CORRELATION OF CLINICOPATHOLOGICAL FEATURES AND DISEASE PROGRESSION IN BREAST CARCINOMA PATIENTS - A MULTINOMIAL LOGISTIC REGRESSION ANALYSIS

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ABSTRACT

Background: Breast carcinoma either progress or regress in response to chemotherapy. Several prognostic factors are known to effect survival but no data exist regarding clinical and pathological entities that predict the pattern of progression of breast carcinoma. The current study addresses this gap.

Objective: To determine correlation between breast carcinoma progression pattern with age, tumor cell receptor status, histopathological diagnoses and stage of disease in carcinoma breast patients.

Materials and Methods: This cohort study was conducted in surgery unit of Khyber Teaching Hospital, from January 2023 to December 2023. Patients diagnosed with breast cancer who did not receive treatment were included while those already on chemotherapy were excluded. Patients received neoadjuvant chemotherapy in Oncology department by consultant Oncologist. Cohort of 54 patients were followed up until completion of chemotherapy. Pre- and post-chemotherapy CT scans were done to re-stage the disease and determine disease progression. Normality of data was recognized by Kolmogorov-Smirnov and Shapiro-wilks test. Association between categorical variables was determined by chi-square test of association. Kruskall-Wallis test was used to determine correlation between nominal and continuous variables. Multinomial logistic regression was applied between nominal variables where correlation was significant. A *p*-value of less than 0.05 was considered statistically significant.

Results: Mean age of fifty-four patients was 44.11±10.87 (range: 17-70) years. Early-stage disease was seen in 20(37%) cases, while 25(46.3%) had locally advanced breast carcinoma and 9 (16.7%) cases had metastatic disease. Disease progression was seen in 19 (35.2%) cases, while 24(44.4%) cases showed regression and 11 (20.4%) cases showed no change in disease progression (*p*-value<0.05). A statistically significant strong association was seen between disease progression and stage of the disease (χ^2=14.7, *p*=0.004). Multinomial logistic regression analysis showed that patients with early disease at diagnosis were more likely to observe disease regression (OR=24.5, *p*= 0.008, CI 95%=2.28-262.5).

Conclusions: Breast carcinoma progression is significantly associated with disease stage at diagnosis. Patients who start therapy at early-stage disease are more likely to undergo tumor regression.

Keywords: Breast carcinoma, early-stage, metastatic disease, progression, regression

INTRODUCTION

Breast carcinoma is notorious for progression and distant metastasis. [1] The progression pattern varies from patient to patient.[2] Despite chemotherapy, certain patients face disease progression, the tumor invades distant tissues. This in turn is associated with significant morbidity. Up till now, there is no predictive tool or investigation to predict the progression or regression of disease in breast carcinoma patients.

Recent research is focused on discovering tools and diagnostic modalities to predict the progression of breast carcinoma. In this regard, the latest research by Huang et al has led to the proposal that tumor-associated macrophages play a role in determining the progression of breast cancer.[3] The research, however, needs further validation studies. More recently, high expression of the N6-Methyladenosine RNA Binding Protein F1 (YTHDF1) gene was reported to be associated with the progression of disease in breast cancer patients. [4] Thus suggesting YTHHDF1 gene expression as a prognostic marker of breast carcinoma progression. Hussen et al has proposed that post-transcriptional modification of micro RNAs

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(mRNA) by non-coding RNAs (ncRNA) can determine the progression of breast cancer.[5] Thus, suggesting miRNA profiling as a prognostic and diagnostic tool to predict the progression of breast cancer.[5] Various researchers have tried to predict breast cancer progression using logistic regression models on microarray gene expression data.[2, 6, 7].

Unluckily, these predictive tools are costly, and thus, cannot be utilized in resource limited countries like Pakistan where majority of the population belongs to low socioeconomic class. Role of environmental chemicals and obesity in determining breast cancer progression is recently reported but it needs further research to validate the findings. [8, 9] Moreover, exercise has been liked to reduced breast progression in pre-clinical trials but it has to be further validated.[10]

To our knowledge, there is no research available regarding correlation of breast carcinoma progression pattern and clinicopathological features i.e. age, tumor cell receptor status, histopathological diagnoses and stage of disease. The current study will fill this gap with the hope of providing data that can help predict progression status of breast cancer from clinicopathological features, which will be cost effective for poor countries like Pakistan. This might help guide clinicians in predicting high risk patients from their clinicopathological features without investing on molecular studies which is a burden for patients in resource limited country like ours.

MATERIALS AND METHODS

This cohort study was carried out in the Surgery unit of the Khyber Teaching Hospital, Peshawar for a one-year period i.e. from January 2023 to December 2023. The ethical approval was obtained from hospital ethical committee. Newly diagnosed cases of breast carcinoma were enrolled in the study. The patients were informed that their data will be collected and the results will be propagated for research purposes. Additionally, they were ensured about confidentiality of their data. Non-consenting patients and those who had already been on chemotherapy were excluded from the study.

Detailed history was taken, and clinical examination was performed by consultant surgeon. True-cut biopsy was performed and the tissue specimen was sent to Pathology department for histopathological review and immunohistochemistry for ER, PR and Her2-neu. The age, diagnosis of breast carcinoma, ER-PR-Her2-neu status was noted. Bone scan and MDCT chest abdomen & pelvis were performed for staging of the disease. Patients were started on neoadjuvant chemotherapy. After completion of the chemotherapy course, CT scan was repeated to re-stage the disease. The staging was categorized into three entities i.e. no change (no change in pre and post therapy staging), progression (increase in post chemotherapy stage) and regression (decrease in post chemotherapy staging).

All the data was noted on the proforma and entered in SPSS software. The data was analyzed by SPSS version 20. The normality of the data was determined by Kolmogorov-Smirnov test, Shapiro Wilks test and by visual inspection of Q-Q charts and histograms. Association between non-parametric nominal variables was determined by chi-square test of association. Association between non-parametric continuous and nominal variables was done by Kruskall-Walis test. *P*-value of <0.05 was considered statistically significant. Multinomial Logistic Regression analysis was performed for variables that showed statistically significant association using 95% confidence interval.

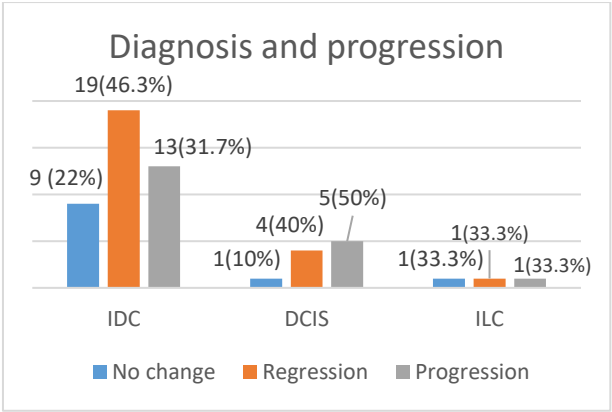
RESULTS

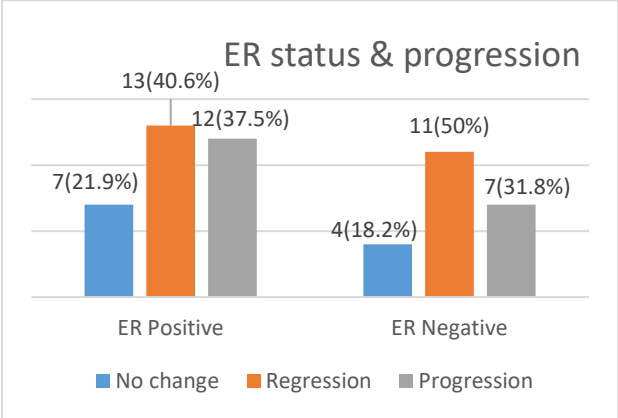
The demographic and clinicopathological features of 54 study participants are shown in table 1. Disease progression with respect to different clinicopathological features is shown in figure 1. Association between disease progression and different clinicopathological characteristics is given in table 2. Multinomial logistic regression analysis for disease progression and stage of disease is given in table 3.

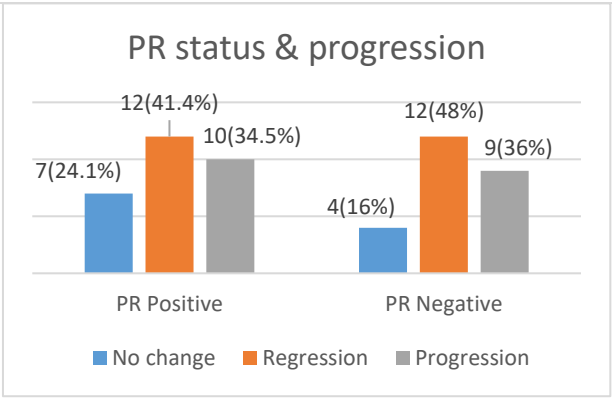
Table 1: Demographic and Clinicopathological features of the study population

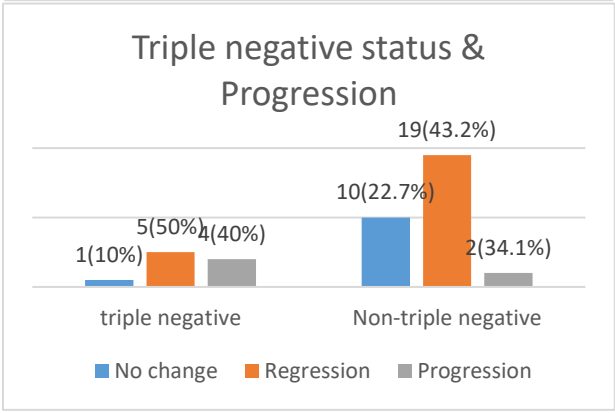
Sample characteristics	Values	*p*-value	Kolmogrov-Simrov & Shapiro-Wilks test statistics
Age	Mean= 44.11±10.87 years Range=17-70 years Median= 42.50 years Mode= 40 years	-	p_{KS}=0.089 p_{SW}=0.660
Menstrual status	Premenopausal= 35 (64.8%) Postmenopausal=19(35.2%)	*p<0.05*	p_{KS}<0.05 p_{SW}<0.05
Histopathological Diagnosis	IDC= 41 (75.9%) DCIS=10 (18.5%) ILC= 3 (5.6%)	*p<0.05*	p_{KS}<0.05 p_{SW}<0.05
ER	Positive=32 (59.3%) Negative=22 (40.7%)	*p>0.05*	p_{KS}<0.05 p_{SW}<0.05
PR	Positive=29 (53.7%) Negative=25 (46.3%)	*p>0.05*	p_{KS}<0.05 p_{SW}<0.05
HER2Neu	Positive=16 (29.6%) Negative=38 (70.4%)	*p<0.05*	p_{KS}<0.05 p_{SW}<0.05
Triple negative status	Triple negative= 10 (18.5%) Non-triple negative= 44 (81.5%)	*p<0.05*	p_{KS}<0.05 p_{SW}<0.05
Stage of disease at diagnosis	Early= 20 (37%) LABC= 25 (46.3%) Metastatic= 9 (16.7%)	*p<0.05*	p_{KS}<0.05 p_{SW}<0.05
Disease progression status	No change= 11 (20.4%) Regression= 24 (44.4%) Progression= 19 (35.2%)	*p>0.05*	p_{KS}<0.05 p_{SW}<0.05
Chemotherapy	NAC= 47 (87%) Adjuvant chemotherapy= 7 (13%)	*p<0.05*	p_{KS}<0.05 p_{SW}<0.05
TNM staging	Tis= 1 (1.9%) T1= 4 (7.4%) T2= 28 (51.9%) T3= 6 (11.1%) T4= (27.8%) N0= 14 (25.9%) N1= 24 (44.4%) N2= 3 (5.6%) N3= 13 (24.1%) M0= 44 (81.5%) M1= 10 (18.5%)	*p<0.05*	p_{KS}<0.05 p_{SW}<0.05

IDC=Invasive ductal carcinoma. DCIS=Ductal carcinoma in situ.ILC=Invasive lobular carcinoma. p_{KS}= kolmogorov smirnov test p value. p_{SW}=Shapiro wilks test p value. p_{KS} and p_{SW} value <0.05 shows that data distribution is non- parametric and vice versa. ER= Estrogen receptor.PR=Progesterone receptor. Triple negative= Negative for ER, PR & Her2neu receptors. LABC= Locally invasive breast carcinoma. NAC= Neo adjuvant chemotherapy


Diagnosis and progression
19(46.3%)
13(31.7%)
9 (22%)
5(50%)
4(40%)
1(10%)
1(33.3%)
1(33.3%)
1(33.3%)
IDC
DCIS
ILC
No change
Regression
Progression


ER status & progression
13(40.6%)
12(37.5%)
7(21.9%)
11(50%)
7(31.8%)
4(18.2%)
ER Positive
ER Negative
No change
Regression
Progression


PR status & progression
12(41.4%)
10(34.5%)
7(24.1%)
12(48%)
9(36%)
4(16%)
PR Positive
PR Negative
No change
Regression
Progression


Triple negative status & Progression
19(43.2%)
10(22.7%)
5(50%)
4(40%)
1(10%)
2(34.1%)
triple negative
Non-triple negative
No change
Regression
Progression

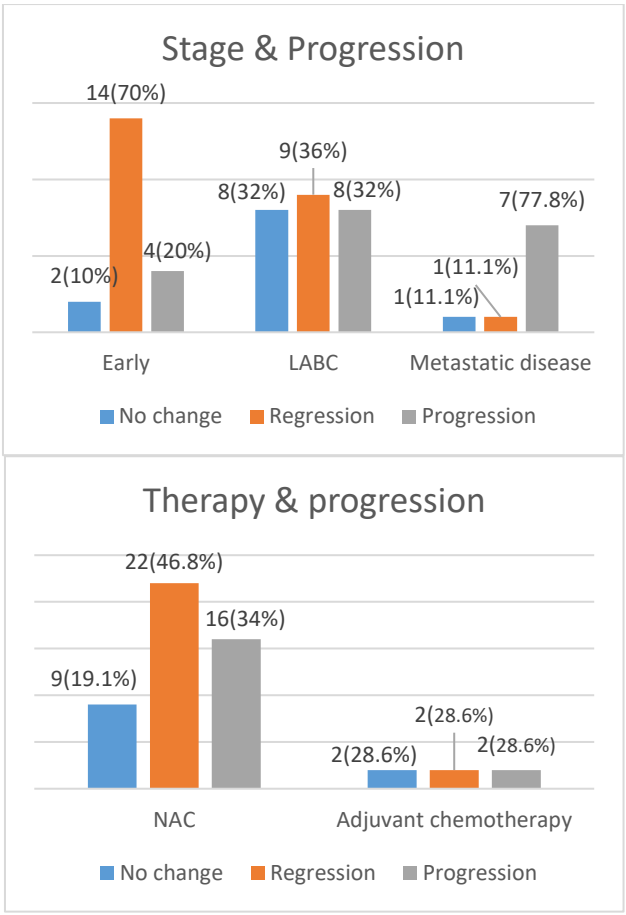


Figure 1: Disease progression with respect to different clinicopathological features

(ER: estrogen receptor. PR: progesterone receptor.LABC:Locally advanced breast carcinoma.NAC: Neo adjuvant chemotherapy)

Table 2: Association between disease progression and different clinicopathological characteristics

Characteristics	Association with disease progression*
Age	X^2= 0.634 , *p*= 0.728
Histopathological Diagnoses	X^2= 0.171 , *p*=0.932
Stage of disease at diagnosis	**X^2=14.78 , *p*=0.004**
Chemotherapy regimen	X^2=0.856 , *p*=0.660
Triple negative status	X^2= 0.814 , *p*=0.666

***Kruskall wallis test for age. Chi square test for association for the rest of variables

Table 3: Multinomial logistic regression model for disease progression and stage of disease

Disease progression	Odd ratio	*p* value	95% Confidence interval	
			Lower limit	Upper limit
No change				
Early	3.5	0.363	0.236	51.8
LABC	7	0.099	0.693	70.74
Metastatic	-	-	-	-
Tumour regression				
Early	24.5	0.008	2.28	262.5
LABC	7.8	0.079	0.788	78.67
Metastatic	-	-	-	-

LABC: Locally advanced breast carcinoma

DISCUSSION

To our knowledge, there is very scanty data regarding prognostic factors that can predict response to chemotherapy in breast cancer patients. Determination of predictive markers in such patients will help pre-treatment stratification of breast cancer patients and hence better management and limited chemotherapy related side effects.

In the current study, median age of the study sample was 44 years and more than half of the cases were pre-menopausal. Invasive ductal carcinoma was the commonest diagnosis. Similar demographic data is reported in a study from India. [11] Disease progression was seen in 35% cases in our study. But a lower rate of 10% is reported from India[11]

The current study showed that almost half of the cases of Invasive ductal carcinoma showed disease regression, while disease progression was seen in half the cases of ductal carcinoma in situ. However, this association between histological diagnosis and disease progressions was statistically not significant (X^2= 0.171, *p*=0.932). When ER, PR and Her 2 neu receptor status was considered, disease regression was seen in almost half the triple-negative cases. However, this association between ER-PR-Her2neu receptor expression and disease regression was statistically not significant (X^2= 0.814, *p*=0.666). Faneyte et al have reported that ER-negative status, but not Her-2-neu status, is associated with significant disease regression[12]. Similar data is reported by Tewari et al. [13] Association of high ER/PR expression with delayed metastasis has been already reported by Aleskandarany et al. [14]

When stage of disease at diagnosis was considered, it was observed that early disease was associated with disease regression and the association was statistically significant (X^2=14.78, *p*=0.004). Multinomial logistic regression analysis showed that patients with early disease were more likely to undergo disease regression with chemotherapy (OR=24.5, *p*= 0.008, CI 95%=2.28-262.5). to our knowledge, this is the first study that highlights the predictive nature of stage of disease on response to chemotherapy in breast cancer. We recommend further studies on larger sample to validate the finding.

To our knowledge, this was the first study that established the association between disease progression pattern and clinical stage of the disease at diagnosis. This may prove to be a predictive tool for determining progression of the disease in patients who cannot afford costly investigations.

CONCLUSION

Early disease at presentation is significantly associated with disease regression in breast cancer patients. Thus, stage of the disease at diagnosis is significant tool to predict breast cancer progression status.

LIMITATION

Enrolling patients from single care center and limited number of patients were the limitations of the study.

RECOMMENDATION

We recommend that stage of the breast cancer at diagnosis be used to predict progression of breast carcinoma patients. Moreover, larger studies are recommended where patients from multiple hospitals can be enrolled and the above findings can be replicated to generate bigger data.

ACKNOLWEDGEMENT

All glories be to Almighty Allah for bestowing knowledge upon the mankind, and for helping me complete the manuscript

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING SOURCE

Nil

REFERENCES

1. Yang S, Wang X, Zhou X, Hou L, Wu J, Zhang W, et al. ncRNA-mediated ceRNA regulatory network: Transcriptomic insights into breast cancer progression and treatment strategies. Biomedicine & Pharmacotherapy. 2023;162:114698.

2. Morais-Rodrigues F, Silv́erio-Machado R, Kato RB, Rodrigues DLN, Valdez-Baez J, Fonseca V, et al. Analysis of the microarray gene expression for breast cancer progression after the application modified logistic regression. Gene. 2020;726:144168.

3. Huang X, Cao J, Zu X. Tumor-associated macrophages: An important player in breast cancer progression. Thoracic Cancer. 2022;13(3):269-76.

4. Chen H, Yu Y, Yang M, Huang H, Ma S, Hu J, et al. YTHDF1 promotes breast cancer progression by facilitating FOXM1 translation in an m6A-dependent manner. Cell & bioscience. 2022;12(1):19.

5. Hussen BM, Hidayat HJ, Salihi A, Sabir DK, Taheri M, Ghafouri-Fard S. MicroRNA: A signature for cancer progression. Biomedicine & Pharmacotherapy. 2021;138:111528.

6. Li Z, Xie W, Liu T. Efficient feature selection and classification for microarray data. PloS one. 2018;13(8):e0202167.

7. Bazzoli C, Lambert-Lacroix S. Classification based on extensions of LS-PLS using logistic regression: application to clinical and multiple genomic data. BMC bioinformatics. 2018;19:1-13.

8. Barone I, Giordano C, Bonofiglio D, Ando S, Catalano S, editors. The weight of obesity in breast cancer progression and metastasis: Clinical and molecular perspectives. Seminars in cancer biology; 2020: Elsevier.

9. Koual M, Tomkiewicz C, Cano-Sancho G, Antignac J-P, Bats A-S, Coumoul X. Environmental chemicals, breast cancer progression and drug resistance. Environmental Health. 2020;19:1-25.

10. Wennerberg E, Lhuillier C, Rybstein MD, Dannenberg K, Rudqvist N-P, Koelwyn GJ, et al. Exercise reduces immune suppression and breast cancer progression in a preclinical model. Oncotarget. 2020;11(4):452.

11. Kunnuru SKR, Thiyagarajan M, Martin Daniel J, Singh K B. A study on clinical and pathological responses to neoadjuvant chemotherapy in breast carcinoma. Breast Cancer: Targets and Therapy. 2020:259-66.

12. Faneyte IF, Schrama JG, Peterse JL, Remijnse PL, Rodenhuis S, Van de Vijver M. Breast cancer response to neoadjuvant chemotherapy: predictive markers and relation with outcome. British journal of cancer. 2003;88(3):406-12.

13. Tewari M, Krishnamurthy A, Shukla HS. Predictive markers of response to neoadjuvant chemotherapy in breast cancer. Surgical oncology. 2008;17(4):301-11.

14. Aleskandarany MA, Soria D, Green A, Nolan C, Diez-Rodriguez M, Ellis IO, et al. Markers of progression in early-stage invasive breast cancer: a predictive immunohistochemical panel algorithm for distant recurrence risk stratification. Breast cancer research and treatment. 2015;151:325-33.