Original Article

Correlation and Expression of ER, PR, HER-2/Neu and Its Association with Clinicopathological Variables in Invasive Ductal Carcinoma of Breast

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DOI: 10.21276/APALM.3374

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Submitted: 19-May-2024
Final Revision: 21-June-2024
Acceptance: 15-Jul-2024
Publication: 11-Aug-2024

Abstract

Background: Invasive ductal carcinoma (IDC) of the breast is the largest group of malignant mammary tumors, comprising approximately 75% of mammary carcinomas. The prognosis of breast cancer depends on the histological type, size of the tumor, tumor necrosis, skin, nipple, and chest wall invasion, lymphovascular invasion, grade, stage, and the status of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. These factors are especially important in planning therapy and for clinical follow-up.

Materials and Methods: A total of 114 cases with IDC who underwent modified radical mastectomy and were diagnosed as malignant on histopathology were collected from the Department of Pathology from January 2022 to January 2024. Immunohistochemistry (IHC) for ER, PR, and HER-2 status was evaluated by histopathologists following the College of American Pathologists (CAP) guidelines. Statistical analysis was performed using SPSS software versions 21 and 23 for Windows, with the chi-square test and Pearson correlation test used to determine the quantitative data.

Results: Our results showed that most of the breast cancer patients (53.6%) were aged 50 and above. The mean age of the patients was 51.1 ± 2.3 years (ranging from 30 to 75 years). Forty-six (40.4%) and 30 (26.3%) cases were positive for ER and PgR, respectively, and 24 cases (21.1%) were positive for HER-2. We also observed a significant positive correlation between ER and PR expression (P = 0.00), and they inversely correlated with HER-2/neu expression (P = 0.02).

Conclusion: The ER/PR/HER2 subtyping is simple, inexpensive, easy to interpret, reliable, reproducible, and readily available for clinicians without additional tests. It provides valuable prognostic information for making the best therapeutic decisions.

Keywords:

Invasive Ductal Carcinoma Breast, Estrogen Receptors, Progesterone Receptor, Her-2/Neu, c-erbB-2 Proto-Oncogene

Introduction

Breast carcinoma is the second most common and leading cause of cancer-related death among women worldwide, comprising approximately 75% of mammary carcinomas [1,2]. Invasive ductal carcinoma (IDC) is a clinically and pathologically heterogeneous hormone-dependent tumor with diverse histopathological types, molecular, and clinical features [2]. The molecular

mechanisms of this hormone dependence have been the focus of studies over the past few decades, primarily to understand the predictive role and prognostic value of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) in breast cancer management [3].

ER, PR, and HER2, routinely available in breast cancer specimens, are reliable, inexpensive, and useful for therapeutic planning and decision-making, which helps clinicians treat patients more effectively for better survival and longevity [4,5,6]. Tumors expressing ER and PR receptors show a good response to hormonal therapy and chemotherapy, leading to a better prognosis, improved survival, and lower mortality compared to women with ER- and/or PR-negative disease [2,7]. Tumors expressing HER2 are histologically high-grade, and HER2 is a promising biomarker associated with a higher likelihood of metastasis and worse prognosis. HER2 is overexpressed in 18%-20% of cases, which has both prognostic and predictive value [8,9,10]. Evaluation of the prognostic and predictive biomarkers ER, PR, and HER2 is recommended in every case of breast carcinoma [9].

The objective of the study is to assess and evaluate the expression and correlation of ER, PR, and HER2/Neu in IDC and its association with prognostically important clinicopathological variables, which helps in understanding the biological and clinical behavior of breast cancer in our population.

Materials and Methods

A total of 114 cases who underwent modified radical mastectomy for invasive ductal carcinoma of the breast, confirmed on histopathology, were collected from the Department of Pathology, GSL Medical College, Hospital & Research Institute, Rajamahendravaram, Andhra Pradesh, from January 2022 to January 2024.

Inclusion Criteria: Patients with histopathologically confirmed IDC, with complete surgical details and information about ER, PR, and HER2 status, were included in the study.

Exclusion Criteria: Data from patients with incomplete histopathological and surgical details, or with no/incomplete information about ER, PR, and HER2/Neu status, were excluded from the study.

Following standard protocols for handling the specimens and reporting, the demographic data, gross, and microscopic findings were recorded. Immunohistochemistry (IHC) for ER, PR, and HER2/Neu was applied to suitable tumor sections, and their status was evaluated by histopathologists using College of American Pathologists (CAP) guidelines.

In brief, 3 μm thick slides were prepared from paraffin-embedded blocks, then sections were deparaffinized in 3 changes of xylene and rehydrated through graded concentrations of alcohol (ethanol). The slides were incubated with immune wash buffer (Tris-EDTA) (pH = 9) for 15 minutes in a microwave for antigen retrieval, then washed with buffer saline and tap water. All slides were incubated in H2O2-methanol solution (1/9) for 12 minutes to inhibit endogenous peroxidases. Next, the slides were covered with primary antibody (Dako, Denmark) for 60 minutes at room temperature, followed by incubation with Envision for 10 minutes at room temperature. Then, all slides were covered with chromogen and diaminobenzidine for 5-7 minutes at room temperature and then washed with wash buffer. Lastly, all these slides were stained with H&E for 3 minutes, dehydrated with graded alcohol, then xylene, dried, and mounted with mounting media.

On IHC, ER and PR were interpreted as positive when the tumor cells showed positive nuclear staining in at least 1% of the tumor cells. Data of all the patients were compiled and assessed for the pattern of expression of ER, PR, and HER2/Neu in IDC. Patients were divided into two age groups: 1) < 50 years and 2) ≥ 50 years. Furthermore, tumor size was divided into 1) ≤ 2 cm, 2) > 2 –5

cm, and 3) > 5 cm. Bloom-Richardson scoring was used for histologic grading (grades I, II, and III).

ER, PR, and HER2/Neu were semiquantitatively evaluated. H score was used for ER and PR (a negative result was defined as a score of ≤ 50, and positive between 51 and 300). The DAKO scoring system for HER2/Neu was defined as negative for scores of 0, 1+, or 2+, and positive for tumors with a score of 3+. The association of ER, PR, and HER2/Neu status with clinicopathological variables such as age, tumor size, tumor grade, necrosis, lymph node status, and lymphovascular invasion was also assessed.

Statistical analysis was done using a Chi-square test and SPSS software version 21 & 23 for Windows to determine the quantitative data, and Pearson correlation test was applied to evaluate P-value (< 0.05 was considered as the significant level).

Results

A total of 114 cases were evaluated for IHC markers: ER, PR, and HER-2/neu on all suitable sections (Figure 1, Figure 2, Figure 3).

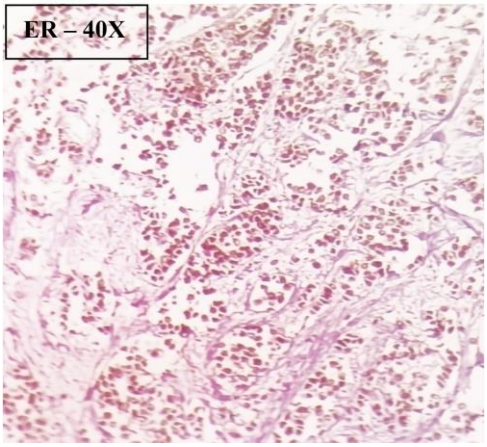

Figure 1: IHC for IDC showed ER positivity

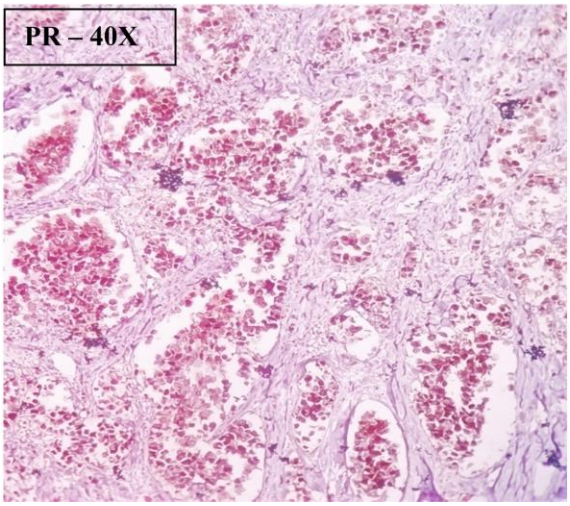

Figure 2: IHC for IDC showed PR positivity

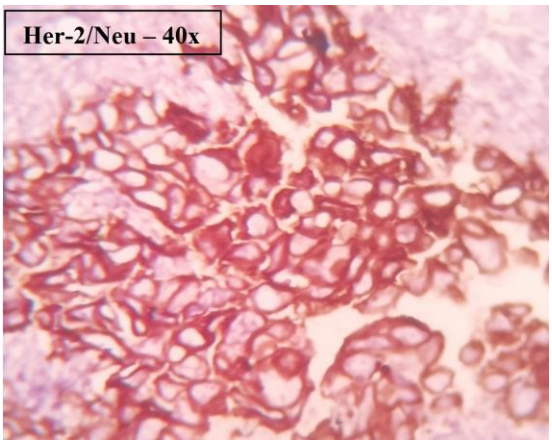

Figure 3: IHC for IDC showed Her-2/neu positivity

The age of the patients ranged from 30 to 75 years. Most of the patients (52.6%) were 50 years and above. The mean age of the respondents was 51.1 ± 10.5 SD (Table 1 & Figure 4).

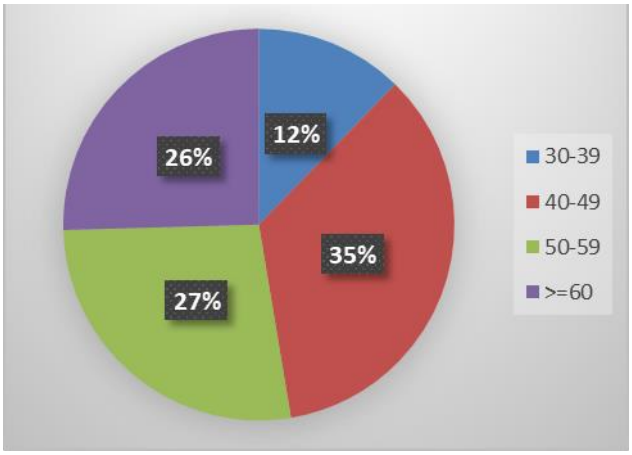

Figure 4: Age distribution among breast cancer patients

Patients aged 50 years and above were the most frequent age group, comprising 60 cases (52.6%). Predominantly, 82 cases (71.92%) belonged to histologic grade II. The tumor size ranged from 1.5 cm to 12 cm, with the majority of the patients (89 cases) presenting with a tumor size of >2-5 cm. The average lymph node involvement was 49 cases, which is 42.98% (Table 2).

Table 1: Age distribution among breast cancer patients

Age in Years	Frequency n=114	Percentage(%)
30-39	14	12.30%
40-49	40	35.10%
50-59	31	27.20%
> = 60	29	25.40%
Total	114	100%
Mean	51.1±10.5SD	

Table 2: Clinical characteristics

Age(years)	N	%
< 50	54	47.4
>=50	60	52.6
Tumor size(cm)		
≤2cm	9	7.90%
>2-5 cm	89	78.10%
>5cm	16	14.04%
Tumor grade		
I	16	14.04%
II	82	71.92%
III	16	14.04%
Lymph node		
Negative	65	57.02%
Positive	49	42.98%

Forty-six (40.4%) cases showed positivity for ER, thirty (26.3%) cases for PR, and twenty-four (21.1%) cases for HER-2/neu. All tumors were graded according to the modified Scarff-Bloom-Richardson grading system. Histologic Grade II predominated with 82 (71.92%) cases, while Grades I and III were found in 16 (14.04%) cases each. Forty-seven (41.2%), fifty-nine (51.75%), and sixty-six (57.89%) cases of histologic Grade II were ER-, PR-, and HER-2/neu- respectively.

The majority of the tumors (89 cases, 78.1%) were >2-5 cm in size, of which 52 cases were negative for ER, 64 cases were negative for PR, and 70 cases were negative for HER-2 hormone receptors. Lymphovascular invasion and tumor necrosis were seen in 53 (40.8%) and 58 (44.6%) cases, respectively. Forty-nine cases (42.98%) showed metastatic tumor deposits in the axillary lymph nodes. Stage 1 lymph nodes were involved in 33 (28.9%) cases, of which 18 (26.47%), 24 (28.5%), and 30 (33.3%) were ER-, PR-, and HER-2-negative. Similarly, Stage 2 involved 13 (11.4%) cases, and Stage 3 involved 3 (2.6%) cases, out of which 7 (6.14%) were negative for ER, PR, and HER-2 receptors. HER-2 was significantly correlated with lymph node status (P = 0.02) (Table 3). A significant positive correlation was also observed between ER and PR expression (P = 0.00), and they were inversely correlated with HER-2/neu expression (P = 0.02).

Out of 114 cases, ER, PR, and HER-2 were expressed in 46 (40.3%), 30 (26.3%), and 24 (21.1%) cases, respectively. Co-expression of ER and PR was seen in 22 (19.3%) cases, while 19 (16.7%) cases were ER-, PR-, HER-2+. Out of 114, 43 (37.7%) cases were triple-negative (ER-/PR-/HER-2-) (Table 4).

Discussion

Breast carcinoma is the most common malignancy in females, with significant differences in ER, PR, and HER2 status around the world, varying by race and ethnicity. The causes of these differences are likely multifactorial, including socio-economic factors and biological differences influenced by genetics, lifestyle, nutrition, or environmental exposure [1][2][3].

Table 3: Association and correlation of Hormone receptors with Clinicopathological Variables.

Clinicopathological variables		ER+ (n=46) 40.3%	ER- (n=68) 59.64%	P-value	PR+ (n=30) 26.3%	PR- (n=84) 73.68%	P-value	Her2 + (n=24) 21.05%	Her2 - (n=90) 78.94%	P-value
Age	<50 yrs	16	38	**0.027**	10	44	0.073	13	41	0.453
	>=50 yrs	30	30		20	40		11	49	
Grade	G-I	9	7	**0.03**	5	11	0.386	2	14	0.18
	G-II	35	47		23	59		16	66	
	G-III	2	14		2	14		6	10	
Tumor size	<=2cm	5	4	0.288	1	8	0.54	1	8	0.708
	2-5 cm	37	52		25	64		19	70	
Lymph node stage	0	23	42	0.14	14	51	0.074	18	47	**0.021**
	1	15	18		9	24		3	30	
	2	8	5		7	6		1	12	
	3	0	3		0	3		2	1	
Lympho vascular invasion	Present	9	10	0.495	6	13	0.568	5	14	0.538
	Not identified	37	58		24	71		19	76	
Necrosis	Present	6	15	0.223	5	16	0.773	5	16	0.732
	Not identified	40	53		25	68		19	74	

Table 4: Proportion of hormone receptor types

S. no	Receptor Type	Frequency N=114	Percentage (%)
1	ER+/PR+/Her2-	22	19.30%
2	ER-/PR-/Her+	19	16.67%
3	ER-/PR-/Her2-	43	37.72%
4	ER+/PR-/Her2-	19	16.67%
5	ER-/PR+/Her2-	6	5.26%
6	ER+/PR-/Her2+	3	2.63%
7	ER+/PR+/Her2+	2	1.75%
	Total	114	100%

Considering the heterogeneity of breast carcinoma, many prognostic and predictive markers have been proposed to determine tumor behavior. A predictive marker provides information about a patient's response to treatment, while a prognostic marker indicates the overall survival of the patient, regardless of therapy [2][10][13].

ER and PR-positive tumors are generally better differentiated, present at an early stage, respond to hormone therapy, and show better prognosis, whereas HER-2-neu expression is associated with poor prognosis and is mostly associated with grade 3 tumors. Adjuvant hormonal therapy is advocated for all women with positive ER/PR status, regardless of their age, menopausal status, grade, stage, axillary lymph node status, or tumor size [9][10]. Positivity for ER and PR receptors in IDC is found to be 70%-80% and 60%-70%, respectively [9]. The management and prognosis depend upon many clinicopathologic variables like histological type, grade, and stage, tumor necrosis, lymphovascular invasion, skin and nipple invasion, lymph node involvement, status of ER, PR, HER2, BRCA 1 status, cell proliferation marker (Ki-67), type of therapy, local recurrence, and gene expression. These are all well-known prognostic and predictive markers [11][12].

In Asian countries, the prevalence of hormone receptor-positive tumors is lower than that in the Western world [2]. However, the number of studies performed on the Asian population is also much less compared to the West.

In our study, the age at the time of diagnosis ranged from 30 to 75 years, with the majority—60 (52.6%)—being over 50 years of age, and those under 50 years constituting 54 (47.4%) of cases. This is comparable to the Sohail SK et al. study performed in Pakistan, which showed 46.9% in >50 years of age and 53.1% in <50 years of age. Zeeshan et al. found that 27.4% of breast cancer patients were even younger than 40 years [2][14].

The majority of the tumors in our study belong to grade II, comprising 82 (71.9%) cases, and T2 stage (>2-5 cm), with 88 (77.2%) cases, 16 (14%) in T3 (>5 cm), and T1 (≤2 cm) in 10 (8.8%) cases, respectively. Hashmi et al. and Nabi MG et al. showed similar results, while Sohail SK et al. reported that 56.92% of the tumors belonged to the T3 category, and 33.85% of the tumors belonged to the T2 category. The possibility of these differences may be due to late presentation at the hospital, illiteracy, lack of resources, and financial problems.

According to Western studies, ER expression has been found in 50%-80% of cases, and PR expression in 60%-70% of cases of IDC [15]. The level of positive expression of hormone receptors was found to be lower compared to a study on the Pakistani population by Mahmood et al., which declared 64.1% positivity for ER and 60.6% positivity for PR [16]. Similarly, a study in Ahmedabad showed a 56.9% positive ER status and a 35.5% PR positive status [10]. Singh et al. reported ER positivity in 44.6% of cases and PR positivity in 40.4% of cases [2]. Hathila et al. reported 53.3% of breast cancer patients positive for ER and 36.6% of patients positive for PR [15]. In our study, ER, PR, and HER-2 positivity was found in 46 (40.3%), 30 (26.3%), and 24 (21.05%) cases, respectively.

Nikbakhsh N and Ghaemian N observed a significant correlation between histologic grade I and II with the expression of ER and PR, and a significant correlation between HER-2/neu expression with grade III tumors and lymph node involvement [1]. In our study, we observed a significant positive correlation between ER and PR expression ($P = 0.00$) in grade I and II tumors, and they inversely correlated with HER-2/neu expression ($P = 0.02$) in grade III tumors, respectively.

Lymphovascular invasion and tumor necrosis are important parameters to determine tumor recurrence after treatment [6]. In our study, lymphovascular invasion was observed in 19 (16.7%) cases, and necrosis in 21 (18.4%) cases, both expressed in the triple-negative category. Sohail SK et al. observed lymphovascular invasion in 53 (40.8%) cases. Similar results were reported by Nabi et al., with lymphovascular invasion seen in 35.2% of cases, the majority belonging to the ER-/PR- subgroup [7]. Shrigondekar et al. reported tumor necrosis in 47.85% of tumors in their study [18].

Certain molecular alterations, such as acquiring access to blood vessels and lymphatics, could potentially correlate with changes in receptor status. This is because endocrine and growth signaling pathways play a crucial role in invasion and metastasis. Such heterogeneity may contribute significantly to treatment failures, as distant diseases are more susceptible to adjuvant systemic therapies following initial surgery and radiotherapy [8].

Dunnwald LK et al. observed increased relative mortality risks among patients with ER-/PR- tumors that were small (<2 cm) or of low grade (grade 1 and 2). These elevated risks are likely attributed to standard adjuvant treatment protocols, where hormonal therapy is typically recommended for women with ER+/PR+ disease, regardless of tumor size. In contrast, adjuvant chemotherapy is not routinely recommended for ER-/PR- patients with small tumors and favorable features such as negative lymph nodes and high differentiation [7].

In our study, the proportion of hormone receptors ER, PR, and HER-2 were divided into eight groups: The majority of the cases are (ER-/PR-/HER2-) (triple-negative), with 43 (37.72%) cases. (ER+/PR+/HER2-) expression was shown in 22 (19.30%) cases, 19 (16.67%) cases for (ER-/PR-/HER+), 6 (5.26%) cases for (ER-/PR+/HER2-), 19 (16.67%) cases showed (ER+/PR-/HER2-), (ER-/PR+/HER2+) showed zero results, (ER+/PR-/HER2+) and (ER+/PR+/HER2+) showed 03 (2.63%) cases and 2 (1.75%) cases, respectively.

Sohail SK et al. studied the proportion of two hormones, ER and PR receptors, dividing them into four categories: (ER+, PR+) seen in 40 (30.8%) of cases, (ER-, PR-) in 63 (48.5%) cases, and (ER+, PR-), (ER-, PR+) in 19 (14.6%) and 8 (6.1%) cases, respectively [2]. Similarly, Nabi et al. showed 59 (42.4%) cases were ER+PR+, 60 (43.1%) cases were ER-PR-, and 10 (7.1%) cases were ER-PR+ and ER+PR-, respectively [9]. Hathila et al. reported co-expression of ER+ and PR+ in 53.3% of cases [17].

In our study, 49 (43%) cases showed metastatic tumor deposits in axillary lymph nodes. Axillary lymph node metastasis had been recorded in 69.2%, 66.9%, and 48.64% of cases, studied by Sohail SK et al., Nabi et al., and Shrigondekar et al., respectively [2][9][18].

Recently, new molecular subgroups of breast cancer have been delineated based on gene expression profiles. Among these, triple-negative breast cancer (TNBC) and basal-like breast cancers are notable for their higher grade and poorer prognosis compared to other molecular subtypes. These subtypes do not express ER, PR, or HER2/neu receptors, making them ineligible for traditional endocrine therapies or targeted treatments like trastuzumab. However, they may exhibit greater sensitivity to chemotherapy regimens that include platinum-based agents [8]. This classification highlights the importance of molecular profiling in guiding treatment decisions for different breast cancer subtypes based on their molecular characteristics and biological behavior.

The patients in our study predominantly originate from rural areas and frequently present with delayed diagnosis and advanced stage breast cancer. This trend can be attributed to several factors, including low levels of awareness about breast cancer, inadequate screening programs, limited access to diagnostic facilities, and lower socioeconomic status.

A notable limitation of our study is that we focused solely on invasive ductal carcinoma (IDC) and did not include other types of breast carcinoma. Future research should consider exploring biomarker expression and correlations in a broader spectrum of breast cancer types to provide a more comprehensive understanding of their clinical implications and management strategies.

Conclusion

We assessed the utility of ER/PR/HER2 expression and correlation in IDC, highlighting its simplicity, cost-effectiveness, ease of interpretation, reliability, reproducibility, and accessibility without the need for additional tests. These characteristics make it valuable for clinicians in providing prognostic information crucial for making optimal therapeutic decisions. Furthermore, we acknowledge the importance of advancing breast cancer classification through gene expression profiling and modern genomic tests. These technologies offer deeper insights into tumor biology, enabling better categorization of breast cancer subtypes. They hold promise for refining treatment strategies tailored to individual patient profiles. Early screening and detection initiatives, along with accurate diagnostics, are essential for improving outcomes through timely diagnosis and targeted treatment approaches, especially in settings where resources and awareness about breast cancer may be limited.

Acknowledgements: Nil

Funding: Self

Competing Interests: None

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