Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 10s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Relationship Between Histomorphological Typing And Immunohistochemistry Expression Of Breast Prognostic Markers (ER, PR, Her2neu) In Breast Carcinoma At A Tertiary Care Hospital

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Cite this paper as: Dr. Vatsala Gupta, Dr. Anshu Gupta Devra, Aheli Chatterjee, Harsh Bishnoi, Dr. Sonam Jain, (2025) Relationship Between Histomorphological Typing And Immunohistochemistry Expression Of Breast Prognostic Markers (ER, PR, Her2neu) In Breast Carcinoma At A Tertiary Care Hospital. *Journal of Neonatal Surgery*, 14 (10s), 336-341

ABSTRACT

Background: Breast cancer remains the most prevalent cancer in Indian women. The histopathological examination by morphology, accompanied by the recommendation to assess hormone receptors—specifically Estrogen Receptor (ER), Progesterone Receptor (PR), and HER2—by the College of American Pathologists and the American Society of Clinical Oncology, are widely recommended due to their prognostic and therapeutic values. Immunohistochemical characterization and gene examination are also essential, as cumulative results reveal the importance of hormone receptors in breast cancer. This study aims to retrospectively analyze the positivity rate of hormone receptors and HER2 in breast cancer patients.

Materials and Methods: The study, conducted over three years, included 51 cases of breast carcinoma, managed at Sharda Hospital, Sharda University. Samples were tested through immunohistochemistry against ER, PR, and HER2, citing ASCO/CAP Guidelines. The results were correlated with clinicopathological and histopathological data.

Results: ER and PR expression were proportionally greater in younger patients (<50 years), similar to HER2. A significant correlation of ER and PR was observed with increasing tumor grade, with p-values of 0.0115 and 0.0378, respectively. No significant correlation was found for Her2neu with tumor grade, with nodal status, or with age/menopausal status. ER and PR involvement significantly decreases as tumor grade increases.

1. INTRODUCTION

Breast lesions are among the most common health problems, accounting for approximately 20% of physician visits by females, but rarely males are also affected.[1] This multifaceted, broad-spectrum disease encompasses various clinical, pathological, and molecular features, each with distinctive prognostic and therapeutic implications for patients. Visually, most of these lesions appear as a breast mass with or without associated pain. Breast carcinoma is the most common cancer among urban women and the second most common in rural women. Epidemiological studies predict that the global incidence of breast carcinoma will reach nearly 2 million by 2030[2]. In India, breast cancers accounted for 13.5% of all cancer cases and 10.6% of all cancer deaths in 2020, according to Globocan data.[3] One in eight women will be diagnosed with breast cancer during their lifetime, and the incidence is increasing, with mortality rates ranging from 6.4 to 11.1 per 100,000 women.[4]

Significant risk factors for breast carcinoma include age, gender, family history, geographic location, race/ethnicity, reproductive history, early menarche, nulliparity, absence of breastfeeding, older age at first pregnancy, radiation exposure, postmenopausal obesity, postmenopausal hormone replacement, mammographic density, and alcohol consumption. Among these, prolonged exposure to estrogen and progesterone plays a significant role.

A definitive diagnosis of a breast lump is crucial for both patients and surgeons. Benign and malignant lesions can be differentiated by triple tests, which include clinical examination, imaging modalities (mammography, breast ultrasound), and fine-needle aspiration cytology (FNAC). When the triple test is insufficient to confirm a diagnosis, additional measures such as biopsy are necessary.

The prognosis of cancer is determined by three markers: Estrogen receptor (ER), Progesterone receptor (PR), and Human epidermal growth factor receptor (HER2), which are evaluated using immunohistochemistry (IHC). These receptors on the cell surface recognize hormone signals and stimulate cell proliferation. It has been observed that patients with similar morphology do not uniformly have predictable prognoses, leading to discussions on breast cancer classification.

At the 12th International Breast Cancer Summit in March 2011 (St. Gallen), breast cancer was classified into four types based on gene expression profiles: luminal-type A & B, HER2 enriched-type, and basal-type. This classification includes molecular markers such as ER, PR, HER2, and Ki-67. [5]

Evaluating ER and PR status in primary invasive breast cancers is crucial because endocrine therapy offers significant benefits for ER+/PR+ tumors.[6] These receptors, located on breast cells, pick up hormonal signals that lead to cell growth. Carcinomas displaying ER and PR positivity respond better to hormonal therapy than tumors with either or both receptors negative. Hormonal therapy is less effective for carcinomas lacking ER or PR, but they respond better to chemotherapy. [7]

HER2/neu, a member of the human epidermal growth factor receptor family (Her2 neu/EGFR/ERBB), is frequently amplified and overexpressed in some of the most aggressive breast cancer subtypes. This is associated with high recurrence and mortality rates. Monoclonal antibody drugs like Herceptin (Trastuzumab) target HER2-positive tumors.[8,9]

Basal-like/Triple-negative breast cancers, which lack ER, PR, and HER2 expression, are most common in BRCA1 mutation carriers and have the highest mortality rates. Chemotherapy is the only treatment option for these cases. [10]

Ki-67 is a nuclear non-histone protein present during all active phases of the cell cycle (G1, S, G2), but low to absent in resting cells (G0). Its association with DNA ploidy status can predict pathological remission rates in breast cancer patients who have received neoadjuvant chemotherapy, as an increased Ki-67 index indicates poor prognosis post-neoadjuvant therapy. From 2000 to 2020, the prevalence of breast cancer in India was found to be 0.33% for Luminal A, 0.17% for Luminal B, 0.15% for HER2 enriched, and 0.30% for Basal type. Basal-like malignancy is higher in India compared to the rest of the world. [11]

2. MATERIAL & METHODS

This retrospective observational study was conducted in the Department of Pathology at Sharda Hospital, following approval from the Institutional Human Ethics Committee. The study included only females with histomorphologically confirmed breast cancer diagnoses. Exclusion criteria were patients with inadequate material, benign pathology, and secondary breast cancers.

Biopsies positive for malignancy (true cut and large specimens) were graded according to Bloom Richardson and histomorphologically classified according to the WHO classification 2022 (5th edition). Tumor blocks were subjected to IHC for ER, PR, and Her2neu. The intensity of color and percentage of cells showing positivity on IHC were noted and scored according to Aldred's score. The expression of prognostic IHC markers was categorized and tabulated according to histomorphology. Clinical details, including patient age, tumor size, laterality of the breast tumor, and histological subtype, were compiled into a data collection proforma and tabulated as a master chart using Microsoft Excel. Informed consent was waived since this was a retrospective study from the tissue archives.

3. RESULTS

In this study, the patients were between 30 and 80 years of age, with a mean age of 46.80 (±11.90SD) years. In this group, 30 patients (58.8%) were younger than 50 years, and 21 patients (41.2%) were 50 years or older. The tumor size ranged from 1.2 to 7.0 cm, with 86% of cases having a size greater than 2 cm. The various histologic types included 41 cases (80.4%) of Infiltrating ductal carcinoma not otherwise specified (IDC NOS), one case (2%) of Medullary carcinoma, and two cases (4%) each of lobular, mucinous, and papillary carcinoma.

Grade I tumors were the most common, consisting of 43.1% (22/51), followed by Grade II tumors at 31.3% (16/51), and Grade III tumors at 25.5% (13/51). ER positivity was observed in 56.8% of cases (29/51), and PR positivity in 47% of cases (24/51). Among the 51 cases, thirteen were positive for Her2neu. ER and PR positivity were observed in 39.2% of cases (20/51). ER positivity alone without PR positivity was observed in 17.6% of cases (9/51). There were only 7.8% of cases (4/51) with PR positivity alone without ER positivity.(Table-2)

Her2neu positivity was seen in thirteen cases. Triple-negative cases were fifteen in number. Of the ER-positive cases (29/51), whether PR positive (20/29) or negative (9/29), ten were Her2neu positive. (Table-1)

Table-1: Percentage of ER/PR and Her2neu positive and negative cases

Status	ER	PR	Her2neu
Positive	29 (56.86%)	24 (47%)	13 (25.49%)

Negative	22 (43.14%)	27 (53%)	38 (74.51%)
Total	51 (100%)	51 (100%)	51 (100%)

Table 2 : Correlation between ER and PR Status

Status	**ER Negative**	**ER Positive**	**Total**
PR Negative	18 (81.82%)	9 (31.03%)	27 (52.94%)
PR Positive	4 (18.18%)	20 (68.97%)	24 (47.05%)
Total	22 (100%)	29 (100%)	51 (100%)

Of the 29 ER-positive cases, 10 (34.48%) were Her2neu positive, and among the 24 PR-positive cases, 6 (25%) were Her2neu positive. There was no significant correlation between Her2neu and ER/PR status. (Table 3)

Table 3 Comparison between Her2neu with ER/PR Status

Her2neu	**ER Positive**	**ER Negative**	**PR Positive**	**PR Negative**
Positive	10 (34.48%)	3 (13.64%)	6 (25%)	7 (25.93%)
Negative	19 (65.52%)	19 (86.36%)	18 (75%)	20 (74.07%)
Total	29 (100%)	22 (100%)	24 (100%)	27 (100%)
P' value	**0.241**		**0.116**	

ER and PR positivity were higher in patients younger than 50 years of age (58.6% and 62.5%, respectively). The 'p' value for ER, PR, and Her2neu did not correlate with the menopausal status. (Table 4)

Table-4: Age Vs ER/PR/Her2neu

			ER Status		**PR status**		**HER2 status**	
			Negative	**Positive**	**Negative**	**Positive**	**Negative**	**Positive**
AGE	**<50**	**Count**	13	17	15	15	23	7
		% within ER Status	59.1%	58.6%	55.6%	62.5%	60.5%	53.8%
	>=50	**Count**	9	12	12	9	15	6
		% within ER Status	40.9%	41.4%	44.4%	37.5%	39.5%	46.2%
Total		**Count**	22	29	27	24	38	13
		% within ER Status	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
P value			0.973		0.615		0.673	

There was no significant association between the histological type of tumor and hormonal receptor status, as IDC NOS constituted the majority (41 cases), along with one case each of medullary carcinoma and two cases each of lobular, mucinous, and papillary carcinomas.

In our study, ER and PR negativity was more common as the tumor grade increased. This was statistically significant for both ER and PR, with p-values of 0.0115 and 0.01, respectively. However, there was no correlation between Her2neu and

tumor grade, as the p-value was 0.215, which was statistically insignificant. (Table 5).

Table 5: Tumour Grade vs ER/PR/Her2neu

Grade	ER Positive	ER Negative	PR Positive	PR Negative	Her2neu Positive	Her2neu Negative
Grade 1	16 (55.2%)	6 (28.6%)	15 (60%)	7 (28%)	7 (53.8%)	15 (40.5%)
Grade 2	10 (34.5%)	5 (23.8%)	8 (32%)	7 (28%)	5 (38.5%)	10 (27.1%)
Grade 3	3 (10.3%)	10 (47.6%)	2 (8%)	11 (44%)	1 (7.7%)	12 (32.4%)
Total	29 (100%)	21 (100%)	25 (100%)	25 (100%)	13 (100%)	37 (100%)
P' value	**0.0115**		**0.01**		**0.215**	

4. DISCUSSION

Breast cancer is a leading worldwide problem among female cancers, with incidence rates expected to increase by 26% in developing countries by 2020. Consistent with results from other studies on Indian and Western populations, the mean age at diagnosis of breast cancer is 49.52 years (±11.2 SD), with a high incidence among postmenopausal patients, accounting for 54% of cases.[13]

Of the 51 total cases in this study, we found that 29 cases (57%) were positive for estrogen receptors. This is consistent with other Indian studies like those of Kaur et al. (36%), Rashmi K et al. (34.5%), and Desai SB et al. (32.6%).[12,14,15] However, the incidence was higher in studies by Western authors compared to those involving Black and Asian populations. This disparity might be attributed to inherent biological differences, and the lower incidence in the Indian population may be due to a presumably lower intake of hormone replacement therapy.[16]

n the present study, 47% of cases were PR positive, closely aligned with findings by Desai SB et al. (46.1%) and Ghosh J et al. (51.2%). However, studies by Kaur et al. (36%), Rashmi K et al. (36.4%), and Haroon S et al. (38.1%) reported lower percentages of PR-positive cases. [12,14,15,17,18]

In the current study, 57% of cases showed ER positivity, and 47% showed PR positivity. The lower PR positivity in the current study could be due to technical reasons like poor antigen retrieval or prolonged cold ischemic time.

Further, there was no significant correlation between Her2neu and ER/PR status or the age of patients, differing from the findings of Thiygarajan M et al.[13]

In the present study, ER/PR and Her2neu showed no significant correlation with tumor size. However, Azizun-Nisa et al. found that ER positivity decreased and Her2neu was over-expressed with increasing tumor size. Similar to our study, reports by Thiygarajan M et al. and Barrios GRM et al. also indicated no correlation between Her2neu and tumor size.[13,22]

The most common pathological type of carcinoma in the present study was IDC NOS (80.4%), similar to findings by Juneja S et al. (92.72%), Bhagat et al. (94.82%), and Thiygarajan M et al. (84.3%).[13,19,23]

In the present study, it was found that ER and PR expression showed a decline with increasing tumor grade, which is statistically significant for both ER and PR but not for Her2neu. A similar trend of decreasing ER and PR positivity with increasing tumor grade was also reported by Thiygarajan M et al., Juneja S et al., Azizun-Nisa et al., Antoniades K et al., Shet T et al., and Fatima et al.[13,19,21,24,25].

Her2neu expression showed no correlation with tumor grade in the current study, similar to findings by Thiygarajan M et al., Almari et al., and Barrios GRM et al.[13,20,22]

No significant correlation was found between ER/PR receptor status and nodal status in the present study, consistent with observations by Thiygarajan M et al., Azizun-Nisa et al., and Fatima et al.[13,21,25,26]

Nodal status was also not significantly correlated with Her2neu status in the present study. This contrasts with findings by Thiygarajan M et al., Azizun-Nisa et al., and Naqvi et al., who reported a significant correlation between Her2neu overexpression and lymph node status.[13,21]

Therefore, it is advisable to test all breast cancer patients for the four markers: ER, PR, Her2neu, and Ki67. The expression

of ER, PR, and Her2neu determines the treatment plan, while Ki67 expression, particularly high Ki67 in ER and PR-negative cases, indicates a poor prognosis. Breast cancers with high Ki67 expression tend to respond better to chemotherapy.

5. LIMITATIONS

In the present study, there was not much correlation observed between the nodal status and ER, PR, or Her2neu receptor status. The study was unable to comment on the status of lymphovascular invasion due to a significant number of samples being core biopsy samples.

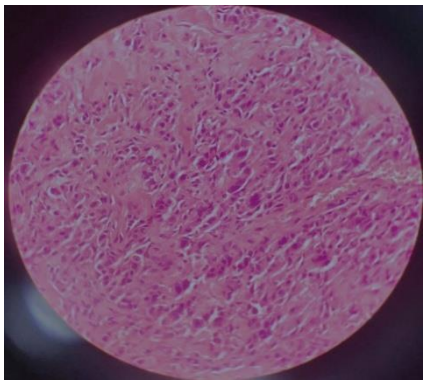

Fig.1: H&E section of Breast IDC

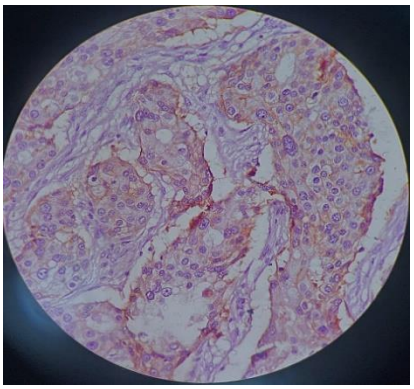

Fig.2: Strong membranous Her2Neu positivity Ca Breast.

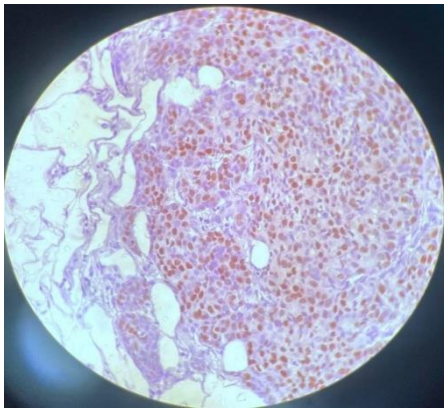

Fig.3: Strong nuclear staining ER positivity Ca Breast

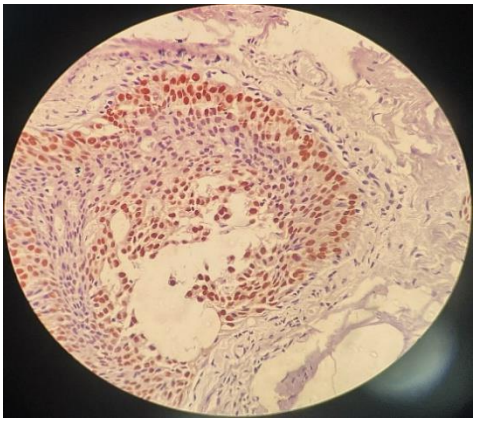

Fig.4: Strong nuclear staining PR positivity Ca Breast

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