening practices or awareness.

Histopathological evaluation showed that infiltrating ductal carcinoma (IDC) constituted the majority (96%) of cases, which is consistent with global literature claiming IDC as the most prevalent breast carcinoma subtype. Other variants such as invasive lobular (3.2%)and mucinous carcinoma (1.8%)were rare in this sample. Tumor grading revealed a predominance of Grade 2 tumors (61%), indicating an intermediate level of differentiation; however, interpretation is limited due to a high proportion (45%) of cases with missing grading data.

Table 2: Characteristics of the Infiltrating BreastCarcinoma Patients.

Parameter	Category	N	%
Age	<40	14	11
	>40	111	89
Menopause	Pre-menopausal	47	38
	Post menopausal	78	62
Tumor size	<2 cm	24	19.2
	2-5 cm	50	40
	>5 cm	30	24
	Not available	21	16.8
Histological Type	Infiltrative ductal carcinoma	120	96
	Invasive lobular carcinoma	4	3.2
	Mucinaus	1	1.8
	Medullary carcinoma	0	0
Tumor grading	Grade1	18	26
	Grade2	42	61
	Grade3	8	11
	Not available	57	45

Table: 3 Comparisons of ER, PR Her2neu test outcome in between premenopausal and post-menopausal age groups

Parameter	Category	Pre-menopausal	Post-menopausal	Total

ER	Positive	15(29%)	36(71%)	51
	Negative	32(36%)	55(64%)	74
PR	Positive	5(26%)	14(74%)	19
	Negative	42(39%)	64(61%)	106
Her2/neu	Positive	15(53%)	13(47%)	28
	Negative	28(32%)	57(68%)	85
	Equivocal	4(33%)	8(67%)	12

Overall, the findings highlight a population where breast carcinoma predominantly affects older, post-menopausal women, with many presenting at later stages. These results emphasize the need for early detection strategies, community awareness, and strengthened screening programs to improve outcomes

The provided data reveals a significant trend toward hormone receptor negativity and post-menopausal prevalence within this patient cohort (N = 125). Regarding Estrogen Receptor (ER) status, only 40.8% of the total population tested positive, with the majority (71.4%) being post-menopausal. Conversely, a substantial 59.2% of patients were ER-negative, a group dominated by post-menopausal women at 64% of the total(p-value<0.05). The Progesterone Receptor (PR) results show an even steeper decline in positivity, with only 15.2% of all patients testing positive, while a staggering 84.8% were PR-negative. Within this negative group, over half of the entire study population (51.2%) consisted of post-menopausal women(p-value<0.05).

The Her2/neu profile presents a more distributed pattern; 22.4% of the total cases were positive, notably showing a slightly higher concentration in pre-menopausal women (12%) compared to post-menopausal women (10.4%). The majority of the cohort, 68%, tested negative for Her2/neu, while 9.6% fell into the "equivocal" category—a clinical gray area where 6.4% of the total patients were post-menopausal and 3.2% were pre-menopausal. Collectively, these percentages suggest a high-risk patient profile, as the overwhelming majority (nearly 70–85%) lack hormone receptor expression, potentially limiting the use of endocrine-based therapies. Here $P < 0.001$, which indicates a highly significant association between age group and HER2/neu positivity.

When HER2/NEU profiles were correlated with ER, PR expression profiles, it derived into a inverse correlation (p value < 0.05). The HER2/NEU positive tumours have less chance of having expression of ER PR. The data of HER2/NEU expression profiles were correlated with 3 BRG histologic grades of the tumours. Although Grade 3 has the smallest sample size (8 cases), it shows the highest prevalence of HER2 positivity at 62.5%. This aligns with clinical expectations, as HER2/neu overexpression is frequently associated with more aggressive, higher-grade tumors.

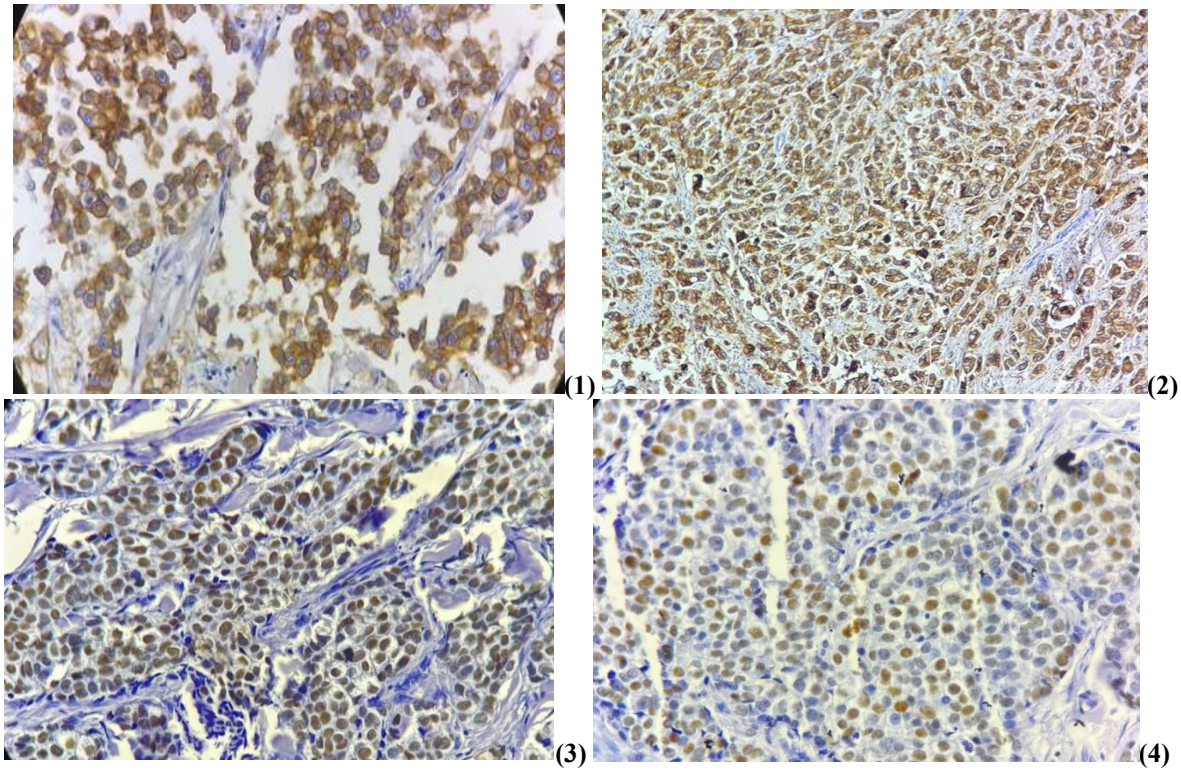
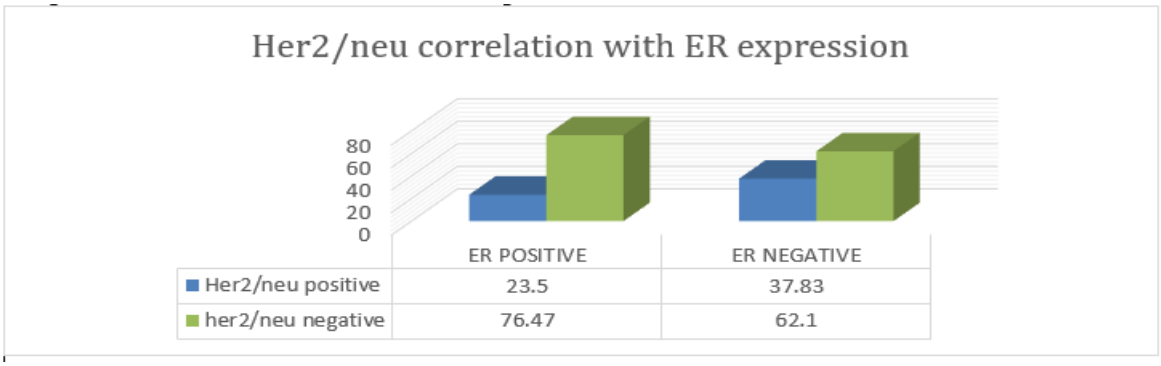
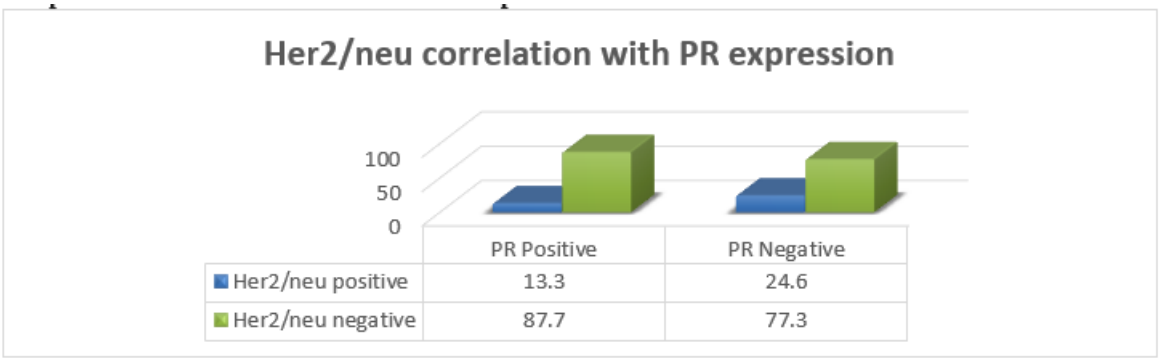


Figure 1: HER2/neu immunohistochemistry (IHC) staining, showing a moderate, complete circumferential brown membrane pattern in the tumor cells, 40x

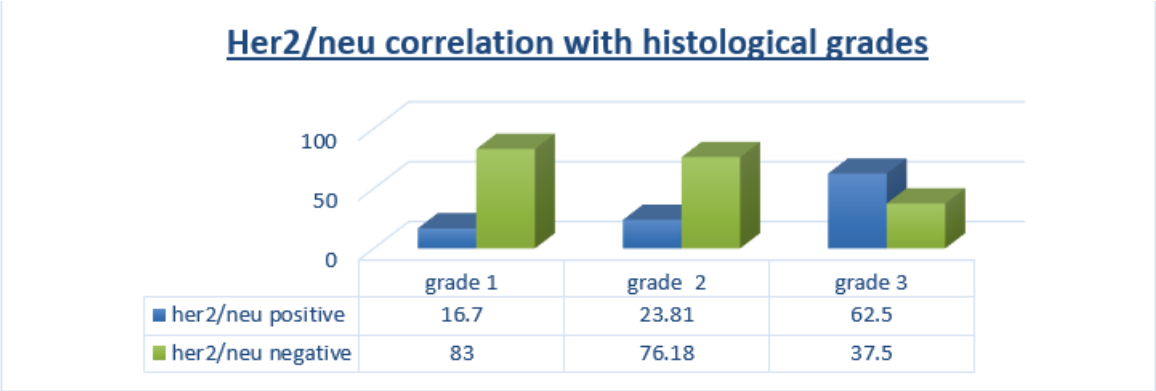
Figure 2: The intense, thick, and complete circumferential staining in more than 10% of the cells signifies a **Positive (3+) result**, Her2neu 10x
Figure 3: Estrogen Receptor (ER) expression, Nuclear Stain, 40x
Figure 4: Progesterone Receptor (PR) expression, Nuclear Stain 40x



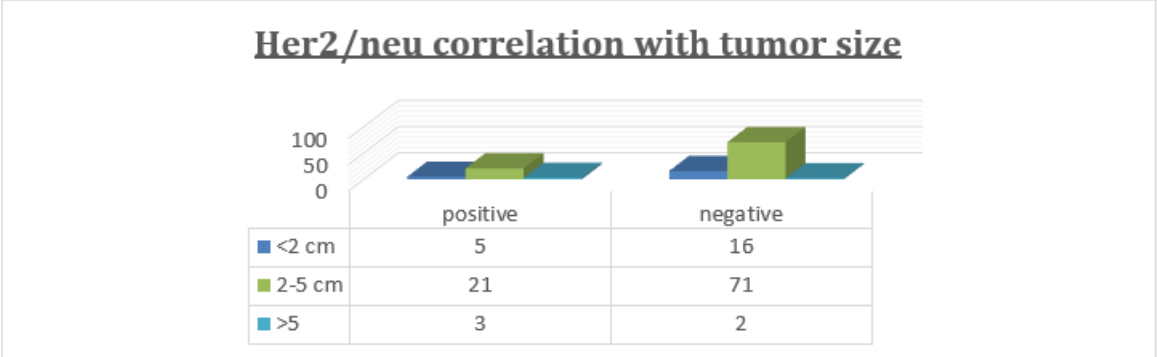
Graph: - 1 Her2/neu correlation with ER expression



Graph: - 2 Her2/neu correlation with PR expression



Graph:3- Her2/neu correlation with histological grades



Graph:-4 Her2/neu correlation with tumor size

DISCUSSION

In this series of 125 cases, the mean age of presentation was 52.76 years (SD ± 11.24), which is notably higher than the mean age of 44.6 years as seen in Gayatri Gogoi et al[3]. We found 53% of HER2/neu positive cases occurred in pre-menopausal women. This aligns with the Li et al[8]. study and the Gogoi et al[3]. study both of which suggest that HER2/neu overexpression is a hallmark of more aggressive disease often seen in younger Indian patients. The fact that more than half of our positive cases are pre-menopausal emphasizes the need for aggressive targeted therapy (like Trastuzumab) in this younger group.

On correlating Her2/neu with ER shows a significant inverse relationship: 76.47% of ER-positive cases are Her2/neu negative, while Her2/neu positivity is nearly twice as common in the ER-negative group (37.83%) compared to the ER-positive group (23.5%).which closely resembles with Gogoi et al[3]. (2015) and Bhaskar et al[9]. (2019) studies. Her2/neu negativity is exceptionally higher among PR-positive cases (87.7%), whereas Her2/neu positivity increases significantly in the PR-negative group (24.6%).This finding is highly consistent with the "inverse correlation" reported in major Indian oncological studies, specifically those by Gogoi et al[3]. and Singhai et al[10].

In this study 62.5% of Grade 3 tumors are Her2-positive is a critical prognostic indicator which is similar to other Indian studies (e.g., Singhai et al.[10] and Chauhan et al[11]). The correlation between Her2/neu status and tumor size in our study (n=125) reveals that Her2/neu positive cases are predominantly associated with larger tumor sizes, specifically in the 2–5 cm (T2) range. Out of 29 Her2/neu positive cases, 72.4% (n=21) fell into this category, while only 17.2% were smaller than 2 cm. Similarly, Chauhan et al[11]. (2016) observed that Her2/neu overexpression was significantly more common in tumors larger than 2 cm. In our study we found that data shows a very high concentration of ER-positive cases in post-menopausal women (71%). In contrast, recent studies like Rajan et al[12]. actually found higher ER positivity in their pre-menopausal group (56.1%).

CONCLUSION

Breast carcinoma patients have good overall survival when treated with combination of surgery, chemotherapy, radiotherapy, targeted therapy, and hormonal therapy as per the indication. Estrogen receptor and progesterone receptor (ER and PR) and c-erb B-2 protein (HER2/neu) status remain one of the most important factors in determining response to treatment and prognosis of disease. The use of various hormonal agents such as selective ER modulators tamoxifen and aromatase inhibitors anastrozole and letrozole depends exclusively on the expression of ER/PR, whereas the use of recently developed novel-targeted agents such as trastuzumab, pertuzumab, and lapatinib depends exclusively on the expression of HER2/neu receptors.

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