Research Article

Clinicopathological Study of Breast Cancer with Correlation of ER, PR and HER2/Neu Immunoreactivity

Dr Ramesh Kalshettty[1]; Dr Kavita P Sawant[2]; Dr Shreya D Badhe[3*]; Dr Subodh V Patil[4]

[1] Assistant professor, Department of Pathology, LTMMC&GH Mumbai
[2] Associate professor, Department of Pathology, LTMMC&GH Mumbai
[3] Senior Resident, Department of Pathology, LTMMC&GH Mumbai
[4] Assistant Professor, Department of Medicine, GMC Buldhana

Corresponding Author:

Dr Shreya D Badhe
Senior Resident, Department of Pathology, LTMMC&GH Mumbai

ABSTRACT

Introduction: Estrogen receptors (ER) and progesterone receptors (PR) are major prognostic factors in breast cancer while HER2/neu is a useful predictive factor to decide on chemotherapy like trastuzumab. They are useful for subtyping, therapeutic planning, and tailoring chemotherapy regimens of patients with breast cancer. Hence, the study was conducted to assess the hormone receptor status in breast carcinoma patients and to correlate this reactivity pattern with histologic grade, tumor stage, and lymph node metastasis.

Materials and methods: This was a prospective observational study conducted for a duration of 3 years among modified radical mastectomy (MRM) specimens from 58 females diagnosed with breast carcinoma. Suitable blocks were chosen for IHC. Association between categorical variables was assessed using Chi-square test.

Results: Mean age of patients was 49.34 years. Invasive Ductal Carcinoma was the most common histological diagnosis. Majority patients presented with grade II (57.69%) and stage II (58.62%). ER, PR and HER2/neu positivity was seen among 53.44%, 41.38% and 13.79% cases respectively.

Conclusion: Significant association was found between ER/PR expression and HER2/neu expression with histological grade and stage of cancer. These findings underscore the importance of assessing hormone receptor and HER2/neu status as essential components in the prognostic evaluation and therapeutic planning for breast cancer patients.

Keywords: Breast cancer, estrogen receptors, HER2/neu, immunohistochemistry, progesterone receptors

INTRODUCTION

Breast cancer encompasses a major impact on the health of women. It is the foremost common cancer among women in many regions in India and has overtaken cervical cancer (1). As per the Indian Council Of Medical Research-Population based Cancer registry (ICMR-PBCR) information, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Kolkata, and Trivandrum where it constitutes >30% of all cancers in females (2). The chances of survival in breast cancer are closely associated with early detection and the initiation of timely, appropriate therapy. Prognostic outcomes are influenced by multiple clinical, pathological, and molecular factors, including tumor stage, histological subtype, tumor grade, and lymph node involvement. Estrogen receptors (ER) and progesterone receptors (PR) are major prognostic factors in breast cancer (3). The current therapeutic approaches for breast carcinoma consist of combinations of surgery, postoperative radiation, hormonal treatment, chemotherapy and Trastuzumab. The choice between hormonal therapy which has minimal side effects and chemotherapy with well-known morbidity and risks is a major responsibility of the clinician. In metastatic breast cancers HER2/neu was concluded as an additional prognostic factor as its gene amplification can lead to over expression of HER2/neu glycoprotein. Hence, HER2/neu is a useful predictive factor to decide on chemotherapy like trastuzumab (3). The immunohistochemistry markers ER, PR, and HER/neu, thus, are useful for subtyping, therapeutic planning, and tailoring chemotherapy regimens of patients with breast cancer (4). With this, the need for accurate and precise assessment of their expression in breast carcinoma is critical in the determination of patients appropriate for treatment with these drugs (5). An immunochemistry is an important tool in precise

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630

histopathological diagnosis. Immunohistochemistry (IHC) is the most commonly used method of testing for ER, PR, and HER2/neu status (5). Survival and response to hormone therapy are most favourable among women who are receptor-positive, intermediate for tumors discordant on receptor status and least favourable for receptor-negative patients. The interaction ER, PR status, along with HER2/neu overexpression, plays a critical role in guiding the management of breast cancer. Considering the above points, this study was aimed at assessing the hormone receptor status in breast carcinoma patients and to correlate this reactivity pattern with histologic grade, tumor stage, and lymph node metastasis.

MATERIALS AND METHODS

Study design, setting and period
A prospective observational study was conducted in Department of Pathology of a tertiary care hospital for a period of 3 years from 2018 to 2021.

Study participants
Modified radical mastectomy (MRM) specimens from 58 females diagnosed with breast carcinoma were taken. All female patients aged 18 and above who underwent modified radical mastectomy and established to be malignant histologically were enrolled for study. Pregnant woman, patients with benign breast disease, recurrent breast lump in previously operated case of breast cancer, inadequate samples and excision and incision biopsies, proven to be malignant histologically were excluded from the study.

Ethical approval
Ethical approval was obtained from the Institutional Ethics Committee (IEC) (IEC/82117/2017)

Study procedure
All cases meeting selection criteria, whose specimen was received during the study period were included. A detailed history regarding age, parity, socioeconomic status, family history, and menstrual history was reviewed in all cases. All the mastectomy specimens received were properly sliced and fixed in 10% formalin for 18 - 24 hours. Detailed gross examination pertaining to the overall size of the specimen, nipple and areola, margin status and nodal status were carefully studied. ER, PR, HER2/neu study was done for 58 cases. Histological grading was done by the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system. Representative samples are taken from tumor, margins, nipple and areola and lymph nodes. The tissues were processed in numerous grades of alcohol and xylene using an automated tissue processor. Paraffin blocks were prepared and sections of 5micron thickness were cut in microtome using disposable blades and stained with hematoxylin and eosin. Suitable blocks were chosen for IHC. The staging of breast carcinoma was done according to the tumor, node, and metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) (6). Scoring was done by Quick Score System (7).

Statistical analysis
Data were entered into an MS Excel spreadsheet and analyzed using Statistical Package for Social Sciences (SPSS) version 25.0. Categorical variables were presented as frequency and percentages (%), while continuous variables were summarized as mean ± standard deviation (SD). Association between categorical variables was assessed using Chi-square test.

RESULTS
Table 1: Clinical profile of patients (N = 58)

Clinical profile	Frequency	Percentage
Age group		
21 – 30	07	12.07
31 – 40	13	22.41
41 – 50	12	20.69
51 – 60	15	25.87
61 – 70	07	12.07
71 – 80	03	5.17
81 – 90	01	1.72
Menstrual status		
Premenopausal	27	46.55
Postmenopausal	31	53.45
Parity		
Nulliparous	03	5.17
≤ 2	47	81.03
> 2	08	13.80
Duration of symptoms		
< 1 year	48	82.76
>1 year	10	17.24
Side involved		
Right	22	37.93
Left	36	62.07

Quadrant involved by the tumor		
Upper outer	27	46.55
Upper inner	06	10.34
Lower outer	07	12.07
Lower inner	04	6.90
Central	14	24.14
Tumor size (cms)		
<2	07	12.07
2-5	29	50.00
>5	22	37.93
Lymph Node Metastasis		
Absent	27	46.55
Present	31	53.45
Histological grade (N = 52)		
I	01	1.92
II	30	57.69
III	21	40.39
Stage		
Stage I	03	5.17
Stage II	34	58.62
Stage III	19	35.76
Stage IV	02	3.45
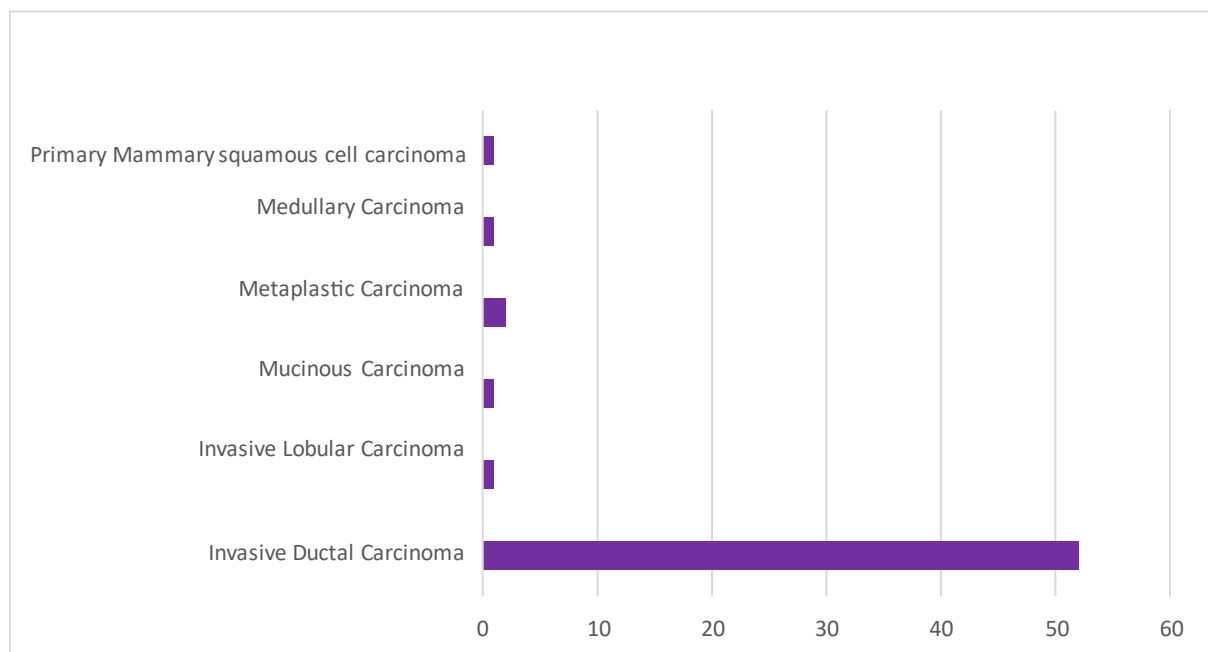
Figure 1: Distribution of histological variants in breast carcinoma

This study dealt with clinicopathological correlation of breast carcinoma in 58 MRM specimens received during the above-mentioned period. Table 1 shows clinical profile of the patients. Maximum number of cases were seen in 51-60 years age group. Mean age was 49.34 years with the youngest patient being 22 years old and oldest being 86 years old. Majority of cases were postmenopausal 31 (53.45%), had parity 2 i.e. 47 (81.03%), had symptoms since less than 1 year 48 (82.76%) and presented with tumor on left side 36 (62.07%).

Most frequently involved quadrant was upper outer quadrant accounting for 27 (46.55%) cases. Only lump was the most common clinical presentation (89.66%), lump with nipple retraction in 03 (05.17%) was also presented followed by skin ulceration in 02 (03.45%) cases, nipple discharge is seen in 1 (1.72%) case.

Figure 1 shows histological variants. Invasive Ductal Carcinoma was the most common histological diagnosis seen in 52 (86.22%). In the present study only, IDC were graded and the other subtypes were not graded therefore histologic grades were available for 52 cases. Most common grade was grade II (57.69%) followed by grade III (40.39%) with minimum cases in grade I tumors (1.92%). 31 out of 58 (53.45%) patients presented with lymph node metastasis. Most common stage was Stage II (58.62%), followed by Stage III (35.76%). 3.45% cases were Stage 4 presenting with distant metastasis to Liver (2 cases), and Lungs (2 cases).
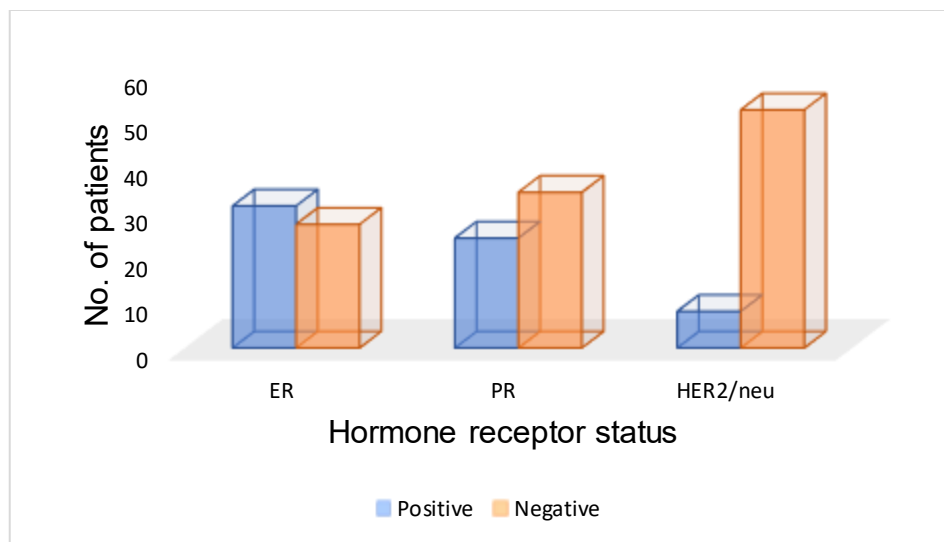
Figure 2: Hormone receptor status of patients. (N = 58)

According to figure 2, total number of ER positive cases were 53.44% whereas it was negative in remaining 46.56% of cases. PR positivity was seen in 41.38% cases. HER2/neu positive cases were 13.79%

Table 2: Association between clinico-pathological parameters and ER/PR status

Clinico-pathological parameters	ER+/PR+ (N = 31)	ER-/PR- (N = 27)	p value
Tumor size			
<2cm	02 (28.57%)	05 (71.43%)	0.05
2-5cm	20 (68.97%)	09 (31.03%)	
>5cm	09 (40.91%)	13 (59.09%)	
Nodal metastasis			
Present	18 (58.06%)	13 (41.94%)	0.45
Absent	13 (48.15%)	14 (51.85%)	
Histological grade (n = 52)			
Grade I	01 (100%)	00 (0%)	**0.01**
Grade II	20 (66.67%)	10 (33.33%)	
Grade III	06 (28.57%)	15 (71.43%)	
Stage			
I	03 (100%)	00 (0%)	**0.04**
II	21 (61.76%)	13 (38.24%)	
III	07 (36.84%)	12 (63.16%)	
IV	00 (0%)	02 (100%)	

Table 3: Association between clinico-pathological parameters and HER2/neu status

Clinico-pathological parameters	HER2/neu +ve (N = 8)	HER2/neu -ve (N = 50)	p-value
Tumor size			
<2cm	02 (28.57%)	05 (71.43%)	0.45
2-5cm	03 (10.34%)	26 (89.66%)	
>5cm	03 (13.63%)	19 (86.37%)	
Nodal metastasis			
Present	06 (19.35%)	25 (80.65%)	0.18
Absent	02 (7.41%)	25 (92.59%)	
Histological grade			
Grade I	00 (0%)	01 (100%)	**0.01**
Grade II	01 (03.33%)	29 (96.67%)	
Grade III	07 (33.33%)	14 (66.67%)	
Stage			
I	00 (0%)	03 (100%)	**0.004**
II	04 (11.76%)	30 (88.24%)	
III	02 (10.53%)	17 (89.47%)	
IV	02 (100%)	00 (0%)	

According to table 2, it was observed that there was significant association found between ER/PR status with histological grade (p = 0.01) and stage (p = 0.04) where more ER-/PR- patients were found with increasing grade and stage.

However, tumor size and nodal metastasis were not found to be significantly associated with ER/PR status.
Similarly, table 3 depicts association between HER2/neu status and some clinicopathological parameters. It was seen that with increasing histological grade and advancing stage of cancer, the frequency of HER2/neu positivity increased and there was significant association found between HER2neu status with histological grade (p = 0.01) and stage (p = 0.004).

DISCUSSION
In the present study the peak was from 51-60 years of age, followed by 31-40 years of age. The mean age was 49.34 years. This finding is similar to studies of Shashidhar M R et al where in their study they had similar finding with maximum cases 30.77% between 51-60 years (8). Majority of the females with breast carcinoma in the present study were postmenopausal 53% and 47% were premenopausal. These findings were similar to the study by Mansour A et al where 59.7% of patients were in the postmenopausal age group (9). 94.83% in our study were parous and 5.17% were nulliparous. Krishnamoorty et al in his study had 88% females who were parous and 12 % nulliparous females (10). Left breast (62.07%) was more commonly involved than right breast. Two large population-based studies conducted by Perkins et al (population size 419.935) and Zeeneldin et al (population size 5459) also found percentage of left breast involvement to be more than right (11,12).

In the present study out of these 58 tumors 50% tumors measured 2-5cm which was similar to findings studied by Vettuparambil A et al (13).

In the present study, IDC (NOS) was the most common subtype in 52 cases (86.22%) which was similar to findings by Saleh F et al where the most common histologic subtype was infiltrating ductal carcinoma (14).

In the present study out of 58 specimens, 31 cases (53.45%) had positive lymph node status. Study done by Mudduwa LK et al (15) showed similar finding. In study done by Vettuparambil A et al they have documented a higher proportion of lymph node positive disease compared to the West (13). The difference could be attributed to the well-established screening programmes in developed countries. Presence of lymph node metastasis indicate poor prognosis. Most common TNM stage at presentation was stage II (58.62%) followed by stage III (35.76%). 5.17% cases were in Stage I and 3.45% in stage IV. Study done by Devi PU et al also shows similar findings (16). However, in a study done by Badopati et al he found that most women presenting at late stage, mostly Stage 3 and 4 (17). Most women in India present at higher stage because of lack in awareness about breast cancer, especially in rural areas and among poor socioeconomic groups. Even despite adequate information, females tend to delay due to reasons like fear, embarrassment, cost, ignorance, negligence but if we compare our data to Western population like United States, most of their cases (57% to 61%), presented in Stage I. Early detection may be due to significant increase in mammographic screening women of all age groups in US.

ER/PR status has gained importance in management of patients who are positive for hormonal receptor and can be treated with targeted Tamoxifene, as the drug is helpful in decreasing breast cancer recurrence and mortality (18). ER and PR status in our study are similar to Ghosh et al but the positivity was more in a study by Ravishankar MC et al (19, 4). In the current study, ER/PR status was found to be significantly associated with grade and stage but not tumor size and nodal metastasis. Slightly contrary to this, Bhimani Z et al in their study found significant association of ER/PR status with all 3 - nodal metastasis, tumor size and stage (20).

The HER2/neu was expressed in 08 (13.79%) out of 58 cases of carcinoma breast in the present study. The HER2/neu expression was higher in a study by Uzun M et al (21). We found significant association between ER/PR status and HER2/neu status with histological grade and stage but Bhimani Z et al found no such association in their study (20).

Strengths and limitations
The findings reinforce the prognostic and therapeutic significance of hormone receptor and HER2/neu status, aligning with current standards in breast cancer management and aiding in treatment stratification. Utilization of immunohistochemistry provides a practical and cost-effective method for biomarker evaluation, which can be readily adopted in most pathology laboratories, including those in resource-limited settings.

The study did have certain limitations as well. As the study was conducted at a single institution and the sample size was small, the findings may not be generalizable to broader or more diverse populations. Since this was not a longitudinal study with no follow-up data, it restricts the ability to correlate receptor status with patient outcomes such as disease-free or overall survival.

CONCLUSION
This clinicopathological study highlights the significant correlation between estrogen receptor (ER), progesterone receptor (PR), and HER2/neu expression with the histological grade and clinical stage of breast cancer. ER and PR positivity were

more commonly associated with lower-grade, early-stage tumors, suggesting a favorable prognosis and potential responsiveness to hormonal therapy. In contrast, HER2/neu overexpression was frequently linked to higher-grade and advanced-stage tumors, indicating a more aggressive disease course. These findings underscore the importance of assessing hormone receptor and HER2/neu status as essential components in the prognostic evaluation and therapeutic planning for breast cancer patients.

Immunohistochemical evaluation of ER, PR, and HER2/neu should be an integral part of the diagnostic workup for all breast cancer patients to guide personalized treatment planning. Larger, multicentric studies are recommended to validate these findings across diverse populations and to explore additional molecular markers that could refine prognostication and therapeutic approaches.

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