To Study the Neutrophil Lymphocyte Ratio As a Predictive Marker of Response to Neoadjuvant Chemotherapy in Locally Advanced Triple-Negative Breast Cancer

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Abstract

Introduction Triple-negative breast cancer (TNBC) is the most aggressive form of invasive breast cancer. A key predictor of positive outcomes is achieving a pathological complete response (pCR) following neoadjuvant chemotherapy (NACT). This study aims to evaluate the role of pre-chemotherapy neutrophil-to-lymphocyte ratio (NLR) as a predictive marker of pCR.

Objective The aim of the study is to study the pCR rate after NACT in relation to NLR in patients with locally advanced TNBC.

Materials and Methods This prospective study enrolled 120 consecutive female patients with locally advanced TNBC who were planned for NACT at the Kidwai Memorial Institute of Oncology from July 2022 to July 2024. Peripheral blood samples were collected before treatment to calculate NLR. The predictive value of NLR for pCR was assessed using descriptive statistics, Chi-square tests, and receiver operating characteristic (ROC) curve analysis.

Results The final analysis included 101 patients. Thirty-one patients (30.7%) achieved pCR. Patients with pCR had a significantly lower mean NLR (2.29 ± 1.21) than the non-pCR group (2.85 ± 1.34). The optimal NLR cut-off for predicting pCR was **2.18**. Low NLR (≤ 2.18) was significantly associated with higher pCR rates (67.74 vs. 32.25% for high NLR, $p < 0.05$).

Conclusion Pre-chemotherapy NLR is a potential predictive marker for pCR in locally advanced TNBC. Patients with a lower NLR were more likely to achieve pCR, suggesting its potential utility in risk stratification.

Keywords
- triple-negative breast cancer
- neutrophil lymphocyte ratio
- pathological complete response
- neoadjuvant chemotherapy
- inflammatory markers

Introduction

Breast cancer is the leading malignancy affecting women globally, representing approximately 25% of all female cancer diagnoses and ranking among the top causes of cancer-related mortality.[1] Several factors influence patient outcomes, including age, tumor stage, ethnicity, molecular characteristics of the tumor, and biomarker expression particularly estrogen

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receptor (ER), progesterone receptor (PR), and HER2 status. Triple-negative breast cancer (TNBC), which constitutes 20% of cases, lacks these receptors and is characterized by aggressive behavior and a lack of targeted therapies.[2]

Neoadjuvant chemotherapy (NACT) is a standard treatment for locally advanced breast cancer, enhancing tumor response and improving the chances of breast-conserving surgery. Achieving pathological complete response (pCR) post-NACT is a key prognostic marker, particularly in TNBC where pCR rates exceed 50%.[3,4] Recent research suggests inflammation plays a critical role in the development of cancer and its progression, with inflammatory cells generating reactive oxygen species that contribute to DNA damage and tumor growth.[5–9] Neutrophils suppress T-cell activity, promoting tumor invasion, while tumor-infiltrating lymphocytes are linked to better chemotherapy responses and improved prognosis.[10–15]

Currently, predictors of response to NACT in breast cancer include traditional factors such as tumor grade, nodal status, receptor subtype, and radiological response (e.g., RECIST [response evaluation criteria in solid tumors] criteria on MRI). However, radiological assessment alone cannot reliably rule out residual disease. Emerging approaches focus on advanced imaging (e.g., computer-extracted MRI features for tumor biology insights) and liquid biopsies (e.g., ctDNA analysis for real-time tumor dynamics).[16–21] Peripheral inflammatory markers like the neutrophil to lymphocyte ratio (NLR) may offer a simple, inexpensive means of predicting response to NACT and disease prognosis. Elevated NLR reflects systemic inflammation and has been correlated with poor outcomes in various cancers, though evidence in breast cancer remains limited.[22–29] NLR is an easily available, reproducible, and inexpensive biomarker of inflammation. Our study enrolled only one subgroup of breast cancer that is non-metastatic locally advanced TNBC. It is one of the very few prospective study that can be found in the literature. This study aims to evaluate the predictive role of pre-chemotherapy NLR in relation to pCR in patients with locally advanced TNBC.

Materials and Methods

Study Design and Patient Population

This was a prospective, observational study. A total of 120 consecutive female patients with newly diagnosed, locally advanced TNBC planned for NACT were recruited between July 2022 and July 2024. ►**Fig. 1** (CONSORT Flowchart) illustrates the patient screening and recruitment process.

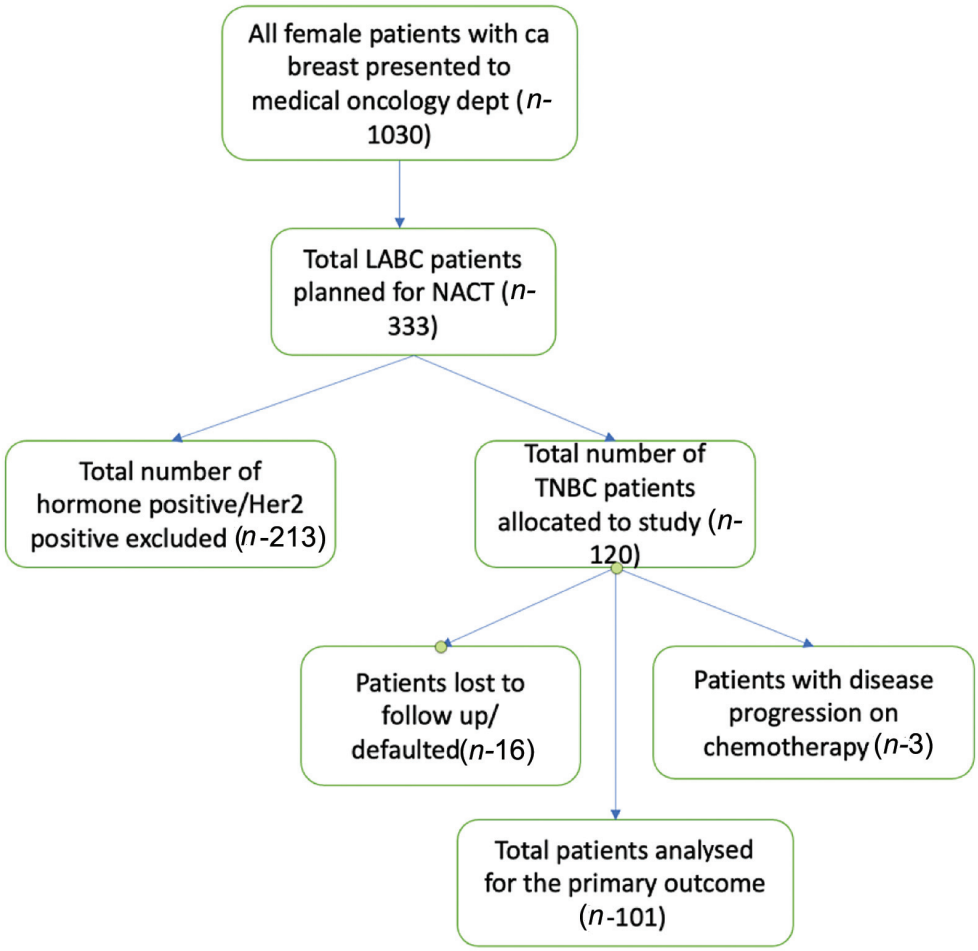

Fig. 1 Receiver Operating Characteristic (ROC) curve for the predictive model. The Area Under the Curve (AUC) is 0.67 (95% CI: 0.55 – 0.79), indicating moderate discriminatory power.

Data Collection

The study was approved by institutional ethical committee. Clinicopathological data were collected including age, menopausal status, clinical stage (AJCC 8th edition), histological type, grade, proliferation index (ki67), ECOG performance status, chemotherapy regimen, and NLR. All patients recruited in the study were pathologically diagnosed with invasive breast carcinoma, with immunohistochemistry (IHC) suggestive of ER-negative/PR-negative/ HER2-negative as per American Society of Clinical Oncology-College of American Pathologist guidelines, 2018.[30] Pre NACT complete blood count was performed from a peripheral venous blood sample drawn within 1 week prior to the initiation of the first cycle of chemotherapy. Absolute neutrophil and lymphocyte count were documented to calculate NLR. NLR is defined as absolute neutrophil count divided by absolute lymphocyte count.

Treatment

After pathological diagnosis, patients received standardized NACT. Those with ECOG performance status 0–1 received either:

1. *Dose-dense chemotherapy*, as per the CALGB 9741 trial protocol, consisted of Adriamycin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) administered every 2 weeks for four cycles, followed by paclitaxel (175 mg/m^2) every 2 weeks for another four cycles with growth factor support as show in ►**Table 1**.[31]
2. *FEC-D regimen*: 5-Fluorouracil, Epirubicin, and cyclophosphamide followed by docetaxel. Patients with ECOG PS 2, as determined by the treating physician based on comorbidities and functional status, received the FEC-D regimen (non-dose-dense), due to better tolerability. A small number of patients ($n = 6$) received docetaxel plus cyclophosphamide (TC) based on physician discretion in specific clinical scenarios (e.g., pre-existing cardiac contraindications to anthracyclines). Following NACT, patients underwent surgical resection, with subsequent radiotherapy and hormone therapy administered as indicated based on receptor status. pCR was strictly defined as the absence of invasive tumor in both breast tissue (ypT0/Tis) and lymph nodes (ypN0) upon postoperative histopathological examination.

Inclusion and Exclusion Criteria

The following inclusion criteria were used to select patient population (1) age >18 years, (2) ECOG 0–2, (3) biopsy-proven locally advanced TNBC. The exclusion criteria were: (1) recurrent breast cancer; (2) metastatic disease; (4) diagnosis of ductal carcinoma in situ; (5) hormone receptor positive or Her2-neu receptor positive breast cancer; (6) patient with impaired hepatic and renal function or cardiovascular disease, as they are less likely to tolerate full-dose chemotherapy and may require frequent dose reductions or treatment interruptions, which can delay treatment and affect outcomes; (7) active infection or inflammatory conditions.

Primary outcome: The primary aim is to study the pCR rate after NACT in relation to neutrophil lymphocyte ratio (NLR) in patients with locally advanced TNBC.

Sample Size Consideration

Given the exploratory nature of this study to determine an NLR cut-off value in a specific population, a formal sample size calculation was not performed a priori. The sample of 120 patients was based on the expected patient accrual over the 2-year study period at our institute. We acknowledge this as a limitation, particularly for the receiver operating characteristic (ROC) analysis, and the results should be interpreted as generating hypothesis for future validation in larger, powered studies.

Statistical Analysis

Statistical analysis was conducted using Python 3.7. Descriptive statistics (means, standard deviations, and percentages) summarized demographic and clinical data. The Chi-square test evaluated associations between clinicopathological factors (including NLR) and NACT response. ROC curve analysis assessed NLR's predictive ability for pCR, while binary logistic regression identified significant predictors ($p < 0.05$ considered statistically significant). The multivariate model included age, menopausal status, clinical stage, tumor grade, K_i-67, lymphovascular invasion, chemotherapy regimen, and NLR.

Ethical Approval

All patient who gave written informed consent were included in the study. Ethical committee of Kidwai memorial institute of oncology has approved the study. Registration no: KMIO/MEC/2022/07/PG/MO/19. This study was conducted in compliance with institutional ethical guidelines and adhered to the principles of the 1964 Helsinki Declaration (including subsequent amendments).

Results

Patient Characteristics

As detailed in the CONSORT flowchart (►**Fig. 1**), 120 patients were enrolled. Of these, 16 were lost to follow-up. Three patients developed distant metastasis during NACT and were excluded from the primary pCR analysis. We acknowledge that excluding these patients, who had high NLR values (mean NLR = 3.4), may introduce a bias; however, for the specific outcome of pCR (a pathological state assessed at surgery), these patients were not evaluable. Their outcomes can be analyzed separately in the context of the secondary survival outcomes. The final analysis for the primary endpoint (pCR) included 101 patients. The baseline characteristics of the 101 patients are summarized in ►**Table 2**. The median age was 49 (24–83) years. The majority of patients (93.1%) had an ECOG performance status of 0 to 1. The predominant histopathology was invasive ductal carcinoma (99.0%). Most tumors were high grade (Grade 2: 55.4%; Grade 3: 42.6%). Regarding chemotherapy regimens, 82 (81.2%) patients received FEC-D, 13 (12.9%) received dose-dense chemotherapy, and six (5.9%) received TC. The majority of patients (98.0%) underwent modified radical mastectomy. pCR was achieved in 31 patients (30.7%).

Table 1 Chemotherapy regimens

Regimen	Drugs and dosage	Frequency	Cycles
(1) FEC-D	5-Fluorouracil 500 mg/m^2, Epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2 (FEC)	Every 3 wk	3 FEC
	Followed by docetaxel 100 mg/m^2	Every 3 wk	3 Docetaxel
(2) Dose-Dense AC-T	Adriamycin 60 mg/m^2, cyclophosphamide 600 mg/m^2 (AC)	Every 2 wk	4 AC
	Followed by paclitaxel 175 mg/m^2	Every 2 wk	4 Paclitaxel
(3) TC	Docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2	Every 3 wk	4 TC

Abbreviations: AC-T, Adriamycin, cyclophosphamide followed by paclitaxel; FEC-D, 5-fluorouracil, Epirubicin, cyclophosphamide followed by docetaxel; TC, docetaxel, cyclophosphamide.

Treatment Response and NLR

The mean NLR for the entire cohort was 2.68. Patients who achieved pCR had a significantly lower mean NLR (2.29 ± 1.21) compared with the non-pCR group (2.85 ± 1.34). The optimal NLR threshold for predicting pCR was 2.18 (AUC = 0.67, sensitivity 67.74%, specificity 67.14%) (►**Table 3**, ►**Fig. 2**). The cohort was divided into high NLR (>2.18; $n = 57$) and low NLR (≤2.18; $n = 44$) groups. pCR rates were significantly higher in the low NLR group (67.74 vs. 32.25%, $p < 0.05$). This association is detailed in the 2×2 contingency table (►**Table 4**). Of the three patients who developed metastasis during NACT and were excluded from the pCR analysis, all had an NLR above the 2.18 cut-off (values: 3.1, 3.5, 3.6). When considering "non-response" as either residual disease or disease progression, the association between high NLR and treatment failure is further strengthened. NLR showed no significant association with baseline characteristics like age or tumor grade (►**Table 5**) but correlated with adverse pathological features (LVI, PNI) in non-responders.

Multiple (Binary) Logistic Regression Analysis

A multivariate binary logistic regression was performed to identify independent predictors of pCR. The model included age, menopausal status, clinical stage, tumor grade, K_i-67, lymphovascular invasion, chemotherapy regimen, and NLR. As shown in ►**Table 6** and ►**Table 7**, a low pre-treatment NLR (≤2.18) remained a significant independent predictor of

Table 2 Baseline clinical and pathological characteristics of the study population ($n = 101$)

Characteristic	Level	Frequency (*n*)	Percentage (%)
Age (years)	Median (range)	49 (24–83)	–
Menopausal status	Premenopausal	55	54.5
	Postmenopausal	46	45.5
ECOG performance status	0–1	94	93.1
	2	7	6.9
Clinical stage	Stage II	45	44.6
	Stage III	56	55.4
Histopathology	Invasive ductal carcinoma	100	99.0
	Other (metaplastic, poorly diff.)	2	2.0
Tumor grade	1	2	2.0
	2	56	55.4
	3	43	42.6
Chemotherapy regimen	FEC-D	82	81.2
	Dose-dense AC-T	13	12.9
	TC	6	5.9
Type of surgery	Breast conserving surgery (BCS)	2	2.0
	Modified radical mastectomy (MRM)	99	98.0

Abbreviation: ECOG, Eastern Cooperative Oncology Group; FEC-D, 5-fluorouracil, Epirubicin, and cyclophosphamide followed by docetaxel.
Note: Percentages may not sum to 100% due to rounding. The "Histopathology" category allows for patients with non-ductal histology to be represented.

Table 3 Pathological response and tumor characteristics post-NACT

Characteristic	Level	Frequency (*n*)	Percentage (%)
Pathological response	Complete response (pCR)	31	30.7
	Non-complete response (Non-pCR)	70	69.3
Residual cancer burden (RCB)	RCB-0 (pCR)	31	30.7
	RCB-1	13	12.9
	RCB-2	22	21.8
	RCB-3	35	34.7
Lymphovascular invasion (LVI)	Negative	56	55.4
	Positive	45	44.6
Perineural invasion (PNI)	Negative	86	85.1
	Positive	15	14.9
Ductal carcinoma in situ (DCIS)	Negative	79	78.2
	Positive	22	21.8
Extranodal extension	Negative	82	81.2
	Positive	19	18.8

Abbreviations: NACT, neoadjuvant chemotherapy; pCR, pathological complete response; RCB, residual cancer burden.

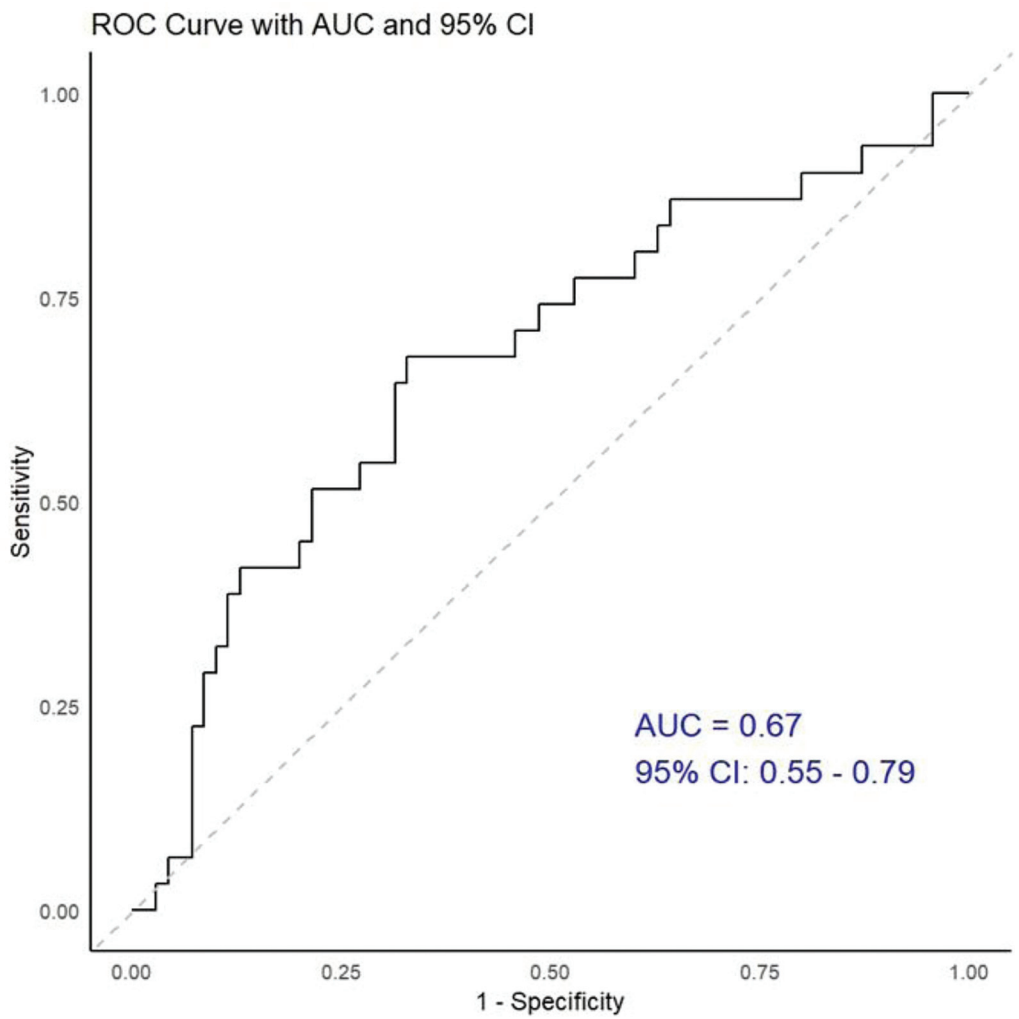

Fig. 2 ROC curve with AUC and 95% CI. AUC, area under the curve; CI, confidence intervals.

Table 4 ROC curve analysis for pretreatment NLR predicting pCR

AUC (95% CI)	Optimal cut-off	Sensitivity	Specificity	PPV	NPV
0.67 (0.55 – 0.79)	**2.18**	67.74%	67.14%	47.73%	82.46%

Abbreviations: AUC, area under the curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; NPV, negative predictive value; pCR, pathological complete response; PPV, positive predictive value; ROC, receiver operating characteristic.

Table 5 Association between pretreatment NLR group and pathological complete response

NLR group	pCR ($n = 31$)	Non-pCR ($n = 70$)	Total ($n = 101$)	*p*-Value
Low NLR (≤2.18)	**21 (67.7%)**	23 (32.9%)	44	<**0.05**
High NLR (>2.18)	10 (32.3%)	**47 (67.1%)**	57	
Total	**31**	**70**	**101**	

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; pCR, pathological complete response.
Note: *p*-Value calculated using Chi-square test.

achieving pCR (odds ratio: 4.27, 95% CI: 1.46 – 12.48, $p = 0.008$). No other variables in the model showed a statistically significant association with pCR.

Discussion

pCR after NACT is the most important goal in TNBC. Failure to reach the endpoint of a pCR is associated with poor clinical outcomes. Hence, it is crucial to identify the patients with higher likelihood of achieving pCR after NACT and further long-term outcomes. NLR is one of those systemic inflammatory markers which can be easily accessed and correlated with aggressive breast cancer outcome specifically TNBC.[32–34] Pre-chemotherapy NLR was assessed in 101 TNBC patients. The result suggests that a lower NLR has high rates of pCR than those with high NLR (67.8 vs. 32.2%, respectively). It is known that the higher NLR is associated with adverse prognosis and thus chances of achieving pCR are unlikely. Our findings align with previous research, including a study by Li et al that examined the relationship between NLR and breast cancer prognosis, particularly its impact on NACT response and survival outcomes. Their results demonstrated that a low pretreatment NLR (specifically <1.8) served as a favorable prognostic marker, correlating with both a higher pCR rate and improved long-term survival.[35] It is reported that patients with NLR of less than 1.8 have a high chance of pCR and overall survival. Similarly, another study showed that high NLR values above 3 resulted in poor disease-free survival DFS and overall survival (OS) status.[36]

Another study found that worse DFS and OS could be predicted by a pretreatment NLR >2.[37] In our study, the optimal cutoff point for NLR was determined to be 2.18, with a sensitivity of 67.74% and a specificity of 67.14%. This differs from cutoff points reported in the literature, likely due to variations in patient demographics, such as age, ethnicity, menopausal status, or overall health. Our study is the first from the Asian subcontinent correlating NLR with pCR in TNBC patients. Furthermore, the retrospective nature of many published studies, leading to different cutoff values for defining high or low NLR along with individual variations in immune response, genetic factors, and other biological factors, could also contribute to the observed differences.

Table 6 Association of baseline characteristics with NLR (mean NLR comparison)

Variable	Level	*N*	Mean NLR	Standard deviation	*p*-Value[a]
Age	≤50 y	56	2.66	1.28	0.896
	>50 y	45	2.72	1.41	
Menopausal status	Premenopausal	55	2.73	1.28	0.546
	Postmenopausal	46	2.62	1.38	
Clinical stage	Stage II	45	2.63	1.30	0.629
	Stage III	56	2.72	1.37	
Tumor grade	1 or 2	58	2.73	1.54	0.648
	3	43	2.60	0.97	
K_i-67 index	≤20%	14	3.13	1.91	0.433
	>20%	87	2.59	1.20	

Abbreviation: NLR, neutrophil-to-lymphocyte ratio.
[a]*p*-Value calculated using Mann-Whitney U test.

Table 7 Univariate and multivariate (binary) analysis of factors predicting pathological complete response (pCR)

Variable	Level	Univariate analysis *p*-Value[a]	Multivariate analysis[b]		
			Odds ratio (OR)	95% CI for OR	*p*-Value
NLR	Low (≤2.18) vs. high (>2.18)	<**0.001**	**4.27**	**1.46 – 12.48**	**0.008**
Age	>50 vs. ≤50 y	1.000	0.75	0.28 – 2.01	0.57
Menopausal status	Post vs. premenopausal	0.869	1.12	0.40 – 3.15	0.83
Clinical stage	III vs. II	0.507	0.64	0.24 – 1.71	0.37
Tumor grade	3 vs. ½	0.239	1.89	0.68 – 5.26	0.22
K_i-67 index	>20% vs. ≤20%	0.215	1.54	0.29 – 8.21	0.61
Lymphovascular invasion	Positive vs. negative	<**0.001**[a]	0.56	0.21 – 1.50	0.25
Chemotherapy regimen	(Reference: FEC-D)	–	–	–	–
	Dose – dense vs. FEC-D	0.344[c]	1.92	0.50 - 7.34	0.34
	TC vs. FEC-D	0.699[c]	1.15	0.18 – 7.26	0.88

Abbreviations: CI, confidence interval; FEC-D, 5-fluorouracil, Epirubicin, and cyclophosphamide followed by docetaxel; LVI, lymphovascular invasion; NLR, neutrophil-to-lymphocyte ratio.
[a]*p*-Value from Chi-square test, unless otherwise indicated. LVI could not be included in the multivariate model due to quasi-complete separation (0 pCR events in the LVI-positive group).
[b]Multivariate analysis performed using binary logistic regression.
[c]*p*-Value from Fisher's exact test due to small cell counts.

The significance of pCR in TNBC is as an indirect parameter for survival benefit. Higher NLR has been associated with poor prognosis which includes increased rates of recurrence and reduced overall survival.[13,14,38] Similarly, a meta-analysis reported that high NLR was linked with poor DFS and OS across all breast cancer subtypes, including TNBC.[15] A study from Australia also showed that low NLR is predictive of pCR and is associated with better DFS and OS.[39,40]

In this population, the proportion of patients achieving pCR was 30.7%, comparable to study conducted in Korea, where the figure was 28.7%. In our multivariate logistic regression analysis, low NLR remained the only significant independent predictor for pCR (odds ratio: 4.274; $p = 0.008$). This highlights the importance of NLR as an indicator of treatment response in TNBC. Recent advances in neoadjuvant therapy for locally advanced TNBC include pembrolizumab-based regimens (KEYNOTE-522 trial), which significantly improve pCR and survival when combined with chemotherapy and radiotherapy.[41] For patients with residual disease, extended adjuvant capecitabine enhances outcomes while germline BRCA-mutated patients benefit from adjuvant olaparib, reducing recurrence risk.[42,43]

Limitations

Our study has several limitations. First, it is a single-center study with a modest sample size. The lack of a prespecified sample size calculation for the ROC analysis is a constraint, and the identified cut-off of 2.18 requires external validation in larger, multi-institutional cohorts. Second, NLR was measured only once before treatment; serial measurements during and after therapy could provide dynamic insights. Third, the exclusion of three patients who progressed during chemotherapy, while necessary for the pathological pCR endpoint, may have biased our results by removing clear non-responders with high NLR. Finally, the use of multiple chemotherapy regimens, although reflective real-world practice, introduces potential confounding.

Conclusion

This prospective study identifies pre-treatment NLR as a potential biomarker for NACT response in locally advanced TNBC. We observed a significant association between low NLR (≤2.18) and improved pCR rates, suggesting that NLR is a promising, cost-effective, and readily available biomarker for predicting response to NACT in locally advanced TNBC, offering a practical and economical approach to risk stratification and treatment planning. Future large-scale, multicenter studies are warranted to validate these findings and standardize the NLR cut-off value.

Authors' Contributions

D.A., L.K.N., P.K.S.K., and M.C.S.B. contributed toward study design, critical revision, and supervision. R.A.H. and R.L.K. collected the data, drafted and revised the manuscript. S.C.S. analyzed the data and edited the manuscript.

Conflict of Interest

None declared.

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