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Research Article

Correlation between estrogen receptor, progesterone receptor, HER-2/neu status and other prognostic factors in carcinoma breast in Indian population

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ABSTRACT

Background: Incidence of breast carcinoma (BC) is increasing all over the world. Contrary to the West where it is more common in the elderly; in India it is more common among the younger women. India accounts for nearly six percent of deaths, due to breast cancers in the world and also that one out of every 22 women in India is diagnosed with breast cancer every year. But no information is available on its biological characteristics in the Indian population. Our aim was to evaluate the estrogen receptor, progesterone receptor and HER-2/neu receptor in single institute patients and to compare the expression of these factors with other prognostic parameters such as menopausal state, size of tumor, grade, histological type, mitotic index, lymphovascular invasion and nodal metastases.
Methods: This is a prospective study conducted in the Department of General Surgery at Sri Ramachandra Medical University Hospital, Chennai, India. A batch of 60 confirmed patients of BC, diagnosed in between 2012 to 2014, were included in this study. ER, PR and HER-2/neu status were studied by immune-histochemistry and were correlated with other prognostic factors.
Results: ER negative and PR negative cases were comparatively high (61.7% and 70%) than the positive cases. 66.7% of the cases were post-menopausal group, 68.3% of cases were T2 tumor and 81.7% cases were ductal carcinoma. There was a significant correlation identified between ER, PR with tumor grade and Mitotic Index of the tumor. HER-2/neu positive cases tended to have significant higher axillary metastasis. There was no significant correlation between ER, PR and HER-2/neu with menopausal state, size, histological type and lymphovascular invasion.
Conclusions: The ER, PR and Her2/neu expression in BC in our patients is comparable with the available international data. ER and PR negative expressions are strongly associated with some known bad pathological factors like high grade tumor and high Mitotic Index. HER-2/neu expression was high in advanced diseases like axillary node positive patients.

Keywords: Breast carcinoma, ER, PR, HER-2/neu, Breast prognostic factors

INTRODUCTION

Breast carcinoma (BC) is the second most common cancers in women and account for 22% of all female cancers, which is more than twice the prevalence of cancer in women at any other site.[1] There are increasing trends of breast cancer in India according to the various Registries of National Cancer –Registry Project.[2] India accounts for nearly six percent of deaths due to breast cancers in the world and also one out of every 22 women in India is diagnosed with breast cancer every year.[3] In India breast cancer rate is more in younger women when compared to other parts of the world where there is more breast cancer in postmenopausal age group.[4] In the absence of systemic therapy, the anticipated outcome of the patient is generally referred to as prognostic factors. But these prognostic factors are also useful to estimate the outcome of systemic therapy and some are useful as predictive factors. Even though there are many prognostic factors for breast cancer, the stage of the disease itself acts as a major prognostic factor. According to the literature, one of the important prognostic factors for recurrence of BC in an early stage is axillary LN involvement. The mortality rate also increased four to eight times in LN positive patients.[5] Microscopic size of the invasive cancer is taken as the tumor size. In patients with negative LN, tumor size is an independent prognostic factor of breast recurrence. The 5-year survival rate completely varies with tumor size. In 1 cm size tumor, the patient's 5-year survival is 99%, whereas it is 86%, in patients with tumor size of 3-5cm.[6] Nottingham applied histological grading system, which is one of the established methodologies to determine the histological grade of the tumor. By using these prognostic factors from pathological reports, the prognosis of the patient can be estimated individually. Histological grade with Nottingham prognostic index is used to plan for an appropriate therapy in individual patients.[7] Age of the patient is one of the important prognostic factors. More aggressive type of tumors is found in young women with BC.[8] Young women with breast cancer are more likely to have negative estrogen receptors, large tumors, lymph node metastasis and high grade of anaplasia.[9] HER2/neu is the major predictive factor in breast cancer. HER2/neu gene amplification can lead to over expression of Her2/neu glycoprotein. In metastatic breast cancers HER-2 /neu was concluded as an additional prognostic factor.[10] HER-2/neu is a useful predictive factor to decide on chemotherapy like trastuzumab. Involvement of lymphovascular space is an independent adverse prognostic factor. It can lead to high rate of lymph node metastasis. Lymphovascular invasion is a pre-requisite for lymph node metastasis. Tumor exposed with micro vessels has more distal metastasis.[11] So it plays an important adverse prognostic factor in both node-positive as well as node-negative patients.

In the breast and the endometrium, the growth kinetics of endothelial linings is mainly regulated by estrogen hormone. Estrogen receptors (ER) and progesterone receptors (PR) are major prognostic factors in breast cancer. It has been shown that tumors expressing estrogen receptors tend to be better-differentiated into low-grade tumors. Remission rate after hormonal therapy in ER+ and PR+ cases was 70%. ER negative status by itself, act as an important predictive factor in the early stages of tumors and are independent of tumor grades. The PR negative status acts as a predictive factor for lymph node metastasis, independent of other clinico-pathological factors.[1,3] On the other hand ER/PR are not reproducible subtypes. PR expression is not a significant independent prognostic factor to the multi-variant model considering ER and other clinico-pathological factors.[12] The triple negative breast cancer (ER/PR/HER-2/neu) has the worst overall survival.[13] Irrespective of age, the high-grade less differentiated tumors showed significant levels of both ER and PR negativity. In younger patients (<53 yrs) with high grade tumors shows more of ER negative status than PR negative status.[14] There are many studies explaining the correlation between hormonal receptors and HER-2/neu and some of the studies explain the correlation of these factors with other risk factors. But neither is there any information available in the Indian population about ER/PR and HER-2/neu expressions nor any comparative study is available with other risk factors in BC.

The aim of the study was to study the relevance of ER/PR and HER-2/neu status in comparison with other clinical and pathological prognostic factors like menopausal status, tumor size, pathological type, histological grading, mitotic index, lymphovascular invasion and nodal status in BC.

METHODS

This was a prospective study done from June 2012 to September 2014 in Sri Ramachandra Medical University Hospital. Sixty patients with confirmed carcinoma breasts were included in this study. All patients under went surgical removal of tumors by modified radical mastectomy. The tissue was sent for receptor study (ER and PR) at low temperature in ice flasks. It was assessed by quantitative analysis (frozen-70°). If value is more than 10 units (f/mols) per gram of tissue then it is called the receptor positive status. Measurement of HER-2/neu is done from a resection specimen by the immunohistochemistry method. The following clinical and pathological risk factors were studied in these 60 patients.

A) Menopausal status
B) Tumor size
C) Pathological type
D) Histological grading
E) Mitotic index
F) Lymphovascular invasion
G) Nodal status

All these risk factors were compared with ER, PR and Her-2/neu status and the correlation were analyzed. Patients who had no menstrual flow since 12 months were considered as postmenopausal and the rest were considered as premenopausal. Patients who had natural menopause were only included in the study population. Patients who had undergone hysterectomy or who were having any other ovarian problems and whose menopausal status was not specified and who had a personal history of cancer other than breast cancer were also excluded from the study. Patients who had undergone neo-adjuvant chemotherapy or had undergone previous breast surgery, outside SRMC, and all cases of metastatic Carcinoma breast were excluded from the study. The size of the tumor was assessed by pathologists from the specimens. Tumors less than 2cm in size were taken as T1, tumors between 2cm to 5cm were taken as T2 and tumor sizes more than 5 cm were taken as T3. Pathologist identified various histological types of the tumors. The Nottingham combined histological system was used for grading. Grade 1 Carcinoma include tumors with combined scores of 3, 4 or 5; Grade 2 includes scores of 6 and 7; and Grade 3 includes tumors with the scores of 8 and 9. Mitotic Index was assessed from 1 to 3. Presence or absence of lymphovascular invasion and positivity or negativity of nodal status was also assessed by the pathologist. Each risk factor was compared with the receptor status and HER-2/neu status individually, and the statistical significance was assessed with the P-value.

Statistical method

The collected data was analyzed with SPSS 17.0 version. To describe about the data descriptive statistics frequency analysis, percentage analysis was used for categorical variables and the mean & S.D were used for continuous variables. To find the significance in the categorical data, the Chi-Square test was used. In the above statistical tool the probability value of 0.05 is considered as a significant level. P-value <0.05 is considered as more significant and P-value <0.01 is considered as highly significant. If P-value is more than 0.5, it is considered as insignificant.

RESULTS

There were 60 patients with BC who attended SRMC during the study period. The mean age of the patients was 51.17 years with standard deviation of 9.859 years. The youngest patient with breast cancer was 32 years of age. About 61.7 % of the cases were ER +ve and another 70% of the cases were PR +ve cases. 56.7% patient had HER-2/neu expression. These results were shown in Table 1.

In this study group, 40 patients (66.7%) were in the postmenopausal age group and 20 patients (33.3%) were in the premenopausal age group. Most of the breast tumor size was from 2cm to 5cm; that is, T2 lesions were 41 cases (68.3%). Only 8 cases (13.3%) were T1 lesions and 11 cases were T3 tumors (18.3%). Four types of histology were found: Ductal Carcinoma, Lobular Carcinoma, medullary Carcinoma and Mucinous Carcinoma were found and Ductal Carcinoma was the most common histological type (81.7%).

Table 1: Number of patient and percentage of ER/PR and HER-2/Neu.

Status	No & Percentage of patients with ER status	No & percentage of patients with PR status	No & percentage of patients with HER-2/neu status
Positive	23 (38.3%)	18 (30%)	26 (43.3%)
Negative	37 (61.7%)	42 (70%)	34 (56.7%)

In our study most number of patients (31 patient 51.6%) had a tumor of Grade 2 and only 11.6% (7 patients) of the cases had Grade 1. Grade 2 patients were 36.6% (22 patients). According to the Mitotic Index, 61.7% of the patients had Mitotic Index 2, 25% had Mitotic Index 3 and only 13.6% of cases had Mitotic Index 1. In 36 patients (60%) lymphovascular invasion was identified and 32 patients (53.3%) had axillary node metastasis. ER, PR receptor status was compared with HER-2/neu expression and no significant correlation was found. Table 2 explains this comparison. But between ER and PR a direct significant correlation was found which was detailed in Table 3.

Table 2: Comparison between HER-2/neu with ER/PR status.

Her-2/neu	ER positive	ER negative	PR positive	PR negative
+Ve	7	19	5	21
-Ve	16	18	13	21
Total	23	37	18	42
P-value		0.112		0.111

Table 3: Correlation with ER status and PR status.

		PR		
		Negative	Positive	Total
ER	Positive	37	0	37
	Negative	5	18	23
Total		42	18	60
P-value: 0.000		0.000		0.000

The estrogen receptor positive cases in both premenopausal and postmenopausal cases were almost equal (40% and 37.5%). But there was a little hike in PR positive cases in premenopausal group (40%) than postmenopausal group (25%). According to the P-value

both ER and PR (0.851 and 0.232) did not correlate with menopausal state. HER-2/neu +ve expression were found to be 55% in premenopausal patients and 62.5% HER-2/neu negativity was found in postmenopausal patients, but it was statistically insignificant (P-value 0.197).

While comparing tumor sizes with the receptor status, the ER negativity increased from T1 (18.9%) to T2 (64.9%) and decreased T3 (16.2%). The P-value was 0.264. Similarly PR negativity with tumor size was: T1-16.7%, T2- 69% and T3- 14.3%. The P-value was 0.297. In T2 and T3 tumors HER-2/neu negativity was more (70.6% and 20.6%) than HER-2 neu Positive cases (65.4%, 15.4%).

On comparing with tumor grade, ER negativity increased significantly with increasing tumor grade (G). In G1 ER-ve was 5.4%, in G2 ER-ve was 43.2% and in G3 ER-ve was 51.4%. The P-value was 0.006. The PR negativity also increased with tumor grade with significant P-value of 0.005. Her-2/neu +ve were increased from G1 to G2 but it decreased in G3 and the P-value was 0.190.These correlation was shown in the Figure 1. Similarly the ER and PR negativity increased along with raising the Mitotic Index and the P-value was 0.042 and 0.018, respectively. But there was increase in HER-2/neu expression from G1 (7.7%) to G2 (69.2%) and again it decreased to 23.1%. The P-value was 0.452. These results were represented in Figure 2.

Table 4: Comparison between ER/PR and HER -2 neu with all other prognostic factors.

Parameter	Number with percentage	Status of ER (P-Value) & %		Parameter	Number with percentage	Status of ER (P-Value) & %	
		Positive	Negative	Positive	Negative	Positive	Negative
Menopause							
Pre-menopause	20(33.3%)	8(40%)	12(60%)	8(40%)	12(60%)	11(55%)	9(45%)
Post-Menopausal	(66.7%)(40)	15(37.5%)	25(62.5%)	10(25%)	30(75%)	15(37.5%)	25(62.5%)
P-Value		0.851	0.232	0.197			
Size							
T1	8(13.3%)	1(4.3%)	7(18.9%)	1(5.6%)	7(16.7%)	5(19.2%)	3(8.8%)
T2	41(68.3%)	17(73.9%)	24(64.9%)	12(66.7%)	29(69%)	17(65.7%)	24(70.6%)
T3	11(18.3%)	5(21.7%)	6(16.2%)	5(27.8%)	6(14.3%)	4(15.4%)	7(20.6%)
P-Value		0.264	0.297	0.479			
Pathological type							
Ductal CA	49(81.7%)	20(87%)	29(78.4%)	15(83.3%)	34(92.3%)	24(92.3%)	25(73.5%)
Lobular CA	3(5%)	1(4.3%)	2(5.4%)	1(5.6%)	2(4.8%)	1(3.8%)	2(5.9%)
Medullary CA	5(8.3%)	0(0.0%)	5(13.5%)	0(0.1%)	5(11.9%)	0(0%)	5(14.7%)
Mucinous CA	3(5%)	2(8.7%)	1(2.7%)	2(11.1%)	1(2.4%)	1(3.8%)	2(5.9%)
P-Value		0.232	0.252	0.195			
Historical grading							
G1	7(11.7%)	5(21.7%)	2(5.4%)	5(27.8%)	2(4.8%)	1(3.8%)	6(17.6%)
G2	15(51.7%)	15(65.2%)	16(43.2%)	11(61.1%)	20(47.6%)	16(61.5%)	15(44.1%)
G3	3(13.1%)	3(13.1%)	19(51.4%)	2(11.1%)	20(47.6%)	9(34.6%)	13(38.2%)
P-Value		0.006	0.005	0.190			
Mitotic Index							
M1	8(13.3%)	5(21.7%)	3(8.1%)	5(27.8%)	3(7.1%)	2(7.7%)	6(17.6%)
M2	37(61.7%)	16(69.5%)	21(56.8%)	12(66.7%)	25(59.5%)	18(69.2%)	19(55.9%)
M3	15(25%)	2	13(35.1%)	1(5.6%)	14(33.3%)	6(23.1%)	9(26.5%)
P-Value		0.042	0.018	0.452			
Lymphovascular invasion							
Absent	36(60%)	14(60.9%)	22(59.5%)	11(61.1%)	25(59.5%)	15(57.7%)	21(61.8%)
Present	24(40%)	9(39.1%)	15(40.5%)	7(38.9%)	17(40.5%)	11(42.3%)	13(38.2%)
P-Value		0.914	0.908	0.750			
Nodal status							
Absent	28(46.7%)	10(43.5%)	18(48.6%)	9(50%)	19(45.2%)	8(30.8%)	20(58.8%)
Present	32(53.3%)	13(56.5%)	19(51.4%)	9(50%)	23(54.8%)	18(69.2%)	14(41.2%)
P-Value		0.696	0.735	0.031			

Lymphovascular invasion compared with ER receptor, which showed ER negative (40.5%) and ER (39.1%) positive cases almost equal in lymphovascular invasion cases. The P-value was 0.914.Similarly, in cases with no lymphovascular invasion ER negative and positive patients, which nearly equalled 40.5% and 38.9% and the P-value was 0.908. HER-2/neu negative (38.2%) and HER-2/neu positive (42.3%) cases nearly the lymphovascular positive cases and there was no significant correlation found (P-value 0.750).

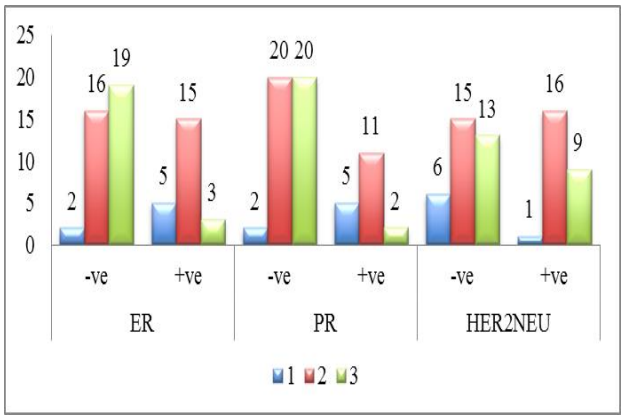

Figure 1: Grade (G) Vs ER/PR/HER-2/neu.

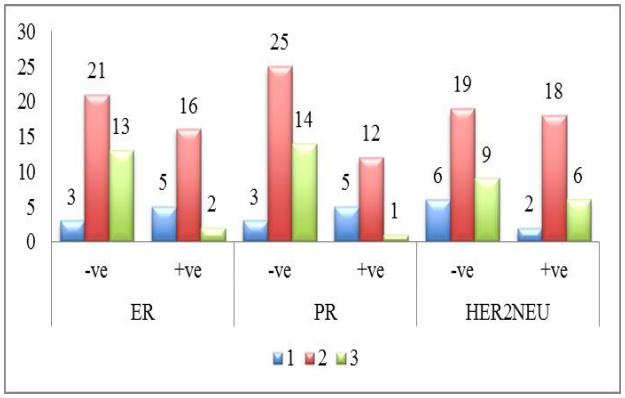

Figure 2: Mitotic index (M) Vs ER/PR/HER-2/neu.

In Axillary lymph nodes, metastasis cases ER+ve (56.5%), ER-ve (51.4%), PR+ve (50%) and PR-ve (54.5%) were almost equal and no statistical significance was found (P-value 0.696 and 0.735). But in node positive cases HER-2/neu expression was high (69.2%) than HER-2/neu –ve cases (41.2%). It was statistically significant with P-value of 0.031. In Figure3 we can see the significant correlation between HER-2/neu status and Axillary lymph node.

DISCUSSION

The history of breast cancer reveals that the Smith Surgical Papyrus (3000-2500 B.C.)is the earliest known document to refer to breast cancer and it had concluded that there was no treatment.[15] In the 1st century in De Medicina, Celsius first explained the benefit of surgery in early breast cancer diagnosed cases.[16] Galen first inscribed the clinical characteristics of breast cancer in the 2nd century itself.[17] In 1773, Bernard Peyrilhe advised surgery for the removal of breast cancer along with axillary contents and Pectoralis Major, the same operation introduced by William Halsted, 100 years later. In the nineteenth century, Moore (1867) of the Middlesex Hospital, London, first emphasized the importance of complete resection of the breast for cancer and stated that removal of auxiliary LN also must be included in surgery.[18] In 1894, Halsted and Meyer reported their Radical removal of breast cancer surgery.[19] Importance of Estrogen receptors in BC was explained by Beatson in the 19th century. In the later part of 19th century a second growth factor HER-2 or erb-B2/neu Protein was discovered.[20]

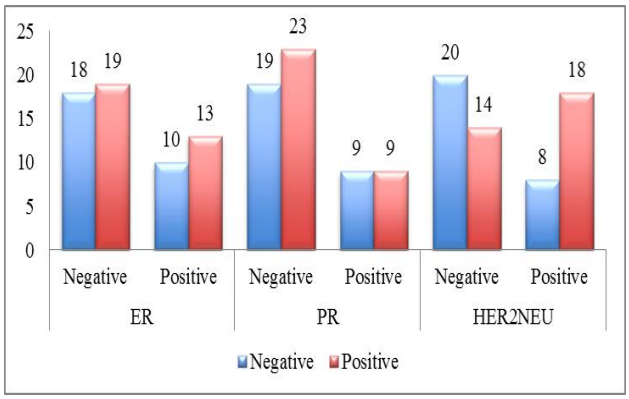

Figure 3: Axillary lymph node Vs ER/PR/HER-2/neu.

The management of breast cancer mainly depends on the knowledge of prognostic factors. The prognostic factors can be taken as first generation prognostic factors which include lymph node metastasis, size of the tumor, tumor grade, hormonal receptor status and second generation prognostic factors which include HER-2/neu growth receptor factors. The presence of hormone receptors is a powerful predictive factor for the likelihood of benefit from adjuvant hormonal therapy including aromatase inhibitors and tamoxifen, an oral selective estrogen receptor modulator.[21,22]

HER 2 is an epidermal growth factor and amplification or over expression of this oncogene associated with aggressive types of breast malignancy. A recent publication by American society of oncology (ASCO) and the College of American Pathologists (CAP) explain a clinical practice guideline on accurate method of testing HER2 in BC HER-2/neu positive cases will have poor prognosis.[23] In Node negative patients presence of HER-2/neu used as prognostive factor and predict the importance of adjuvant chemo in these patients. Trastuzumab is added to Paclitaxel Chemotherapy which may benefit in Her-2/neu positive patients and used as a

targeted Chemotherapy. Age is probably the most important risk factor that clinicians use in everyday clinical practice.[24] Younger patients are more likely to have higher-grade tumors. Younger age also appears to be an independent adverse prognostic risk factor.[25]

In our study, the mean age of BC is 51.2 (+/-9.8), which is similar to the western population studies, and incidence of BC is high in postmenopausal patient (66.7%). According to cancer research UK, between 2009 and 2011, an average of 80% of breast cancer cases were diagnosed in the age group of over fifty. But in one of study of Azizun- Nisa et al shows 66 % of cases are less than 50 years of age.[26] In our study 56.7% patient had HER-2/neu expression. It is comparatively higher than the other studies like Zineb Bouchbika et al (29%) and in Ayadi et al (18%).[27,28]

Several studies show significant ER /PR and HER-2/neu expressions with menopausal state. In Mohammad Faheem et al. postmenopausal women have a higher incidence of ER and PR positivity and Her 2 Neu negativity.[29] In Hussein et al a significantly high mean ($P<0.05$) of ER and PR positively stained cells was observed in postmenopausal females compared to premenopausal women.[30] In contrast, high HER-2/neu expression values were seen only in premenopausal females. Our study did not permit for this correlation. HER-2/neu expression was high (62.5%) in post-menopausal age than premenopausal (45%). But it is not statistically significant.

Tumor size is one of the important prognostic factors which are directly correlated with survival. In Hussein et al showed that 69.8% of the patients had breast tumor size of T2 (2-5 cm) which is similar to our study where 68.2% cases are T2 breast lesions.[30] There is no significant changes demonstrated with ER/PR and HER-2/neu to size of the tumor. In Azizun-Nisa et al ER positivity decreased and HER- 2/neu is over-expressed with increasing tumor size.[26] The over expression of HER-2/neu in larger tumors was demonstrated in other studies like J. M. Bhatavdekar et al and T. Ivkovic-Kapicl et al.[31,32] Similar to our study there is no correlation of HER2/neu with tumor size as per G. R. Molina Barrios et al.[33] Most of the patients in our study presented with a tumor Grade 2 (51.6%). Similar observations were made in a study done by Hussein et al where 55.2% were Grade 2 and Azizun- Nisa et al where 55.3% of patients were Grade 2.[26,30]

In our study as the grade of the tumor increased, the ER/PR negativity significantly increased. Similar observations were made in studies done by Azizun- Nisa et al and Fatima et al.[26,34] In contrast In Almari et al no co-relation was detected between the grade of the tumors and expression of ER and PR.[35] There is no correlation between Her2/neu with tumor grade in our study which is similar to G. R. Molina Barrios et al and Almari et al.[33,35]

In our study the most common pathological type of carcinoma was Ductal carcinoma NOS (81.6%). Similar observations were made in a study done by Hussein et al where 90.5% of the patients were diagnosed to have Ductal Carcinoma.[30] There is no significant correlation between receptor statuses with histological types in our study. Most of the patients in our study were node positive (53.3%). Similar observations were made in a study done by Azizun- Nisa et al where the maximum number of patients was node positive (71.3%).[26]

In our study there was not much of a correlation between the nodal status and ER/PR receptor status. This observation was similar to the study done by Fatima et al and Azizun- Nisa et al where no significant correlation of receptor status and lymph node metastasis was seen.[26,34] In contrast higher rates of ER and PR expression in lymph node positive cases in Wasseen in Mg Mostafa et al.[36] In our study HER-2/neu over expression was found to be high in node positive patients. Similar observation were made in a study done by Naqvi et al and Azizun-Nisa et al where a significant correlation was found between HER-2/neu over expression and lymph node status.[26,37]

In our study most number of patients came under Mitotic Index 2 (61.6%). In our study ER negativity and PR negativity significantly increased with increase in Mitotic Index. But there was no correlation with HER2/neu with Mitotic Index which is similar to Molina Barrios et al where there was no correlation between Her2/neu with Mitotic Index.[33]

In our study most number of patients presented with absent lymphovascular invasion (60%). There was no significant correlation noted between the receptor status and the lymphovascular invasion. In Zahra MA Mohammed et al Lymphovascular invasion was independently associated with poorer survival in patients with ER positive but not ER negative invasive ductal breast cancer.[38]

CONCLUSION

The ER, PR and HER-2/neu expression in the breast cancer in Indian population is comparable with the available international data. Larger studies are required to analyze the biological characteristics of BC in this population. The frequency of carcinoma of breast is high in post-menopausal group. The most common tumor pathology found in the study was Ductal Carcinoma. Definitive correlation was found in ER and PR receptors with grade of the tumor and mitotic index. HER-2/neu expression was high in advanced diseases like axillary node positive patients. The clinical importance of these prognostic markers in the management of breast cancer in clinical practice is strongly recommended.

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