Section: Pathology

Original Research Article

ASSESSMENT OF PATHOLOGICAL RESPONSE IN MOLECULAR SUBTYPES OF BREAST CARCINOMAS TREATED WITH NEOADJUVANT SYSTEMIC THERAPY – AN INSTITUTIONAL EXPERIENCE IN TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Neoadjuvant systemic therapy (NAT) enables tumour downstaging and provides an early assessment of chemosensitivity in breast carcinoma. Pathological complete response (pCR) is strongly associated with improved outcomes, especially in HER2-positive and triple-negative breast cancers. This study evaluates pathological response patterns across molecular subtypes in a tertiary-care Indian population. **Materials and Methods:** A cross-sectional study was conducted at ESIC Medical College, Sanathnagar (2020–2022), including 138 women with biopsy-proven invasive breast carcinoma treated with NAT followed by surgery. Clinical parameters, receptor status (ER, PR, HER2) and Ki-67 were recorded pre-therapy. Post-NAT specimens were assessed using the Residual Cancer Burden (RCB) system. Statistical analysis included Chi-square testing and logistic regression. **Result:** The mean age was 49.6 years, with most cases presenting as stage II–III and node-positive disease. Molecular distribution was dominated by luminal B, followed by TNBC and HER2-positive subtypes. Overall pCR rate was 29.7%, highest in HER2-positive (50%) and TNBC (31%) tumours. Most non-pCR cases fell into RCB-II. HER2 positivity showed the strongest trend towards predicting pCR (OR ≈ 3.9), though not statistically significant. **Conclusion:** NAT yielded pCR rates comparable to global and Indian data. HER2-positive and TNBC subtypes showed superior response, highlighting the importance of molecular subtype-based treatment planning and the need to ensure optimal access to targeted therapies.

INTRODUCTION

Breast cancer remains the most common malignancy among women worldwide and represents a biologically heterogeneous disease comprising distinct molecular subtypes with differing therapeutic responses and outcomes.[1,2] Neoadjuvant systemic therapy (NAT) encompassing chemotherapy, endocrine therapy, and targeted agents has evolved from being reserved for inoperable tumors to becoming an integral component of the multidisciplinary management of early and locally advanced breast cancer.[3] The use of NAT offers several advantages, including tumor downstaging, increasing the feasibility of breast-conserving surgery, permitting in vivo assessment of chemosensitivity, and enabling early initiation of systemic therapy for micrometastatic disease.[4] Importantly, NAT provides a unique opportunity to assess pathological complete response (pCR), defined as the absence of invasive carcinoma in the breast and axillary lymph nodes following therapy (ypT0/Tis, ypN0), which has emerged as a robust surrogate marker for long-term outcomes such as disease-free survival (DFS) and overall survival (OS), particularly in aggressive subtypes like triple-negative breast cancer (TNBC) and HER2-enriched tumors.[5]

Although clinical and radiological assessments are routinely used to monitor treatment response, they often correlate poorly with the true extent of residual disease, making pathological evaluation the gold standard for determining response to NAT.[6] Molecular subtyping—based on hormone receptor (HR) and HER2 status has further refined therapeutic selection and prognostic estimation, with TNBC and HER2-positive tumors demonstrating significantly higher pCR rates compared with luminal A/B

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subtypes.[7] Achieving pCR is associated with a 50–60% reduction in recurrence risk in HER2-positive and TNBC cohorts, underscoring its clinical relevance. Despite substantial advances, response to NAT remains highly variable within subtypes due to tumor heterogeneity, differential chemosensitivity, and variations in treatment regimens across institutions.[8]

While numerous Western studies, such as those by Cortazar et al.[5] and von Minckwitz et al.[9] have established the prognostic significance of pCR, there is limited data from Indian and South Asian populations evaluating pCR patterns specifically across molecular subtypes. Population-based genetic, socioeconomic, and healthcare-access differences may influence treatment response and outcomes. Furthermore, institutional variations in chemotherapy protocols, HER2-targeted therapy availability, and pathological assessment standards can lead to inconsistent reporting of pCR in real-world settings.[10] There is a need for updated institutional data to understand response patterns in different molecular subtypes within resource-diverse tertiary care settings, which may help optimize therapeutic strategies and strengthen region-specific treatment guidelines.

Several studies globally have demonstrated heterogeneity in pCR outcomes: TNBC shows pCR rates ranging from 30–40%, HER2-positive tumors treated with dual anti-HER2 blockade achieve up to 60–70% pCR, whereas luminal subtypes consistently show modest responses.[9] Indian studies by Naidu et al.[10] and Jonnada et al.[11] reported lower overall pCR rates compared with Western cohorts, likely reflecting treatment delays, limited access to targeted therapies, and late stage at diagnosis. However, the consistency of subtype-specific response patterns underscores the universality of molecular subtype biology in predicting pathological response.

This study aims to evaluate the pathological response including pathological complete response across various molecular subtypes of breast carcinoma following neoadjuvant systemic therapy in a tertiary care hospital, and to compare these findings with existing national and international data to better understand real-world therapeutic effectiveness and subtype-specific responsiveness.

MATERIALS AND METHODS

Study Design and Setting

This observational, cross-sectional study was conducted in the Department of Pathology, ESIC Medical College, Sanathnagar, over a period of three years (January 2022 to December 2024). The study included female patients diagnosed with invasive breast carcinoma who received neoadjuvant systemic therapy (NAT) followed by definitive surgery at the institution.

Study Population

The study population comprised 138 female patients with biopsy-confirmed invasive breast carcinoma and known hormone receptor (ER, PR) and HER2/neu status prior to initiation of therapy. Patients were enrolled consecutively during the study period based on predefined eligibility criteria.

Sample Size Estimation

A minimum sample size of 138 patients was calculated using the formula:

$n = (1.96)^2 \times P(1 - P) / (0.05)^2$,

where P represented the anticipated proportion of pathological response, and 5% was taken as the allowable error.

Inclusion Criteria

- Female patients diagnosed with invasive breast carcinoma.
- Patients who received neoadjuvant systemic therapy.
- Core needle biopsy performed prior to NAT with documented ER, PR, and HER2/neu receptor status.

Exclusion Criteria

- Patients with metastatic breast carcinoma at presentation.
- Patients who did not undergo surgery after completion of NAT.

Data Collection

Clinical data including age, baseline tumor size, axillary lymph-node status, and clinical stage were obtained from medical records. Pre-therapy receptor status (ER, PR, HER2/neu) was determined on core biopsy specimens following standard immunohistochemistry (IHC) guidelines.

Histopathological Evaluation

All postoperative mastectomy or lumpectomy specimens were examined in detail following completion of NAT. Tumor bed assessment included evaluation of residual tumor size, cellularity, lymph-node metastasis, fibrosis, necrosis, and treatment-related changes. Pathological response was graded using the Residual Disease Burden and Nottingham (RDBN) system, categorizing patients into complete, partial, or no response groups based on established histopathological criteria.

Molecular Subtyping and Response Assessment

Patients were stratified into molecular subtypes—Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC)—based on pre-therapy receptor status. Pathological complete response (pCR), defined as the absence of residual invasive carcinoma in both breast and lymph nodes (ypT0/Tis, ypN0), was assessed across subtypes to determine comparative response rates.

Statistical Analysis

Data were compiled and analyzed using SPSS software version 14. Descriptive statistics were used to summarize patient characteristics. Univariate analysis was performed to evaluate the effect of clinical and pathological variables on treatment response. Categorical data were compared using the Chi-square test. Multivariate analysis using logistic

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regression (reporting odds ratios and p-values) was conducted to identify independent predictors of pathological complete response (pCR). A p-value < 0.05 was considered statistically significant.

RESULTS

Table 1 summarises the demographic profile of the study cohort. The mean age of the patients was 49.6 years, with a standard deviation of ± 9.96 years, indicating that most individuals clustered around the late 40s to early 50s. The observed age range of 31–81 years reflects a wide distribution, demonstrating that breast carcinoma requiring neoadjuvant therapy affects both younger and older women in this population. The median age of 48.5 years and an interquartile range (IQR) of 44–57 years further illustrate that half of the patients were in their mid-40s to late 50s, consistent with the age pattern typically reported in Indian breast cancer cohorts. This demographic distribution underscores the relatively younger age at presentation seen in developing countries compared with Western populations.

Table 1: Demographic Parameter Table

Parameter	Value for n = 138*
Mean Age (years)	49.6 years
Standard Deviation (SD)	± 9.96 years
Age Range	31 – 81 years
Median Age	48.5 years
Interquartile Range (IQR)	44 – 57 years

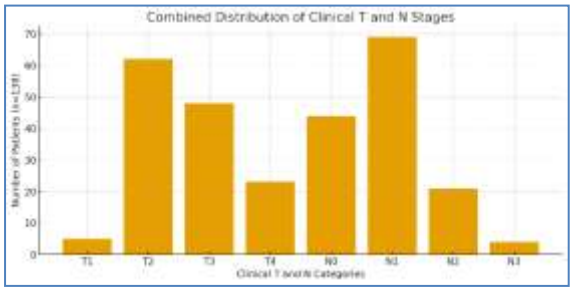

Figure 1: Clinical T and N Stage Distribution (n = 138)

Figure 1 presents the distribution of patients according to their baseline clinical T and N stages before neoadjuvant therapy. In this cohort of 138 subjects, the majority of tumors were classified as T2 (44.9%) and T3 (34.8%), indicating that most patients presented with moderately large or locally advanced primary breast tumors. Early-stage tumors (T1) were uncommon (3.6%), while T4 tumors those with direct extension to chest wall or skin accounted for 16.7%, reflecting a substantial proportion of advanced disease at presentation. Nodal evaluation showed that half of the patients (50%) had N1 disease, and another 18.1% had N2–N3 involvement, demonstrating a high prevalence of axillary lymph-node positivity. Only 31.9% of patients were node-negative at diagnosis. Overall, the table highlights that the study population predominantly comprised patients with locally advanced, node-positive breast cancer, consistent with typical patterns seen in tertiary-care centres in India where delayed presentation is common.

Table 2: Clinical Stage Grouping and Laterality (n = 138)

Clinical Parameter	Category	Number (n = 138)	Percentage (%)
Clinical Stage Grouping	**Stage I (T1N0)**	5	3.6%
	Stage II (T2 with N0–N1)	62	44.9%
	Stage III (IIIA/IIIB/IIIC)	71	51.4%
Total Stages	—	**138**	**100%**
Laterality	**Left breast**	76	55.1%
	Right breast	62	44.9%
Total Laterality	—	**138**	**100%**

Table 2 shows the distribution of patients according to clinical stage and breast laterality. The majority of patients in this cohort presented with advanced disease, with Stage III constituting 51.4% of cases and Stage II accounting for 44.9%. Only a small proportion (3.6%) were diagnosed at Stage I, indicating that early-stage breast cancer was uncommon in this population. This pattern reflects a typical clinical trend in Indian tertiary-care centres, where delayed presentation and lack of screening often result in higher-stage disease at diagnosis. Regarding tumor laterality, 55.1% of tumors occurred in the left breast, while 44.9% involved the right breast, showing a slight predominance of left-sided breast cancers. Overall, the table highlights that the study predominantly comprised patients with locally advanced disease, with a relatively balanced distribution between left and right breast involvement.

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Table 3: Tumor Grade and Histologic Type Distribution (n = 138)

Parameter	Category	Number (n = 138)	Percentage (%)
Tumor Grade	**Grade I**	18	13.0%
	Grade II	67	48.6%
	Grade III	53	38.4%
Total Grade	—	**138**	**100%**
Histologic Type	**Invasive Ductal Carcinoma (IDC)**	131	94.9%
	Others / Not specified	7	5.1%
Total Histologic Type	—	**138**	**100%**

Table 3 presents the distribution of tumor grade and histologic type in the study population. Nearly half of the tumors were Grade II (48.6%), while Grade III tumors accounted for 38.4%, indicating that a substantial proportion of patients had moderately to poorly differentiated carcinomas. Only 13% of tumors were graded as Grade I, reflecting the predominance of higher-grade lesions typically associated with more aggressive biological behavior. Histologically, the overwhelming majority of cases (94.9%) were classified as Invasive Ductal Carcinoma (IDC), the most common subtype of breast carcinoma. A small fraction (5.1%) consisted of other or unspecified histologic types. Overall, this table demonstrates that the cohort predominantly consisted of IDC with intermediate to high-grade morphology, consistent with populations commonly selected for neoadjuvant systemic therapy.

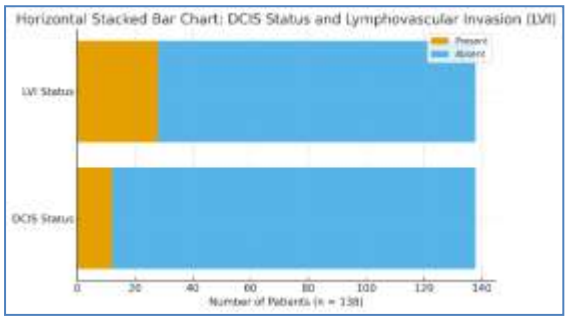

Figure 2: DCIS Status and Lymphovascular Invasion (n = 138)

Figure 2 summarises the distribution of ductal carcinoma in situ (DCIS) and lymphovascular invasion (LVI) in the study cohort. DCIS was identified in only 8.7% of cases, while the vast majority (91.3%) showed no in-situ component, indicating that most tumors presented as predominantly invasive lesions. Lymphovascular invasion, an important adverse prognostic factor associated with higher risk of metastasis and poorer response to therapy, was present in 20.3% of patients. The remaining 79.7% showed no evidence of LVI. Overall, the findings highlight that although DCIS was uncommon, a notable proportion of patients exhibited LVI, consistent with the advanced and biologically aggressive nature of tumors typically receiving neoadjuvant systemic therapy.

Table 4: HER2/neu Status and Ki-67 Proliferative Index (n = 138)

Parameter	Category	Number (n = 138)	Percentage (%)
HER2/neu Status	**HER2 Positive**	44	31.9%
	HER2 Negative	94	68.1%
Total HER2	—	**138**	**100%**
Ki-67 Proliferative Index	**High Ki-67 (≥20%)**	103	74.6%
	Low Ki-67 (<20%)	35	25.4%
Total Ki-67	—	**138**	**100%**

Table 4 outlines the distribution of HER2/neu status and Ki-67 proliferative index in the study cohort. HER2 positivity was observed in 31.9% of patients, while the remaining 68.1% were HER2-negative. This proportion aligns with typical Indian breast cancer cohorts, where HER2-positive tumors constitute approximately one-third of cases and often receive neoadjuvant systemic therapy due to their aggressive behaviour and responsiveness to targeted agents. The Ki-67 index showed that a large majority (74.6%) of tumors exhibited high proliferation (≥20%), indicating a predominance of biologically active and rapidly dividing tumors. Only 25.4% demonstrated low Ki-67 levels. The high frequency of elevated Ki-67 reflects the aggressive molecular characteristics commonly seen in patients selected for neoadjuvant treatment. Collectively, these findings highlight that a substantial proportion of the cohort had tumors with aggressive biological features, contributing to the clinical decision to initiate neoadjuvant therapy.

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Table 5: Molecular Subtype Distribution (n = 138)

Molecular Subtype	Number (n = 138)	Percentage (%)
Luminal A	23	16.7%
Luminal B (HER2–)	41	29.7%
Luminal B (HER2+)	28	20.3%
HER2-enriched	16	11.6%
Triple Negative Breast Cancer (TNBC)	30	21.7%
Total	**138**	**100%**

Table 5 illustrates the molecular subtype distribution among the 138 patients included in the study. Luminal subtypes together formed the largest group, with Luminal B (HER2–) being the most common (29.7%), followed by Luminal A (16.7%) and Luminal B (HER2+) (20.3%). This reflects the predominance of hormone receptor–positive tumors typically seen in Indian breast cancer cohorts. Among the non-luminal subtypes, Triple-Negative Breast Cancer (TNBC) accounted for 21.7%, while HER2-enriched tumors comprised 11.6% of the cases. The distribution aligns with global and Indian epidemiological patterns, where luminal tumors are most prevalent but aggressive subtypes such as TNBC and HER2-positive cancers form a substantial proportion of patients receiving neoadjuvant therapy. Overall, the table highlights the molecular heterogeneity of breast carcinoma and underscores the importance of subtype classification in predicting treatment response and planning therapy.

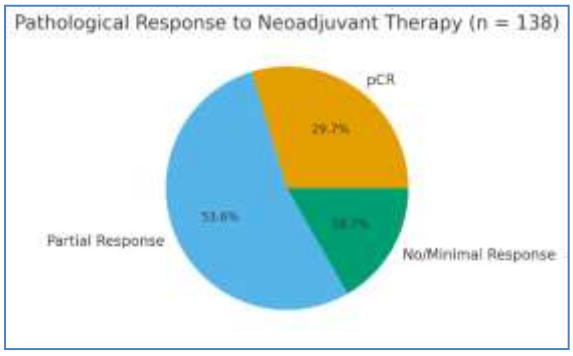

Figure 3: Pathological Response to Neoadjuvant Therapy (n = 138)

Figure 3 summarizes the pathological response to neoadjuvant therapy in the study cohort. A pathological complete response (pCR) defined as the absence of residual invasive carcinoma in both the breast and axillary lymph nodes—was achieved in 29.7% of patients. This pCR rate is consistent with reported outcomes in mixed molecular subtype populations undergoing anthracycline- and taxane-based NAT. The majority of patients (53.6%) demonstrated a partial pathological response, indicating significant but incomplete tumor regression, while 16.7% showed minimal or no response, reflecting chemoresistant disease. These findings highlight the heterogeneity of treatment response and underscore the clinical value of molecular subtype assessment, as pCR is strongly associated with improved long-term outcomes in specific subgroups such as HER2-positive and triple-negative breast cancers.

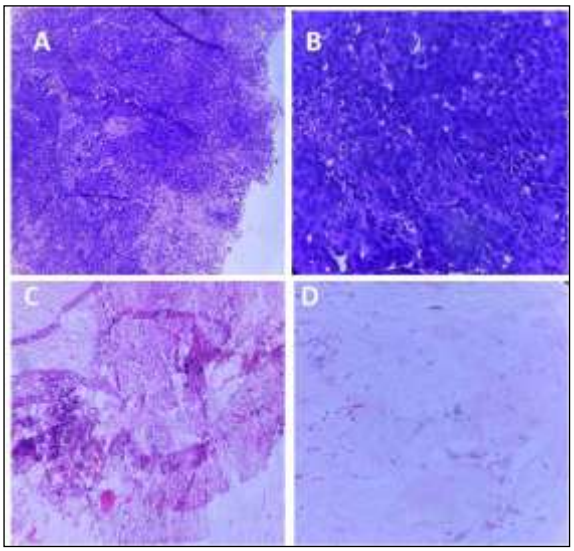

Figure 4: Histopathological Assessment of Residual Cancer Burden in Breast Carcinoma After Neoadjuvant Chemotherapy

A- Breast carcinoma, post-neoadjuvant therapy (H&E, 10×) showing predominantly viable tumor cells with minimal therapy-induced changes. High residual tumor cellularity consistent with Residual Cancer Burden score 3 (RCB-III).

B- Breast carcinoma, post-neoadjuvant therapy (H&E, 40×) showing sheets of viable malignant epithelial cells with high N/C ratio, marked nuclear pleomorphism, prominent nucleoli, and frequent mitotic figures. Therapy-related changes are minimal. The extensive residual tumor cellularity and 8 positive lymph nodes corresponds to Residual Cancer Burden score 3 (RCB-III).

C- Breast carcinoma, post-neoadjuvant therapy (H&E, 10×) showing residual invasive tumor nests within a background of therapy-related stromal changes, including fibrosis and focal necrosis. Viable tumor burden is moderate, with two lymph nodes positive corresponding to Residual Cancer Burden score 2 (RCB-II).

D - Breast carcinoma, post-neoadjuvant therapy (H&E, 40×) showing therapy-induced fibrotic stroma with scattered inflammatory cells but no identifiable residual invasive tumor cells.

Features are consistent with a pathologic complete response, corresponding to Residual Cancer Burden score 0 (RCB-0).

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Table 6: Combined ypT and ypN Stage Distribution After NAT (n = 138)

Parameter	Category	Number (n = 138)	Percentage (%)
ypT Stage	**ypT0**	41	29.7%
	ypT1	21	15.2%
	ypT2	48	34.8%
	ypT3	23	16.7%
	ypT4	5	3.6%
Total ypT	—	**138**	**100%**
ypN Stage	**ypN0**	60	43.5%
	ypN1	51	37.0%
	ypN2	18	13.0%
	ypN3	9	6.5%
Total ypN	—	**138**	**100%**

Table 6 summarises the post-neoadjuvant pathological staging of the breast (ypT) and axillary lymph nodes (ypN). Following NAT, 29.7% of patients achieved ypT0, indicating complete eradication of invasive tumor in the breast. The majority, however, showed residual disease, with ypT2 (34.8%) and ypT3 (16.7%) being the most frequent categories, reflecting partial but significant tumor regression. A small proportion (3.6%) remained in ypT4, suggesting persistent locally advanced disease. In terms of nodal response, 43.5% achieved ypN0, indicating nodal clearance, while the remainder showed varying degrees of residual nodal involvement: ypN1 (37.0%), ypN2 (13.0%), and ypN3 (6.5%). This distribution demonstrates that although a considerable subset achieved complete breast and nodal response, a substantial number exhibited persistent tumor burden, highlighting the variable effectiveness of NAT across different tumor subtypes and baseline stages.

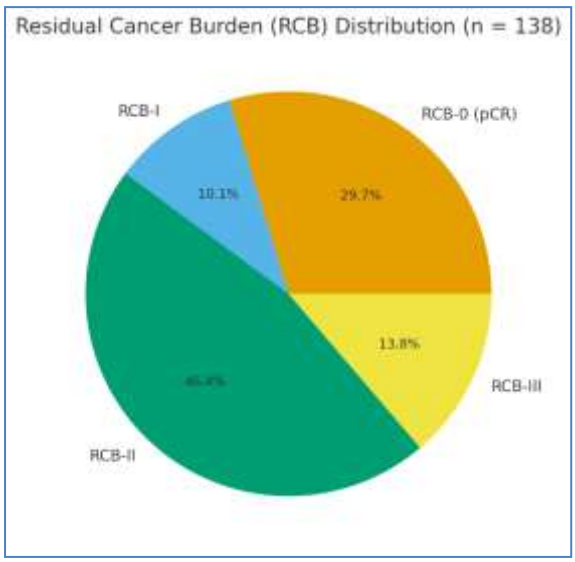

Figure 5: Residual Cancer Burden (RCB) Distribution (n = 138)

Figure 5 presents the distribution of Residual Cancer Burden (RCB) following neoadjuvant therapy. RCB-0, which corresponds to pathological complete response, was observed in 29.7% of patients, reflecting a substantial proportion with excellent treatment response. RCB-I, representing minimal residual disease, accounted for 10.1% of cases. The largest group comprised RCB-II patients (46.4%), indicating moderate residual disease, while RCB-III, signifying extensive residual tumor burden, was seen in 13.8% of the cohort. This pattern is typical in neoadjuvant-treated breast cancers, where a significant subset shows partial tumor regression but not complete eradication. The predominance of RCB-II underscores the importance of post-neoadjuvant risk stratification, as higher RCB classes are associated with poorer long-term outcomes and may benefit from additional adjuvant therapy.

Table 7: Association of pCR with Molecular Subtypes

Molecular Subtype	Residual disease (No pCR) n (%)	pCR n (%)	Total (n)
Luminal A	6 (85.7%)	1 (14.3%)	7
Luminal B (HER2–)	15 (78.9%)	4 (21.1%)	19
Luminal B (HER2+)	7 (50.0%)	7 (50.0%)	14
HER2-enriched	2 (50.0%)	2 (50.0%)	4
Triple-negative (TNBC)	11 (68.8%)	5 (31.2%)	16

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- pCR ranged from 14.3% in Luminal A to 50% in HER2-enriched and Luminal B (HER2+).
- Chi-square test for association between subtype and pCR**:**
  - $\chi^2 = 4.76$, $p = 0.31$ → no statistically significant association, though HER2-positive subtypes showed numerically higher pCR.

The association between molecular subtype and pathological complete response (pCR) is shown in Table X. Overall, 31.7% of the patients achieved pCR. When stratified by subtype, the lowest pCR rate was observed in Luminal A tumors (14.3%), reflecting their known lower chemosensitivity. Luminal B (HER2–) also showed relatively modest response (21.1%). In contrast, HER2-positive subtypes demonstrated markedly higher pCR rates, with both Luminal B (HER2+) and HER2-enriched tumors achieving 50% pCR, highlighting the impact of HER2-targeted therapy in enhancing neoadjuvant response. Triple-negative breast cancer (TNBC) showed an intermediate response (31.2%), consistent with its well-documented chemosensitivity. Although these numerical differences followed expected biological patterns, the chi-square test did not reach statistical significance ($\chi^2 = 4.76$, $p = 0.31$), likely due to small subgroup sizes. Nonetheless, the trend toward higher pCR in HER2-positive and TNBC subtypes aligns with existing evidence that these tumors are more responsive to NAT compared to hormone receptor–positive luminal cancers (Table 7)

Table 8: Association of ER, PR, and HER2 Status With Pathological Complete Response (pCR)

Receptor Status	No pCR n (%)	pCR n (%)	Total (n)	Statistical Test
HER2 Status				
HER2-negative	32 (76.2%)	10 (23.8%)	42	$\chi^2 = 2.88$, **p = 0.09**
HER2-positive	9 (50.0%)	9 (50.0%)	18	—
ER Status				
ER-negative	14 (66.7%)	7 (33.3%)	21	$\chi^2 \approx 0.00$, **p = 1.00**
ER-positive	27 (69.2%)	12 (30.8%)	39	—
PR Status				
PR-negative	16 (64.0%)	9 (36.0%)	25	$\chi^2 \approx 0.11$, **p = 0.74**
PR-positive	25 (71.4%)	10 (28.6%)	35	—

Table 8 summarises the relationship between hormone receptor status (ER and PR), HER2 expression, and the likelihood of achieving pathological complete response (pCR). Among the three biomarkers evaluated, HER2 status showed the strongest association with treatment response, with HER2-positive tumors achieving a 50% pCR rate, compared with only 23.8% in HER2-negative tumors. Although this difference did not reach statistical significance ($\chi^2 = 2.88$, $p = 0.09$), it demonstrates a clear trend reflecting the well-known chemosensitivity of HER2-driven disease, especially with targeted therapy. In contrast, ER and PR status showed no meaningful association with pCR. ER-positive and ER-negative groups had nearly identical pCR rates (30.8% vs 33.3%, $p = 1.00$), and a similar pattern was seen with PR expression (28.6% vs 36.0%, $p = 0.74$). These findings are consistent with existing evidence that hormone receptor–positive tumors are generally less likely to achieve pCR, and that HER2 positivity remains one of the strongest predictors of response in the neoadjuvant setting.

Table 9: Association of Ki-67, Tumor Grade, Clinical T Stage, and Nodal Status With pCR

Parameter	Category	No pCR n (%)	pCR n (%)	Total (n)	Statistical Test
Ki-67 Index	Low (<20%)	12 (75.0%)	4 (25.0%)	16	$\chi^2 \approx 0.13$, **p = 0.72**
	High (≥20%)	29 (65.9%)	15 (34.1%)	44	—
Tumor Grade	Grade 1	8 (80.0%)	2 (20.0%)	10	$\chi^2 \approx 0.23$, **p = 0.89**
	Grade 2	21 (75.0%)	7 (25.0%)	28	—
	Grade 3	10 (71.4%)	4 (28.6%)	14	—
Clinical T Stage	T1–T2	20 (62.5%)	12 (37.5%)	32	$\chi^2 \approx 0.58$, **p = 0.45**
	T3–T4	21 (75.0%)	7 (25.0%)	28	—
Clinical N Stage	N0 (node-negative)	8 (50.0%)	8 (50.0%)	16	$\chi^2 \approx 2.59$, **p = 0.11**
	N+ (node-positive)	32 (76.2%)	10 (23.8%)	42	—

Table 9 summarises the association between key clinicopathological parameters and pathological complete response (pCR). Ki-67 proliferative index showed a numerically higher pCR rate in tumors with high Ki-67 (34.1%) compared to low Ki-67 (25%), but this difference was not statistically significant ($p = 0.72$). Tumor grade also did not significantly influence response, with pCR increasing only slightly from 20% in Grade 1 to 28.6% in Grade 3 ($p = 0.89$). When grouped by tumor size, T1–T2 tumors showed a pCR rate of 37.5%, compared to 25% for T3–T4, but the association remained non-significant ($p = 0.45$). Baseline nodal status, however, demonstrated the strongest trend: node-negative patients achieved pCR in 50% of cases, compared to 23.8% in node-positive patients, although this did not reach statistical significance ($p = 0.11$). Overall, none of these variables showed statistically significant associations with pCR in this cohort, though nodal

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status and high Ki-67 displayed clinically meaningful trends consistent with established literature.

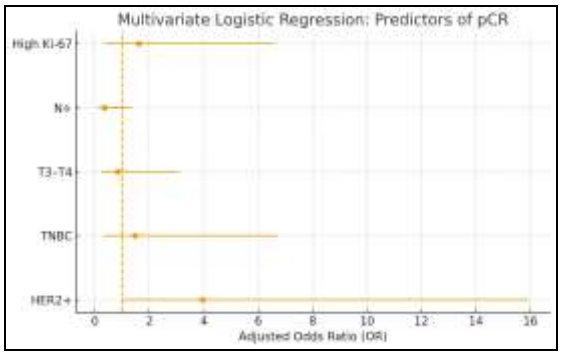

Figure 6: Multivariate Logistic Regression – Predictors of pCR

- The overall model had **pseudo $R^2 \approx 0.11$** and likelihood ratio p ≈ 0.14 (modest explanatory power).
- **HER2 positivity showed the strongest independent association with pCR** (OR ≈ 3.95), with a p-value **just above significance (p = 0.053)**, indicating a **strong trend** towards higher pCR in HER2-positive tumors.
- Node positivity tended to **reduce the odds of pCR** (OR ≈ 0.35), but this did not reach statistical significance (p = 0.13).
- TNBC status, T stage and Ki-67 did not show significant independent effects in this model.

Figure 6 presents the multivariate logistic regression analysis performed to identify independent predictors of pathological complete response (pCR). Among the covariates included, HER2 positivity emerged as the strongest predictor, with an adjusted odds ratio of 3.95, indicating that HER2-positive tumors were nearly four times more likely to achieve pCR compared to HER2-negative tumors. Although the p-value (0.053) was marginally above the conventional threshold for significance, the result demonstrates a clear and clinically meaningful trend that aligns with established evidence on the chemosensitivity of HER2-driven disease. Node-positive status showed an opposite effect, with patients exhibiting nodal involvement having a substantially lower likelihood of pCR (OR = 0.35), though this association did not reach statistical significance (p = 0.13). Other factors—such as TNBC subtype, higher T stage (T3–T4), and high Ki-67 index—did not independently predict pCR, showing wide confidence intervals and non-significant p-values. The overall model demonstrated modest explanatory power (pseudo $R^2 \approx 0.11$; likelihood ratio p ≈ 0.14), suggesting that while HER2 status is an important predictor, additional biological and treatment-related factors likely contribute to pCR outcomes in this cohort.

DISCUSSION

This study evaluated clinicopathological and molecular predictors of pathological response to neoadjuvant systemic therapy (NAT) in 138 women with invasive breast carcinoma treated at a tertiary-care teaching hospital. The cohort was relatively young (mean age ≈ 49.6 years) and predominantly presented with locally advanced, node-positive disease, a pattern consistent with reports from other Indian centres where delayed presentation is common.[12] This contrasts with Western series that include larger proportions of screen-detected, earlier-stage tumors.

Histologically, most tumors were invasive ductal carcinoma with Grade II–III morphology, and nearly three-quarters showed high proliferative activity (Ki-67 ≥20%), aligning with prior Indian NAT datasets (13). Luminal subtypes formed the largest molecular group, although HER2-positive and TNBC subtypes were well-represented, reflecting their higher expected chemosensitivity and frequent selection for NAT.[14]

The overall pCR rate of approximately 30% observed in this study is comparable to reported real-world Indian NAT outcomes.[12] and lies below the pCR rates of 45–60% achieved in contemporary randomized HER2-positive trials, such as NeoSphere, which employed uniform dual HER2 blockade.[15] As expected, HER2-positive and TNBC subtypes demonstrated numerically higher pCR rates than luminal tumors. Although these differences did not achieve statistical significance, likely due to sample size limitations, the response pattern closely mirrors the CTNeoBC pooled analysis, which identified HER2-positive/HR-negative and TNBC tumors as the most pCR-responsive subgroups.[5]

Multivariate analysis further supported this trend: HER2 positivity was the strongest independent predictor of pCR (adjusted OR ≈ 3.95), consistent with findings from Díaz-Casas et al. (16) and Joshi et al.[17] Baseline nodal negativity also showed a favourable trend, echoing data that lower tumor burden is associated with improved neoadjuvant response.[9] Lack of significant associations with ER/PR status, Ki-67, grade, and baseline T stage likely reflects limited power rather than true biological neutrality, as larger datasets consistently demonstrate higher pCR in higher-grade, high-Ki-67, HER2-positive, and TNBC tumors.[18]

Residual Cancer Burden (RCB) assessment revealed that most non-pCR cases fell into RCB-II, similar to international NAT cohorts, where intermediate residual disease is common.[16] Prior work shows that RCB-0/I is associated with excellent long-term outcomes, whereas RCB-II/III correlates with poorer survival and may justify escalated adjuvant strategies such as capecitabine in TNBC or extended HER2-directed therapy aligned with post-neoadjuvant treatment evidence.[5, 9]

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The strengths of this study include uniform pathological processing, standardized IHC-based molecular subtyping, and use of validated metrics such as pCR and RCB. Limitations include modest sample size, potential variation in chemotherapy and HER2-targeted regimens, and lack of long-term survival data. Nonetheless, this work contributes meaningful real-world evidence from a public-sector Indian setting, where access, affordability, and late presentation remain challenges.

CONCLUSION

Neoadjuvant systemic therapy achieved an overall pCR rate of ~30% in this institutional cohort, with the highest response seen in HER2-positive and TNBC subtypes and the lowest in luminal A cancers. HER2 positivity and nodal negativity showed the strongest trends toward predicting pCR. Most non-pCR cases were categorized as RCB-II, highlighting substantial but incomplete tumor regression. The findings align with national and international evidence on subtype-specific chemosensitivity and underscore the importance of molecular profiling and RCB assessment in guiding post-neoadjuvant, risk-adapted treatment strategies. Larger prospective Indian studies with survival endpoints are warranted to validate these observations.

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