

# Determination of Estrogen Receptor, Progesterone Receptor & Human Epidermal Growth Factor Receptor 2 Status in Breast Cancer: A Single-Center Experience

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## ABSTRACT

**Objective:** To determine the frequency of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expressions and to compare them with certain morphological parameters of breast tumors.

**Methodology:** It was a retrospective record-based study carried out in the Pathology Department of Akhtar Saeed Medical & Dental College, Lahore. A total of 45 cases of breast cancer from January 2021 to May 2022 were included in this study. The cases included needle core biopsies and mastectomy specimens. The sections were processed and examined under a microscope. Grading of tumors was done by the Bloom Richardson grading system and tumor characteristics for mastectomy specimens such as tumor size and lymph node status were noted. The luminal classification was done and frequencies were calculated. The immunohistochemical analysis was performed for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Scoring was done according to the breast cancer template of the College of American Pathologists. The frequencies were calculated for ER, PR, and HER2 status, Bloom grades, and tumor characteristics.

**Results:** In our study, the mean age of the patients was 46.31 years and most of the cases were seen in the age group of 55 to 64 years. The frequency of ER-positive cases was 29(64.4%) while the frequency of ER-negative cases was 16(35.6%), the frequency of PR-positive cases was 19(42.2%), and PR-negative cases was 26(57.8%). In contrast, the frequency of HER2-positive cases was 13(28.9%) and the frequency of HER2-negative cases was 28(62.2%). Most ER-positive cases were observed in the age group 45 to 64 years and most of the HER2-negative cases were seen in the age group 55 to 64 years. The majority of the cases (95.6%) were invasive ductal carcinoma. Most of the cases of breast cancer were of grade II (87%) and luminal A type (40%) was the most frequent one. In the mastectomy specimens, the size of the tumor in most of the cases (55.6%) was 2 to 5 cm and a majority of the cases (33.3%) had  $\geq 4$  lymph nodes positive.

**Conclusion:** Estrogen receptor was most frequently expressed along with loss of HER2 receptor. Invasive ductal carcinoma was the most common histological type and the majority of breast cancer cases showed grade II. The most common type of carcinoma was the luminal A type.

**Keywords:** Breast carcinoma. Estrogen receptor. Progesterone receptor.

## INTRODUCTION

Breast cancer is the fifth leading cause of cancer-related deaths, globally. According to some recent statistics, almost 2.3 million cases of breast cancer and 685,000 deaths were reported in the year 2020.<sup>1</sup> The total number of cases may rise to 4.4 million by the year 2070.<sup>2</sup> In the year 2020, this deadly cancer has already taken over other malignancies among females with a reported incidence of a total of 24.5% cases and mortality of 15.5% worldwide.<sup>1</sup> Pakistan with 90,000 cases annually and nearly 40,000 breast cancer-related deaths, remains the leading country among other Asian countries.<sup>3</sup> According to the annual report of Nuclear Medicine, Oncology & Radiotherapy Institute, Islamabad, breast cancer accounts for 33% of all cancers in females admitted to the center.<sup>4</sup> In urban India, the incidence of breast cancer in women is about 25 to 33%.<sup>5</sup>

Breast cancer was once considered a disease of elderly females. But according to several recent studies, the incidence is steadily increasing in young females, with 47.3% of total breast cancer cases in developing countries. The age group most prone to develop the disease is 45-49 years with an incidence of 45.42%.<sup>6</sup> Majority of such cases are attributed to loss of hormonal influence leading to abnormal expression of estrogen receptor and progesterone receptor. The hereditary factors contribute to only 10% of breast cancers while other risk factors like socio-demographic factors, reproductive health, and lifestyle constitute the most.<sup>5,7</sup>

There are various markers used to identify breast cancer including estrogen and progesterone receptors. Breast cancers with positive ER and PR status are associated with improved outcomes and response to therapy. On the contrary, another marker is a tyrosine kinase receptor (HER2) related to the epidermal growth factor receptor family. If HER2 is over-expressed, it is associated with relapse and resistance to therapies as compared to ER & PR-positive cases.<sup>5</sup> Therefore, it is imperative to evaluate ER, PR, and HER2 status of breast carcinomas diagnosed on hematoxylin and eosin (H & E) staining.<sup>8</sup> The purpose of this study was to analyze the frequency of ER, PR, and HER2 receptor

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Received: August 29, 2022; Accepted: October 17, 2022

expression, and their correlation with established clinicopathological prognostic criteria (age, histological type, and grade) to improve the medical care provided to breast cancer patients.

**METHODOLOGY**

It was a retrospective record-based study carried out in the Pathology Department of Akhtar Saeed Medical & Dental College, Lahore. A total of 45 cases of breast cancer from January 2021 to May 2022 were included in this study. The cases were received from Akhtar Saeed Trust Hospital and Farooq Hospital, Lahore. The specimens included formalin-fixed needle core biopsies and mastectomies (27 needle cores and 18 mastectomies). The poorly preserved specimens were not included in this study. All the relevant information from patients was collected on a predesigned proforma. Grading of tumors was done by the Bloom Richardson grading system. The tumor characteristics for mastectomy specimens such as tumor size and lymph node status were recorded. The luminal classification was also done and frequencies were calculated. The immunohistochemical analysis was performed for ER, PR, HER2, and scoring was done according to the breast cancer template of the College of American Pathologists. The frequencies were calculated for ER,

PR, and HER2 status, Bloom grades, and tumor characteristics.

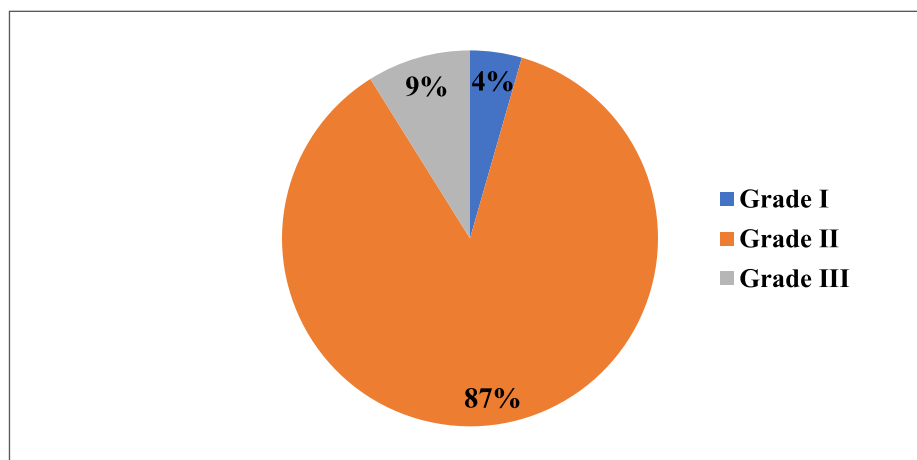
**STATISTICAL ANALYSIS**

The collected data was analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0. The mean and standard deviation was used to summarise the statistics of continuous variables. Categorical variables were reported as frequencies and percentages.

**RESULTS**

In our study, the mean age of the patients was 46.31 years and most of the cases were seen in the age range of 55 to 64 years. The majority of the cases (95.6%) were of invasive ductal carcinoma and 4.4% of the cases were diagnosed as invasive lobular type. According to Bloom’s grade, most of the cases were of grade II (87%) (Figure 1).

The frequency of ER-positive cases was 29(64.4%) while the frequency of ER-negative cases was 16(35.6%), the frequency of PR-positive cases was 19(42.2%), and that of PR-negative cases was 26(57.8%). In contrast, the frequency of HER2-positive cases was 13(28.9%) as reported in Table 1.



**Figure 1: Distribution of Cases (Needle Core Biopsy & Mastectomy) according to Bloom’s Grade**

**Table 1: Receptor Expression Pattern in all Age Groups**

Receptor Type	Positive Frequency & Percentage	Negative Frequency & Percentage
Estrogen Receptor	29(64.4%)	16(35.6%)
Progesterone Receptor	19(42.2%)	26(57.8%)
HER2	13(28.9%)	28(62.2%)
Equivocal Frequency & Percentage	4(8.9%)	

The frequency of receptor-positive cases among various age groups was compared. Most ER-positive cases (n=18) were observed in the age group 45 to 64 years and most of the HER2-negative cases (n=9) were recorded in the age range of 55 to 64 years (Table 2).

Considering the luminal classification of breast cancer, it was found that most of the cases were of luminal A type (40%) and HER2-enriched cases were of minimum frequency (8.9%). The triple negative cases comprised 22.2% (Table 3).

In the mastectomy specimens, the size of the tumor in most of the cases [10(55.6%)] was 2 to 5 cm. In 6(33.3%) cases, the size of the tumor was more than 5 cm and 2(11.1%) cases had a tumor of size less than 2 cm. The lymph node status of the mastectomy specimen revealed that most of the cases (33.3%) had  $\geq 4$  lymph nodes positive (Table 3). This study also depicted that as the tumor size increased, the frequency of HER2-negative status also increased (Table 4).

**Table 2: Receptor Expression Pattern in Patients according to Age Groups**

Age (Years)	ER-Positive (n)	ER-Negative (n)	PR-Positive (n)	PR-Negative (n)	HER2-Positive (n)	HER2-Negative (n)
25 to 34	5	2	5	2	2	4
35 to 44	5	6	6	5	2	8
45 to 54	7	5	3	9	6	6
55 to 64	11	3	5	9	3	9
$\geq 65$	1	0	0	1	0	1

**Table 3: Distribution of Cases according to Luminal Types and Lymph Node Metastasis**

Distribution of Needle Core Biopsy & Mastectomy Specimens according to Luminal Types	
Luminal Classification	Frequency & Percentage
Luminal A	18(40%)
Luminal B	9(20%)
HER2-Enriched	4(8.9%)
Triple Negative	10(22.2%)
Distribution of Mastectomy Specimens according to Lymph Node Metastasis	
Lymph Node Status	Frequency & Percentage
Not Identified	5(27.8%)
Negative (0)	2(11.1%)
Positive (1-3)	5(27.8%)
Positive (4 or more)	6(33.3%)

**Table 4: Receptor Status according to Tumor Size**

Tumor Size (cm)	No. of Cases	ER-Positive	ER-Negative	PR-Positive	PR-Negative	HER2-Positive	HER2-Negative
<2	2(11.1%)	2	0	2	0	1	0
2 to 5	10(55.6%)	8	2	7	3	1	9
>5	6(33.3%)	2	4	1	5	1	5

### DISCUSSION

A multidisciplinary approach involving a surgeon, pathologist, and oncologist is required for the appropriate management of breast carcinomas. The hormone receptors play a critical role in the

determination of a therapeutic plan, treatment response, and prognosis.<sup>8</sup> The patients can be categorized into two groups based on the receptor positivity status. One group of those who can benefit from adjuvant chemotherapy and the other group of

those who are less likely to respond. Therefore, the hormone receptor status should be determined in all breast carcinomas.

In a study by Singh et al., the frequency of ER-positive cases was observed to be 56% and ER-negative cases 44%, PR-positive cases 38% and PR-negative cases 62%. Human epidermal growth factor receptor 2 positivity was observed in 30% of total cases, HER2-negative in 70%, and triple-negative in 30%, respectively.<sup>9</sup> Another study conducted by Khalid et al., showed that the frequency of ER-positive cases was found to be 53.3%, ER-negative 46.7%, PR-positive 55.1%, PR-negative 44.9%, HER2-positive 30.8%, and HER2-negative 39.3%.<sup>10</sup> Some other studies also reported similar observations, showing a relatively higher percentage of ER and PR-positivity in breast cancer cases.<sup>11,12</sup> All these findings support the findings of the current study where ER-positive and negative cases were 64.4% & 35.6%, respectively, PR-positive in 42.2%, and negative in 57.8%, and HER2 positivity was observed in 28.9% & negativity in 62.2% cases.

Our study showed that most of the cases were of luminal A type (40%) and HER2-enriched cases were of minimum frequency (8.9%). The triple negative cases comprised 22.2%. Another study reported that more than half of the total tumor cases (51.9%) fall in the category of grade II, 42.9% in grade III, and only 5.2% in grade I. Luminal A subtype was found to be the most prevalent (38.8%). Triple-negative hormone receptors and luminal B cases were 15.5% each, however, 14.9% of cases were HER2-enriched.

In an Indian study carried by Bhardwaj et al., the mean age of development of carcinoma breast was 50.28±12.83 years. The majority of the cases (53.52%) were in the age group of 35 to 54 years. The most frequent type (76.64%) was invasive ductal carcinoma not otherwise specified (NOS) and the most frequent grade was grade II (47.88%) followed by grade III (32.39%). The results of this study showed that 38(53.52%) of the cases were ER/PR-positive, 9(12.67%) were ER-positive/PR-positive/HER2-positive, and 22(30.98%) were ER-negative/PR-negative/HER2-negative, respectively.<sup>13</sup>

Another study showed a majority of patients in the age group of 40 to 59 years. The most frequent type was invasive ductal carcinoma NOS (83.9%) and the most frequent grade was I (49%) followed by grade III (40%). In addition, the frequency of ER & PR expression was found to be 48.39% and 41.9%, respectively.<sup>14</sup>

In a Malaysian study, the median age for carcinoma breast was 55 years, and infiltrating ductal carcinoma (IDC) was found to be the most common histological type (6.8%).<sup>15</sup> Similarly, African researchers conducted a study on 343 breast cancer patients. It showed that the

mean age for breast cancer was 49.7 years and the common histological type was invasive ductal carcinoma of no special type (89%). More than half percent of the total cases (51.9%) had tumor sizes ranging from 2-5 cm and some (39.1%) with >5 cm. A greater percentage of these tumors were of grades II and III types.<sup>16</sup>

A study on the population of Pakistan indicated that ER and PR-positive cases were present in 45.4% and 36.9%, respectively, of breast cancers. The most common histological type was invasive ductal carcinoma, not otherwise defined, which made up 95.4% of all cases. Age at diagnosis ranged from 24 to 78 years, with the majority of cases (53.1%) being under 50 years old. In the same study, 40(30.8%) of the cases showed positive results for both receptors (ER, PR) while 63(48.5%) of the cases showed negative results for both receptors. Among other findings 6.1% of cases had ER-negative, PR-positive while 14.6% of all cases had ER-positive, PR-negative.<sup>17</sup> All of these conclusions are consistent with the current research.

## CONCLUSION

The present study showed that ER receptor was most frequently expressed along with the loss of HER2. Invasive ductal carcinoma was the most common histological type of breast cancer and a majority of the cases showed grade II morphology. Luminal A type of breast cancer was the most common among other subtypes in our setting.

## LIMITATIONS & RECOMMENDATIONS

This was a single-centered study and the sample size was relatively small due to time constraints. Therefore, the findings of the present study cannot be applied to the general population. Further large-scale studies on a single biopsy type are recommended to validate these results.

## REFERENCES

1. Soerjomataram I, Bray F. Planning for tomorrow: global cancer incidence and the role of prevention 2020-2070. *Nat Rev Clin Oncol.* 2021; 18(10):663-72. doi:10.1038/s41571-021-00514-z.
2. Malik SS, Baig M, Khan MB, Masood N. Survival analysis of breast cancer patients with different treatments: a multi-centric clinicopathological study. *J Pak Med Assoc.* 2019; 69(7):976-80. Available from: <https://jpma.org.pk/PdfDownload/9232>.
3. Arshad S, ur Rehman M, Abid F, Yasir S, Qayyum M, Ashiq K, et al. Current situation of breast cancer in Pakistan with the available interventions. *Int J Biosci.* 2019; 14(6):232-40. doi:10.12692/ijb/14.6.232-240.
4. Venkatesh N, Jayaram R, Venkatesan V. Case study of infiltrating carcinoma of the breast in correlation with the incidence of the estrogen receptor [ER], progesterone receptor

- [PR] and HER2<sup>neu</sup> status. *JMSCR*. 2019; 7(8):699-703. doi:10.18535/jmscr/v7i8.118.
5. Zaheer S, Shah N, Maqbool SA, Soomro NM. Estimates of past and future time trends in age-specific breast cancer incidence among women in Karachi, Pakistan: 2004-2025. *BMC Public Health*. 2019; 19(1):1001. doi:10.1186/s12889-019-7330-z.
  6. Ahmad W, Firasat S, Akhtar MS, Afshan K, Jabeen K, Amjad RA. Demographic variation and risk factors regarding breast cancer among females in Southern Punjab, Pakistan. *J Pak Med Assoc*. 2021; 71(7):1749-56. doi:10.47391/JPMA.1091.
  7. Kuroda H, Muroi N, Hayashi M, Harada O, Hoshi K, Fukuma E, et al. Oestrogen receptor-negative/progesterone receptor-positive phenotype of invasive breast carcinoma in Japan: re-evaluated using immunohistochemical staining. *Breast Cancer*. 2019; 26(2):249-54. doi:10.1007/s12282-018-0898-9.
  8. Blackwood O, Deb R. Multidisciplinary team approach in breast cancer care: benefits and challenges. *Indian J Pathol Microbiol*. 2020; 63(Supplement):S105-12. doi:10.4103/IJPM.IJPM\_885\_19.
  9. Singh M, Kumar J, Omhare A, Mishra V, Kala C. Study on histopathological correlation with ER, PR, and HER2 neu receptor status in breast carcinoma and its prognostic importance. *Int J Life Sci*. 2019; 5(1):2130-6. doi:10.21276/SSR-IIJLS.2019.5.1.3.
  10. Khalid F, Zafar G, Afzal S, Chughtai A, Fatima B, Chughtai AS. Frequency of different molecular subtypes of breast cancer in Pakistani population: a single center study. *Pak J Pathol*. 2020; 31(2):50-4. Available from: <https://pakjpath.com/index.php/Pak-J-Pathol/article/view/558/469>.
  11. Sleightholm R, Neilsen BK, Elkhatib S, Flores L, Dukkipati S, Zhao R, et al. Percentage of hormone receptor positivity in breast cancer provides prognostic value: a single-institute study. *J Clin Med Res*. 2021; 13(1):9-19. doi:10.14740/jocmr4398.
  12. Rouge TD, Frenel JS, Hardy-Bessard AC, Bachelot T, Pistilli B, Delalogue S, et al. 167MO association between ER, PR and HER2 levels and outcome under palbociclib (Pal)+ aromatase inhibitors (AIs) as first-line therapy for ER+ HER2-metastatic breast cancer (MBC): an exploratory analysis of the PADA-1 trial. *Ann Oncol*. 2022; 33(S3):S200. doi:10.1016/j.annonc.2022.03.186.
  13. Bhardwaj H, Khandelwal M, Mittal S, Sharma RK. A study of hormone receptor status in breast carcinoma and their histopathological correlation. *JMSCR*. 2021; 9(5):19-25. doi:10.18535/jmscr/v9i5.05.
  14. Mittal A, Prasad C, Sreeramulu PN, Srinivasan D, Khan NA, Joshi RU. Histopathological grade versus estrogen and progesterone receptor status in carcinoma breast - a single center study. *Open Access J Surg*. 2017; 4(3):555639. doi:10.19080/OAJS.2017.04.555639.
  15. Tan KF, Adam F, Hussin H, Mohd Mujar NM. A comparison of breast cancer survival across different age groups: a multicentric database study in Penang, Malaysia. *Epidemiol Health*. 2021; 43:e2021038. doi:10.4178/epih.e2021038.
  16. Oluogun WA, Adedokun KA, Oyeniye MA, Adeyeba OA. Histological classification, grading, staging, and prognostic indexing of female breast cancer in an African population: a 10-year retrospective study. *Int J Health Sci (Qassim)*. 2019; 13(4):3-9. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6619457/pdf/IJHS-13-3.pdf>.
  17. Sohail SK, Sarfraz R, Imran M, Kamran M, Qamar S. Estrogen and progesterone receptor expression in breast carcinoma and its association with clinicopathological variables among the Pakistani population. *Cureus*. 2020; 12(8):e9751. doi:10.7759/cureus.9751.

