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Original Research Article.

Co-Relation of HER-2 Status with ER, PR & Histological Features in Invasive Breast Carcinomas: A Single Center Experience in Bangladesh

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ABSTRACT

Background: ER and PR are the hormone receptors of breast cells that pick-up hormone signals resulting in cell growth. And positive Her2/neu status of breast carcinoma means the gene making too many Her2/neu proteins, which acts as receptors on the cell surface and helps the cells to grow and divide. These hormone-receptor i.e ER, PR, and Her2/neu are routinely done in breast carcinoma disease. It helps in the prognosis and treatment of the tumor or breast cancer.

Objective: The objective of this study was to evaluate the co-relation of Her2 status with ER, PR & histological features in invasive breast carcinomas.

Methods and Materials: This cross-sectional study was conducted in the department of surgical oncology in a tertiary cancer hospital, Dhaka, Bangladesh from March 2015 to April 2016. All the patients of breast cancers for surgery/ biopsy for invasive breast carcinoma followed by evaluation of ER, PR, and Her2 status. In total 121 cases analyzed retrospectively for documentation of ER, PR, and Her2 status, using ASCO/CAP guideline.

Results: In analyzing the co-relation of Her2 status with ER, PR receptor status in invasive breast carcinomas we found only 10.74% patients with all positive whereas 28.10% were with all negative. Besides these, 23.97% of participants were Her2 negative whereas both ER and PR were positive. In 23.14% of participants, Her2 was positive whereas both the ER and PR were negative. On the other hand, 4.13% of participants were with ER-positive whereas PR and Her2 were negative and only 2.48% of patients were found with PR negative but both the ER and Her2 positive.

Conclusion: In conclusion, we can say that the receptor status of breast cancer, including ER, PR, and Her2 play a crucial role in the development of the treatment plan of breast cancer.

Keywords: HER-2/neu, ER, PR, Breast Carcinomas.

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INTRODUCTION

Worldwide, breast cancer is the most prevalent cancer as well as the most common female neoplasm accounting for 11.7% of all cancers in Bangladesh.[1] According to the world cancer report, more than one million cases occur worldwide each year, and 45% of these are in developing countries.[2] In South Asia, it is estimated that each year, 76,000 women die of breast cancer.[3] In Bangladesh, there is no national cancer registry but estimate an annual new breast cancer case burden of 30,000 women. It is projected that global breast cancer cases will grow from 1.4 million in 2008 to over 2.1 million cases in 2030.[4] According to receptor status biological classifications of breast cancer are introduced. The peculiar 'classification' of breast cancer that may be best seen as a kind of working formulations for clinical use included three main classes. They are 1) Tumor considered to be highly endocrine responsive, 2) Tumor not endocrine responsive, 3) Tumor with uncertain endocrine responsiveness. Endocrine treatment is the best therapeutic option for highly endocrine responsive tumors. Cytotoxic drugs and Transtuzumab in case of Her2 overexpression are the treatment modalities of a non-endocrine responsive tumor. Chemotherapy, as well as hormone therapy, is effective in the case of ER-positive and Her2 negative disease.[5] The original molecular classification has been derived from investigations on fresh frozen tissue based on the molecular expression of ER, PR, Her2 and Ki-67. Breast cancer can be categorized as five majors subtypes associated with different molecular alterations and distinct clinical outcomes including

therapeutic response: luminal A, luminal B, Her2 enriched, triple-negative breast cancer (TNBC) and basal/normal-like breast cancer.[6] Following this discovery, additional subgroups of breast cancer were identified such as the interferon-enriched and the molecular apocrine[7] subgroups and several subgroups of triple-negative breast cancer.[8] Molecular characteristics of the luminal A subtype is ER + and/or PR+, Her-2-and low proliferation rate, while the luminal B subtype is characterized by ER+ and/or PR+, Her2+ and high proliferation rate. The Her2+ subtype characteristics are ER/PR and Her-2+ expression; meanwhile, the triple negative-basal-like subtype is characterized by negative expression of ER/PR and Her2. Sixty percent of breast cancers are luminal subtype cancers arising from luminal epithelial cells that lined the duct of the mammary gland. The luminal subtypes of breast cancer tend to have a better prognosis compared with the non-luminal subtype because the luminal subtype is a hormone receptor-positive. Therefore, it is more sensitive to the hormone therapy approach. Her2+ and triple-negative/basal-like molecular subtypes arise from the basal cell of the mammary gland. These subtypes of breast cancer have a fairly poor prognosis and more prone to early and frequent recurrence and metastasize. Prognosis of Her2+ subtype is better compared with a triple-negative/basal-like subtype. In 2007, a new intrinsic subtype was described, the claudin-low subtype (CL), through the combined analysis of murine mammary carcinoma models and human breast cancer.[9] This subtype represents 6% of breast cancer samples analyzed (13/232). Notably, the molecular subtypes display highly significant differences in the prediction of overall survival, as well as disease-free survival with the basal-like/triple-negative (ER-/PR-/ErbB2-) subtype having the shortest survival.[10] The triple-negative phenotype has been associated with a higher rate of recurrence and distant metastasis, poorer Nottingham prognostic index, and a higher frequency of spinal cord and meninges, brain, liver, and lung metastases compared with other types of breast cancer. The biologic, predictive, and prognostic importance of assessment of estrogen receptor (ER) expression in breast cancer is well established. The added value of assessment of progesterone receptor which is a surrogate marker of estrogen receptor activity assessment remains controversial.[11]

METHODS AND MATERIALS

This cross-sectional study was conducted in the department of surgical oncology in a tertiary cancer hospital, Dhaka, Bangladesh during the period from March 2015 to April 2016.

All surgery or core biopsy patients of breast cancer was performed for invasive breast carcinoma followed by evaluation of ER, PR, and Her 2 status were included in the study. In total 121 cases were analyzed retrospectively for documentation of ER, PR, and Her2 status, using American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) interpretation guidelines. In this current study, the patient population comprises of all the cases underwent surgery or core biopsy for invasive breast cancers in the study place.

The inclusion criteria were: cases that (1) had undergone a mastectomy or breast conservation (2) core biopsies to start chemotherapy and hormone therapy before surgery (3) had complete immunohistochemistry data for ER, PER, and Her2. The study was performed at the department of laboratory medicine, NICRH. Data include age, size of the tumor, histopathological typing, and grade. All cases were subjected to immunohistochemistry for ER, PR, Her 2 on formalin-fixed, paraffin-embedded breast tumor sections by using ready to use monoclonal antibody and HRP polymer detection system with 3'-3' di-aminobenzidinehydrochloride (DAB) as the chromogen. Adequate tissue fixation in 10% buffered formalin for 6-24 hours was ensured and thin paraffin (3-4 µ thickness) sections with maximum invasive tumor components were selected for IHC. Both H&E and IHC slides were reviewed by two independent pathologists and results were interpreted with positive and negative controls. For ER and PR results were interpreted as positive when more or equal to 1% of tumor cells showed positive nuclear staining as per the ASCO/CAP interpretation guidelines 2010. Initial immunohistochemistry for Her2 was carried out in all cases and Her2 scoring was categorized as 0, 1+, 2+, and 3+. The result was considered positive for Her2 (score 3+) if uniform intense membrane staining of >30% of invasive tumor cells was seen. The test was considered negative if there was no staining (score 0) or incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumor cells (score 1+). Equivocal results (score 2) was labeled when circumferential membrane staining that is incomplete and/or weak/moderate and within >10% of the invasive tumor cells; or complete and circumferential membrane staining that is intense and within ≤10% of the invasive tumor cells was noticed as per ASCO–CAP Her2 Test Guideline 2013 Recommendations. In all equivocal results (score 2) reflex tests as confirmation by fluorescence in situ hybridization (FISH) was advised. Due to financial constraints and loss of follow up for FISH testing the correlation in 22 cases with Her2 (score 2+) could not be performed. The data were prepared on an excel sheet and analyzed manually for interpretation of results.

Table 1: Key Outcomes of the Participant Patients (N=121)

Variables	N	%	Mean(±SD)
Age group of Patients			
≥ 30 years	12	9.83	42.85
31 - 40 years	48	39.67	(±9.6)
41 - 50 years	43	35.53	
51- 60 years	14	11.57	
>60 years	4	3.4	
Base	121	100.0	
Educational Qualification of Patients			
Illiterate	5	4.15	
Primary	40	33.05	
SSC	41	33.88	
HSC	35	28.92	
Base	121	100.0	
Patients Menopausal Status			
Pre-menopausal stage	69	57.0	
Post-menopausal stage	52	43.0	
Base	121	100.0	
Patients Clinical status			
Mass	119	98.34	
Nipple discharge	33	27.27	
Pain	19	15.7	
Others	11	9.09	

Table 2: Distribution of baseline characteristics (N=121)

Variables	n	%
Tumor stage		
I	43	35.54
II	68	56.20
III	10	8.26
Cancer Type		
Ductal	88	72.73
Lobular	15	12.40
Ductal & lobular	9	7.44
Inflammatory	1	0.83
Others	8	6.60
Histological grade		
Well differentiated	25	20.66
Moderately differentiated	46	38.02
Poorly differentiated	50	41.32
Tumor Size		
≤2 cm	6	4.96
2.1 – 5 cm	86	71.07
>5 cm	29	23.97
Lymph node status		
Positive	58	47.93
Negative	63	52.07
Receptor status		
ER (+)	74	61.16
ER (-)	47	38.84
PR (+)	71	58.68
PR (-)	50	41.32
Her2 (+)	46	38.02
Her2 (-)	75	61.98
Tumor Subtypes		
Luminal A (ER/PR+Her2-)	38	31.40
Luminal B (ER/PR+Her2+)	16	13.22
TNBC (ER/PR-Her2-	37	30.58
Her2 (ER/PR-Her2+	26	21.49
Others	4	3.31

Table 3: Correlation of ER, PR and Her2 receptor (N=121)

ER/PR/HER2 Status		n	%
Status-1	ER (+ve) PR (+ve) HER2 (+ve)	14	11.98
Status-2	ER (-ve) PR (-ve) HER2 (-ve)	36	29.35
Status-3	ER (+ve) PR (+ve) HER2 (-ve)	31	25.22
Status-4	ER (-ve) PR (-ve) HER2 (+ve)	29	24.38
Status-5	ER (+ve) PR (-ve) HER2 (-ve)	6	5.37
Status-6	ER (+ve) PR (-ve) HER2 (+ve)	5	3.73

RESULTS

In this study in total 48 (39.67%) patients belonged to the age group of 31-40 years followed by 41-50 years of age group by 43(35.53%) and the mean age of the patients was 42.85 (±9.6). Regarding the educational qualification of the patients, 41(33.88%) were SSC passed, followed by 40(33.05%) were primary school passed and 35(28.92%) were HSC passed. In total 69 (57%) patients were in the pre-menopausal state and rest 52(43%) patients were in the post-menopausal state. Almost 98.34% of patients had breast mass, 27.27% of patients had associated features of nipple discharge with breast lump and pain were in (15.7%) cases.

This study manifests that luminal A 38(31.4%), Luminal B 16 (13.22%), TNBC 37(30.57%), Her2 enriched 26 (21.48%), other 4(3.3%) out of 121 respondents. Other features denoted as nipple retraction, deviation, ulceration, etc. In this study, the commonest site of the lump was upper outer quadrant (43.69%) followed by the lower outer quadrant (31.93%). The considerable figure of the lump was also seen in the lower inner quadrant (11.76%) and central zone (8.4%). The lowest number of patients revealed in the upper inner quadrant (4.2%). The baseline characteristics of tumor-like staging, grading, histopathological status, receptor status and molecular subtypes.

Among the molecular subtypes, 31.4% tumor was luminal A type followed by 30.57%, tumor with triple negative breast cancer (TNBC). A considerable percentage of tumors belong to Her2 enriched molecular subtypes (21.48%) on the contrary Luminal B subtypes.

In this study, we found the relation of tumor size (T staging) and molecular subtypes of breast cancer. In T staging I the Luminal A, Luminal B TNBC, Her2 enriched were found in 3, 1, 1, 1 and 0 cases respectively. In T staging 2 the Luminal A, Luminal B TNBC, Her2 enriched were found in 24, 10, 31, 18 and 3 cases respectively.

On the other hand, In T staging 3 the Luminal A, Luminal B TNBC, Her2 enriched were found in 11, 5, 5, 7 and 1 cases respectively. According to the lymph node status, where the lymph node was present there the Luminal A, Luminal B TNBC, Her2 and others were in 21, 6, 21, 10 and 0 cases respectively.

On the other hand, where the lymph node was absent there the Luminal A, Luminal B TNBC, Her2 and others were in 17, 10, 16, 16 and 4 cases respectively. According to the grading of a tumor, in well-differentiated tumors, the Luminal A, Luminal B TNBC, Her2 and others were observed in 7, 3, 11, 4 and 0 cases respectively.

Besides these, in moderately differentiated tumors the Luminal A, Luminal B TNBC, Her2 and others were observed in 28, 9, 6, 3 and 0 cases respectively. On the other hand, in poorly differentiated tumors the Luminal A, Luminal B TNBC, Her2 and others were observed in 3, 4, 20, 19 and 4 cases respectively. In analyzing the co-relation, Her-2 status with ER, PR receptor status in invasive breast carcinomas we found only 10.74% patients with all positive whereas 28.10% were with all negative. Besides these, 23.97% of participants were Her2 negative whereas both ER and PR were positive. In 23.14% of participants, Her2 was positive whereas both the ER and PR were negative. On the other hand, 4.13% of participants were with ER-positive whereas PR and Her2 were negative and only 2.48% of patients were found with PR negative but both the ER and Her2 positive.

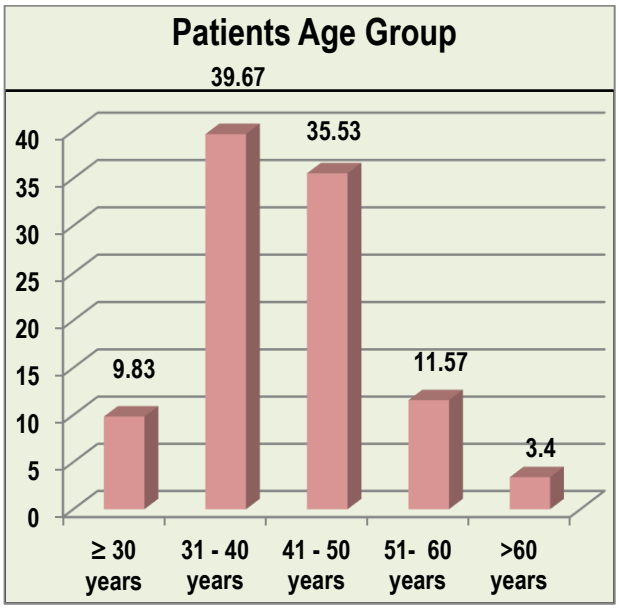

Figure I: Patients Educational Status (N=121)

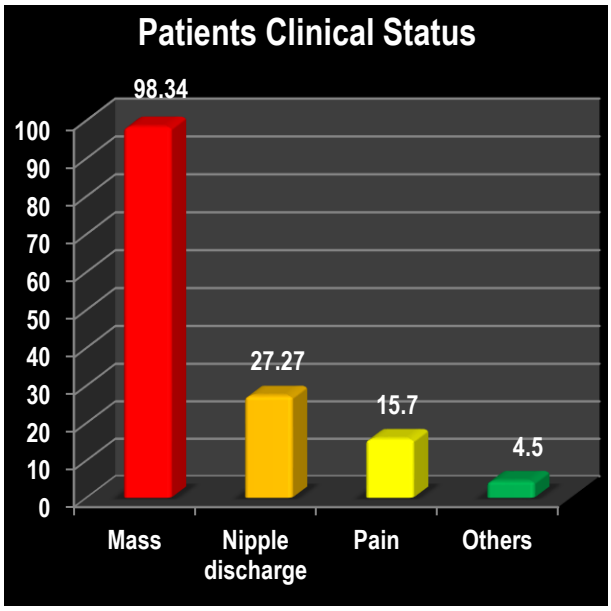

Figure IV: Patients Clinical Status (N=121)

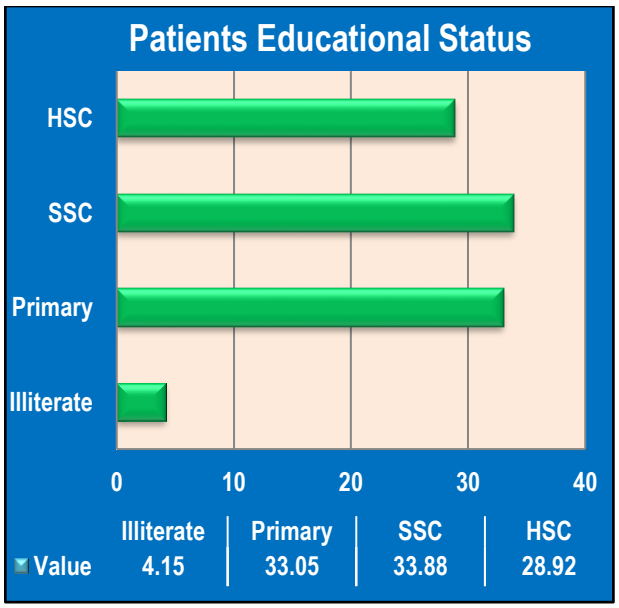

Figure II: Patients Educational Status (N=121)

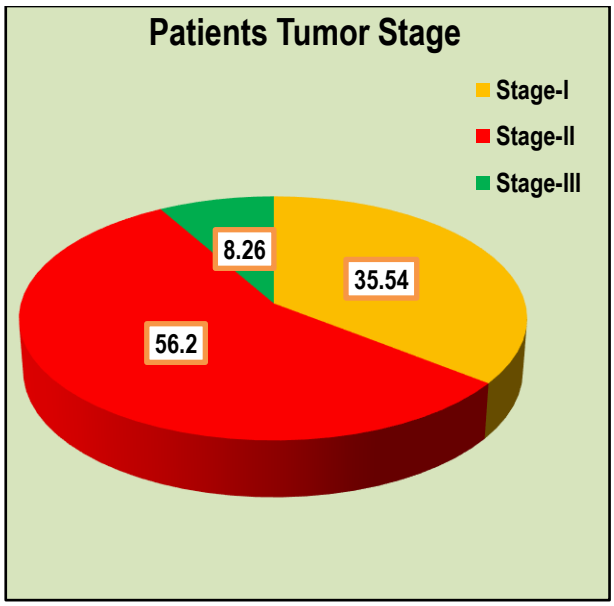

Figure V: Patients Tumor Stage (N=121)

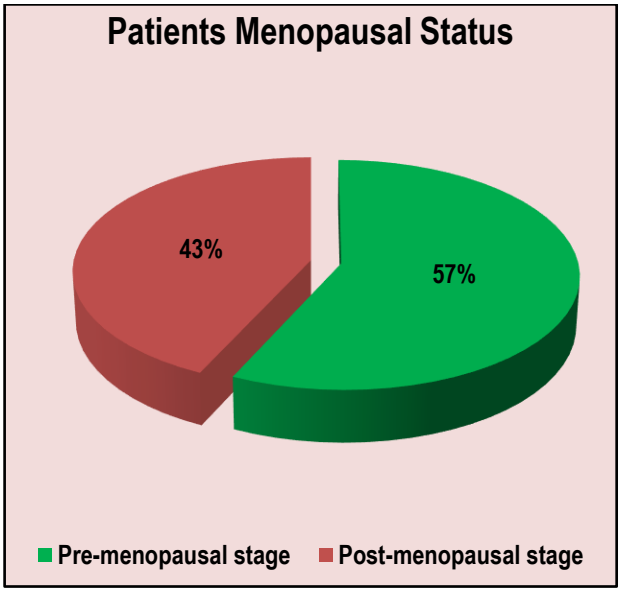

Figure III: Patients Menopausal Status (N=121)

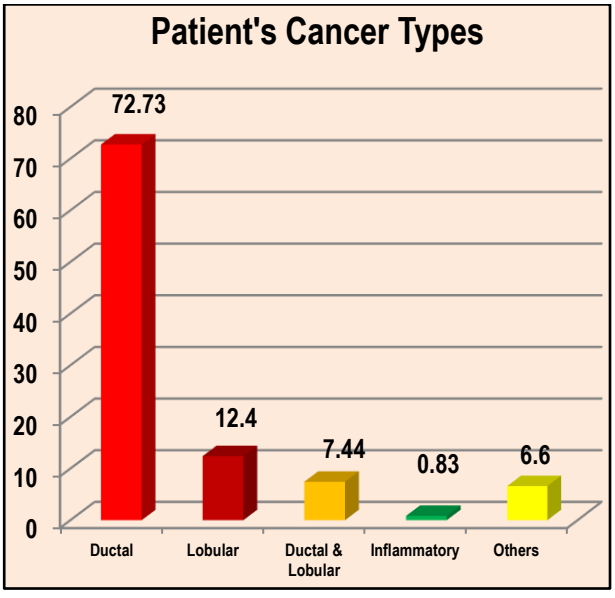

Figure VI: Patients Cancer Types (N=121)

DISCUSSION

Breast cancer is a multifaceted disease comprised of distinct biological subtypes with diverse natural history which are increasingly recognized as presenting a multidimensional spectrum of clinical, pathological and molecular features with different prognostic and therapeutic implications.[12] Breast cancer is the most common cancer in women worldwide and is a major health concern especially in developing countries where a majority of cases are being diagnosed in late stages. Global cancer rates, in general, are estimated to rapidly rise from 14 million in 2012 to 20 million over the next two decades, thus making breast cancer a significant health emergency.[13] The major objective of this study was to evaluate the co-relation of Her2 status with ER, PR & Histological features in invasive breast carcinomas. These subtypes, however, be complemented with the many other important traditional prognostic variables for the individual such as age, tumor size, lymph node status, co-morbidity, etc. The commonest way of molecular subtyping is microarray way of molecular subtyping the study place had no such a facility; so the optional way of molecular subtyping had to be used. The immunohistochemistry classification of both ER/PR and Her2 status provides prognostic and therapeutic information not achievable from either alone. Prior sub-classifications separating breast cancer into one of two categories based on ER expression is less discriminatory in terms of prognosis, and the additional sub-classification based on Her2 expression provides enhanced and important therapeutic guidance. Breast cancer has also sometimes been dichotomized into triple negativity or other.[14] Determining the molecular subtype of breast cancer by IHC markers has some limitations.[15] There is no consensus on how to define exactly the basal-like breast cancer and overlap categories exist. Although majorities of basal-like breast cancers are triple-negative; ER or Her2 expression has been reported in about 15%-45% of the basal-like cancers.[6] Cancers; often have lower expression levels of hormone receptors, higher Nottingham grade, and higher proliferative rates; and can be Her2 positive.[16] There is clinical interest in distinguishing the luminal B cancers from luminal A cancers because they may be a subset of ER-positive cancers that derive benefit from more aggressive therapy.[17] Here the Her2 enriched group patients were found 21.48% of the total population. The study in Shanghai[18] and Taiwan showed separately the figure of Her2 in their studies was 31% and 26% respectively. But a Taiwan study report was found almost similar to our study where the Her2 enriched molecular subtype patients were found in the case of 21% cases. These variations are may be due to underreporting of our patients, skill, and expertise variation from the laboratory to a laboratory in different centers of the world. Clinically, luminal A has the characteristics of common occurrence[19] Luminal B tumor may benefit from taxanes in the adjuvant settings.[20] So, a vivid picture of subsequent treatment response so, it can be predicted from this study that 38 patients out of 1212 of this study may show recurrence whereas 16(13.22%) out of 121 of this study may respond better with adjuvant taxanes. The independent prognostic and predictive role of PR expression regardless of ER has been a topic of great controversy as demonstrated by the report from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant trial, a large worldwide trial comparing the efficacy of tamoxifen with that of the aromatase inhibitor anastrozole, showing overall that patients with ER+/PR+ tumors had a lower recurrence rate than those with tumors.[21] The observation from the same study that patients with ER tumors respond nearly as well to anastrozole as those with ER+/PR+ tumors suggests that the ER signaling pathway is functional in many ER tumors, consistent with the well-known fact that the PR gene is regulated by the estrogen pathway. The prognosis of carcinoma depends on several factors including ER/PR/Her2 status. The biologic, prognostic, and predictive importance of assessment of estrogen receptor (ER) expression in carcinoma is well established that ER-positive tumors are related to better overall survival compared to ER-negative tumors. There is a direct correlation between the levels of expression and response to hormone therapies, and even tumors with very low levels (≥1% positive cells) have a significant chance of responding. Western literature showed that by immunohistochemistry, about 70-80% of invasive breast carcinoma express nuclear ER during a proportion starting from ≥1% to 100% positive cells and like ER, PR is expressed in the nuclei of 60-70% of invasive breast cancers, with an expression that varies in a continuum ranging from 1% to 100% positive cells.[22] So it is clear that the receptor status of breast cancer, including ER, PR, and HER 2 play a crucial role in the development of the treatment plan of breast cancer.

CONCLUSION

According to the findings of this study, it is clear that the receptor status of breast cancer, including ER, PR, and Her2 plays a crucial role in the development of the treatment plan of breast cancer. This was a single centered study with small sample size. So the findings of this study may not reflect the exact scenario of the whole country.

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