

## Original Research Article

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# Immunohistochemistry profile and its relation with prognosis in locally advanced breast cancer

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## ABSTRACT

**Background:** Breast cancer is one of the most common malignancy and leading cause of cancer related deaths in women worldwide. Immunohistochemistry (IHC) is done to characterize intracellular proteins or cell-surface antigens and is used to assess tumour subtypes, confirm diagnosis, predict prognosis and response to therapy. The aim of the present study was to evaluate the relationship of IHC profile- ER, PR and HER2 neu and prognosis of patients who underwent modified radical mastectomy for locally advanced breast cancer.

**Methods:** A retrospective cohort study was conducted at MES Medical College Hospital from October 2015 to November 2017 in patients who underwent modified radical mastectomy for locally advanced breast carcinoma. A total of 65 women were enrolled in the study. 5 years survival was taken as the prognostic indicator.

**Results:** Majority of the patients belong to the age group of 40-49 years with 40% patients followed by 33.84% patients in the age group of 50-59 years. Maximum number of patients was found in 2B stage of tumour. Maximum patients belonged to the ER/PR+, HER2- subgroup (27), followed by triple negative (ER/PR-, HER2) subgroup (16). There was no disease related mortality in ER/PR+, HER2+ and ER/PR+, HER2- subgroups. There were 1 and 2 disease related mortality in ER/PR-, HER2+ and triple negative subgroups respectively.

**Conclusions:** In the present study the worst prognosis was observed in triple negative (ER/PR-, HER2-) IHC subgroup followed by the HER2 enriched (ER/PR-, HER2+) subgroup.

**Keywords:** IHC, Locally advanced breast cancer, Modified radical mastectomy, 5 year survival, Prognosis

## INTRODUCTION

Breast cancer is considered to be the most common cancer in women and the second most common cause of death after lung cancer.<sup>1</sup> The World Cancer Report issued by the International Agency for Cancer on Research tells us that cancer rates are increasing at an alarming rate globally. Cancer rate could increase by 50% to 15 million new cases as per 2020.<sup>2</sup> According to Globocan, the annual age standardized incidence rate of breast cancer was 43.1/100,000.<sup>3</sup> In breast carcinoma,

hormone receptors and human epidermal growth factor receptor 2 are assisted to predict the prognosis.<sup>4</sup>

Immunohistochemistry (IHC) is a special staining process which is performed on fresh or frozen breast cancer tissue removed during biopsy or surgery. The most common IHC markers used in breast cancer which has prognostic values are estrogen receptor (ER), progesterone receptor (PR), HER 2 neu, Ki-67 and p53. There are many ER/PR scoring systems based on percentage of positive staining cells and staining intensity. According to St Gallen treatment guidelines, breast cancer is divided into 3

groups based on percentage of positive cells- responsive (10%), uncertain response (1-9%) and non-responsive (0%). According to Allred scoring system, a total score of 3 (characterize the lowest positive result- corresponds to uncertain response in St Gallen) or more is recommended for hormone therapy.<sup>5</sup> HER 2 neu is a marker of sensitivity to Herceptin (trastuzumab) and resistance to tamoxifen. The IHC reactions for HER2 are scored by the Hercep test where a score of 0 to 3+ that measures the amount of HER2 receptor protein on the surface of cells in a breast cancer tissue sample. If the score is 0 to 1+, it's called "HER2 negative". If the score is 2+, it's called "borderline". A score of 3+ is called "HER2 positive".<sup>5</sup> Immunohistochemistry markers are used to guide treatment decisions, to classify breast cancer into subtypes and both as predictive and prognostic factors.<sup>6</sup>

### Objectives

The objective of the present study was to study the relationship between IHC profile and prognosis in locally advanced breast cancer.

### METHODS

A retrospective cohort study was conducted at MES Medical College Hospital from October 2015 to November 2017 with modified radical mastectomy. Patients who underwent modified radical mastectomy for locally advanced breast cancer during 1 January 2009 to 31 May 2012 were included in the study. Patients with inadequate post modified radical mastectomy data were excluded from the study. A total of 65 cases of locally advanced breast cancer were enrolled in the study. The study was approved by institutional ethics committee.

The details of initial clinical laboratory and survival were collected from the relevant files and evaluated using imaging techniques and follow up visits were done. Data was supplemented using phone calls and mails if required.

Data collected was entered and tabulated in Microsoft Excel sheet. Patients were distributed into four subgroups based on the IHC profile. Prognosis was taken as 5 year survival in which each subgroup was assessed and it was expressed in percentages for ease of comparison between groups.

### RESULTS

A total of 65 women underwent modified radical mastectomy for locally advanced breast cancer during the study period. Table 1 presents the demographic characteristics. Majority of the patients belong to the age group of 40-49 years with 40% patients followed by 33.84% patients in the age group of 50-59 years. The least number of patients were observed in age group of 20-29 years. The mean age patients were 52.29 years with a standard deviation of 12.03. 37 out of the total 65

patients belonged to the premenopausal group and the remaining 28 belonged to the postmenopausal age group. 55 (84.61%) out of 65 patients were parous. Only 1 (1.53%) patient had a past history of opposite breast cancer. None of the other patients had any past history of malignancy. Family history of ovarian cancer was found in 6 (9.23%) patients and breast cancer in 3 (4.61%) patients. Right breast cancers were found in 37 (56.92%) patients as compared to left breast cancer in 28 (43.07%) patients. Maximum number of patients was found in stage 2B with 54 (83.07%) patients.

**Table 1: Demographic and clinical characteristics of the studied patients.**

Demographic characters	N (%)
<b>Age group (in years)</b>	
0-19	0 (0)
20-29	3 (4.61)
30-39	9 (13.84)
40-49	26 (40)
50-59	22 (33.84)
60-69	5 (7.69)
<b>Menopausal status</b>	
Premenopausal group	37 (56.92)
Postmenopausal group	28 (43.07)
<b>Parity</b>	
Parous	55 (84.61)
Nulliparous	10 (15.38)
<b>Past history of breast cancer</b>	
Present	1 (1.53)
Absent	64 (98.46)
<b>Family history of malignancy</b>	
Carcinoma breast	3 (4.61)
Ovarian malignancy	6 (9.23)
Other malignancy	0 (0)
Absent	56 (86.15)
<b>Side and site of lesion</b>	
Right breast	37 (56.92)
Left breast	28 (43.07)
Upper outer quadrant	30 (46.15)
Upper inner quadrant	16 (24.61)
Lower outer quadrant	10 (15.38)
Lower inner quadrant	5 (7.69)
Central	4 (6.15)
<b>Stage of tumor</b>	
2B	54 (83.07)
3A	9 (13.84)
3B	2 (3.07)

38 out of 65 patients did not have any co morbidities, and the remaining 27 patients had the following co morbidities, the maximum number of patients having systemic hypertension (31%) as observed in Figure 1. In our study population, majority of the patients were belonging to ER/PR+ and HER2- subgroup, 27 (42%) out of the total 65 patients (Figure 2).

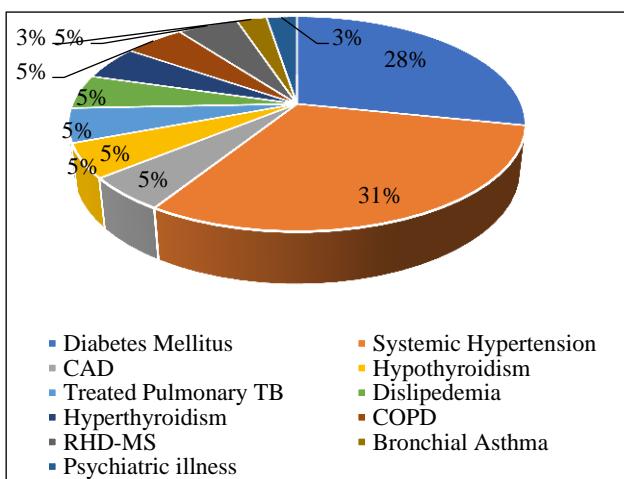


Figure 1: Comorbidities.

All patients below the age group of 30 were belonging to triple negative (ER/PR- and HER2-) category. With the advancement of age, there was fall in the percentage of patients with triple negative IHC subgroup and along with that a rise in the percentage of patients with ER/PR+

and HER 2+ IHC subgroup with 27 (87.06%) patients (Table 2). 5-year survival in ER/PR+, HER2+, ER/PR+, HER2-, ER/PR-, HER2+ and ER/PR-, HER2- subgroups were found to be 100%, 96.29%, 83.33%, and 87.5% respectively as provided in Table 3. But breast cancer related death was maximum in triple negative subgroup which was 12.5%.

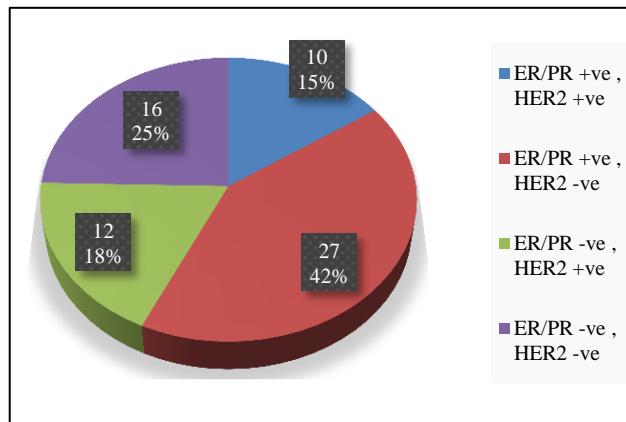


Figure 2: IHC profile.

Table 2: Relationship between age group, stage of tumour and IHC profile.

	Age group (in years)				
	20-29	30-39	40-49	50-59	>60
	N (%)	N (%)	N (%)	N (%)	N (%)
<b>Stages of tumour</b>					
T2B	2 (3.07)	8 (12.30)	21 (32.3)	19 (29.23)	4 (6.15)
T3A	1 (1.53)	1 (1.53)	4 (6.15)	3 (4.61)	0 (0)
T3B	0 (0)	0 (0)	1 (1.53)	0 (0)	1 (1.53)
<b>IHC</b>					
ER/PR+, HER+	0 (0)	1 (1.53)	4 (6.15)	4 (6.15)	1 (1.53)
ER/PR+, HER-	0 (0)	3 (4.61)	12 (18.46)	10 (15.38)	2 (3.07)
ER/PR-, HER+	0 (0)	2 (3.07)	5 (7.69)	4 (6.15)	1 (1.53)
ER/PR-, HER-	3 (4.61)	3 (4.61)	5 (7.69)	4 (6.15)	1 (1.53)

Table 3: Prognosis of 5 year survival of each immunehistochemistry subgroups.

IHC subgroup	5 year survival		Died of disease	Died due to unrelated cause
	N (%)	N (%)		
ER/PR+, HER2+	10 (100)	0 (0)	0 (0)	0 (0)
ER/PR+, HER2-	26 (96.29)	0 (0)	0 (0)	1 (3.7)
ER/PR-, HER2+	10 (83.33)	1 (8.33)	1 (8.33)	1 (8.33)
ER/PR-, HER2-	14 (87.5)	2 (12.5)	2 (12.5)	0 (0)

Table 4: Relationship between stage and prognosis.

Prognosis	Stages of tumour		
	II B	III A	III B
	N (%)	N (%)	N (%)
Died due to unrelated cause	2 (3.07)	0 (0)	0 (0)
Died of disease	1 (1.53)	1 (1.53)	1 (1.53)
5 year survival	51 (98.1)	8 (88.9)	1 (50)

Table 4 represents the relationship between stage of tumour and prognosis. There was a steep fall in prognosis as noticed in 5 year survival as stage advances, in our study which is 98.1%, 88.9% and 50% for stage IIB, IIIA and IIIB respectively.

## DISCUSSION

A hospital based retrospective cohort study was conducted with 65 patients who underwent modified radical mastectomy for locally advanced breast cancer. The current study findings had dominance on the age group of 40-49 years with 40% patients followed by 33.84% patients in the age group of 50-59 years whereas the study was in contrast to the study findings by Khalis et al in which was observed the maximum number of incidence rate in the age group ranging from 50-59 years.<sup>7</sup> The mean age of patients was observed to be  $52.29 \pm 12.03$  which was similar to the study conducted by Lee et al in which the mean age of women was found to be  $46 \pm 10.1$  years.<sup>8</sup> The presents study showed a prevalence of maximum number of patients belonging to premenopausal group with 56.92% patients similar to the study findings by Surakasula et al.<sup>9</sup> In the current study, 55 (84.61%) out of 65 patients were parous, similar to the study results by Gogai et al in which maximum number of patients were found to be multiparous with 408 out of 509 patients.<sup>10</sup> The current study had maximum number of patients in right breast as compared to the results obtained by Gogai et al in which left breast had majority of patients. The site of lesions was found to be more in upper quadrant with 46.15% patients similar to the study results observed by Sandhu et al in which maximum was found to be 47.7% patients.<sup>11</sup>

The present study observed that risk of breast cancer was maximum in patients with systemic hypertension followed by 28% patients with diabetes mellitus. Thus, the present study was supported by No et al in which the risks of developing ischemic heart disease, heart failure, depression, diabetes, osteoporosis and hypothyroidism were higher in women with breast cancer compared to women without cancer.<sup>12</sup>

The maximum proportion of patients were belonging to ER/PR+, and HER2- subgroup, 27 (42%) out of the total 65 patients in our study supported by the study of Gogai et al in which ER/PR+ and HER2- subgroup had 236 (43%) patients.<sup>10</sup> The overall receptor expression pattern in our patients suggested higher fraction of ER/PR- and HER2- (triple negative) IHC subgroup in the age group of 20-29 years with decrease in number of patients as the age increases. The present study had 10 (15.36%) ER/PR+, HER+ subgroup in comparison to the study by Gogai et al.<sup>10</sup> The hormone receptor positivity was seen in 63.4% patients, while 23.8% of tumors were triple negative in a study by Doval et al.<sup>13</sup>

The present study considered 5 years survival as the prognostic indicator; the worst prognosis was observed in

triple negative IHC subgroup followed by the HER2 enriched (ER/PR+, HER2-) subgroup and good prognosis was in the remaining 2 subgroups, ER/PR+, HER2+ and ER/PR+, HER2-. The ER/PR-, HER2- had the worst survival in all the three stages supported by the study conducted by Onitilo et al.<sup>14</sup>

## CONCLUSION

In this study maximum number of patients was in ER/PR+, HER2- subgroup and the percentage distribution of the same was increasing as the age of the patient advances. All the three patients in 20-29 age groups were belonging to triple negative subgroup and distribution of the same was decreasing with age. The ER/PR-, HER2- had the worst survival in all the three stages.

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