International Journal of Research in Medical Sciences
Walke V et al. Int J Res Med Sci. 2019 May;7(5):1796-1802
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20191679

Original Research Article

Immunohistochemical profile and its association with clinicopathological parameters in carcinoma breast: a prospective study in central India

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Received: 03 March 2019
Revised: 20 March 2019
Accepted: 28 March 2019

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ABSTRACT

Background: Carcinoma breast is one of the most common malignancies of women in India. The current study was conducted with the objective of assessing estrogen receptor (ER), progesterone receptor (PR), Her-2/neu (human epidermal growth factor receptor-2) expression and Ki67 index of breast carcinomas and its correlation with histological grade, tumour size and lymph node metastasis.
Methods: Forty-seven lumpectomy or modified mastectomy specimens diagnosed as Infiltrating duct carcinoma (IDC): NOS, were selected for panel of imuno histochemistry (IHC) markers on tissue microarray blocks prepared from each case.
Results: Maximum of our patients belonged to premenopausal 24/47 (51%) and 20% to younger age group (<30 year). Tumour size of 2-5 cm was observed in maximum females 29 (61%); while 13(27%) had size >5.0cm. The majority of cases diagnosed as grade I (40%) and lymph node involvement was seen in 31/47 (65%). Molecular classification revealed 10 (21%) luminal A, 4 (8%) luminal B, 9 (19%) Her2/neu positive, while triple negative phenotype comprised of maximum 24 (51%) patients. Most of the Luminal group tumours were low grade (14/15); while majority of Her2/neu positive 7/9(77%) and triple negative tumours 19/24 (80%) belonged to higher grades.
Conclusions: Breast carcinoma among our patient is characterized by a large percentage of triple negative phenotype that is less susceptible to hormonal therapy. The empirical treatment with tamoxifen should therefore be reconsidered as it would be less effective. Assessment of prognostic markers in breast carcinoma is strongly advocated in order to provide the best therapeutic options.

Keywords: Breast carcinoma, Histological grade, Immuno histochemistry, Molecular classification, Triple negative

INTRODUCTION

Carcinoma breast is the commonest cancers in women worldwide.[1] Amongst Indian females; it is second most common next to carcinoma cervix. The cumulative incidence in females until the age of 64 year is 1-2%.[2,3] There has been a slight decline in the overall breast cancer mortality, which can be attributed both to success of early detection programs and advances in treatment modalities.[1] Breast cancer being a heterogeneous disease reveal varied clinical and pathologic features. These include clinical stage, tumour type, histological grade, hormone receptor status, DNA ploidy, cell proliferation markers and expression of oncogenes which also

determine prognosis in a given patient.[1,2] The approach in managing breast cancers has undergone enormous changes over the last 20 years. Estrogens (ER)/progesterone (PR) receptor and Her-2/neu (human epidermal growth factor receptor type 2) analysis have been accepted as established procedures in routine management of the patients with breast cancer. The combined expression of these three receptors and Ki 67 index has become most informative in the molecular classification of breast tumours and their clinical assessment for treatment and further outcome.[4] The proposed molecular subtypes of breast cancer determined by gene expression profiling are luminal A, luminal B, Her2 positive and basal like. These molecular subtypes have prognostic and predictive value.[5,6] The Her2/neu-overexpression and basal-like phenotypes have poor outcomes. Triple negative tumour are aggressive, associate with BRCA 1 mutation and constitute about 15-20%. Within estrogen/progesterone receptor (ER/PR) positive subtypes, the luminal B cohort is seen in younger age and has a significantly worse prognosis than luminal A which is associated with best prognosis and low recurrence rate.[7,8] Follow-up studies have shown these subtypes to be conserved across diverse patient series and array platforms have shown that different gene expression based predictors are likely tracking a similar, common set of biological subtypes, with significant agreement in predicting patient outcome.[9,10] Cost and complexity issues have to date rendered gene expression profiling impractical as a routine hospital diagnostic tool. However, there are immunohistochemistry surrogate panels proposed that can potentially identify these molecular subtypes. Luminal A is characterized by ER/PR positivity, non-reactivity for Her2 neu and low Ki67 index while luminal B shows ER/PR positivity, non-reactivity for Her2 neu and high Ki67 index. The HER2 neu positive cohort can either be ER/PR positive or negative but show consistent overexpression for Her2/ neu. The basal-like phenotype is ER/PR negative and Her2/neu negative (triple- negative (TNP)) but can either show epidermal growth factor receptor (EGFR) or cytokeratin 5/6 (CK5/6) positivity (five-marker method).[5,11,12]

An attempt has been made in the present study to classify invasive breast carcinomas on the basis of biomarkers such as ER, PR, Her2/neu expression and Ki67 index. It aims to correlate these molecular classes with tumour size its grade and lymph node status in invasive breast carcinomas in our institution. Authors also aim to correlate Ki67 index with various tumour grades. Authors tried to categorize triple negative basal like phenotype on the basis of CK 5/6 expression into five-marker negative cohort or core basal type.

METHODS

The study included total 47 cases of histologically confirmed invasive breast carcinoma IDC (NOS) and excluded patients who received preoperative chemotherapy or radiotherapy for breast carcinoma. The lumpectomy or mastectomy specimens received were immediately and adequately fixed in 10% buffered formalin for 12-48hours. The cold ischemia time was minimal (<1hour). The tissues were processed, and sections stained with hematoxylin and eosin (H and E). The Nottingham modification of bloom-Richardson method (MBR) was applied for histological grading. The mitotic figures were counted towards the peripheral invasive margin of tumour in most mitotically active area per 10 hpf (40x) using Nikon microscope (field diameter 0.44mm).[13] Tissue blocks (paraffin embedded) with tumour checked on H and E slides were selected for IHC by tissue microarray (TMA). The procedure was performed on randomly selected 47 cases of IDC (NOS) from various grades of tumour, in private accredited pathology laboratory. The expenses incurred for TMA were born by the investigators and no financial assistance was taken from anyone else. Three tissue cores were taken from each block (each case) of size of 1mm and were spaced 2mm away from each other. Single recipient block prepared and was subjected to various immunohistochemical (IHC) stains. The reporting was made on stained slides for each of the marker like ER, PR, Her2/neu and KI-67 and CK 5/6 as per the spreadsheet in excel format to identify the exact location of each case (tissue). The scoring for ER, PR, HER2neu was done as per American society of clinical oncology and the college of American pathologist guidelines (ASCO/ CAP) guidelines by taking an average of three and is considered for analysis.[14]

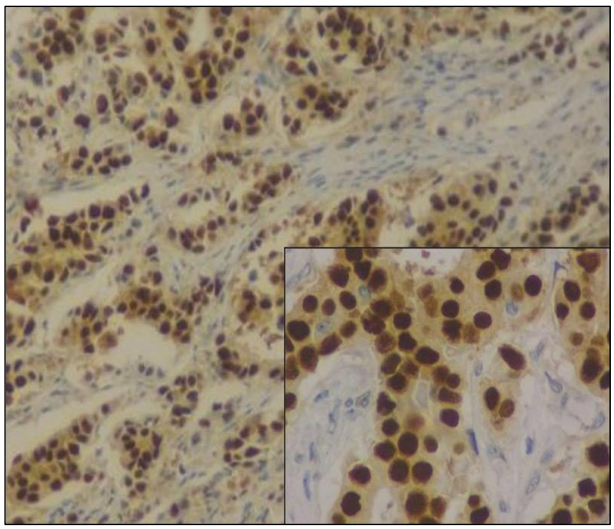

Figure 1: Strong nuclear positivity: Allred score of 8. (IHC (ER): (20X)) inset (40X).

The Allred score was used for interpretation of ER (Figure 1) and PR staining (Figure 2).[14] For interpretation of HER2/neu, ASCO/CAP guidelines were similarly followed.[14] The score of 0 and 1+ was considered negative for HER2 expression.

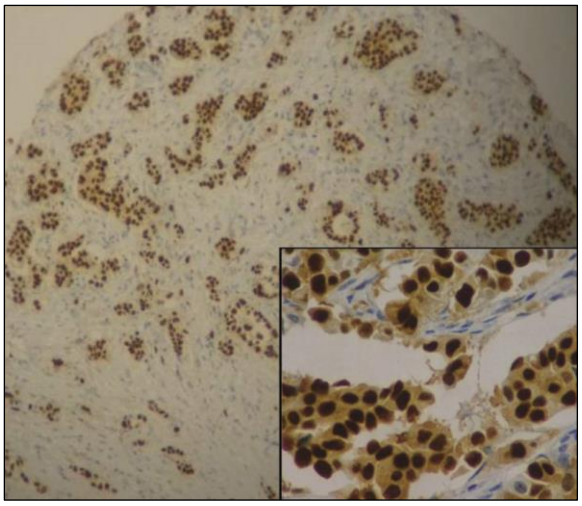

Figure 2: Strong nuclear positivity: Allred score of 8. (IHC (PR): (20X)) Inset (40X).

Tumours with score of 2+ or 3+were considered as positive for Her-2 overexpression (Figure 3). (2+were scored as positive for statistical calculation).[15]

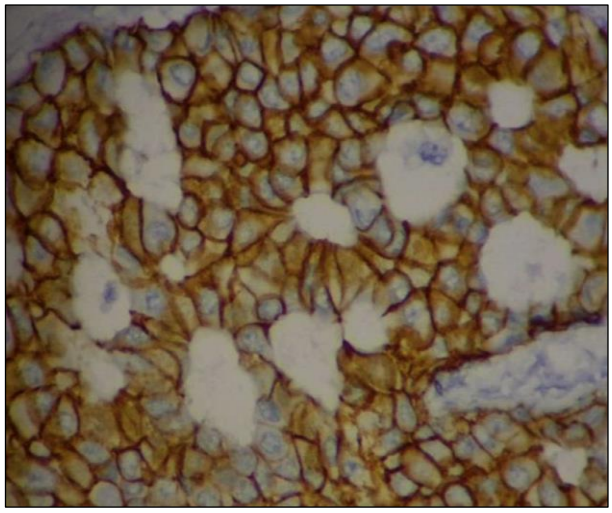

Figure 3: Strong, uniform, complete membrane positivity in >10% of tumor (3 + positivity) (IHC (Her2/neu): 40X).

Interpretation of KI-67 staining was as per recommendations from international KI-67 in breast cancer working group, nuclear staining is considered positive. Scoring involved counting of at least 500 malignant invasive cells and expressed as percentage of positively staining cells among the total number of invasive cells in the given area.[16]

The IHC study was carried out using polymer labelling technique on i6000 Biogenex automated IHC staining system. The antibodies used were: ER- clone 6f 11 Leica; PR-clone pa 0312 Leica; Ki-67- clone MIB 1 Dako; Her2-clone CB 11-Biogenex and CK 5/6- clone D5/16B4 -Dako (Figure 4).

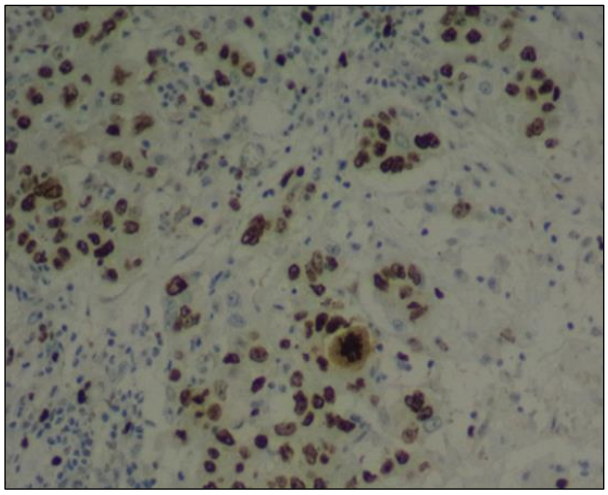

Figure 4: Nuclear positivity >15% (IHC (Ki67): (20X)).

Statistical analysis

The probability value $p<0.005$ was considered significant. Association of molecular classes and histological (MBR) grading was assessed by Pearson's chi-square test. Statistical software STATA version 13.0 was used for statistical analysis.

RESULTS

The present prospective, cross sectional study included total 47 female patients which were classified depending on ER/PR, Her2/neu, Ki67 score into various subtypes. Luminal A cases were 10 (21%) and 4 (8%) were Luminal B. The HER2 neu positive cohort consisted of 9 (19 %) cases, while triple negative phenotype comprised of maximum 24 (51%) patients (Table 1).

Out of these, maximum patients 24 (51%) were in premenopausal age group (<50years) and 5 (20%) of which were below 30 years of age. In triple negative cohort, maximum cases 14 (58%) were in premenopausal group; while in luminal types maximum cases belong to postmenopausal (>50yrs) cohort (Table 1). Majority patients 29 (61%) had tumour size in the range of 2-5cm, followed by 13 (27%) with tumour size>5cm. In luminal A type, most patient had tumour size<2cm; while in triple negative phenotype, all patients had size >2cm; of which 11 had tumour size >5cm (45%) and 13 had it in the range of 2-5cm (Table 1). The lymph node metastasis was evident in total 31 cases (65%). The highest number of patients with node metastasis was observed in HER2 positive cohort 9/9 (100%) followed by triple negative phenotype 17/24(70%). Most of the patients of luminal types A and B, 6 (60%) and 3 (75%) respectively had no evidence of lymph node metastasis (Table 1).

The tumour grade revealed maximum cases in grade I, followed by II and III. When tumour grade was assigned to molecular classes; all the luminal A cases 10 (100%)

belonged to grade I; so also, majority cases 3/4(75%) in luminal B, belonged in grade I. In Her2/neu positive cohort maximum patients, 5 were in grade II (55%). The triple negative phenotype has higher number 11 (45%) of cases in grade III, followed by grade II (37%) (Table 2).

Table 1: Age, tumour size and lymph node involvement in various molecular subtypes.

	Age (years)		Tumour size (cm)			Lymph node	
Molecular types	**<50**	**>50**	**≤ 2cm**	**>2-5 cm**	**>5cm**	**Positive**	**Negative**
Luminal A: (ER/PR +, Her2/neu -, Ki 67<10)	2	8	4	6	0	4	6
Luminal B: (ER/PR +, Her2/neu -, Ki 67>10)	0	4	1	2	1	1	3
Her 2 positives :(Her2+ (ER/PR ±))	7	2	0	8	1	9	0
Triple Negative: (Her2- (ER/PR -))	8	16	0	13	11	17	7
Total	17	30	5	29	13	31	16

Table 2: Tumour Grade-wise distribution of cases in various molecular types.

	Histological tumour grade			Total
Molecular classes	**I**	**II**	**III**	
Luminal A: (ER/PR +, Her2/neu -, Ki 67 index <10)	10 (100%)	0	0	10
Luminal B: (ER/PR +, Her2/neu-, Ki 67index ≥10)	3(75%)	1(25%)	0	4
Her2 positive: Her2/neu+, (ER/P ±)	2(22%)	5(55%)	2 (22%)	9
Basal like/Triple Negative: (ER/PR -, Her2 /neu-)	4(16%)	9 (37%)	11 (45%)	24
Total	19	15	13	47

The triple negative cohort of 24, was subclassified on the basis of CK 5/6 staining. The 7 cases with cytokeratin positivity were labelled as core basal while 17 negative cases were considered as 5 NP; however, EGFR staining not done in our cases. Low Ki67 index (<15%) observed in 83% cases of grade I tumour, while intermediate to high Ki67 value (>30%) was noted in (38%) of grade III tumour (Table 3).

Table 3: Ki 67 index correlation with tumour grade.

	Tumour grade			Total
Ki 67 index	**Grade I**	**Grade II**	**Grade III**	
Low (<15)	15 (83%)	9 (56%)	0 (23%)	24
Intermediate (15-30)	3 (16%)	5 (31%)	8 (38%)	16
High (>30)	0	2 (12%)	5 (38%)	07
Total	18	16	13	47

DISCUSSION

Biomarkers expression in breast cancer is used as a prognostic indicator and predictor of response to hormonal and chemotherapy. To date, the leading parameters that guide adjuvant therapy in breast cancer are estrogen receptor (ER), progesterone receptor (PR) and Her2/neu.[17] Few Studies have found consecutive decrements of ER, PR expression as a measure of differentiation of tumour with grade I (well differentiated) having the highest and grade III (poorly differentiated) having the lowest ER/PR expression. Her 2/neu over expression is associated with poor tumour grade so also the triple negative breast carcinomas.[4,18,19] Though hormone receptor analysis is a prerequisite for management and prognosis; histological grading has a bearing on prognosis, as high grade has poor prognosis and vice versa.[4,18-20] The triple negative breast cancers therefore would not be expected to benefit from anti estrogens therapy nor from trastuzumab.[19] Approximately 15% of breast cancers are basal-like and are associated with poor relapse-free and overall survival.[20,21] These Basal-like breast cancers are mitotically active, high-grade and are associated with younger age of the patient.[7,8] A readily available prognostic immunohistochemical surrogate marker, easily applied on formalin-fixed, paraffin embedded tissues, would therefore identify these molecular subtypes of breast cancer patients.[14] Study by Sofi GN et al, in their study of 101 cases, observed ER/PR positivity in 63 % cases.[22] They correlated ER, PR status with tumour grade. According to them in the ER/ PR+ cohort; 71.4% cases were in grade I, 64.45% in grade II and 52.5% in grade III. Higher positivity of ER, PR expression is observed in low grade tumour as compared to high grade tumour. Geethamala K et al, studied 100 cases out of which 19 were in grade I, 54 in grade II and 27 in grade III.[23] Amongst ER, PR positive tumours; 78.9% were in grade I, 64.9% in grade II and 7.4% in grade III. Similar to this study, low grade tumours were predominant and expressed higher percentage of ER and PR positivity. The prevalence of hormone receptor positive breast cancer in Asian countries has been found to be lower than Western world where ER positivity is 70-80% while PR positivity

is 60-70%.[22] A prevalence of 32.6% for ER positive and 46.1% for PR positive breast cancers has been documented by a study carried out in India (Desai et al, 2000).[24] Patnayak R et al, noted ER positivity in 47.6% and PR positivity in 48.8% cases.[15] In the present study, hormone receptor status for ER/PR was evaluated in 47 cases; amongst which expression of ER was seen in 38% cases and PR expression in 23% cases. The reasons for Indian-western disparity includes parameters such as differences in techniques of evaluation, high tumour grade, postmenopausal status. So also, ER seems to be more vulnerable to pre analytical variables. Authors compared receptor positivity with tumour grade and found that patient with lower grade had higher expression of ER/PR and vice versa. In the present study there is inverse relationship between tumour grade and ER/PR expression which is statistically significant. The inter relationship of ER, PR and Her2 has come to have an important role in the management of breast cancer. In has been shown that patients of breast carcinoma overexpressing Her2 (Her2 positive cohort) do respond to targeted therapy such as herceptin.[5-8] Consistent with most widely accepted clinical practice, authors considered a tumour Her2: 2+as being scored as Her2: 3 +on IHC. FISH (Fluorescent In Situ Hybridization) was not done in. The prevalence of Her 2 neu positive cohort in present study (Table 1) is 19% (9/47). Distribution of Her2 positive cases are (2/9) 22% in grade I, (5/9); maximum 55% cases in grade II and (2/47) 22% in grade III. The correlation of tumour grade and Her2 amplification was studied in a large series of cases by Rilke F et al, was found overexpression rate were 3.9%, 20.4% and 38.9% in tumours of grade I, II and III respectively.[25] More recently Hoff ER et al, in their study of 388 cases observed Her2 positivity in 1% of grade I, 10% of grade II and 23% of grade III tumours.[26] The frequency of Her2 positivity varies among Indian studies. In a study by Vaidyanathan K et al, they observed 43.2% Her2 positivity by IHC and 25.5% by genomic PCR.[27] The results of Her2 positivity by various authors show direct relationship with grade of the tumour; higher tumour grade is associated with overexpression of Her2 which are identical with our observations and are statistically significant with p-value 0.041 (<0.05), in spite of the fact that Her 2 expression is scattered amongst grade II invasive duct carcinomas.[25-27] In the present study, we classified 47 cases, based on the ER/PR and Her2status and KI 67 index into various categories (Table 1). Triple negative cases (ER/PR-, Her2/neu-) were predominant; out of total 24 (51%); 11 belong to grade III, 9 to grade II and 4 cases to grade I. Second predominant phenotypic group was luminal type (ER+PR+; Her2/neu-) which has 14 (29%) cases. This class was further subdivided into luminal A and luminal B depending on proliferation activity as determined by KI 67 index (cut off of 10). In luminal A type, all the cases belonged to grade I (10/10); while in luminal B group, 3 out of 4 cases in grade I. In Her2positive (ER/PR±, Her2 +) cohort, out of 9, maximum cases (5/9) were in grade II Comparing these classes with various studies, researchers found majority of cases in ER+, PR+, Her2/neu-category (Table 4).

Table 4: Molecular subtypes: comparison with various studies.

Molecular subtypes	Onitilo AA et al [29]	Ambroise et al [4]	Ghosh et al[28]	Geethamala K et al[23]	Present study 2016
Luminal A: (ER/PR +, HER2-, Ki 67 index <10)	68.9 % (luminal A and B)	48% (luminal A and B)	51.2% (luminal A and B	54% (Luminal A and B)	(21%)
Luminal B:(ER/PR +, HER2-, Ki67 index >10)					(08%)
Her2/neu positive: (HER2neu+ ER/PR ±)	17.7%	27%	24.8 %	26%	(19%)
Basal like: Triple negative: (ER/PR-, HER2-)	13.4%	25%	29.8%	20%	(51%)

Ambroise M et al, showed 47%, Geethamala K et al, 52% Ghosh J et al, 51.2% and Onitilo AA et al, 68.9 %.[4,22,28,29] Authors observed maximum Triple negative cases in contrast to other studies.

The reasons for this disparity could be, high tumour grade, menopausal status, or smaller sample size. The triple negative basal like phenotype is further classified depending on staining with cytokeratin 5/6. Out of 24 cases, 7 showed CK5/6 positivity and categorized as core basal while 17 were negative and classified as 5NP group, however EGFR staining was not done in this study. This sub categorization will aid us to understand the response to treatment.

Authors tried to correlate various molecular classes with respect to tumour size, grade and lymph node status. When Luminal A versus Her2 positive groups were compared with respect to tumour size, statistically significant difference was observed in tumour size <2cm. Statistically significant difference was also observed between luminal A Vs triple negative group for tumour size <2cm. This clearly states that luminal group category is associated with smaller tumour size as tumour as compared to Her2 positive and Triple negative class

which are known for their aggressive behavior. Similar findings were quoted by Kumar N et al, and Pandey D et al, Luangxay T et al.[30-32] When these groups were similarly compared with respect to lymph node status, no statistically significant difference was observed in each of them. Tumours are categorized into low (grade I) and high grade (grade II and III). Various molecular classes when compared with reference to tumour grade, we observed statistically significant difference between luminal A Vs Her2 positive group (<0.05 for LG and <0.005 for HG), Luminal A versus triple negative group in both low and high grade (<0.005). These findings favour that lower tumour grade is a feature of luminal group in contrast; triple negative and Her2 positive cohort is associated with higher grade. Within the cohort of luminal A and luminal B, no significant difference was obtained with respect to tumour size, grade and lymph node status. Role of Ki 67 index as a prognostic and predictive marker in breast cancer is being investigated.[17] The simplest and most widely used method is mitotic count. In recent times, IHC for Ki 67 is being used to determine tumour proliferation. In present study, significant correlation was found between Ki-67 (index<15) and tumour grade on histology. There were 15/18 (83%) cases in grade I am having Ki-67 index<15. Similarly, Ki 67 index of >15 correlated with 7/16 (43%) cases of grade II and 10/14 (71%) grade III tumours (Table 4). The grade II and grade III tumours are clubbed together as high grade for statistical analysis. Then the comparison within tumour grade and Ki67 was made. Authors established statistically significant association of Ki67 expression with tumour grade, (Table 5) well evident from p-value (<0.05). Haroon S et al, studied 194 cases breast carcinoma correlated different tumour characteristics with mean Ki-67 value.[17] They concluded that with increasing grade, there was a rise in Ki-67 index and the correlation was statistically significant (p<0.05).

Table 5: Association Ki 67 index and tumour grade: statistical analysis.

	Tumour grade		P value
Ki 67 index	Low grade	High grade	
Low (≤15)	15	9	0.014
High (>15)	3	20	0.012
Total	18	29	

CONCLUSION

This study allows characterization of immunohistochemical subgroups in patients with breast cancer in central India, using a recently updated classification. It also allowed the assessment of subgroup distribution in relation to the clinicopathological characteristics like tumour size lymph node status and histologic grade. In this sense, it is noteworthy that the association between the histological diagnosis and immunohistochemistry can help to determine the phenotypic profile of breast cancer, aiming to guide treatment and, consequently, to improve the therapeutic response. Our findings could provide fundamentally useful data for national policies in order to control breast cancer in the future. Larger studies are required to determine the biological behavior of breast cancer in this population. The clinical importance of these prognostic markers in the management of breast cancer patients is strongly advocated in our population to improve the dismal prognosis of triple negative and Her2/neu positive cases and to provide better therapeutic options.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Walke V, Gunjkar G. Immunohistochemical profile and its association with clinicopathological parameters in carcinoma breast: a prospective study in central India. Int J Res Med Sci 2019;7:1796-802.