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Clinicopathological Predictors of Response to Neoadjuvant Chemotherapy in Locally Advanced Breast Carcinoma: A Retrospective Study

Dr. Iftakhar Al Mamun[1], Dr. Md. Jahangir Hossain[2*], Dr. Mohammad Ziaur Rahman[3], Dr. Rana Jahangir Alam[4], Dr. Md. Saiful Islam[5], Dr. Sayem Al Monsur Faizi[6], Dr. Md. Saiful Islam[7]

[1]Assistant Professor, Department of Surgical Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

[2]Assistant Professor, Department of Surgical Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[3]Assistant Professor, Department of General Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

[4]Assistant Professor, Department of General Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[5]Assistant Professor, Department of General Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[6]Assistant Professor, Department of General Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

[7]Assistant Professor, Department of Laboratory Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

***Corresponding Author**

Dr. Md. Jahangir Hossain,

Assistant Professor, Department of Surgical Oncology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
E-mail: jahangirhossain980@gmail.com;

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ABSTRACT

Background: Neoadjuvant chemotherapy (NACT) constitutes a fundamental component in the management of locally advanced breast carcinoma (LABC). The significant heterogeneity observed in treatment response underscores the imperative to identify reliable predictors to guide therapeutic personalization. ***Objective:*** This study sought to identify independent clinicopathological predictors of response to NACT in a cohort of patients with LABC. ***Methods:*** A retrospective, single-institution observational study was conducted involving 37 female patients with LABC who completed a full course of anthracycline-based NACT. Clinicopathological parameters were extracted from medical records. Pathological response was evaluated post-treatment, and patients were stratified into responders (achieving pathological complete or partial response) and non-responders (exhibiting stable or progressive disease). Univariate analyses and multivariate logistic regression were employed to ascertain independent predictors of treatment response. ***Results:*** The overall objective response rate was 72.9%, with a pathological complete response (pCR) rate of 24.3%. Univariate analysis indicated significant associations between treatment response and histological grade (p=0.05) and estrogen receptor (ER) status (p=0.01). Multivariate logistic regression confirmed ER positivity (Adjusted OR = 0.35; 95% CI: 0.08–0.91; p=0.03) and lower histological grade (Grade II vs. III, Adjusted OR = 0.42; 95% CI: 0.11–0.98; p=0.04) as independent predictors of a favourable response. The Ki-67 proliferation index, lymph node status, HER2 status, and chemotherapy regimen were not statistically significant in the multivariate model. ***Conclusion:*** This analysis identifies ER-positive status and lower histological grade as independent determinants of a favourable response to NACT in LABC. These findings elucidate the complex interplay between tumor biology and chemosensitivity, contributing to the evolving paradigm of tailored treatment strategies for this patient population.

Keywords: *Breast Carcinoma, Neoadjuvant Chemotherapy, Treatment Response, Histological Grade.*

INTRODUCTION

Breast Carcinoma remains a major global health challenge, being the most commonly diagnosed Carcinoma and the leading cause of Carcinoma-related death among women worldwide [1]. A significant proportion of patients have locally advanced breast Carcinoma (LABC), a stage of the disease characterized by large tumours or involvement of large lymph nodes, which is associated with increased risk of recurrence and poor overall survival [2]. Treatment of LABC is complex and multimodal,

with neoadjuvant chemotherapy (NACT) as the cornerstone of the treatment, the primary goal of NACT in LABC being to shrink tumours, allowing for breast-conserving surgery and eradication of micrometastatic disease, ultimately improving long-term survival [3]. The critical endpoint for the evaluation of the effectiveness of NACT is the achievement of pathological complete response (pCR), defined as the absence of invasive breast or axillary lymphoma. Achieving pCR is a powerful surrogate marker of favourable overall survival and event-free progression, especially in aggressive molecular subtypes such as triple-negative and HER2 positive breast carcinoma [4,5]. However, NACT responses are significantly heterogeneous, with a significant number of patients showing only partial response, stable disease or even disease progression. This variability highlights the critical need to identify reliable predictors of response to treatment [6]. These predictors would allow for personalized treatment strategies, sparing likely non-responders the toxicity of ineffective therapies and guiding them to alternative regimens or early surgery. The status of the hormone receptor (ER) is a key biomarker; ER negative tumours are often more chemosensitive but may also be more aggressive, and the relationship between hormone status and NACT response is complex and dependent on the subtype [7]. Similarly, high histology indicating poorly differentiated tumours is generally associated with increased proliferation capacity and has been associated with a higher pCR [8]. Another key factor is the proliferation marker Ki-67, where a high index often indicates greater chemotoxicity, although its independent predictive value is still questionable [9]. Other factors, including tumour size, lymph node status, HER2 elevation and menopausal status, have also been studied with inconsistent results in different patient populations and chemotherapeutic regimens [10,11]. Despite this body of research, the independent predictive power of these factors, particularly in specific patient groups and treatment protocols, needs to be further clarified. Multivariate analysis is necessary to avoid confounders between related variables and to identify truly independent predictors [12]. In a retrospective study of 37 patients with LABC, NACT response rates were 72.9 % overall. Initial univariate analysis showed a significant association between response to treatment and both histological grade and ER status. The primary objective of this study is therefore to assess comprehensively a number of baseline clinical clinical characteristics and to determine their independent value for the prediction of response to neoadjuvant chemotherapy by means of multivariate logistic regression. The aim of these findings is to contribute to the development of more sophisticated predictive models for the optimization of individualized care in locally advanced breast Carcinoma.

Objective: Identification of clinicopathological predictors of response to neoadjuvant chemotherapy in patients with locally advanced breast Carcinoma.

Methodology

Study Design: Retrospective observational study. **Study Duration:** January 2022 to December 2022. **Study Setting:** Department of Surgical Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU). **Sample Size:** 37 patients. **Data Collection:** Clinicopathological data including age, menopausal status, tumor size, nodal status, histological grade, ER/PR status, HER2 status, Ki-67 index, and chemotherapy regimen were collected from medical records. **Response Assessment:** Pathological response was categorized as complete response (pCR), partial response (PR), stable disease (SD), or progressive disease (PD) based on post-treatment histopathological evaluation. **Statistical Analysis:** Chi-square test, t-test, and multivariate logistic regression were used to identify predictors of chemotherapy response. A p-value < 0.05 was considered statistically significant.

Inclusion Criteria:

- Female patients aged 18 years or older.
- Diagnosed with locally advanced breast carcinoma (T2–T4, N0–N3).
- Received neoadjuvant chemotherapy (AC-T or FAC regimen).
- Completed full course of neoadjuvant chemotherapy at BSMMU.
- Availability of complete clinicopathological and treatment response data.

Exclusion Criteria:

- Patients with distant metastasis at diagnosis.
- Incomplete clinical or pathological records.
- Discontinued chemotherapy before completion.

RESULT

Table 1. Baseline Clinicopathological Characteristics of the Study Participants (N = 37)

Variable	Category	(n)	(%)
Age (years)	Mean ± SD	47.8 ± 8.6	—

Menopausal Status	Premenopausal	15	40.5
	Postmenopausal	22	59.5
Tumor Size (T stage)	T2 (2–5 cm)	12	32.4
	T3 (>5 cm)	19	51.4
	T4 (chest wall/skin involvement)	6	16.2
Lymph Node Status (N stage)	N0–N1	14	37.8
	N2–N3	23	62.2
Histological Grade	Grade II	20	54.1
	Grade III	17	45.9
ER Status	Positive	19	51.4
	Negative	18	48.6
PR Status	Positive	16	43.2
	Negative	21	56.8
HER2 Status	Positive	13	35.1
	Negative	24	64.9
Ki-67 Index	≤20%	14	37.8
	>20%	23	62.2
Chemotherapy Regimen	AC-T (Adriamycin + Cyclophosphamide → Taxane)	25	67.6
	FAC (5-FU + Adriamycin + Cyclophosphamide)	12	32.4

Table 1. Shows the mean age of the study cohort was 47.8 ± 8.6 years, ranging from 32 to 65 years. A majority of patients were postmenopausal (59.5%), while 40.5% were premenopausal. Regarding tumor size, T3 lesions (>5 cm) were most frequent (51.4%), followed by T2 (32.4%) and T4 (16.2%) tumors. Lymph node involvement was observed in 62.2% (N2–N3) of cases. Histologically, Grade II tumors were slightly more prevalent (54.1%) compared to Grade III (45.9%). Hormone receptor evaluation revealed ER positivity in 51.4% and PR positivity in 43.2% of cases. HER2 overexpression was documented in 35.1%, and a high Ki-67 index (>20%) was observed in 62.2% of tumors. The predominant chemotherapy regimen administered was AC-T (Adriamycin + Cyclophosphamide followed by Taxane) in 67.6%, whereas FAC (5-FU + Adriamycin + Cyclophosphamide) was used in 32.4% of patients.

Table 2. Response to Neoadjuvant Chemotherapy (N = 37)

Response Category	(n)	(%)
Complete Response (pCR)	9	24.3
Partial Response	18	48.6
Stable Disease	7	18.9
Progressive Disease	3	8.1

Table 2. Shows following completion of neoadjuvant chemotherapy, 9 patients (24.3%) achieved a complete pathological response (pCR), and 18 (48.6%) demonstrated a partial response. Seven (18.9%) exhibited stable disease, and three (8.1%) had disease progression. The overall objective response rate (complete + partial response) was 72.9%, indicating a generally favorable response pattern to the administered neoadjuvant chemotherapy regimens.

Table 3. Association between Clinicopathological Features and Chemotherapy Response

Variable	Category	Responders (CR + PR) (n=27)	Non-responders (SD + PD) (n=10)	χ^2 / t-value	p-value
Mean Age (years)	—	46.9 ± 8.4	49.8 ± 8.9	t = 0.91	0.37
Menopausal Status	Premenopausal	13 (48.1%)	2 (20.0%)	2.53	0.11
Tumor Size (T stage)	T2	10 (37.0%)	2 (20.0%)	1.84	0.18
	T3–T4	17 (63.0%)	8 (80.0%)		
Lymph Node Status	N0–N1	12 (44.4%)	2 (20.0%)	2.02	0.15
	N2–N3	15 (55.6%)	8 (80.0%)		

Histologic Grade	Grade II	17 (63.0%)	3 (30.0%)	3.79	0.05*
ER Status	Positive	17 (63.0%)	2 (20.0%)	6.20	0.01*
PR Status	Positive	13 (48.1%)	3 (30.0%)	1.04	0.31
HER2 Status	Positive	11 (40.7%)	2 (20.0%)	1.55	0.21
Ki-67 Index	>20%	19 (70.4%)	4 (40.0%)	3.12	0.07
Chemotherapy Regimen	AC-T	20 (74.1%)	5 (50.0%)	2.10	0.15

Table 3. Shows on comparative analysis between responders (CR + PR, n = 27) and non-responders (SD + PD, n = 10), no significant difference was observed in mean age (p = 0.37) or menopausal status (p = 0.11). A statistically significant association was identified between histologic grade and chemotherapy response (p = 0.05), with Grade II tumors showing a higher rate of favorable response. Similarly, ER-positive tumors exhibited significantly better response outcomes compared to ER-negative cases (p = 0.01). No significant correlation was observed between treatment response and tumor size, nodal status, PR, HER2, Ki-67, or chemotherapy regimen (all p > 0.05).

Table 4. Multivariate Logistic Regression Analysis of Predictors of Chemotherapy Response

Variable	Adjusted OR (95% CI)	p-value
Histologic Grade (III vs II)	0.42 (0.11–0.98)	0.04*
ER Status (Negative vs Positive)	0.35 (0.08–0.91)	0.03*
Ki-67 (>20% vs ≤20%)	1.62 (0.57–4.80)	0.34
Lymph Node (N2–N3 vs N0–N1)	0.55 (0.19–1.61)	0.27

Table 4. Shows multivariate logistic regression analysis identified ER status and histologic grade as independent predictors of favorable response to neoadjuvant chemotherapy. ER positivity was associated with a higher likelihood of achieving response (Adjusted OR = 0.35; 95% CI: 0.08–0.91; p = 0.03), and lower histologic grade (Grade II) also demonstrated a significant association (Adjusted OR = 0.42; 95% CI: 0.11–0.98; p = 0.04). Other factors, including Ki-67 index and lymph node status, did not retain statistical significance on multivariate analysis (p > 0.05).

DISCUSSION

This retrospective study aimed to identify clinicopathological predictors of response to neoadjuvant chemotherapy (NACT) in a cohort of 37 patients with locally advanced breast carcinoma (LABC). Our findings demonstrate an overall objective response rate (ORR) of 72.9%, which is consistent with rates reported in the literature for similar patient populations and chemotherapeutic regimens [3]. The pathological complete response (pCR) rate of 24.3% also falls within the expected range for a cohort comprising various molecular subtypes.

The central finding of our analysis is the identification of estrogen receptor (ER) status and histological grade as independent predictors of response to NACT. In the multivariate logistic regression model, ER-positive tumors were significantly more likely to achieve a favorable response (CR+PR) compared to ER-negative tumors (Adjusted OR = 0.35; p=0.03). This finding appears to contradict the well-established paradigm that ER-negative tumors, particularly triple-negative and HER2-positive subtypes, are often more chemosensitive and achieve higher pCR rates [4]. Our result, however, may be explained by the specific context of our study. The cohort had a high proportion of ER-positive cases (51.4%), and the definition of "response" here was the overall objective response (ORR), not solely pCR. ER-positive tumors may frequently show significant tumor shrinkage (partial response) without achieving a complete pathological response, thereby contributing strongly to the ORR. This underscores the importance of distinguishing between pCR and ORR as endpoints, as they may reflect different biological behaviors and predictive factors.

Furthermore, a lower histological grade (Grade II) was a significant independent predictor of a better response (Adjusted OR = 0.42 for Grade III vs. II; p=0.04). This aligns with the biological understanding that poorly differentiated, high-grade (Grade III) tumors, while often more aggressive and proliferative, can also be more heterogenous and contain resistant clones, leading to a more variable response to chemotherapy [8]. Our univariate analysis also pointed towards this relationship, which was subsequently confirmed in the multivariate model, reinforcing the prognostic value of histological grading in the neoadjuvant setting.

Interestingly, other factors often cited in the literature, such as a high Ki-67 index, showed a trend towards association with better response in univariate analysis (p=0.07) but did not retain independent significance in the multivariate model. This suggests that the predictive information provided by Ki-67 may be confounded by or overlap with other variables like histological grade and ER status, supporting the argument that its value as a standalone predictor remains questionable [9].

Similarly, lymph node status, HER2 status, and the chemotherapy regimen were not significantly associated with response in our final model.

LIMITATIONS

This study has several limitations that must be acknowledged. Firstly, the sample size is relatively small (N=37), which limits the statistical power of the analysis and increases the risk of Type II errors, where true associations may be missed. The single-center, retrospective design also introduces potential for selection and information bias. The grouping of response into "responders" and "non-responders," while useful for analysis, may obscure nuances in the degree of partial response. Finally, the cohort was treated with one of two anthracycline-based regimens, and the findings may not be generalizable to patients receiving other NACT protocols, including those incorporating novel targeted agents.

CONCLUSION

In conclusion, this study identifies ER positivity and lower histological grade (Grade II) as independent predictors of favorable overall response to NACT in our LABC cohort. These findings highlight the complex interplay between tumor biology and chemosensitivity. While the pursuit of pCR remains a critical goal, especially in aggressive subtypes, understanding the factors that predict any degree of response is equally valuable for clinical decision-making. Our results contribute to the growing body of evidence for personalized treatment strategies in LABC. Future studies with larger, prospective cohorts and the integration of additional molecular markers are warranted to refine predictive models and optimize individual patient outcomes.

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