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NEUTROPHIL-TO-LYMPHOCYTE RATIO AND PLATELET-TO-LYMPHOCYTE RATIO IN PREDICTING THE PATHOLOGICAL COMPLETE RESPONSE IN PATIENTS WITH BREAST CANCER RECEIVING NEO-ADJUVANT CHEMOTHERAPY

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Abstract

Objective: *To determine the predictive value of baseline neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) for pathological complete response (pCR) in breast cancer patients receiving neoadjuvant chemotherapy (NACT).*

Study Design: *Prospective observational study.*

Place and Duration of Study: *Oncology Department, Fauji Foundation Hospital, Rawalpindi, from March 2024 to January 2025.*

Methodology: *A total of 74 biopsy-proven breast cancer patients receiving NACT were enrolled using consecutive non-probability sampling. Baseline clinical data and hematological parameters were recorded prior to chemotherapy. NLR and PLR were calculated from complete blood counts. Following NACT, patients underwent definitive surgery, and pCR was assessed histopathologically.*

Results: *The median age of patients was 52.5 years, with the majority presenting with stage III disease (62.2%). Pathological complete response was achieved in 33.8% of patients. The mean total leukocyte count was 8.36 ± 2.0 ×10³/µL, neutrophil count 5.13 ± 1.97 ×10³/µL, lymphocyte count 2.46 ± 0.68 ×10³/µL, and platelet count 286.3 ± 87.2 ×10³/µL. There was no statistically significant difference in NLR (p=0.437) or PLR (p=0.414) between pCR and non-pCR groups. Logistic regression analysis also demonstrated no significant association of NLR (OR=0.7, p=0.170) or PLR (OR=1.001, p=0.927) with pCR.*

Conclusion: *Baseline NLR and PLR are not significant predictors of pathological complete response in breast cancer patients receiving neoadjuvant chemotherapy and should not be used as standalone biomarkers in clinical practice.*

Introduction

Breast cancer is one of the most prevalent cancers that is affecting women all over the world. The American Cancer Society has estimated that in 2024, there will be 310,720 new cases of invasive breast cancer in women in the United States and 42,250 deaths.(1) In 2020, Globocan updated the data and there were 178,388 reported cases of

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breast cancer in Pakistan and this rate is expected to rise more in the coming years.(2) Neoadjuvant Chemotherapy (NACT) is generally recognized as a treatment for breast cancer that is given before definitive cancer surgery.(3) It is presently acknowledged as a standard therapeutic approach for patients with high-risk early-stage, including aggressive subtypes such as triple-negative and HER2-positive breast cancer, and locally advanced breast cancer.(4) It is globally established as an effective and evidence-based treatment strategy.(5) The intent of this NACT are multifaceted which include minimizing the overall tumor burden, downstaging axillary lymph node involvement, improving the feasibility of surgical resection and achieving pathological complete response (pCR). Moreover, with NACT chances of achieving successful breast-conserving surgery are enhanced.(6) Among these, pCR is one of the important prognostic markers.

Achieving pCR is a vital factor in anticipating overall survival and disease-free survival in breast cancer after NACT.(7) Traditionally, different characteristics of tumors, mainly including the molecular subtypes were used to predict the response to NACT.(8) However, now inflammatory biomarkers are also being explored for their effect on pCR prediction. Neutrophil-lymphocyte ratio (NLR) and Platelet-lymphocyte ratio (PLR) are the inflammatory markers which affect long term survival in malignancies, and these are also described to be predictive of chemosensitivity.(9) Beside malignancy, the NLR and PLR values are utilized as prognostic and survival markers in different diseases as well.(10)

Accomplishing a pathological complete response (pCR) following NACT is closely linked with enhanced survivorship and thus the ability to predict pCR has significant clinical value.(11) Although genomic assays and tumor-infiltrating lymphocytes indicated potential predictive biomarkers, their expensiveness and limited accessibility narrow their widespread use in clinical practice esp. in low and middle-income countries (LMIC) like Pakistan. On the other hand, systemic inflammatory indices originated from complete blood counts, especially the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inexpensive, reproducible, and routinely available.(11) The progressively clear relationship linking breast cancer response to therapy and its immune microenvironment recently prompted researchers to analyze the role of the peripheral immune system in breast cancer.(12) A recent study revealed that a lower hematological parameter, like NLR & PLR, indicates reduced immune and inflammatory system activation, which can lead to variable clinical outcomes. The response of these specific immune/inflammatory biomarkers to NACT, particularly when considered alongside other factors like, molecular subtypes, chemotherapy regimen, grading, and Ki-67, remains unanalyzed in our setting.(13) Keeping in view these facts, we decided to study the role of NLR and PLR in predicting pCR in breast cancer patients undergoing NACT, to identify practical, readily available and low-cost predictors for chemotherapy response among our patients.

Objective:

- To determine the frequency of pathological complete response in breast cancer patients
- To evaluate mean neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with pCR and non pCR.
- To determine if baseline NLR and PLR values differ significantly between pCR and non-pCR achievers, assessing their potential as predictive biomarkers for NACT outcome in breast cancer

Methodology

A prospective comparative cross-sectional study was performed at the Oncology Department, Fauji Foundation Hospital, Rawalpindi from March 2024 to January 2025 after obtaining approval from the ethical review board. We recruited 74 patients with breast cancer from the out-patient and in-patient departments between 2024 and 2025. The sample size was determined using the World Health Organisation (WHO) sample size calculator, with an expected population

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proportion of 19.2%, a confidence level of 95% and a margin of error of 9%, which gave a total sample size of 74 patients. A consecutive non-probability sampling method was used to select the study participants. The study participants were chosen based on the inclusion and exclusion criteria. The criteria for inclusion were biopsy-proven invasive breast cancer, patients with early and locally advanced disease who were receiving neoadjuvant chemotherapy (NACT), normal liver and renal function tests, treatment-naïve, and age less than 70 years. Exclusion criteria were recurrent, relapsed, or metastatic breast cancer, patients with genetically linked breast cancer, autoimmune diseases, active infections, immunodeficiencies, patients receiving immunosuppressants, and patients with chronic liver disease.

Data Collection:

Data collection was commenced after obtaining approval from the Institutional Ethical Review Committee and verifying the eligibility criteria. Following this, informed consent was obtained from all participants, and a total of 74 patients were enrolled in the study. The variables recorded, included patients' age at diagnosis, clinical stage, hormonal receptor and HER2neu status, type of chemotherapy received and surgery performed. Baseline complete blood counts of the patients were assessed prior to neoadjuvant chemotherapy. Patients subsequently received NACT, followed by definitive surgery in the form of modified radical mastectomy (MRM) or breast-conserving surgery (BCS). Postoperative specimens were subjected to histological assessment to determine pathological complete response (pCR). The baseline hematological parameters were compared with the postoperative histopathological findings to evaluate treatment response. Patients after surgery underwent adjuvant radiotherapy followed by 3 monthly opd visits for history, physical examination, annual mammograms and other imaging as required. Medical records that lacked complete blood count data, cases with recurrent disease, or patients who previously received chemotherapy for another primary malignancy were excluded from the analysis.

Data Analysis:

All the collected data was entered and analyzed with IBM SPSS statistics version 21. Descriptive statistics were calculated for qualitative and quantitative variables. Qualitative variables like stage, receptor status, type of chemotherapy, type of surgery and histopathological response were measured in terms of frequency and percentages. Quantitative analysis like age, baselines hematological measures (total leukocyte count, absolute neutrophil count, absolute lymphocyte count, platelets, neutrophil to lymphocyte ratio and platelet to lymphocyte ratio) were analyzed via calculation of mean and standard deviations. Effect modifiers like age, clinical stage, receptor status, chemotherapy type and type of surgery were stratified by using post stratified Chi square test for histopathological response. Mann Whitney U test was used for NLR and PLR for both groups i.e. CR and PR. For these tests $p < 0.05$ was considered significant and ROC analysis was planned if correlation identified.

Results

The analysis comprised 74 consecutive breast cancer patients who received neo-adjuvant chemotherapy between 2024 and 2025. As detailed in Table 1, the cohort had a median age at diagnosis of 52.5 years (range: 31–74), with the predominant age group being 50–59 years (43.2%). Most patients presented with locally advanced disease –stage 3, with a total percentage of 62.2% (n=46), while 37.8% (n=28) were Stage 2. Analysis of the hormonal profiles revealed that HR-positive tumors were the most prevalent subtype, accounting for 40.5% (n=30) of the study population. This was followed by triple-negative cases at 23% (n=17) and HER2neu positive cases at 20.3% (n=15).

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Table 1- Baseline characteristics of breast cancer patients treated between 2024 and 2025 and included in the present study (n = 74).

Characteristics		n=74
Median Age at diagnosis (range)		52.5 years (31-74)
Stage (n%)	Stage 2	28 (37.8)
	Stage 3	46 (62.2)
Hormonal types (n%)	HR positive	30 (40.5)
	Triple positive	12 (16.2)
	HER2neu positive	15 (20.3)
	Triple negative	17 (23)
Type of Chemotherapy (n%)	DDAC x IV F/B DDpacil x IV	20 (27%)
	AC x IV F/B pacil x IV	37 (50 %)
	TCH x VI	9 (12.2 %)
	TCHP x VI	1 (1.3%)
	FEC III F/B Doce x III	5 (6.8 %)
	Weekly Pacli carbo x IV followed by AC x IV	2 (2.7%)
Type of Surgery (n%)	MRM	52 (70.3 %)
	BCS + ALND	22 (29.7 %)
Histopathological Response (n%)	CR	25 (33.8 %)
	PR	49 (66.2 %)

The descriptive statistics for these parameters are presented in Table 2. The mean total leukocyte count was 8.36 ± 2.0 x10³/µL. The derived counts for the primary inflammatory components revealed a mean absolute neutrophil count of 5.13 ± 1.97 x10³/µL and a mean absolute lymphocyte count of 2.46 ± 0.68 x10³/µL. The mean platelet count was 286.3 ± 87.2 x10³/µL.

Table 2 – Descriptive statistics of hematological parameters

	Mean & Std. Deviation
Total leukocyte count	8.36 ± 2.0
Absolute neutrophil count	5.13 ± 1.97
Absolute lymphocyte count	2.46 ± 0.68
Platelets	286.3 ± 87.2
Hemoglobin	14.01 ± 13.62

To assess the predictive utility of pre-treatment inflammatory markers, pre-chemotherapy Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) were compared between patients achieving pathological complete response (CR; n=25) and those with partial response (PR; n=49) using the Mann-Whitney U test. As shown in Table 3, no significant difference in median NLR (U=544.50, p=0.437) or PLR (U=541.00, p=0.414) was observed between response groups.

Table 3 – Mann-Whitney U Test for NLR and PLR by Histopathological Response

	NLR	PLR
Mann-Whitney U	544.50	541.00
Z value	-0.777	-0.817

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p Value	0.437	0.414

As detailed in Table 4, neither Neutrophil-to-Lymphocyte Ratio (NLR) nor Platelet-to-Lymphocyte Ratio (PLR) demonstrated a significant association with CR. The model yielded a non-significant odds ratio (OR) of 0.7 for NLR (p=0.170; 95% CI: 0.421–1.165), indicating no meaningful predictive effect. Similarly, PLR showed an OR of 1.001 (p=0.927; 95% CI: 0.989–1.013), confirming the absence of a clinically relevant association.

Table 4 – Binary Logistic Regression Analysis of NLR and PLR With Histopathological Complete Response

	Sig.	OR	95% Confidence Interval	
			Lower	Upper
NLR	0.170	0.7	0.421	1.165
PLR	0.927	1.001	0.989	1.013

Discussion

The host immune landscape impacts advance tumor progression and malignant transformation. Neutrophils, being short-lived effector cells of the innate immune system, are increasingly recognized as significant contributors in cancer progression. The tumor cells release cytokines such as TGF-beta, IL-6, and G-CSF which recruits the neutrophils into the tumor microenvironment. These tumor-associated neutrophils (TANs) suppress the anti-tumor activity of lymphocytes, particularly CD8+ cytotoxic T-cells and Natural Killer (NK) cells, through the release of reactive oxygen species (ROS), arginase-1, and the expression of programmed death-ligand 1 (PD-L1).(17) This myeloid-derived suppression creates a biological "shield" that allows tumor cells to withstand the genotoxic stress induced by chemotherapy, thereby reducing the likelihood of achieving pCR.(17,18)

A key mechanism by which platelets exert carcinogenic effects is through the molecular mimicry between platelet-derived growth factors and the products of oncogenes. Due to functional homology with oncogene products, the PDGF receptor facilitates the expression of cellular homologs of myc and fos upon PDGF stimulation.(19) Benoy et al. provided evidence that a high platelet count promotes angiogenesis in tumors.(20) Platelets also secrete pro-invasive enzyme metalloproteinase-9 that accelerates tumor growth.(21) By producing pro-inflammatory mediators like IL-1, IL-3, and IL-6, cancer cells directly promote the proliferation of platelet progenitor cells. The antitumor function of lymphocytes in the tumor microenvironment is well-established, and recent evidence confirms that greater tumor infiltrating lymphocytes (TIL) is a positive prognostic indicator for breast cancer outcomes.(22) Effective antitumor immunity relies on a two-phase cellular mechanism. In the priming phase, $CD4^+$ T helper-1 cells license antigen-presenting cells through cytokine release, amplifying tumor antigen visibility. In the effector phase, activated $CD8^+$ cytotoxic T cells infiltrate the tumor and mediate its direct destruction.(23) Given the evidence for breast cancer's immune-dependent nature, monitoring systemic inflammatory markers can be an essential component of effective treatment monitoring. Therefore, their ratios like the NLR and PLR are the upcoming systemic inflammatory indices, which are easily measurable and evolving promising prognostic tools in breast cancer management.

Hence, studies have been carried out determining the prognostic value of the NLR and PLR in breast cancer. Koh et al. established that elevated levels of the systemic inflammatory markers NLR and PLR serve as robust predictors of poor breast cancer prognosis.(24) The prognostic utility of the NLR has been explored in relation to molecular subtypes, with evidence indicating it serves as an adverse marker in luminal A breast cancers.(25) Conversely, separate research supports its prognostic relevance in triple-negative breast

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cancer (TNBC) populations.(26) The prognostic utility of the PLR remains a subject of debate. However, our results align with a segment of literature that questions the universal applicability of these inexpensive biomarkers.

Conclusion

In conclusion, our findings suggest that baseline NLR and PLR alone are not significant predictors of pCR in a mixed Pakistani breast cancer cohort receiving NACT. The conflicting results across the literature indicate that the predictive value of these inexpensive biomarkers may be population-specific, subtype-dependent, and enhanced by combined marker approaches. Future research should focus on larger, multi-center prospective studies in South Asian populations, with standardization of cut-off values, stratification by molecular subtype, and inclusion of composite inflammatory markers to determine their true predictive potential in routine clinical practice.

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