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Association of Neutrophil to Lymphocyte Ratio with Clinicopathological Features in Breast Cancer

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Authors' contributions

This work was carried out in collaboration between both authors. Author RS selected the topic, collected the data, reviewed and edited and re-edited the manuscript. Author NC wrote the manuscript and did a literature search. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Even with the advances in the diagnosis and treatment of breast malignancy, to date breast cancer is still the number one cause of death in women in Pakistan. Various researches proved that prolonged inflammatory conditions played a part in progression of malignancy, these factors also promote growth leading to poor prognosis. This study shows the analysis of peripheral blood neutrophil to lymphocyte ratio (NLR) in breast malignancy and its association with disease characteristics

Methods: The cross-sectional study was done in Liaquat National Hospital and Medical College, Karachi. Pakistan. A total of 2059 female patient population with breast cancer hit the criteria. The patients were asked to undergo a complete blood count with leukocyte differential preoperatively. Patients' complete data was collected preoperatively including specimen-related histopathology reports. Patients excluded were those with clinical evidence of ongoing active infection/sepsis, any blood disorders, any previous or ongoing inflammatory or autoimmune diseases, and steroid therapy.

Results: No association was seen between the NLR with the age, grade, and luminal subtypes. However, NLR had a significant association with the size and stage of the disease. With an increase in NLR, the stage increased.

Conclusion: The study identifies the usefulness of the NLR ratio, which in the future can be used as a diagnostic adjunct in the preoperative workup of patients with breast malignancy.

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Keywords: Neutrophil to lymphocyte ratio; breast malignancy; biomarkers; staging.

1. INTRODUCTION

The malignancy of the breast which is increasingly common in females worldwide signifies approximately 30% of all new cancers found in women [1]. 5-7% of the woman being diagnosed before the age of 40 [2].

With the recent advancements and increased awareness, more patients are being diagnosed early, and with the initiation of early treatment, the majority are being successfully cured. Heterogeneity in breast cancer is usually caused by various factors involving patient characteristics, co-morbidities, histological, immunochemical, and molecular typing of the disease-causing diversity in the array of management, therefore various inflammatory markers such as neutrophils, lymphocytes, NLR, RD width, circulating tumor cells are currently studied as prognostic factors that have been identified and hence proved helpful as an evidence to determine the outcome in patients [3] Usually a small tumor at presentation, a low histological grade, negative axillary status, positive expression of hormone receptors, Her-2-neu negative and a low Ki-67 indicate favorable outcome [4] compared to a tumor of greater size (more than 5 cm) at initial presentation, high grade, positive axillary nodes and estrogen receptor, progesterone receptor-negative, Her2Neu positive, high Ki-67 (> 20) and triple-negative which are considered poor prognostic factors with a negative impact on the outcome even with the current treatment modalities [5].

Multiple studies showed evidence related to the association between the activation of systemic inflammatory markers which includes cytokines and neutrophil- to- lymphocyte ratio with poor prognosis in various types of breast malignancy [6]. A peripheral neutrophil-to-lymphocyte (NLR) ratio, which is calculated as the absolute neutrophil count divided by the absolute lymphocyte count, obtained from a routine complete blood picture test, has been recognized as a poor prognostic factor in various cancers such as gastric, urinary bladder, and lung [7-9].

NLR was superior to independent leukocyte parameters [10] due to its stability as it is not altered drastically by various factors such as physiological and pathological, and it represented the inflammatory and immune reactions simultaneously that co-existed in a diseased patient.

Although the detailed mechanism underlying the role of NLR for patient prognosis remains unclear, it is speculated that cancer-related chronic inflammation increases the production of factors promoting carcinogenesis [11]. Obtaining the NLR requires a minimally invasive blood test which is inexpensive and can be measured conveniently [12].

Therefore, in this study, we aim to investigate and study the association of the NLR ratio with the various prognostic clinicopathological features.

2. MATERIALS AND METHODS

A total of 2059 breast cancer patients with histologically confirmed breast cancer were included in this study. All were treated between the years 2018-2020, at the Breast unit, Department of General Surgery, Liaquat National Hospital, Karachi. Patients who were female with a biopsy-proven diagnosis of breast cancer were included. Inclusion criteria were patients aged between 18 to 70 years with Breast cancer of all stages. All patients underwent workup before the surgery. The detailed information about patients' histopathology type, grade, tumor size, nodal status, ER, PR, Her 2 neu, and Ki67 was collected. The laboratory data including complete blood picture, focusing on neutrophil and lymphocyte counts were also obtained preoperatively. Neutrophil/lymphocyte ratio (NLR) was calculated by absolute Neutrophil count divided by absolute lymphocyte count.

The Luminal classification was done based on St. Gallen's criteria [13]. Patients with Inflammatory breast cancer (diagnosed clinically), those diagnosed with any systemic or auto-immune or chronic illness, patients on steroid therapy, or pregnancy-induced breast malignancy, and patients concurrently diagnosed with cancers in other organs were excluded from the study. Histopathology reports showing tumor pathology like size and tumor type were also noted. Data analysis was performed by SPSS 23 for windows. The qualitative variables such as tumor histopathology and axillary status are presented as percentages and frequency. The quantitative variables such as age, stage, size, ER and PR, Her-2-Neu, Ki-67, and NLR ratio are presented as mean +/- SD. The Association of NLR is calculated with outlined clinic-pathological

features of breast cancer by using the chi-square test and the P-value of less than 0.05 is considered significant. The cut-off value for the NLR ratio is 2.5 as quoted by other authors [14,15] Univariate logistics regression was applied for variables found significant by the chi-square test.

3. RESULTS

2059 females with breast malignancy were included in the current research. The mean age of patients was identified as 50.39±12.37 ranging from 15 years to 89 years. Most of the patients (54.8%) were from age≤50 years. Mean neutrophil and lymphocyte counts were 78.59±93.69 unit and 29.33±8.91 unit respectively while mean neutrophil to lymphocyte ratio (NLR) was 55±11.29 ranging from 0.16 to 340.54. Most of the patients (66.7%) were found with tumor sizes 2 to 5 cm. ER, PR and Her2 neu were positive for 64.4%, 51.3%, and 34.5% respectively. Among 2059 patients, 350(17.1%) were luminal A, 515(25.2%) were luminal B, 486(23.8%) were luminal B (Her 2 positive), 459(22.5%) were triple-negative and 231(11.3%) were Her2 Neu positive and hormone negative. In our study, 1270(61.7%) have NLR<2.5 and 789(38.3%) have NLR≥2.5. A detailed description of study characteristics is presented in Table 1. Detailed results of NLR associations are presented in Table 2. No association was noted of NLR with the age, pathology type, and histologic grade However significant association was noted with the tumor size and stage of the disease. No association was seen with luminal subtypes (Table 3) and lymph node status (Table 4). It was found that patients with T1 (OR=0.595), T3 (OR=0.973) are less likely to have low NLR in comparison to Tx. It was also found that patients with grade-I (OR=0.552), grade-III A (OR=0.745), III B (OR=0.888), and IIIC(OR=0.595) are less likely to have low NLR in comparison to grade-IV. Detailed results of odds for low NLR and high NLR are presented in Table 5.

Table 1. Descriptive statistics of study characteristics

	n (%)
Age(in years)↕	50.39±12.37 (15 to 89 years)
NLR ratio↕	3.55±11.29 (0.16-340.54)
Age Groups	
≤50 years	1129(54.8)
>50 years	930(45.2)
Pre-op Ki67 (n=2059)	
<14%	334(19.2)
≥14%	1408(80.8)
Tumor Size (n=2059)	
<2.0 cm	378(22.1)
2-5 cm	1143(66.7)
>5 cm	192(11.2)
Clinical Diagnosis	
Ductal	1728(83.9)
Invasive Ductal	90(4.4)
Invasive Lobular	79(3.8)
Invasive Mucinous	162(7.9)
T	
Tx	45(2.2)
T1	98(4.8)
T2	1031(50.1)
T3	310(15.1)
T4	525(25.5)
Not Available	50(2.5)
Stage	
Stage-I	81(3.9)
Stage IIA	615(29.9)
Stage IIB	460(22.3)
Stage IIIA	214(10.4)
Stage IIIB	471(22.9)
Stage IIIC	10(0.5)
Stage IV	126(6.1)
Not Available	62(3.0)

Number of AXLN Involved (n=1713)	
No AXLN found	1086(63.4)
1-3	310(18.1)
4-10	176(10.3)
>10	141(8.2)
Grade	
Grade-I	74(3.6)
Grade-II	495(24)
Grade-III	579(28.1)
NA	911(44.2)
ER	
Positive	1327(64.4)
Negative	732(35.6)
PR	
Positive	1056(51.3)
Negative	1003(48.7)
Her 2 Neu	
Positive	711(34.5)
Negative	1348(65.5)
Luminal (n=2059)	
Luminal A	350(17.1)
Luminal B	515(25.2)
Luminal B Like	486(23.8)
Tripple Negative	459(22.5)
Her2 Neu	231(11.3)
NLR ratio group	
<2.5	1270(61.7)
≥2.5	789(38.3)
↕Mean±SD (Range)	

Table 2. Patients' characteristics of tumour group (n=2059)

Characteristics	Overall (%)	NLR, *n* (%)	NLR, *n* (%)	*p*-value
		<2.5	≥2.5	
Age				0.608
≤50	1129(54.8)	702 (55.3)	427(54.1)	
>50	930(45.2)	568 (44.7)	362 (45.9)	
Pathology				0.243
DCIS	1728(83.9)	1059(83.4)	669 (84.8)	
IDC	90(4.4)	64 (5.0)	26 (3.3)	
ILC	79(3.8)	51(4.0)	28(3.5)	
OTHERS	162(7.9)	96(7.6)	66(8.4)	
Grade				0.146
I	74(3.5)	46 (3.6)	28 (3.5)	
II	495(24)	322(25.4)	173 (21.9)	
III	579(28.1)	364(28.7)	215 (27.2)	
NA	911(44.2)	538(42.4)	373 (47.3)	
Tumor status				0.000
Tx	45(2.2)	26(2.0)	19(2.4)	
T1	98(4.8)	44 (3.5)	54 (6.8)	
T2	1031(50.1)	682 (53.7)	349(44.2)	
T3	310(15.1)	177 (13.9)	133(16.9)	
T4	525(25.5)	316(24.9)	209(26.5)	
N/A	50(2.4)	25(2.0)	25(2.0)	
Stage				*0.008*
I	81(3.9)	39 (3.1)	42(5.3)	
IIA	615(29.9)	399(31.4)	216(27.4)	
IIB	460(22.3)	303(23.9)	157(19.9)	
IIIA	214(10.4)	119(9.4)	95(12.0)	
III B	471(22.9)	282(22.2)	189(24.0)	
IIIC	10(0.5)	5(0.4)	5(0.6)	
IV	126(6.1)	79(6.2)	47(6.0)	
N/A	82(4.0)	44(3.5)	38(4.8)	

Table 3. Neutrophil to Lymphocyte ratio in luminal subtypes of the tumor

N/L ratio	Luminal A	Luminal B	Luminal B (Her2 positive)	Triple Neg	HER 2 NEU+	P – value
<2.5	230 (18.1%)	335(26.4%)	308 (24.3%)	260 (20.5%)	137(10.8%)	.081
>2.5	135 (17.1%)	183 (23.2%)	178 (22.6%)	199 (25.2%)	94(11.9%)	

Table 4. Neutrophil/ Lymphocyte ratio in the number of lymph nodes involved. Data presented percent

N/L ratio	0 LN	1-3 LN	4-9 LN	>10 LN	N/A	P – value
<2.5	661 (52.0)	208 (16.4)	110 (8.7)	82(6.5)	209(16.5)	.081
>2.5	425(39.1)	102 (12.9)	66 (8.4)	59(7.5)	137(17.4)	

Table 5. Odds ratios for Low NLR and High NLR

	Low NLR		High NLR	
	P-value	**Odds (95% CI)**	**P-value**	**Odds(95% CI)**
Tumor status				
T1	0.154	0.595(0.292-1.215)	0.154	1.679(0.823-3.426)
T2	0.249	1.428(0.779-2.616)	0.249	0.700(0.382-1.283)
T3	0.931	0.973(0.516-1.831)	0.931	1.028(0.546-1.936)
T4	0.751	1.105(0.596-2.047)	0.751	0.905(0.488-1.677)
N/A	0.448	0.731(0.325-1.644)	0.448	1.368(0.608-3.078)
Tx®		1		1
Stage				
I	0.040	0.552(0.314-0.973)	0.040	1.810(1.028-3.188)
IIA	0.641	1.099(0.739-1.635)	0.641	0.910(0.612-1.354)
IIB	0.508	1.148(0.763-1.729)	0.508	0.871(0.578-1.311)
IIIA	0.201	0.745(0.475-1.170)	0.201	1.342(0.855-2.106)
III B	0.565	0.888(0.592-1.331)	0.565	1.127(0.751-1.690)
IIIC	0.431	0.595(0.164-2.164)	0.431	1.681(0.462-6.113)
N/A	0.196	0.689(0.392-1.212)	0.196	1.452(0.825-2.553)
IV ®		1		1

Reference group
Univariate binary logistic regression was applied.
P-value<0.05, considered as significant

4. DISCUSSION

Globally Breast cancer is the most common cancer identified among the female population [16]. Accumulating evidence suggests that chronic inflammation, in general, was linked with tumor progression [17] i.e. high number of leukocytes such as neutrophils and lymphocytes were associated with an increase in tumor advancement [18]. In the NLR ratio in our study, there was a significant variation in NLR association with various disease characteristics. Like the Elyasinia group showed that a high NLR ratio was associated with a higher stage, we also noted a significant relationship with the disease stage, and no significant association was noted with ER, PR, and Her 2 neu [19]. Ethier, JL et al noted higher NLR to be associated with poor outcome irrespective of disease stage, and greater effect on outcome was noted in ER, and Her2 neu patients [20], whereas others have noted a relationship in Triple-negative patients. [21,22]. Our results also coincided with the study of Yilmaz [23] which proved no significance between preoperative NLR with breast cancer subtypes. The findings in this paper also corroborate the results of prior studies which showed that patients with high NLR >2.5 as an independent predictive factor for worse prognosis.

Our findings are consistent with showing a significant relationship between increasing NLR ratios with the T stage of the disease [24].

Although various cutoff values were used in previous studies, the pooled analysis proved that elevated NLR is inclined to poor overall outcome [25-26]. Although numerous inflammatory markers have been studied to date as a diagnostic adjunct [27] none have entered still in the clinical setting, either due to expensiveness and unavailability in a various laboratory setup, on the contrary, NLR can be used as a marker of inflammation to predict the outcomes due to its potential usefulness and inexpensiveness and availability [28].

Though it is not possible to fully identify whether the advanced stages produced more inflammatory reactions, or chronic inflammatory condition caused an increase in NLR which accelerated progression and metastasis, although one proposed mechanism is that Neutrophils consist of a significant part of the phagocyte system and one of the killing mechanisms of neutrophils to the pathogens includes phagocytosis with remarkable potential is to release the reactive oxygen species (ROS) through phagolysosome [29], though which is itself a pro-apoptotic effect. It is said that with tumor progression the neutrophils increase and possess different characteristics affecting tumor cytotoxicity and immune suppression explaining the mechanism behind the elevated risk of worsening outcomes in malignancy, with increasing blood concentration levels of neutrophils [30]. Raised NLR can help and alert clinicians about prognosis and help in selecting appropriate therapy.

The limitation is that it is a single Centre design and that the data regarding the chemotherapy is not available in this analysis. Another limitation is the inability to explore the NLR breast cancer survival which though has been confirmed by multiple previous studies.

Therefore further studies to identify the role of NLR in rectifying its usage in prognostic scoring and outcomes are still warranted.

5. CONCLUSION

NLR can be used as a marker of subclinical inflammation in breast malignancy, which can be easily assessed using laboratory white blood cell counts. An increase in preoperative NLR is associated with the disease characteristics i.e. stage of the disease and may be an indicator of poor outcome in breast malignancy. Therefore pre-operative neutrophils to lymphocytes could be used as a marker for surgeons as a prognostic adjunct in the management of breast malignancy.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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