ORIGINAL ARTICLE

Prognostic significance of pretreatment inflammatory biomarkers in non-metastatic breast cancer

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ABSTRACT

Background: Recently, peripheral blood inflammatory biomarkers such as neutrophil-lymphocyte ratio (NLR) have been identified for their prognostic role in many types of cancers. Elevated NLR was associated with poor prognosis & increased mortality rates. This study assessed the predictive value of pretreatment NLR in non-metastatic breast cancer.
Objective: To assess the role of pretreatment NLR in non-metastatic breast cancer and their effect on prognosis in terms of 5 years disease-free survival and overall survival.
Methods: This retrospective cross-sectional study was conducted in Suez Canal University Hospitals in Ismailia, Egypt. 105 patients with pathologically proven breast cancer were recruited from January 2015 to December 2016. Patients & tumor characteristics were collected from medical records. Five-year overall survival & disease-free survival were analyzed.
Results: Mean patients' ages were 47.82 $\pm$ 11.65. The age ranges were between 25 & 78 years. There was no statistical significance between patients with low & high pretreatment NLR in terms of patients' characteristics & tumor variables. With the ROC curve, the cut-off points for NLR were 1.65 & 1.55 for DFS and OS, respectively. In terms of patients' DFS & OS, no statistically significant difference was found between non-metastatic breast cancer patients with low & high NLR ($p_{long-rank}$ = .357 and .236, respectively). No statistically significant difference was found between patients with low & high pretreatment NLR in the period of five years OS & DFS.
Conclusions: Pretreatment NLR is an inflammatory biomarker that might affect patient prognosis and survival. Further research is required to confirm the prognostic significance.

Key Words: NLR, Inflammatory biomarker, Prognosis, Breast cancer

1. INTRODUCTION

Breast cancer (BC) is the most common malignant tumor among females and one of the most common causes of mortality worldwide.[1,2]

In Egypt, Breast cancer represents 38.8% of cancer among females. The number of cases was approximately 22,700 in 2020 & expected to be about 46,000 in 2050.[3] Breast cancer, following liver cancer, is the second cause of mortality among Egyptian females, with a mortality rate about 11%.[4]

Patient's ages & stages at the time of presentation were compared between Gharbia Cancer Registry (GCR) and the U.S. Surveillance, Epidemiology, and End Results (SEER) Program database (for 2004–2008). Results revealed that GCR cases were an entire decade younger than SEER, with a mean age of 51.0 versus 61.4 years.[5,6]

About 19% of patients were less than or equal to 40 years

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in Gharbia Cancer Registry. In SEER, only 6% of cases were less than or equal to 40 years. In addition, a significant difference in the patient's stage at the time of diagnosis exists among both groups. Those results should be taken into consideration and would put the cornerstone for planning a breast cancer screening program.[6]

Management and prognosis depend upon tumor characteristics, patient characteristics, and response to treatment.[7] However, tumor microenvironment, inflammatory mediators, and immune response play a significant role in treatment outcome and patient prognosis.[8,9]

Inflammatory mediators and immune response to cancer in the tumor microenvironment are the significant hallmarks of malignancy.[8] Recently, more efforts have been performed, leading to the development of immunotherapy, a new promising treatment modality. The Inflammatory response in the tumor microenvironment affects the survival of the tumor cell, tumor cell growth, and tumor angiogenesis.[10]

Breast cancer tumor microenvironment has cellular, soluble, and physical components. The cellular features include local, regional, and metastatic compartments. The Local (intratumoral) component consists of the tumor-infiltrating inflammatory cells within the tumor tissue. The regional (breast) components consist of the infiltrating edges of cancer with the interaction between the tumor cells and the adjacent host cells. The host cells at the adjacent lymphatics and distant organs are the metastatic compartment of the tumor microenvironment. The soluble and physical components include various enzymes, cytokines, and growth factors playing a significant role in tumor progression.[11]

Many meta-analyses revealed that elevated pretreatment NLR & PLR represent poor breast cancer prognosis.[12–14] The NLR is a well-known prognostic factor in many types of cancer and in early-stage breast cancer, with an elevated level being associated with worse prognosis in Asian and Western populations as well.[15–19]

We conducted this study to assess the role of pretreatment NLR in non-metastatic breast cancer and their effect on prognosis in terms of DFS and OS.

2. METHODS

2.1 Study design

A retrospective cross-sectional study was conducted in Clinical Oncology & Nuclear Medicine department, in Suez Canal University Hospital, Ismailia, Egypt between January 2015 to December 2016, with a follow-up period of five years after that.

2.2 Target population

The target population includes Histo-pathologically proven non-metastatic breast cancer patients who received first-line chemotherapy treatment.

Inclusion criteria:

(1) Patients diagnosed with non-metastatic breast cancer from January 2015 to December 2016.
(2) Patients with documented pretreatment neutrophils & lymphocytes were included.
(3) ECOG Performance status ≥ 2.

Exclusion criteria:

(1) Patients diagnosed with other cancer rather than breast cancer.
(2) Patients with metastasis from the start were excluded.
(3) Male Breast cancer patients were excluded.
(4) Patients who received neoadjuvant chemotherapy.
(5) Patients without available pathology reports and laboratory test results.
(6) Patients with hematological disorders, long-term corticosteroid use, or any acute or systemic chronic inflammatory disease were excluded.
(7) Patients with ECOG PS > 2.

2.3 Sample size justification

The equation for sample size calculation (n = 20, see equation 1):

$$n = \frac{(Z_{1-\frac{\alpha}{2}})^2 \times p(1-p)}{d^2} \quad (1)$$

Where: n = the sample size;
$Z_{1-\frac{\alpha}{2}}$ = 1.96 when the type one error is 5% (confidence interval);
p = the 5-year disease-free proportion among breast cancer patients of NLR ≥ 3 equals 47.8% based on previous literature. (Ramos-Esquivel et al, 2017);
d = often equal 10% (precision or absolute error).

The sample size was 105 participants.[21,22]

2.4 Sampling technique

Simple random sample method was used.

2.5 Data collection tool and study procedure

Data were collected from patient's medical records. A list of all eligible patients from January 2015 to December 2016, with follow-up five years after that, was retrieved from the patient's records.

Data collected include:

Personal data: age at diagnosis; TNM staging system at the time of presentation; ECOG Performance status; Comorbidities (Diabetes, Hypertension, Cardiac diseases, chronic kidney disease, Rheumatoid arthritis, HCV); Tumor variables: histological subtype, degree of differentiation, pathological characteristics & hormonal receptors were collected from patient's files; Baseline investigations: chest X-ray, abdominal ultrasound; Management received with the assessment of treatment response and management outcomes were determined.

Procedure:

Patient's pretreatment complete blood count (with differential WBC) were collected from medical records. The WBC count, the percentage & total count of neutrophils and lymphocytes were calculated. The NLR was estimated by dividing the absolute neutrophil count by the absolute lymphocyte count.

2.6 Data management and statistical analysis

Analyses were done using SPSS with Windows version 22.0. Descriptive data were analyzed as mean ± *SD* or percentages. We used the chi-square test for statistical analysis of categorical variables. We assessed means differences by independent *t*-test.

Since no validated cut-off points for NLR were recognized in previous data, the optimal cut-off points were determined by both receiver operative curves (ROC) analysis (the maximum specificity and sensitivity) for five years' DFS and OS. Survival curves stratified were analyzed using the Kaplan-Meier plots and compared with the log-rank test. *P* value > .05 was statistically significant.

2.7 Ethical considerations

The Research ethics committee in FOMSCU has approved this work. We analyzed data collection and analysis confidentially.

3. Results

We conducted this study to assess the role of pretreatment NLR in non-metastatic breast cancer and their effect on prognosis in terms of 5 years DFS and OS. We included 105 non-metastatic breast cancer patients.

Patient characteristics: The mean patient's age was 47.82 ± 11.65. patient's ages ranged between 25 & 78 years old. Most patients (34.3%) had at least a history of one chronic illness. 20% of patients were hypertensive, and 15.2% were diabetic. About 90% of the patients had invasive ductal carcinoma and grade II disease. Most patients were stage IIA, and about 25% had stage IIIA and IIIC. About 22% of the patients had a multicentric tumor. Two-thirds of the patients had luminal receptors, while about 23% had Her2 enriched receptors, and about 16% had triple negative receptors. More than 85% of the patients had modified radical mastectomy. We illustrated patient's characteristics in Table 1.

Table 1. Baseline characteristics of the studied sample (n = 105)

Variables	N (%)
Age (years)	
Mean ± *SD*	47.82 ± 11.65
Median (range)	45 (25–78)
Chronic illnesses	
Absent	69 (65.7%)
Present	36 (34.3%)
Hypertension	21 (20%)
Diabetes mellitus	16 (15.2%)
Cardiac	6 (5.7%)
HCV	5 (4.8%)
Rheumatoid arthritis	1 (1%)
Histological subtype	
IDC	94 (89.5%)
ILC	8 (7.6%)
Mixed	3 (2.9%)
Multicentricity	23 (21.9%)
Grade	
I	4 (3.8%)
II	94 (89.5%)
III	7 (6.7%)
Tumor size	
T_1	21 (20%)
T_2	71 (67.6%)
T_3	12 (11.4%)
T_4	1 (1%)
Nodal involvement	
N_0	30 (28.6%)
N_1	28 (26.7%)
N_2	22 (21%)
N_3	25 (23.8%)
Stage	
IA	7 (6.7%)
IIA	43 (41%)
IIB	5 (4.8%)
IIIA	25 (23.8%)
IIIC	25 (23.8%)
EXE	46 (43.8%)
PNI	3 (2.9%)
LVI	24 (22.9%)
Receptor	
ER	68 (64.8%)
PR	59 (56.2%)
Her 2neu	23 (21.9%)
Molecular classification	
Luminal	64 (61%)
Her2 enriched	24 (22.9%)
Triple-negative	17 (16.2%)

Table 2. Treatment characteristics of the studied sample (n = 105)

Variables	N (%)
Surgery	
Modified radical mastectomy (MRM)	92 (87.6%)
Conservative breast surgery (CBS)	13 (12.4%)
Radiotherapy	
No	2 (1.9%)
Yes	103 (98.1%)
Hormonal therapy	
No	34 (32.4%)
Yes	71 (67.6%)
Target therapy	
No	93 (88.6%)
Yes	12 (11.4%)

Table 3. The pattern of metastasis among patients with breast cancer

Variables	N (%)
Recurrence	
Absent	71 (67.6%)
Present	34 (32.4%)
The Pattern of metastasis (n = 34)	
Locoregional	1 (2.9%)
Distant	28 (82.4%)
Mixed	5 (14.7%)

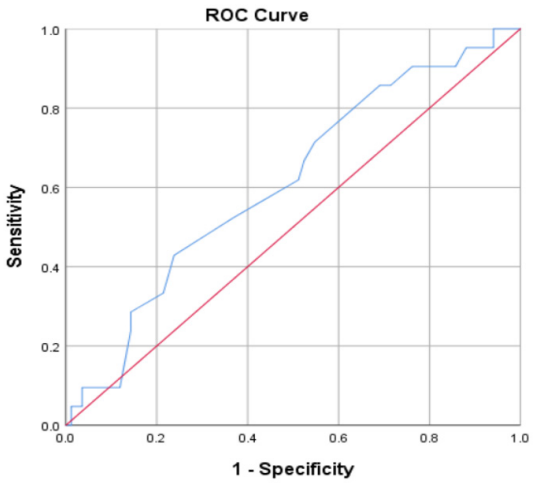

Figure 1. ROC curve of NLR for overall survival

Moreover, almost all patients had chemotherapy and radiotherapy, and about two-thirds had hormonal therapy after that. Only 11.4% of the patients had target therapy (see Table 2). 32.4% had recurrence. Distant metastasis was the most typical pattern of metastasis (see Table 3).

NLR values and association with clinical and pathological variables: Neutrophil lymphocyte ratio cut-off point for overall survival was determined as 1.55 with the ROC curve (see Figure 1). We found no correlation with the age of the patient. High NLR was 53.3% of the total sample with a mean value 1.86 ± 0.97 & median value of 1.60. Low NLR was 46.7% of the studied sample. Patients with high NLR were 53.3% of the total sample (see Table 4).

Table 4. The NLM among the studied sample (n = 105)

NLR	N (%)
Mean ± *SD*	1.86 ± 0.97
Median (range)	1.60 (0.40–6.20)
Low NLR, n (%)	49 (46.7%)
High NLR, n (%)	56 (53.3%)

Analysis of patient's demographic & treatment characteristics are shown in Table 5. Results revealed no statistically significant difference between patients with low NLR and high NLR regarding patients' demographic, tumor pathological, and treatment characteristics (see Table 5).

Progression-free and overall survival association with NLR: Analysis of overall survival revealed that the mean patient's overall survival was 54.16 months (95%CI 50.91–57.40) & 57.33 months (95%CI 55.36–59.31) in patients with low & high NLR, respectively (see Table 6). Mean DFS was 54.589 (95%CI 51.606–57.572) & 57.388 months (95%CI 55.133–59.642) for patients with low and high NLR, respectively (see Table 7).

The Neutrophil lymphocyte ratio cut-off point for OS was determined as 1.55 with the ROC curve & cut-off point for DFS was 1.65. No statistically significant difference presents between patients with low & high NLR in the OS & DFS ($p_{log-rank}$ = .236, .357, respectively) (see Figures 2 and 3).

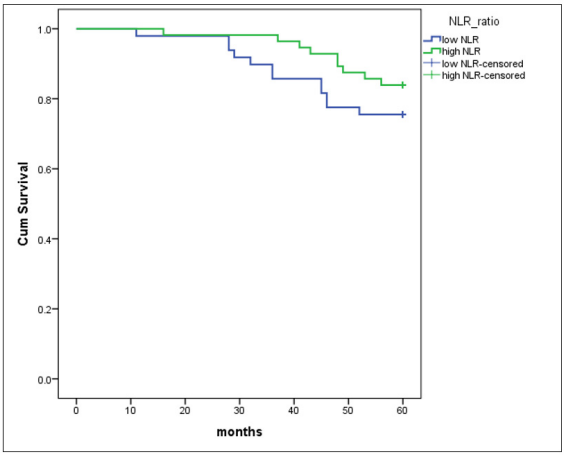

Figure 2. Kaplan–Meier curve of overall survival of patients with low NLR and high NLR

Table 5. Comparison between low NLR and high NLR regarding patients' & tumor characteristics

Variables	Low NLR (n = 49)	High NLR (n = 56)	*p*-value
Age (years)			
Mean ± *SD*	49.04 ± 11.678	46.75 ± 11.633	.317[a]
Median (range)	51 (30–69)	45 (25–78)	
Chronic illnesses			
Absent	32 (65.3)	37 (66.1)	.934[b]
Present	17 (34.7)	19 (33.9)	
Pathological features			
Histological subtype			
IDC	44 (89.3)	50 (89.3)	.686[b]
ILC	3 (6.1)	5 (8.9)	
Mixed	2 (4.1)	1 (1.8)	
Multicentricity			
No	38 (77.6)	44 (78.6)	.900[a]
Yes	11 (22.4)	12 (21.4)	
Grade			
I	1 (2.0)	3 (5.4)	.587[b]
II	44 (89.8)	50 (89.3)	
III	4 (8.2)	3 (5.4)	
Tumor size			
T_1	9 (18.4)	12 (21.4)	.838[a]
T_2	35 (71.4)	37 (66.1)	
Nodal involvement			
N_0	14 (28.6)	16 (28.6)	
N_1	12 (24.5)	16 (28.6)	.853[a]
N_2	12 (24.5)	10 (17.9)	
N_3	11 (22.4)	14 (25)	
Stage			
IA	3 (6.1)	4 (7.1)	
IIA	24 (42.9)	22 (39.3)	
IIIA	14 (28.6)	11 (19.6)	.245[b]
IIB	0 (0)	5 (8.9)	
IIIC	11 (22.4)	14 (25)	
EXE	23 (46.9)	23 (41.1)	.545[a]
PNI	2 (4.1)	1 (1.8)	.481[b]
LVI	12 (24.5)	21 (21.4)	.709[a]
Receptor			
ER	28 (57.1)	40 (71.4)	.126[a]
PR	25 (51)	34 (60.7)	.318[a]
Her 2neu	11 (22.4)	12 (21.4)	.900[a]
Molecular classification			
Luminal	26 (53.1)	38 (67.9)	
Her2 enriched	11 (22.4)	13 (23.2)	.090[b]
Triple-negative	12 (24.5)	5 (8.9)	
Management			
Surgery			
MRM	46 (93.9)	46 (82.1)	.082[a]
CBS	3 (6.1)	10 (17.9)	.082[a]
Radiotherapy			
No	1 (2)	1 (1.8)	.924[b]
Yes	48 (98)	55 (98.2)	
Hormonal therapy			
No	19 (38.8)	15 (26.8)	.190[a]
Yes	30 (61.2)	41 (73.2)	
Target therapy			
No	44 (89.8)	49 (87.5)	
Yes	5 (10.2)	7 (12.5)	.767[b]

Note. [a] *p*-values are based on Mann Whitney *U* test. Statistical significance at $p < .05$; [b] *p*-values are based on Chi square test. Statistical significance at $p < .05$; [c] *p*-values are based on Fisher Exact test. Statistical significance at $p < .05$

Table 6. Overall survival of patients with low and high NLR

Variables	Mean (months)	Standard error	95%CI	*p*-value
Low NLR	54.16	1.656	(50.91–57.40)	.236
High NLR	57.33	1.01	(55.36–59.31)	

Table 7. Disease-free survival of patients with low and high NLR

Variables	Mean (months)	Standard error	95%CI	*p*-value
Low NLR	54.589	1.522	(51.606–57.572)	.357
High NLR	57.388	1.150	(55.133–59.642)	

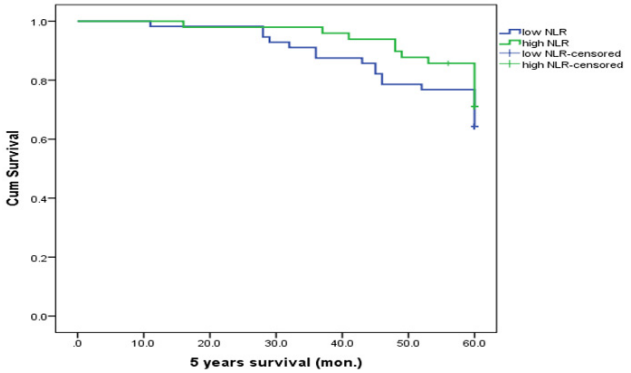

Figure 3. Kaplan–Meier curve of disease-free survival of patients with low NLR and high NLR

4. Discussion

Recently, peripheral blood inflammatory biomarkers have been used as new predictive and prognostic factors in breast cancer, mainly NLR and PLR. pretreatment-elevated NLR was associated with poor responses to treatment and poor prognosis.[23,24] We recruited One hundred and five non-metastatic breast cancer patients between January 2015 and December 2016. We calculated NLR from pretreatment complete blood counts. We collected and analyzed the patient's clinical & pathological characteristics, and received plan of management. Follow up period was five years.

The mean age of the patients was 48 years. We found no statistically significant difference in both patient's groups. Similarly, in a previous study assessing NLR prognostic values for breast cancer, the mean age was 54 years, and there was no statistical significance of age to low or high NLR.[21]

In our study, only 34% of patients had chronic illnesses, with no statistical association with NLR. The same was found in a previous study showing pretreatment NLR ratio as a predictor of poor prognosis and survival in breast cancer. There was no statistical significance of patients' co-morbidities to NLR.[19]

In the current study, disease clinical and pathological characteristics, including histological subtypes, multicentricity, tumor grade, tumor size, nodal involvement, tumor stage, extranodal extension, perineural invasion, lymph vascular invasion, ER, PR, Her2, and molecular subtypes, were not significantly associated with NLR. On the contrary, in a study evaluating NLR in different stages of breast cancer, there was a significant association between NLR and LN staging, LVI, and tumor staging. Yet, there was no association between NLR and estrogen receptor and HER2 status. Invasive ductal carcinoma of the breast was not significantly correlated with NLR, but there was a significant relation between invasive lobular carcinoma and NLR < 1.8 and NLR > 3.3.[25]

Hong et al. assessed elevated preoperative NLR to DFS and prognosis in Chinese women with breast cancer; nodal involvement, and tumor stage were the only significant clinicopathological factors associated with NLR.[26] This may be explained by the larger sample size, the larger mean of age, and the higher NLR cut-off value in these studies compared to our research.

In the current study, patients' treatment strategies, including radiotherapy, hormonal, and targeted treatment, were all insignificant associated with NLR. While in Azab et al.'s study, only radiotherapy was significantly associated with NLR.[19]

In the current study, a high NLR > 1.55 was associated with higher five years OS, and > 1.65 was associated with higher DFS, yet this was not statistically significant, and it was against many studies found that higher NLR was significantly associated with poor patient prognosis. Whereas Azab et al. found that pretreatment NLR is an independent predictor of long-term mortality in breast cancer.[19] This difference can be justified as that study was a cohort with a larger sample size, and their patients were categorized into quartiles; in addition, they used the Cox proportional hazards model to build a multivariate model to evaluate the independent effect

of NLR on mortality.

In another study assessing neutrophil-lymphocyte ratio as a prognostic factor in non-metastatic breast cancer from a Hispanic population, they didn't find a significant relation between NLR and OS and DFS, indicating that NLR may be affected by different population characters.[21] Another study done over 350 breast cancer patients with five years of follow-up showed that NLR has no prognostic effect on overall and disease-free survival.[27]

In a study done by Losada et al., over 104 elderly breast cancer patients' pretreatment NLR was assessed. There was no statistical difference in OS and DFS with varying levels of NLR. Results show a potentially different effect in old-age patients.[28]

In the current study, a combination has been assessed between low and high NLR; it revealed no significant relation to OS or DFS when they are analyzed. In Graziano et al. 373 breast cancer patients were retrospectively analyzed. Patients received neoadjuvant chemotherapy. Results showed that NLR and PLR were not significantly associated with complete pathological response in each case analyzed independently. However, when combining NLR and PLR, patients with low NLR/ low PLR achieved a significantly higher rate of pCR compared to those with high NLR or high PLR.[29] The authors justified that an immunologic response, not an inflammatory one, has occurred.

5. Conclusions

(1) NLR is an inflammatory biomarker, which may affect prognosis in breast cancer patients.

(2) The pretreatment neutrophil-lymphocyte ratio was not significantly associated with patients' socio-demographic characteristics or co-morbidities.

(3) Clinicopathological characteristics of breast cancer were not statistically significant with NLR.

(4) High NLR was associated with Higher OS and DSF, yet we found no statistical significance.

(5) The Statistical combination of low NLR versus high NLR did not add any significance regarding OS and DFS.

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Nil.

Authors' contributions

SHS, MMA, AMMS performed the design of this work. SHS, MMA, AMMS shared the interpretation of the data, analysis & acquisition of the results. SHS, MMA revised and supervised the work. SHS, MMA wrote the initial draft of the manuscript. All authors contributed to the manuscript revision. All authors revised & approved the final manuscript version.

Availability of data and materials

Data supporting those findings & results are available with the corresponding author upon reasonable request.

Ethics approval

Approval by the Research Ethics Committee of Suez Canal University Department of Clinical Oncology & Nuclear Medicine, Suez Canal University was obtained.

(1) Clinical data were collected after approval of the research ethics committee of (FOMSCU).
(2) Confidentiality of the information and privacy.
(3) No personal data was published.
(4) Data were used only in that research.
(5) Analysis of data was done secretly without mentioning the participant's name.

Consent for publication

Not applicable.

Conflicts of Interest Disclosure

The authors declare that they have no competing interests.

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