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**The role of baseline peripheral neutrophil to lymphocyte
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The role of baseline peripheral neutrophil to lymphocyte ratio in predicting response to neoadjuvant chemotherapy in breast cancer

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ABSTRACT

Background: Breast cancer is a major health problem all over the world. Neutrophil-to-lymphocyte ratio (NLR) is an easy, cost-effective, readily available diagnostic tool for systemic inflammation. **Aim:** We aimed to evaluate whether baseline peripheral neutrophils to lymphocytes ratio in the peripheral blood of breast cancer patients are correlated with pathological complete response (pCR) following neoadjuvant chemotherapy. **Patients & Methods:** This Observational prospective cohort study was carried out in the Clinical Oncology Department, Helwan University Hospitals from October 2022 to September 2023. The study involved 50 females with breast cancer who underwent treatment with neoadjuvant chemotherapy protocol. **Results:** In this study, 17 patients (34%) achieved statistically significant pCR following neoadjuvant chemotherapy among the patients with lower NLR as compared to the patients with high NLR. Our study showed also that 12 (66.7%) patients in the lower NLR (<1.69) achieved pCR, while only 5 (15.6%) patients in the high NLR (≥ 1.69) achieved pCR (P value=0.002). **Conclusion:** Lower baseline peripheral NLR is associated with better rates of pCR in breast cancer patients receiving neoadjuvant chemotherapy, reflecting better treatment outcomes.

Keywords: Breast cancer, Neutrophil-to-lymphocyte, ratio, pathological complete response

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INTRODUCTION

Breast cancer is the most often diagnosed malignancy and ranks second in the leading causes of death amongst women globally. In 2020, about 2.3 million women were diagnosed with breast cancer and around 0.7 million passed away from the disease (Sung *et al.*, 2020).

In Egypt, breast cancer accounts for 33% of all female malignancies. Every year there are more than 22,000 newly diagnosed cases. With this increasing incidence, physicians' goal is to establish the standard of care for breast cancer (Sung *et al.*, 2020).

Neoadjuvant chemotherapy has become the standard of care for locally advanced breast cancer, TNBC, and HER2-enriched subtypes, with a subsequent rise in the breast conservative surgeries rates and improved aesthetic outcomes. Furthermore, the response to neoadjuvant chemotherapy tells us

important information about the biology and prognosis of the tumor and guides the management after surgery (Korde *et al.*, 2021).

Studies found that patients with pathological complete response (pCR) tend to have a favorable prognosis and overall survival than those who have residual disease (Yau *et al.*, 2022). Researchers studied clinicopathological variables linked to pCR in breast cancer patients who received neoadjuvant chemotherapy, with tumor size and molecular subtype being two of the most well-known factors (Li *et al.*, 2017).

Inflammation is a key player in the biology of cancer. In 2011, Hanahan and Weinberg identified inflammation as one of the hallmarks of cancer development and this led to the acceptance that tumor-induced inflammation contributes to cancer progression (Hanahan and Weinberg 2011).

Neutrophils have direct and indirect pro-tumor effects during the early stages of tumor

initiation and growth while lymphocytes are responsible for anti-tumor immune responses. The interaction between neutrophils and lymphocytes in inflammatory responses holds significant clinical importance in the development of cancer. Therefore, the neutrophil-to-lymphocyte ratio (NLR) may serve as an indicator of the equilibrium between the activation of inflammatory pathways and the antitumor immune response in breast cancer (Li *et al.*, 2018).

Many researchers have studied the relationship between basal NLR and the response of breast cancer to neoadjuvant chemotherapy and whether they will achieve a pathological complete response or not. While many studies found that NLR is an independent prognostic factor, there is still some controversy over its value (Hernández *et al.*, 2018).

AIM OF THE WORK

The objective of this study was to assess if the baseline peripheral neutrophil-to-lymphocyte ratio (NLR) in breast cancer patients is associated with pathological complete response (pCR) after neoadjuvant chemotherapy or not.

PATIENTS & METHODS

This is a prospective observational cohort study which involved 50 patients and was conducted at the Clinical Oncology Department of Helwan University Hospitals from October 2022 to September 2023. Approval was obtained from Helwan University Institutional Review Board (Ethical Approval Number :61-2022). Consents from all patients before participating in the study were obtained. This study adhered to the Declaration of Helsinki, which serves as the ethical guideline established by the international Medical Association for research involving human participants. The inclusion criteria were 1) female patient with pathologically proven breast cancer 2) performance status 0 to 1 according to ECOG score 3) patients who are indicated for neoadjuvant chemotherapy. The exclusion criteria were 1) male patient with breast cancer 2) metastatic breast cancer 3) Patients with breast carcinoma in situ. 4) Suffers from any chronic autoimmune or inflammatory disease

or any disease affecting NLR. 5) Pregnant patients.

Sample size

Through using z score table with confidence interval (95%) and power at 80% with consideration of estimated prevalence ratio of the disease in Egypt; it is estimated that sample size of 50 women can detect whether breast cancer patient baseline peripheral neutrophil to lymphocyte ratio (NLR) values are correlated with pathological complete response (pCR) following neoadjuvant chemotherapy treatment.

Methods

1. Before starting neoadjuvant chemotherapy, all patients underwent:
 - full labs included (CBC-liver functions test-renal functions test)
 - Echocardiography
 - Either PET/CT or CT scan with contrast of abdomen, pelvis and chest along with a bone scan
 - Biological profile (ER – PR – HER 2 – Ki 67).
 - Patients were categorized into four distinct molecular subtypes:
 - Luminal A: characterized by estrogen receptor positivity (ER+) and progesterone receptor strong positivity (PR+), negative for HER2 (HER2–), and a Ki67 level of less than 20.0%.
 - Luminal B: defined as ER+ and/or PR+, HER2– with a Ki67 level of 20.0% or greater, or ER+ and/or PR+ with HER2+ regardless of Ki67 levels.
 - HER2 enriched: identified as ER–, PR–, and HER2+.
 - Triple-negative breast cancer (TNBC): classified as ER–, PR–, and HER2–.
2. The neutrophil to lymphocyte ratio (NLR) was determined by calculating the ratio of absolute neutrophil counts to absolute lymphocyte counts obtained from a peripheral blood sample prior to starting the first dose of neoadjuvant chemotherapy with a cut-off value of 1.69 based on a recent study by Zhu *et al.*, 2021.
3. A standardized neoadjuvant chemotherapy protocol was given to all enrolled patients; The treatment regimen consisted of Adriamycin and Cyclophosphamide,

administered on day 1 with Doxorubicin at a dosage of 60 mg/m² intravenously, and Cyclophosphamide at 600 mg/m² intravenously. This cycle was repeated every 21 days for a total of four cycles. Subsequently, Paclitaxel was given at a dosage of 80 mg/m² on a weekly basis for a duration of 12 weeks. Her 2 positive patients received trastuzumab + pertuzumab along with chemotherapy. And TNBC received carboplatin weekly alongside paclitaxel.

- Response to neoadjuvant chemotherapy was evaluated by radiological and pathological examination and correlated to NLR.

Pathological complete response (pCR) is defined as no evidence of residual invasive carcinoma in the fully resected breast specimen and in all examined regional lymph nodes, regardless of whether residual ductal carcinoma in situ (DCIS) is present or absent (ypT0/is ypN0) (Gradishar *et al.*, 2021).

Statistical analysis

The data gathered from various sources, including (history records, basic clinical examinations, laboratory tests, and outcome measures) were systematically coded, entered, and subsequently analyzed using Microsoft Excel software. Following this, the data were imported into the Statistical Package for the Social Sciences (SPSS version 20.0) for further analysis. Qualitative data were expressed in terms of numbers and percentages, while quantitative data were presented as mean ± standard deviation (SD). The Chi-square test and Mann–Whitney U test was employed to compare qualitative and quantitative variables, respectively. A significant value was established at $p < 0.05$ for statistically significant results and $p < 0.001$ for highly significant results.

RESULTS

Baseline clinicopathological characteristics

This study involved 50 females with breast cancer, their mean age was 45.5±10.17 years. 60% were premenopausal and 50% of tumors were left sided and 50% were right sided. For pathological parameters, the predominant classification was cT2 (38%). cN1 was the

prevalent category (50%). Stage III constituted the largest proportion of patients (60%) and Luminal B accounted for the majority (48%) of cases. As for histopathological subtype, ductal carcinoma comprised 98.0% of cases and grade 2 accounted for 84% as illustrated in Tables 1 and 2.

Relation between NLR level and clinicopathological parameters

No significant correlation was found between NLR and clinical parameters (age, menopausal status and site) or between NLR and histopathological parameters (T status, N status, stage, molecular subtype, and histopathological subtype and grade) as shown in Tables 3 and 4.

Table 1. Clinical parameters of- the studied group

		Age	
Mean± SD		45.10±10.17	
Median (Range)		44.0 (25-70)	
		N	%
Menopausal status	Pre	30	60.0
	Post	20	40.0
Site	Left	25	50
	Right	25	50
	Total	50	50

Table 2. Histopathological parameters of the tumor in the studied group

		N=50	%
T status	cT1	3	6.0%
	cT2	19	38.0%
	cT3	14	28.0%
	cT4	14	28.0%
LN status	cN 0	10	20.0%
	cN 1	25	50.0%
	cN 2	9	18.0%
	cN 3	6.	12.0%
Stage	I	1	2.0%
	II	19	38.0%
	III	30	60.0%
Molecular subtype	HER2 enriched	9	18.0%
	Luminal A	9	18.0%
	Luminal B	24	48.0%
	Triple -ve	8	16.0%
Histopathological subtype	Ductal	49	98.0%
	Mucinous	1	2.0%
Grade	Grade 1	1	2.0%
	Grade 2	42	84.0%
	Grade 3	7	14.0%

Table 3. Relation between NLR level clinical parameters

			Low NLR	High NLR	t/ X ²	P
Age			42.9±9	46.3±10.7	-1.13	0.265
Menopausal status	Post	N	6	14	0.52	0.470
		%	33.3%	43.8%		
	Pre	N	12	18		
		%	66.7%	56.3%		
Site	Left	N	12	13	3.12	0.077
		%	66.%	40.6%		
	Right	N	6	19		
		%	33.3%	59.4%		

Table 4. Relation between NLR level histopathological parameters

			Low NLR	High NLR	t/ X ²	P
T status	cT1	N	2	1	2	0.571
		%	11.1%	3.1%		
	cT2	N	6	13		
		%	33.3%	40.6%		
	cT3	N	6	8		
		%	33.3%	25.0%		
	cT4	N	4	10		
		%	22.2%	31.3%		
N status	cN0	N	3	7	1.6	0.657
		%	16.7%	21.9%		
	cN1	N	11	14		
		%	61.1%	43.8%		
	cN2	N	2	7		
		%	11.1%	21.9%		
	cN3	N	2	4		
		%	11.1%	12.5%		
Stage	I	N	1	0	2.55	0.279
		%	5.6%	0.0%		
	II	N	8	11		
		%	44.4%	34.4%		
	III	N	9	21		
		%	50.0%	65.6%		
Molecular subtype	HER2 enriched	N	5	4	6.36	0.096
		%	27.8%	12.5%		
	luminal A	N	3	6		
		%	16.7%	18.8%		
	luminal B	N	5	19		
		%	27.8%	59.4%		
	Triple negative	N	5	3		
		%	27.8%	9.4%		
Histopathological subtype	Mucinous	N	0	1	0.574	0.448
		%	0.0%	2.0%		
	Ductal	N	18	31		
		%	100.0%	98.0%		
Grade	Grade 1	N	0	1	2.05	0.359
		%	0.0%	3.1%		
	Grade 2	N	14	28		
		%	77.8%	87.5%		
	Grade 3	N	4	3		
		%	22.2%	9.4%		

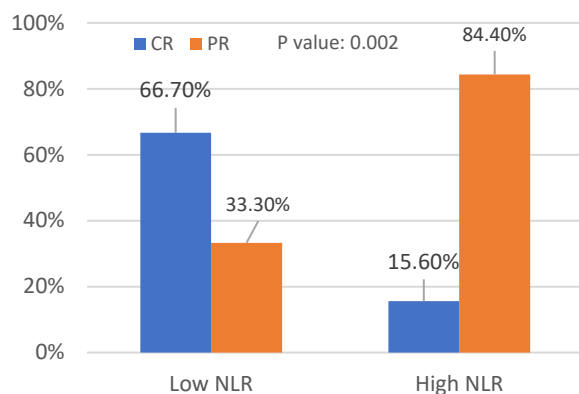


Figure 1. Relation between NLR and response in the studied group

Relation between NLR and response

17 patients (34%) achieved pCR following neoadjuvant chemotherapy with statistically significant higher pCR rates among the group with a lower NLR in comparison to the group with a higher NLR. These results demonstrate that 12 (66.7%) patients in the lower NLR (≤ 1.69) achieved pCR while 5 (15.6%) patients in the high NLR (≥ 1.69) achieved pCR (P value=0.002) as shown in Figure 1.

DISCUSSION

The current study did not reveal any statistically significant correlation between the baseline NLR and clinical parameters (age, menopausal status, and tumor site) or histopathological parameters (T status, N status, stage, molecular subtype, and histopathological subtype and grade). In contrast to Zhu *et al.*, 2021 who found that low NLR was associated with older age and postmenopausal women but no correlation with other clinicopathological parameters.

Jadoon *et al.*, 2023 retrospectively studied 2050 breast cancer patients found that higher NLR was correlated with higher clinical tumor stage, triple negative subtype, HER 2 positive subtype, younger age, positive lymph node status. Nakano *et al.*, 2014 conducted a retrospective analysis involving 167 Japanese female patients diagnosed with stage I to III breast cancer and found a correlation between higher NLR and higher grade and younger age but no correlation with other clinicopathological parameters. Takeuchi *et al.*, 2017 carried out a retrospective review of 269 patients who had surgery for localized breast cancer. The relation

between clinicopathological characteristics and NLR was evaluated and found that higher NLR was associated with higher tumor stage only but not with other clinicopathological parameters. The variation in the relation between NLR and clinicopathological parameters in different studies may be attributed to different NLR cut off value between different studies and different patient characteristics.

In the current study, 17 patients (34%) achieved pCR following neoadjuvant chemotherapy with statistically significant higher pCR rates in the group with lower NLR compared to the high NLR group (P value=0.002). These results agreed with a meta-analysis of 11 studies conducted by (Xue *et al.*, 2019) incorporating 2107 breast cancer patients. The meta-analysis indicated a significant correlation between elevated NLR and unfavorable responses to neoadjuvant chemotherapy. The findings were consistent with a meta-analysis conducted by (Cullinane *et al.*, 2020) which examined eight studies involving 1,586 patients. Among these patients, 363 (22.88%) had a pathological complete response (pCR) following neoadjuvant chemotherapy. The analysis revealed that a lower neutrophil-to-lymphocyte ratio (NLR) correlated with an increased likelihood of achieving pCR (odds ratio, 1.83; 95% confidence interval, 1.15-2.91; P < 0.0003). This meta-analysis identified NLR as a significant predictor of pCR in individuals diagnosed with breast cancer. These results are also aligned with Chen *et al.*, 2016 who retrospectively analyzed a total of 215 patients and found that patients with lower pretreatment NLR had higher pCR rates compared to those with higher NLR levels (24.5 % vs.14.3 %, p < 0.05).

In the same way Zhou *et al.*, 2021 identified a total of 19 studies. The effect of NLR on pCR was extracted and combined from each study. The findings suggested that patients with a low NLR experienced higher pCR rates (odds ratio, 1.620, 95% confidence interval, 1.209-2.169, p < 0.001). Similarly, Zhu *et al.*, 2021 retrospectively analyzed outcomes from 1435 primary breast cancer patients who underwent neoadjuvant chemotherapy and found that higher pCR rates were associated with low NLR (P = 0.005). A further multivariate logistic regression analysis showed that NLR was an

independent predictor of patient pCR (odds ratio, 2.034, 95% confidence interval, 1.178–3.512, $P = 0.011$).

In contrast to the results in this study Muñoz-Montaño *et al.*, 2020 and Suppan *et al.*, 2015 examined the pretreatment NLR of patients undergoing neoadjuvant chemotherapy and did not observe a relationship between pCR and NLR. This difference might be due to different patients' characteristics and different regimen of chemotherapy that were used and different NLR cut-off value. The current study's strengths lie in its prospective design with a standard chemotherapy regimen used for all patients and no patients with chronic inflammatory or autoimmune disease were included. The limitation of this study consists of being conducted at only one center, as well as having a rather small sample size and it did not study the effect of NLR on DFS and OS.

CONCLUSION

In conclusion, a lower baseline peripheral neutrophil-to-lymphocyte ratio is correlated with increased rates of pathological complete response (pCR) in breast cancer patients receiving neoadjuvant chemotherapy which reflects better treatment outcomes.

LIMITATION

Further multicenter prospective research studies with larger sample size are necessary to ascertain the role of baseline peripheral NLR in predicting response among breast cancer patients receiving neoadjuvant chemotherapy and its role in predicting DFS and OS in conjunction with other inflammatory biomarkers, including platelet-lymphocyte ratio (PLT), C-reactive protein (CRP) and tumor necrosis factor (TNF).

CONFLICT OF INTEREST

All authors of this work declared that there was no conflict of interest.

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The current study is self-funded.

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