

ORIGINAL RESEARCH

Evaluation of the Breast Carcinoma by Immunohistochemical Profile Analysis – For Prognostic and Therapeutic Usage

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ABSTRACT

Background: Breast cancer is the most common type of cancer in women with increasing incidence in India. Infiltrating ductal carcinoma is the most common type of breast carcinoma amongst various histological entities. Immunohistochemical markers of prognosis and predictors for therapy include estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu). Immunohistochemistry was used to evaluate how ER, PR, and HER2/neu were expressed in invasive ductal carcinomas of the breast. The objective was to study the correlation of these markers with one other and to various parameters like the patient's age, the tumor size, histological grading, and its spread to axillary lymph nodes.

Material and Methods: 50 cases diagnosed with infiltrating ductal carcinoma were taken for this prospective study. Histopathological examination revealed diagnosis of infiltrating ductal carcinoma and further evaluation was done with immunohistochemical profile-ER, PR, HER2/neu and their expression. For ER/PR expression, the Allred scoring system was used, and for HER2/neu expression the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) guidelines were used. Using the Chi square test, a statistical analysis was done.

Results: Most of the tumors were positive for ER and PR but negative for HER2/neu expression. ER and PR were having strong correlation with each other, age, tumor size, and tumor grade, but HER2/neu was only strongly correlated to tumor size. No correlation was studied with respect to axillary lymph node metastatic deposits. Expression of ER and PR was correlated with one other, but neither of them correlated to HER2/neu.

Conclusion: As most tumors are ER and PR positive, correlating with one other, tumor size, and grade. Hereby it is recommended that breast carcinoma patients have their hormone receptors evaluated for their further prognosis and procuring best treatment regimens available.

Keywords: Immunohistochemical markers, estrogen receptors, progesterone receptors, human epidermal growth factor, Allred scoring system.

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INTRODUCTION

The most common type of malignancy in women is breast carcinoma seen more in developed countries. There are many histological types of breast carcinomas, but infiltrating ductal carcinoma is the most common type. Surgery is the main stay treatment for breast cancer patients followed by chemotherapy (if needed), radiotherapy, and adjuvant hormonal therapy for tumors with positive expression of estrogen receptor (ER) and progesterone receptor (PR). Early-stage diagnosis leads to better prognosis. Routine morphological prognostic factors include the size and grade of the tumor and its spread to the axillary lymph nodes. Recently biological molecular prognostic factors have gained clinical significance because a lot of people with early-stage breast cancer already have microscopic metastasis at the time they are diagnosed.^[1] Hormone receptors (ER and PR) and human epidermal growth factor receptor 2 (HER 2) are the most important clinical biomarkers that are widely used to manage breast cancer cases.^[2] HER 2 expressions and hormonal receptors are very important for therapeutic management of breast cancer. Therefore, prognostic factors and predictive factors are evaluated thoroughly thereby play a role as important indicators for further treatment options and in evaluating overall outcome of the patient.

Estrogen receptor: Breasts are hormonally influenced as an important physiological change. There are two types of ER: ER α and ER β . ER α is a well-known prognostic factor in breast carcinoma. Most ER-positive subtypes of breast carcinoma have both ER α and ER β expression and very few have only ER β expression. It has been seen that the expression of ER decreases during breast carcinogenesis.^[3]

Progesterone receptor: PR comes in two different types: PR A and PR B. Progesterone acts as a modulator of estrogen function.^[19] It has been seen that ER-positive breast cancers that don't express PR respond less to hormonal treatment than PR-positive cancers. ER and PR both are not stable phenotypes. These can change as the disease progresses or because of the treatment.

Human epidermal growth factor receptor-2/neu (c-erbB-2): It is one of four members growth factor receptors. The other three are the epidermal growth factor receptors (HER1, HER3, and HER4). In breast carcinoma, oncogenic transformation and tumorigenesis are caused by the over expression or amplification of HER2/neu receptors. When receptors are overexpressed, the increased signaling causes uncontrolled cell proliferation, increased tumor cell motility and neo angiogenesis making the contribution of these factors for the worsening of the prognosis. Currently ER, PR, and HER2/neu receptors are a panel of markers done for a biopsy diagnosed cases of breast cancer for further adjuvant hormonal/chemotherapy management of cases. Cases with strong ER positivity can get better with hormonal therapy, in contrast to cases with low to moderate ER positivity. Patients in whom tumor is ER and PR negative carry worse prognosis when compared to tumors with both ER and PR positive expression. Therefore, this study was done to see if correlation between the expression of ER, PR, and HER2/neu and various parameters like the age of the patient, the histological grade of the tumor, the size of the tumor, and axillary lymph node metastasis [Figure 1].

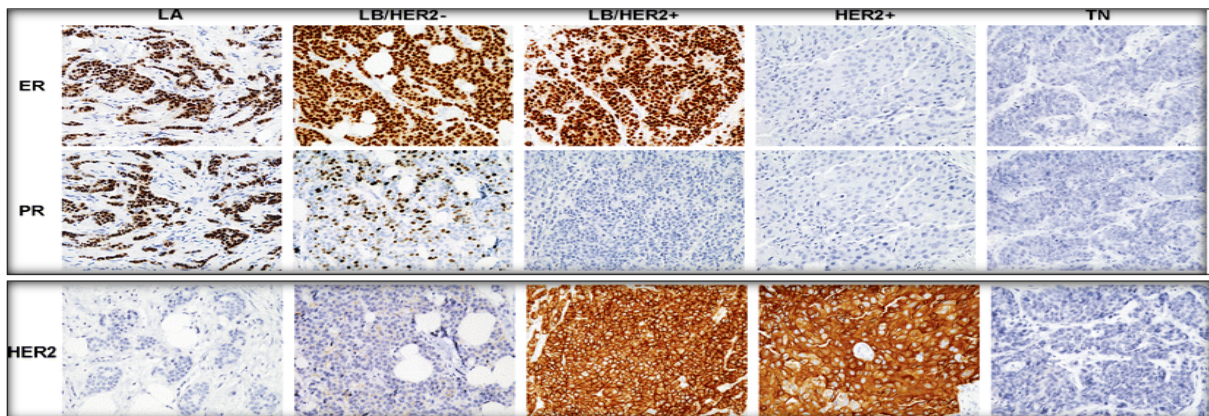


Figure 1: Representative examples of the different IHC breast carcinoma subtypes

MATERIALS & METHODS

The study included 50 cases who had been diagnosed in histopathological examination as infiltrating ductal carcinoma. Immunohistochemistry (IHC) was done as a further confirmatory diagnostic test to compare the expression of ER, PR, and HER2/neu with each other and with different clinicopathological parameters. The study was carried out for a period of 18 months from November 2020 to April 2022 at Malla Reddy institute of medical sciences, Suraram, Hyderabad, Telangana, India.

Inclusion criteria: All patients with infiltrating ductal carcinoma of the breast confirmed by histopathological examination were included in the study.

Exclusion criteria: Patients with inflammatory breast lesions, benign proliferative breast lesions and breast cancer patients who had received neoadjuvant chemotherapy were not included in the study.

Procedure: Histopathology examination was done with the help of formalin fixed paraffin embedded blocks and diagnosis of infiltrating ductal carcinoma is reported. Immunohistochemical staining for ER, PR, and HER2/neu was carried out for further confirmation.

Preparation of slides: Paraffin embedded sections were taken on silanized slides and deparaffinization done and further washed with distilled water after the tissues were rehydrated. The slides were then put into a fresh aqueous solution of 3% peroxide for 3 minutes and rinsed with Tris buffer.

Retrieval and detection of antigens: Heat retrieval was done with citrate buffer for 40 minutes at 95°C in the Decloaking chamber. After taking the slides out of the Decloaking chamber the temperature was brought back to room temperature by immersing them in Tris Saline buffer. To stop nonspecific immunostaining, 1% mouse serum was added to the tissue. The primary antibody was put on the sections for about an hour, and then the Tris buffer was used to wash away the primary antibody.

Secondary detection of the primary antibody: Further the sections are incubated in biotinylated mouse antibodies for 10 minutes and then rinsed in Tris buffer. The slides are then immersed in 3,3' diaminobenzidine (DAB) chromogen solution of 1mg/ml added in Tris buffer with 0.016% fresh H₂O₂ and wash the DAB off of the slides with tap water.

Counter staining: Hematoxylin mixed in 1:1 with distilled water was used to stain slides. The slides were then washed with distilled water and steps of dehydration were carried by dipping them in ethanol, washed in xylene, and mounted.

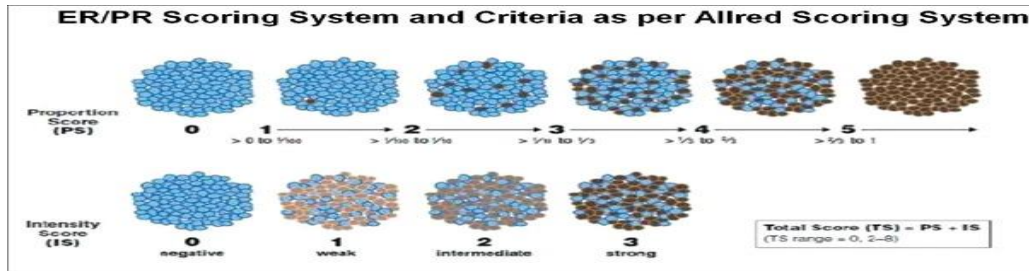


Figure 2: Allred Scoring System for Estrogen Receptor/Progesterone Receptor Scoring

Interpretation:

Reporting done as per ER/PR scoring system and criteria as per Allred scoring system [Figure 2].^[4]

Proportion score

0 – No cells are ER +ve.

1 – $\leq 1\%$ of cells is ER +ve.

2 – 1%–10% of cells are ER +ve.

3 – 11%–33% of cells are ER +ve.

4 – 34%–66% of cells are ER +ve.

5 – 67%–100% of cells are ER +ve.

Intensity score

0 – Negative.

1 – Weak.

2 – Intermediate.

3 – Strong.

Interpretation-Total (proportion score + intensity score).

0–2 = Negative; 3–8 = Positive.

Human epidermal growth factor receptor-2/neu scoring system and criteria according to the American Society of clinical Oncology College of American pathologists guidelines.^[5]

0- No staining or Incomplete faint and barely perceptible in $<10\%$ of tumor cells.

1+= incomplete membrane staining which is faint and barely perceptible with in $>10\%$ of tumor cells.

2+= Circumferential membrane staining; incomplete and /or weak/Moderate and within $>10\%$ of in value tumor.

Reporting

Reporting done as per ER/PR Scoring System and Criteria as per Allred scoring system⁽⁴⁾.

Proportion score 0- no cells or ER +ve.

1- $\leq 1\%$ of cells are ER +ve

2- 1%-10% of cells are ER +ve

3- 11%-33% of cells are ER +ve

4- 34%-66% of cells are ER +ve

5- 67%-100% of cells are ER +ve

Intensity score

0-Negative

1-Weak

2-Intermediate

3-Strong

Statistical analysis: The Chi-square test was used to determine the statistical significance between the ER/PR and the HER2/neu receptor status and correlation between hormonal

status and different clinicopathological parameters, like the patient's age, the status of the axillary lymph nodes, the size of the tumor, and the grade of the tumor. p value of <0.05 was considered to be statistically significant.

RESULTS

Age: Patients were between 24 and 75 years old, on average, with a mean age of 55.28 years. Most of them (66% of them) were older than 50 years. About 96% of people who tested positive for ER and PR were older than 40. Majority HER2/neu positive were of age less than 40 years [as shown in Table 1]. Based on the numbers, it was clear that ER, PR, and HER2/neu expression was strongly correlating with age.

Table 1: Estrogen receptors, progesterone receptor and human epidermal growth factor receptor expression compared to age

Age (years)	ER Positive	ER Negative	Total	PR Positive	PR Negative	Total	HER2/neu Positive	HER2/neu Negative	Total
<40	02	05	07	02	06	08	04	07	11
41 - 50	05	05	10	04	05	09	00	08	08
51 - 60	12	04	16	12	05	17	01	13	14
>60	14	03	17	12	04	16	01	16	17
Total	33	17	50	30	20	50	06	44	50
χ^2 , df, p		18.476, 3, 0.0003			17.666, 3, 0.0005			21.789, 3, 0.000	

ER: Estrogen receptors, PR: Progesterone receptor, HER2/neu: Human epidermal growth factor receptor.

Table 2: Estrogen receptors, progesterone receptor and human epidermal growth factor receptor expression compared to tumor size

Tumor size (cm)	ER Positive	ER Negative	Total	PR Positive	PR Negative	Total	HER2/neu Positive	HER2/neu Negative	Total
<2	10	04	14	10	04	14	05	09	14
2 - 5	14	07	21	14	07	21	02	19	21
>5	04	11	15	06	09	15	02	13	15
Total	28	22	50	30	20	50	09	41	50
χ^2 , df, p		16.218, 2, 0.0003			9.3374, 2, 0.009			26.296, 2, 0.000	

ER: Estrogen receptors, PR: Progesterone receptor, HER2/neu: Human epidermal growth factor receptor.

Table 3: Estrogen receptors, progesterone receptor and human epidermal growth factor receptor expression compared to tumour grade

Grade	ER Positive	ER Negative	Total	PR Positive	PR Negative	Total	HER2/neu Positive	HER2/neu Negative	Total
I	09	04	13	09	04	13	03	10	13
II	12	09	21	12	09	21	02	19	21
III	06	10	16	06	10	16	04	12	16
Total	27	23	50	27	23	50	09	41	50
χ^2 , df, p		8.852, 2, 0.011			11.95, 2, 0.002			25.7278, 2, 0.028	

ER: Estrogen receptors, PR: Progesterone receptor, HER2/neu: Human epidermal growth factor receptor.

Table 4: Expression of estrogen receptors, progesterone receptor and human epidermal growth factor receptor compared to axillary lymph node status

Lymph node status	ER			PR			HER2/neu		
	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total
Positive	12	09	21	12	09	21	01	20	21
Negative	17	12	29	16	13	29	03	26	29
Total	29	21	50	28	22	50	04	46	50
χ^2 , df, p		3.0833 1, 0.0805			2.2857, 1, 0.13057			38.377, 1, 0.583	

ER: Estrogen receptors, PR: Progesterone receptor, HER2/neu: Human epidermal growth factor receptor.

Table 5: Estrogen receptors and progesterone receptor expression compared to human epidermal growth factor receptor expression

ER	HER2/neu positive	HER2/neu negative	Total	PR	HER2/neu positive	HER2/neu negative	Total
ER positive	01	30	31	PR positive	01	28	29
ER negative	03	16	19	PR negative	03	18	21
Total	04	46	50	Total	04	46	50
κ , p	0.053, 0.059		-0.052, 0.203				

ER: Estrogen receptors, PR: Progesterone receptor, HER2/neu: Human epidermal growth factor receptor.

Tumor size: On average, the size of the tumor was 4.3cms. Most ER/PR-positive tumors were between 2 and 5 cm in size (50%), and most HER2/neu-positive tumors were less than 2 cm in size (56%). [Table 2] shows that there was a statistically significant link between the expression of ER, PR, and HER2/neu and the size of the tumor.

Tumor grade: Based on the Nottingham Modified Bloom–Richardson System score, most of the tumors in our study were Grade II (42%), Grade III (30%), and Grade I (28%). Most ER/PR-positive tumors (44-45%) were Grade II, and most HER2/neu-positive tumors (44.4%) were Grade III. [Table 3] shows the relationship between the amount of ER, PR, and HER2/neu and the grade of the tumor. It was decided that the correlation between ER/PR expression and tumor grade was statistically significant, but that HER/neu was not.

Axillary lymph node status: All of the cases were examined for spread to the axillary lymph nodes, and 21 of the patients were found to have spread to the lymph nodes. Out of the 29 ER positive cases, 12 had positive axillary lymph nodes, while only 12 of the 28 PR positive cases had positive axillary lymph nodes. One of the four cases who were positive for HER2/neu had positive axillary lymph nodes. As shown in [Table 4], there was no significant

link between the expression of ER, PR, and HER2/neu and the status of the axillary lymph nodes.

Estrogen receptor status: ER was found in 29 of the tumors, but not in 21 of them. >1% of the cells in ER positive tumors showed weak, moderate, or strong nuclear positivity.

Progesterone receptor status: PR was present in 28 tumors, but not in 22 of them. In more than 1% of tumor cells in PR-positive cases, the nucleus stained weak, moderate, or strong pattern. Out of 50 cases, 29 had positive ER and PR, 16 had negative ER and PR, and 5 had different ER and PR expressions. Using, p value and kappa value as a measure of agreement, it was found that ER and PR expressions agree with each other in a significant way.

HER2/neu expression: Only four patients had HER2/neu that was positive, and the other did not. Only one of these cases was positive for ER, PR, and HER2/neu. There were 16 cases that did not have either ER or HER2/neu. ER and HER2/neu showed up in different ways in 34 cases [as shown in Table No 5]. Only one case of the 50 cases was both PR and HER2/neu positive. The other 16 cases were both PR and HER2/neu negative. The PR and HER2/neu expressions were different in 33 cases. Statistical analysis using kappa as a measure of agreement shows that ER/PR and HER2/neu expressions did not correlate.

DISCUSSION

Breast carcinoma is the most common cancer in women, as a cause of death making up 25% of all cases around the world. The results of breast cancer vary a lot depending on the type of cancer, how far it has spread, and age of the case. In the developed world, the five-year survival rates are high: 80% in England and 90% in the United States. Survival rates are low in places like Africa and Asia. This is because there aren't enough effective screening programs and people aren't aware of the signs and symptoms of a breast lump. This means that when the disease is diagnosed, it has already progressed to an advanced stage, with an extensive involvement of lymph nodes. Based on information from India, the cervix is the most common cancer with breast cancer in the second place. Surgery -Mastectomy is the main stay of treatment on diagnosis of carcinoma breast. This is followed by chemotherapy (if needed), radiotherapy, and, for tumors that are ER and PR positive- hormonal therapy. Immunohistochemical markers of prognosis and therapy response include ER, PR, and HER2/neu. Determining the ER, PR, and Her2/neu receptor status in breast cancer is also common practice now, because patients who have a positive ER, PR, or Her2/neu status have prolonged life if they are treated with hormones or chemotherapy. Patients whose tumors are ER PR positive have a better chance of getting better than those whose tumors are ER PR negative.^[6] This study was done to see how the expression of ER, PR, and HER2/neu related to each other and to different clinicopathological parameters, such as the patient's age, the tumor's size, and whether it had spread to lymph nodes.

Age: More than two thirds of women with breast carcinoma are 50 years or older, and most of these cases were encountered in developed countries. In developing countries, twice as many women ages 15–49 are diagnosed with breast cancer as in developed countries. In places where mammography is a feasible easily available diagnostic modality and cost effective, routine screening is advised. In our study, infiltrating ductal carcinoma was found in people between the ages of 20 and 60, with a mean age of 55.28 years. This is the same as what Sengal et al,^[2] and Kaul et al,^[7] found in their studies. A study by Alzaman et al.^[8] showed that most ER and PR-positive cases were over 60 years old. About 67% of HER2/neu-positive cases were under 40 years old, which is similar to what Alzaman et al,^[8] analysed. Studies by Dodiya et al,^[9] and Ghosh et al,^[10] showed that there was a strong link between the age of the patient and how much ER and PR were being made.

Tumor size: Size ranged from 0.1 cm to 12 cm, with 4.3 cm being the average. Tumor sizes of 21 cases ranged from 2 cm to 5 cm. 50% of ER+ tumors and 47% of PR+ tumors were between 2 and 5 cm in size. 56% of HER2/neu tumors were smaller than 2 cms. In this study, there was a strong link between the size of the tumor and how much ER ($P = 0.003$) and PR ($P = 0.009$) were being made. In this study, like the one by Almasri and Hamad et al,^[11] there was a strong link between tumor size and HER2/neu expression ($p = 0.000$).

Tumor grade: 21 were Grade II, 16 were Grade III, and 13 were Grade I. Most ER-positive (44.41%) and PR-positive (44%) tumors were Grade II, but most HER2/neu-positive (54%) tumors were Grade III. Siadati et al,^[12] did a study that came to the same conclusions. There was a strong correlation between the size of the tumor and ER ($p = 0.011$) and PR ($p = 0.002$). The results of the study by Dodiya et al,^[9] were the same.

Axillary lymph node status: Metastasis was found in 21% of patients' axillary lymph nodes. About 41.3% of the ER and PR-positive cases had metastasis in the axillary lymph nodes. About 25 percent of HER2/neu-positive cases had metastasis in the axillary lymph nodes. Ali et al,^[13] study came to the same conclusion. [Table No 4] shows that there was no significant link between the status of the axillary lymph nodes and the expression of ER ($p = 0.805$), PR ($p = 0.130$), or HER2/neu ($p = 0.583$), which is approximately correlating with Azizun-Nisa et al.^[14]

Receptor positivity: In this study, the ER positivity rate was 82%, which was close to what Idirisinghe et al,^[15] found, and the PR positivity rate was 58%, which was close to what Engstorm et al,^[16] found. HER2/neu positivity was only 8%, which was a lot less than what other studies analysed. This could be because people in different populations presented with different. Also, the results of a HER2/neu assay are affected by several biological, technical, and performance factors. Since many parts of HER2/neu assays have not been standardized, it is not possible to separate the effects of these different factors. ER and PR were linked ($p = 0.000$), but HER2/neu expression was opposite to ER expression ($p = 0.059$) and PR expression ($p = 0.203$). Studies by Siadati et al,^[17] Maha et al,^[18] etc., all came with similar conclusions.

CONCLUSION

Infiltrating ductal carcinomas of breast were found in women between the ages of 25 and 60, with the average age being 55.28 years. The most cases were seen in people who were over 50 years old (66%). Most of the tumors were positive for ER and PR but negative for HER2/neu. Most tumors that were positive for ER and PR were Grade II, while most tumors that were positive for HER2/neu were Grade III. The current study confirmed that ER and PR are correlated to age, tumor size, and tumor grade, but not to lymph node status. HER2/neu expression was correlating to age and the size of the tumor, but not to the grade of the tumor or the number of lymph nodes. Expression of ER and PR was correlated to each other, but neither correlated to HER2/neu. With adjuvant hormonal therapy, cases that test positive for ER and PR may have a good outcome. It is strongly suggested that a case of breast carcinoma have their hormone receptor status evaluated timely in order to further know about their prognosis and treatment protocols for early and better management.

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