International Surgery Journal
Yadav P et al. Int Surg J. 2022 Apr;9(4):828-834
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20220942

Original Research Article

Immunohistochemical profile of carcinoma breast and its association with clinicopathological features: a single institutional experience

Parul Yadav[1]*, Shaitan Singh Rathore[2], Vijay Verma[1], Mukesh Kumar Yadav[2], Yogesh Sangwan[1]

[1]Department of General Surgery, Dr. S.N. Medical College, Jodhpur, Rajasthan, India
[2]Department of Dermatology, ESIC Model Hospital, Jaipur, Rajasthan, India

Received: 20 February 2022
Revised: 08 March 2022
Accepted: 14 March 2022

***Correspondence:**
Dr. Parul Yadav,
E-mail: parulyadavjalsu93@gmail.com

ABSTRACT

Background: Breast cancer is a systemic disease which has different biological subtypes with vast natural history, clinical presentation, various pathological types and molecular features which has impact on prognostic profile and outcome. Present study aims to evaluate correlation of receptor status (ER, PR and HER 2neu) with other tumor characteristics.
Methods: The present study was a prospective observational study of 50 breast cancer patients and was conducted from January 2020 to June 2021 in surgical unit of the department of general surgery at MDM hospital attached with Dr. S. N. medical college, Jodhpur, Rajasthan.
Results: Most common age group was 41-50 years in 38% cases. Majority of patients were females (49, 98%). The 88% cases had invasive duct carcinoma. ER, PR and HER 2neu positivity had statistically significant correlation with age ($p<0.0001$), histological grade ($p<0.0001$) and tumor size ($p=0.04$). HER 2neu had statistically significant negative correlation with ER and PR ($p<0.05$).
Conclusions: Immunohistochemistry (IHC) markers (ER, PR, HER 2neu) are positively correlated with increasing age, tumor size, tumor grade and positive axillary lymph nodes, also there is statistically significant correlation between HER 2neu overexpression and hormone receptor (ER, PR) negativity in study population.

Keywords: Breast cancer, Hormone receptor, HER 2neu, IHC

INTRODUCTION

Breast cancer is the most common malignancy and leading cause of death among women resulting in more than 1000,000 cases found worldwide annually.[1] As per WHO guideline, India has cancer mortality of 79 per 1000,000 cases and accounts for 6% of total deaths.[2] Carcinoma breast is a biologically heterogeneous disease and patients with similar clinical and diagnostic prognostic profile, can have diverse clinical outcome.[3] Breast cancer is a systemic disease which has different biological subtypes with vast natural history, clinical presentation, various pathological types and molecular features which has impact on prognostic profile and outcome.[4] Classical prognostic factors of carcinoma breast includes tumor size, lymph nodes involvement, pathological types, grade hormone receptor status and HER 2neu expression.[5] There has been advancement in management of breast cancer which leads to early diagnosis and more efficacious treatment resulting in significantly decrease in deaths due to breast cancer and enhancement in lifespan for women having breast cancer.[6] Oestrogen is an important mitogen which shows its effect by binding to its receptor (ER) and its positivity seen in 50-80% of breast cancer. Endocrine therapies are targeted to these receptors.[7] PR is also having equal

importance as ER in prognosis of breast cancer with its expression is seen in 60-70% of invasive cancer.[8] HER 2neu is a proto-oncogene which is an amplified protein and it is overexpressed in 15-25% cases of carcinoma breast and it is associated with poor prognosis.[9] Present study aims to evaluate correlation of receptor status (ER, PR and HER 2neu) with other tumor characteristics.

METHODS

The present study was a prospective observational study of 50 breast cancer patients and was conducted from January 2020 to June 2021 in department of general surgery at tertiary care hospital Rajasthan. All patients were included according to the inclusion criteria and excluded according to exclusion criteria.

Inclusion criteria

Patients with histopathologically confirmed diagnosis of carcinoma breast, presented in surgical OPD and underwent modified radical mastectomy included.

Exclusion criteria

Patients who were with breast lump which made diagnosis obvious to be benign, patient with no primary tumour found, diffuse disease, Paget's disease of the nipple, or *in situ* disease and patient not willing for the study were excluded from the study.

The study started after taking approval from college ethical committee. Detailed clinical history, clinical examination including primary tumor size and axillary nodal status were carried out followed by laboratory and radiological investigations for diagnosis. All patients had undergone modified radical mastectomy (MRM) with level II axillary nodal dissection. Specimen sent to pathology department for detailed histopathological examination including histopathological type, no. of lymph nodes retrieved and no. of positive axillary nodes IHC staining for ER, PR and HER 2neu receptors and histological grade. For ER/PR, nuclear staining of more than 10% in tumor cells considered as positive and for HER 2 neu a test score of +3 considered to be positive. All paraffin blocks studied for grading according to Scarff-Bloom Richardson grading system of breast cancer with Nottingham modification. Staging of breast tumor done according to tumor node metastasis classification.

Collected data was analysed using SPSS version 18 and then correlation of hormone receptors (ER, PR) and HER 2neu were tested with age, tumour size, histopathological types, tumour grade and positive axillary lymph node involvement using Chi-square test.

RESULTS

This study included 50 patients of carcinoma breast who had undergone modified radical mastectomy (MRM). Majority of patients were females (49, 98%). Age of presentation ranged from 28-70 years. Most common age group was 41-50 years in 38 % cases. Mean age of presentation was 45.58 years. The 19 cases (38%) had age <40 years and 31 cases (62%) had age >40 years. The 49 cases (98%) presented with complaint of breast lump, out of 49 cases, 11 cases (22%) had associated pain, 7 cases (14%) had dimpling/puckering, 5 cases (10%) had associated nipple discharge, 4 cases (8%) had associated nipple retraction, 3 cases (6%) had associated ulceration of overlying skin of lump and only 1 case (2%) had inflammatory carcinoma without any associated lump. Majority of cases 28 (56%) presented in duration of 4-6 months after noticing disease, 15 patients (30%) presented in duration of <3 months and only 7 patients (14%) presented in duration of 7-9 months. None of the patient presented before 2 months. the 33 (66%) cases presented with right sided disease. 2 cases (4%) had previous history breast cancer on contralateral side and had undergone MRM for same. Only 2 patients (4%) had family history of carcinoma breast. Majority of patients 35 (71.42%) presented in premenopausal age group. Mean age at menarche was 12.5 years. Mean age at menopause was 51.5 years.

Majority of lumps 35 (71.43%) were in upper outer quadrant, 10 lumps (20.41%) were in upper inner quadrant, 4 (8.16%) were present beneath nipple areola complex.35 cases (71.43%) had lump size between 3-5 cm and 14 cases (28.57%) had size between 6-7 cm. No case presented with lump size <2 cm. the 27 cases (54%) had palpable axillary lymph nodes.

In histopathological examination, 44 cases (88%) had invasive duct carcinoma, 3 cases (6%) had invasive lobular carcinoma, 2 patients had invasive papillary carcinoma (4%), 1 patient had inflammatory carcinoma. The 31 cases (62%) had positive axillary nodes. Majority of cases 27 (54%) had histological grade II followed by grade III (34%) and 6 patients (12%) had grade I. ER positivity seen in 27 (54%), PR positivity in 22 (44%) and HER 2neu positivity in 16 (32%) cases. Majority of patients presented in stage II (66%) and the stage III (34%).

ER, PR and HER 2neu positivity had statistically significant correlation with age ($p<0.0001$), histological grade ($p<0.0001$) and tumor size ($p=0.04$). IHC markers (ER, PR HER 2neu) showed no significant correlation with histopathological types and number of positive axillary nodes ($p>0.05$) HER 2neu had statistically significant negative correlation with the ER and PR ($p<0.05$).

Table 1 showing prevalence of clinicopathological characteristics of carcinoma breast in study population. Table 2 showing correlation of IHC markers with tumor characteristics and the Table 3 showing correlation between IHC markers (hormone receptors and HER 2neu).

Table 1: Prevalence of clinicopathological characteristics.

Variables	Number of patients	Percentage (%)
Age (years)		
<40	19	38
>40	31	62
Mean age	(45.5)	
Most common age group (41-50)	19	38
Symptoms		
Lump	49	98
Lump with pain	11	22
Lump with nipple discharge	4	8.16
Laterality		
Right	33	66
Left	17	33
Site of Lump		
Upper outer	35	71.43
Upper inner	10	20.41
Central	4	8.16
Histopathology		
Invasive duct carcinoma	44	88
Invasive lobular carcinoma	3	6
Invasive papillary carcinoma	2	4
Inflammatory carcinoma	1	2
Histological grading		
Grade I	6	12
Grade II	27	54
Grade III	17	34
Palpable axillary lymph nodes	27	54
Positive axillary lymph nodes	31	62
1-3 nodes	18	36
4-9 nodes	9	18
>10 nodes	4	8
Size of tumor (cm)		
<3	0	0
3-5	35	71.43
6-7	14	28.57

Table 2: Correlation of IHC markers with tumor characteristics.

Variables		ER+ (n=27)		PR+ (n=22)		Her 2neu+ (n=16)		P value
		N	%	N	%	N	%	
Age (years)	≤40	2	7.41	1	4.55	15	93.75	<0.0001
	41-49	14	51.85	12	54.55	0	0.00	
	≥50	11	40.74	9	40.91	1	6.25	
Grade	I	6	22.22	4	18.18	0	0.00	<0.0001
	II	20	74.07	17	77.27	7	43.75	
	III	1	3.70	1	4.55	9	56.25	
Histopathological types	Invasive duct carcinoma	25	92.59	21	95.45	14	87.50	0.117
	Invasive lobular carcinoma	0	0.00	0	0.00	2	12.50	
	Invasive papillary	2	7.41	1	4.55	0	0.00	
	Inflammatory carcinoma	0	0.00	0	0.00	0	0.00	
Lymphnodes	No LN	8	29.63	6	27.27	10	62.50	0.05
	1-3	19	70.37	16	72.73	6	37.50	
	4-9	0	0.00	0	0.00	0	0.00	
	≥10	0	0.00	0	0.00	0	0.00	
Tumor size (cm)	3-5	19	70.37	15	68.18	2	12.5	<0.05
	>5	8	29.63	7	31.82	14	87.50	

Table 3: Correlation between IHC markers.

Her 2 neu	ER+	ER-	PR+	PR-
Positive	1	15	2	14
Negative	26	8	20	14
Total	27	23	22	28
P value	<0.0001		0.002	

Figures 1-3 are show photomicrographs of ICH of ER, PR and HER 2neu receptors.

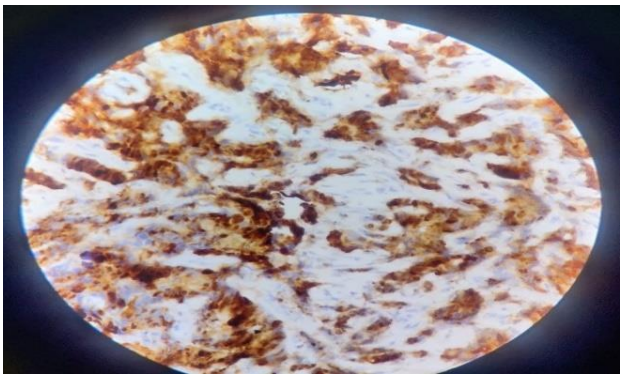

Figure 1: ICH of invasive duct carcinoma ER positive (40x).

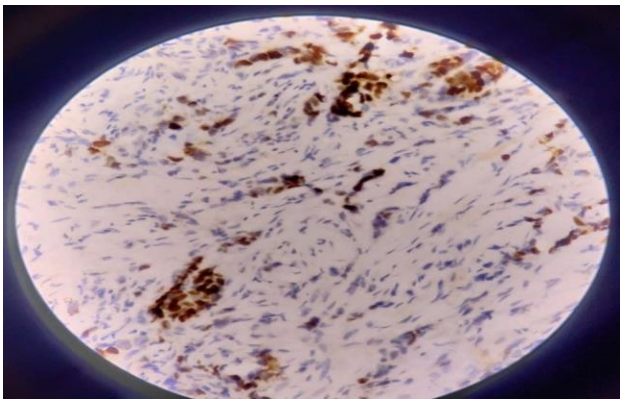

Figure 2: ICH of invasive duct carcinoma PR positive (10x).

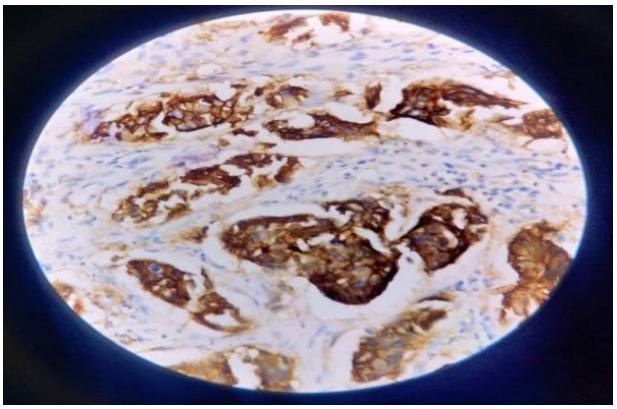

Figure 3: ICH of invasive duct carcinoma HER 2neu positive (40x).

DISCUSSION

Our study included 50 patients of breast cancer with mean age of presentation was 45.5 years. Most common age group was 41-50 years. Mean age of presentation in Indian patients is found to be lower than western countries which is seen in western studies; Takalkar et al and Sandhu et al.[10,11] In our study majority of patients 49 (98%) presented with breast lump, lump associated with pain in 11 (22%), 3 patients (6%) presented with ulceration, five (10.0%) had a nipple discharge, four (8.0%) showed nipple retraction whereas one (2.0%) presented with Peau'd orange. Our results correlate with study done by Nath et al.[12] Tumor size of 3-5 cm was observed in majority of cases (35, 71.43%) followed by tumor size of >5 cm in 14 cases (28.57%). In our study tumor size was >3 cm in all patients which was comparable to other Indian and Asian studies; Acharya et al and Kumar et al.[13,14] In contrast, in a study from western countries Taucher et al the tumors are predominantly less than 2 cm.[15] This could be due to awareness and the early detection programs prevalent in the western countries. In our study 31 cases (62%) had positive axillary nodes which correlates with Indian and Asian studies; Mahalakshmi et al and Shoeb et al.[16,17] In western countries majority of patients have negative axillary nodes seen in study done by Stead et al.[18] Most common histological type was invasive duct carcinoma in 88% cases which was similar to other Indian and western studies; Kumar et al, Naeem et al and Kohler et al.[18-20] In our study majority of cases 27 (54%) had histological grade II followed by grade III (34%) and 6 patients (12%) had grade I. Our findings correlate with other Indian studies; Ambroise et al and Acharya et al.[13,21]

In our study ER positivity was present in 27 (54%) and PR positivity was in 22 (44%). Our results correlate with studies done by Vedashree et al and Munjal et al.[22,23] In contrast, Lal et al concluded higher ER and PR expression in western population.[24] A study from Mumbai also showed that hormone receptor expression in India is lower compared to the West; Shet et al and Suvarchala et al concluded that hormone receptor expression is associated with decreased cancer related mortality independently of various clinical tumor factors and patients' demographic factors.[25,26]

HER 2neu overexpression was present in 16 (32%) cases in our study. The 26.89% and 24.8% cases had HER 2neu over expression in studies done by Lal et al and Azizun-Nisa et al respectively.[24,27]

Correlation of hormone receptors (ER, PR) and HER-2/neu receptor status positivity with other prognostic variables

Our study showed strong correlation of ER and PR expression. In our study ER and PR expressions were highest in age group >50 years. HER 2neu expression was highest in age group <40 years. In our study

hormone receptor expression was associated with increasing age inverse relation was seen with HER 2neu overexpression. Other studies done by Saleh et al, Azizun-Nisa et al and Ambroise et al also found that percentage of ER positivity increases with age whereas PR expression does not seem to have any significant variation and HER 2neu overexpression was associated with decreasing age.[21,27,28]

In this study correlation of ER, PR and HER 2eu expression with histological grade was statistically significant. ($p<0.0001$) majority of ER and PR positive tumor had grade II respectively, 74.07% and 77.27% followed by grade I in 22.22% and 18.18% respectively. Other studies done by Fatima et al and Azizun-Nisa et al concluded that ER and PR expression decreases with increasing tumor grade as seen in our study.[27,29] There was strong inverse correlation between hormone receptor expression and tumor grade in our study as well as in others.

Most of the cases of HER 2neu overexpression was associated with higher tumor grade as observed in 0, 43.75% and 56.25% grade I, II and III tumors respectively. whereas in a study done by Azizun-Nisa et al HER 2neu positivity was shown in 0%, 22.89%, and 31.58%. Similar results were found in study done by Lal et al.[27, 24]

In this study increasing tumor size was significantly associated with HER 2neu overexpression ($p<0.05$). HER 2neu overexpression was seen with increasing tumor size; 87.5% HER 2neu+ cases had tumor size >5 cm. Similar results obtained in other studies; Naeem et al and Fatima et al.[19,29]

Significant correlation was seen between ER, PR expression and tumor size ($p<0.05$) EP and PR expression decreased with increasing tumor size. Similar results found in other studies done by Bhaskar et al, Ambroise et al and Azizun-Nisa et al.[21,27,30]

A strong correlation was seen between HER 2neu overexpression and hormone receptors negativity ($p<0.05$). Majority of ER and PR negative cases had HER 2neu overexpression; 65.22% and 50% respectively. Our findings were correlated with other studies done by Naeem et al, Toucher et al, Almasri et al and concluded that HER 2neu overexpression was correlated significantly with ER and PR negativity.[15,19,31]

In this study correlations of ER, PR and HER 2neu with number of positive axillary lymph nodes and histopathological types were statistically not significant ($p>-0.05$). Ivkovic-kapicl et al showed non-significant correlation of HER 2neu with histopathological types and number of positive axillary nodes.[32] Tokatli et al has reported a significant association between HER-2/neu and increasing number of involved axillary lymph nodes ($p=0.014$).[33] Bhaskar et al reported non-significant correlation between hormone receptors and HER 2neu with positive axillary nodes ($p<0.05$).[30]

It is obvious from above discussed literature that HER-2/neu over expression is significantly associated with ER/PR negativity, young age, high tumour grade, large tumour size and increased number of axillary lymph node involvement. Hormone receptor positivity is significantly associated with increasing age, lesser tumor grade, decreasing tumor size. Assessment of hormone receptors positivity and HER-2/neu over expression in breast cancer patients has an impact on treatment modality.

The principal limitation of study was that patients were from a single centre. The sample size was relatively small. Moreover, the relatively presentation at younger age indicates a selection bias in favour of lower hormone receptor expression and higher Her2 neu expression. Large sample study is required for further assessment of molecular biological behaviour of breast cancer in our region.

CONCLUSION

Hormone receptor expression is slightly lower in our study as compared to other studies where as HER 2neu expression is slightly higher which can be attributed to younger age at presentation in western world. IHC markers (ER, PR, HER 2neu) are positively correlated with increasing age, tumor size, tumor grade and positive axillary lymph nodes, also there is statistically significant correlation between HER 2neu overexpression and hormone receptor (ER, PR) negativity in study population.

ACKNOWLEDGEMENTS

Authors would like to thank to Dr. Kishor Kumar Khatri, associate professor, department of pathology for his support and proving photomicrographs.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Makki J. Diversity of breast carcinoma: histological subtypes and clinical relevance. Clin Med insights Pathol. 2015;8:CPath-S31563.
2. Rajpal S, Kumar A, Joe W. Economic burden of cancer in India: Evidence from cross sectional nationally representative household survey-2014. PLoS ONE .2018;13(2):1-17.
3. Perou CM, Sørlie T, Eisen MB, Van De Rijn M, Jeffrey SS, Rees CA et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747-52.

4. Glass AG, Lacey JV Jr, Carreon JD, Hoover RN. Breast cancer incidence, 1980-2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. J National Cancer Institute. 2007;99:1152-61.
5. Rampaul RS, Pinder SE, Elaston CW, Ellis IO. Prognostic and predictive factors in primary breast cancer and their role in patient management; the Nottingham breast team. Eur J Surg Oncol. 2001;27:229-38.
6. Ravdin PM, Cronin KA, Howlader N, Berg CD, Chlebowski RT, Feuer EJ et al. The decrease in breast-cancer incidence in 2003 in the United States. N Eng J Med. 2007;356:1670-4.
7. Yamauchi H, Stearns V, Hayes DF. When is a tumor marker ready for prime time? A case study of c-erbB-2 as a predictive factor in breast cancer. J Clin Oncol. 2001;19:2334-56.
8. McGuire WL, Clark GM. The prognostic role of progesterone receptors in human breast cancer. In Seminars in oncology. 1983;10(4):2-6.
9. Hung MC, Lau YK. Basic science of HER-2/neu: a review. In Seminars in oncology. 1999;4(12):51-9.
10. Takalkar UV, Asegaonkar SB, Kulkarni U, Kodlikeri PR, Kulkarni U, Saraf M, Advani S. Clinicopathological profile of breast cancer patients at a tertiary care hospital in Marathwada region of Westen India. Asian Pacific J Cancer Prev. 2016;17(4):2195-8.
11. Sandhu DS, Sandhu S, Karwasra RK, Marwah S. Profile of breast cancer patients at a tertiary care hospital in north India. Indian J Cancer. 2010;47:16-22.
12. Pervin MM, Nath HD, Bahar MM, Alam A, Bhowmik J. Study on clinical presentation of breast carcinoma of 50 cases. ChattagramMaa-O-Shishu Hospital Med College J. 2014;13(2):8-11.
13. Acharya SC, Jha AK, Manandhar T. Clinical Profile of Patients Presenting with Breast Cancer in Nepal. Kathmandu Uni Med J. 2012;39(3):3-7.
14. Kumar A, Singh D, Gupta ML. Correlation of morphological profile and receptor status in breast carcinoma: An institutional study in tertiary care hospital. J Med Sci Clin Res. 2020;8(1):545-9.
15. Taucher S, Rudas M, Mader RM. Do we need HER2/neu testing for all patients with primary breast carcinoma? Cancer. 2003;98:2547-53.
16. Mahalakshmi P, Krishnaswamy B, Gopalakrishnan KR, Dhanalakshmi M, Shyamala E. A Clinicopathological Evaluation of Breast Carcinoma in a Rural Tertiary Care Hospital. J Med Sci Clin Res. 2020;8(11):44-8.
17. Shoeb MFR, Pinate AR, Shingade PP. Risk factors and clinical presentations of breast cancer patients: a hospital based study. Inte Surg J. 2017;4:645-9.
18. Stead LA, Lash TL, Sobieraj JE. Triple-negative breast cancers are increased in black women regardless of age or body mass index. Breast Cancer Res. 2009;11:R18.
19. Naeem M, Nasir A, Aman Z, Ahmad T, Samad A. Frequency of Her-2/neu receptor positivity and its association with other features of breast cancer. J Ayub Med College Abbottabad. 2008;20(3):23-6.
20. Kohler RE, Moses A, Krysiak R, Liomba NG, Gopal S. Pathologically confirmed breast cancer in Malawi: a descriptive study: Clinical profile of breast cancer. Malawi Med J. 2015;27(1):10-2.
21. Ambroise M, Ghosh M, Mallikarjuna VS, Kurian A. Immunohistochemical profile of breast cancer patients at a tertiary care hospital in South India. Asian Pac J Cancer Prev. 2011;12(3):625-9.
22. Vedashree MK, Rajalakshmi V. Clinico-pathological study of breast carcinoma with correlation to hormone receptor status & HER2/neu. Indian J Pathol Oncol. 2016;3(4):690-5.
23. Munjal K, Ambaye A, Evans MF. Immunohistochemical analysis of ER, PR, Her2 and CK5/6 in Infiltrative Breast Carcinomas in Indian Patients. Asian Pacific J Cancer Prev. 2009;10:773-8.
24. Lal P, Tan LK, Chen B. Correlation of HER-2 status with estrogen and progesterone receptors and histologic features in 3,655 invasive breast carcinomas. Am J Clin Pathol. 2005;123,541-6.
25. Shet T, Agrawal A, Nadkarni M, Palkar M, Havaldar R, Parmar V et al. Hormone receptors over the last 8 years in a cancer referral center in India: what was and what is? Indian J Pathol Microbiol. 2009;52(2):171.
26. Suvarchala SB, Nageswararao R. Carcinoma breast-histopathological and hormone receptors correlation. J Biosci Tech. 2011;2(4):340-8.
27. Azizun-Nisa BY, Raza F, Kayani N. Comparison of ER, PR and HER-2/neu (C-erb B 2) reactivity pattern with histologic grade, tumor size and lymph node status in breast cancer. Asian Pacific J Cancer Prev. 2008;9(4):553-6.
28. Saleh F, Abdeen S. Pathobiological features of breast tumours in the State of Kuwait: a comprehensive analysis. J Carcinogenesis. 2007;6:12.
29. Fatima S, Faridi N, Gill S. Breast cancer: steroid receptors and other prognostic indicators. Journal of the College of Physicians and Surgeons-Pakistan: JCPSP. 2005;15(4):230-3.
30. Bhaskar S, Rastogi K, Gupta S, Jindal A, Bhatnagar AR, Jain S. A study of hormone receptor status in breast carcinoma and use of HER2-targeted therapy in a tertiary care center of India. Indian J Med Paediatr Oncol. 2019;40(S 01):S54-60.
31. Almasri NM, Al Hamad M. Immunohistochemical evaluation of human epidermal growth factor receptor 2 and estrogen and progesterone receptors in breast carcinoma in Jordan. Breast Cancer Res. 2005;7:R598-604.
32. Ivkovic-Kapicl T, Knezevic-Usaj S, Djilas-Ivanovic D, Panjkovic M. Correlation of HER-2/neu protein overexpression with other prognostic and predictive factors in invasive ductal breast cancer. Anticancer Res. 2007;21(4):673-8.

33. Tokatli F, Altaner S, Uzal C, Ture M, Kocak Z, Uygun K et al. Association of HER-2/neu overexpression with the number of involved axillary lymph nodes in hormone receptor positive breast cancer patients. Exp Oncol. 2005;27:145-9.

Cite this article as: Yadav P, Rathore SS, Verma V, Yadav MK, Sangwan Y. Immunohistochemical profile of carcinoma breast and its association with clinicopathological features: a single institutional experience. Int Surg J 2022;9:828-34.