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Original Article

Pathology Section

Neutrophil-lymphocyte Ratio as Independent Prognostic Factor among Breast Cancer Patients in a Tertiary Care Hospital, Kolkata, India

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ABSTRACT

Introduction: The most important prognostic factor for breast cancer is tumour stage and tumour grade. However, the assessment of the above parameters are time-consuming and require expertise. Thus evaluation of the prognosis of breast cancer is still limited to tertiary care hospitals, with appropriate facilities for histopathological techniques. Recently, inflammatory blood markers have shown a role as a prognostic factor. Out of all the inflammatory blood markers, Neutrophil-Lymphocyte Ratio (NLR) has emerged as the most useful. Abundant evidence suggests the role of NLR as an adverse prognostic factor in breast cancer. NLR is simple and inexpensive. It can be easily obtained, as the differential count of every patient is done routinely. Thus it can act as an indicator of high-risk patients who are likely to show poor prognosis. Though NLR has been found to play a role in prognosis prediction in breast cancer, much is unknown in this field.

Aim: To assess the effectiveness of Neutrophil-Lymphocyte Ratio (NLR) as an independent prognostic parameter among breast cancer patients in a tertiary care hospital in Kolkata, India.

Materials and Methods: This observational cross-sectional study was conducted in Department of Pathology, Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal, India, where 140 female patients undergoing mastectomy for breast cancer were studied from 1st February 2019 to 31st January 2020. The clinicopathological parameters, histopathological parameters, and molecular subtypes were evaluated. NLR was calculated and related with the other prognostic parameters. Data entry was done in Microsoft Excel and analysis was done using Statistical Package for Social Sciences (SPSS) software version 20.0. One way Analysis of Variance (ANOVA) test and Chi-square test was used to assess the relationship of NLR with various other prognostic factors.

Results: Out of 140 patients, 78 patients showed NLR values within 1.8 to 3.33. Higher NLR (>3.33) was associated with poor prognostic factors like higher T stage (T4) {17 (53.1%)}, higher stage (stage III) 95 (67.8%), skin involvement 19 (47.5%), Lymphovascular involvement in 23 (39.7%), perineural involvement in 10 (71.4%) and in patients with Human Epidermal Growth factor Receptor 2 (HER 2) positive molecular subtype in 8 (5.7%).

Conclusion: This study suggests that a high NLR value was associated with poor prognosis in breast cancer patients. Thus, it can be used as an independent marker of poor prognosis and can help guide the treatment of breast cancer patients. The more we study the role of NLR, the more useful it will be in predicting the course of breast cancer as early as possible.

Keywords: Blood inflammatory biomarkers, Invasive ductal carcinoma, Prognosis, Total leukocyte count

INTRODUCTION

Inflammatory cells can cause modification of the tumour microenvironment by direct interaction with tumour cells, stromal fibroblasts, and endothelial cells. Inflammatory cells can be both tumour-promoting as well as tumour antagonising. The predominant inflammatory cells are neutrophils which secrete growth factors and proteases that help in the invasion, angiogenesis, and metastases [1,2]. The antigen-presenting cells present tumour antigens to cytotoxic T lymphocytes which attack tumours cells and kill them. Thus neutrophils promote tumour spread whereas T lymphocytes are protective against cancer.

Previous studies have shown pretreatment Neutrophil-Lymphocyte Ratio (NLR) to be an independent prognostic marker in different types of malignancies [3-7]. NLR is the ratio obtained by dividing Absolute Neutrophil Count (ANC) as the numerator and Absolute Lymphocyte Count (ALC) as the denominator [8]. It is a simple ratio that can be easily calculated from the complete blood count of the patient.

This ratio can be affected by any condition of the body which affects the blood cell counts. Inflammation due to any cause leads to an increase in the NLR of the patients. Similarly in cancer patients, this ratio has been found to increase. Thus inflammation plays an important role in the mechanism of neoplasm and recently many studies are focusing on the role of cancer-associated inflammation and its role in predicting the role in disease progression and survival. The various systemic inflammatory response markers that have been studied are C-Reactive Protein, hypoalbuminaemia, and circulating leukocyte [9,10]. Based on these, certain markers are becoming the center of many studies, evaluating their role as a predictor of prognosis [11,12]. These markers are Glasgow Prognostic Score (GPS) [13], modified GPS [14], neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and lymphocyte-monocyte ratio. Thus as can be deduced from this study, high NLR is associated with a poor prognosis in cancer.

Neutrophil-lymphocyte ratio has been studied in many cancers, like renal carcinoma, colon cancer but very few studies have been done on breast cancers [15-17]. The objective was to find out the relation between pretreatment NLR with the prognosis of breast cancer and whether it can be used as an independent prognostic marker.

MATERIALS AND METHODS

This observational cross-sectional study was conducted in the Department of Pathology at Nil Ratan Sircar Medical College and Hospital, Kolkata, West Bengal, India, from 1st February 2019 to 31st January 2020. The study was conducted after receiving approval from the Institutional Ethics Committee of Nil Ratan Sircar Medical College and Hospital (IEC No- No/NMC/10020) and after taking proper informed consent from all the patient.

Sample size calculation: In a similar study done in India, mean NLR was found to be 1.8±1.08 [18]. Assuming this approximate mean and standard deviation of NLR in this study, the sample size was calculated taking 95% confidence level (Zα) and 10% relative precision (l) by applying the formula:

$$(Z_\alpha)^2 * S^2/l^2$$

The sample size was calculated to be 140 female breast cancer patients.

Inclusion criteria: All female patients undergoing mastectomy for breast cancer during the study period were included in the study.

Exclusion criteria: All those patients whose treatment was already started before the pretreatment NLR was determined were excluded from the study.

Data collection: For all the patients age, tumour laterality, family history and the clinical presentation (mass, nipple discharge, bleeding) were recored. Routine blood examination reports was done including Complete Blood Count (CBC), Differential Count (DC), Absolute Neutrophil Count (ANC), Absolute Lymphocyte Count (ALC) were obtained and NLR was calculated. The normal total leukocyte count lies in the range of (4000-10,000/cmm). The normal absolute neutrophil count lies in the range of (2000-7000/cmm). The normal absolute lymphocyte count lies in the range of (1000-3000/cmm).

Procedure

Mastectomy specimens received were grossed, formalin-fixed paraffin-embedded blocks were cut into 3-5 µ thick sections and stained with Haematoxylin and Eosin (H&E) stain to examine under light microscopy for diagnosis of tumour and proper staging and grading. Then appropriate sections were used for immunohistochemical study for Oestrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth factor Receptor 2 (HER 2) and were scored by Allred scoring [19], and molecular profiling of breast cancer was done into luminal A, luminal B, HER 2 enriched, and triple-negative groups. For NLR, patients were grouped into four groups based on previous studies [20,21]:

- <1.8,
- 1.8-2.45,
- >2.45-3.33,
- >3.33

The association between the mean NLR and the following prognostic factors was analysed:

- Patients age,
- Size of the tumor (T-stage)
- Skin invasion
- Lymphovascular invasion
- Axillary lymphnode metastases (N stage)
- HER 2 expression

STATISTICAL ANALYSIS

Data entry was done in Microsoft excel and analysis was done by Statistical Package for Social Sciences (SPSS) version 20.0. Differences of NLR with various variables like stage and molecular subclassification were evaluated by applying the Analysis of Variance (One-way ANOVA test). A Chi-square test was used to assess the relationship between the clinicopathological parameter of prognostic significance with NLR. A Receiver Operating Characteristic (ROC) curve has been plotted to determine the sensitivity of various NLR values in the study. Statistical significance was determined at p-value <0.05.

RESULTS

In this study, 140 breast cancer patients were included and the clinical features are presented in [Table/Fig-1]. Majority of the cases were between 40-49 years (50.7%). The peripheral blood analysis results are as seen in [Table/Fig-2].

Clinical presentation		Findings
Mean age (year)		48.9
Location of tumor (with respect to the quadrant of breast involved)		
Surrounding areola		15 (10.71%)
Lower inner		16 (11.43%)
Upper		11(7.86%)
Upper outer		26 (18.57%)
Central		15 (10.71%)
Upper interior		24 (17.14%)
Lower outer		19 (13.57%)
Lower		10 (7.15%)
Not specified		4 (2.86%)
Family history		
Yes		9 (6.4%)
No		131 (93.6%)
Nipple discharge/bleeding present		7 (5%)
Histologic type		
Invasive ductal carcinoma {No Special Type/ Not Otherwise Specified (NOS/NST)}		123 (87.9%)
Ductal carcinoma		7 (5%)
Mucinous carcinoma		3 (2.1%)
Ductal Carcinoma In-situ (DCIS)		5 (3.6%)
Residual		2 (1.4%)
Mean tumour size		4.7±1.8 cm
Laterality		
Right		54 (38.57%)
Left		86 (61.43%)
Lymphovascular Invasion		
Involved		58 (41.4%)
Not involved		82 (58.6%)
Perineural invasion		
Involved		14 (10%)
Not involved		126 (90%)
Margin status		
Free margins		106 (75.7%)
Deep resection margin		15 (10.7%)
Superior-medial		2 (1.4%)
Inferior		4 (2.9%)
Superior-lateral		2 (1.4%)
DRM-inferior		4 (2.9%)
Superior		2 (1.4%)
Superior-DRM		3 (2.1%)
Medial		2 (1.4%)
Skin involvement		
Not involved		100 (71.5%)
involved		40 (28.5%)
Stage		
Tumour stage	T1a	4 (2.8%)
	T1c	8 (5.6%)
	T2	70 (50%)
	T3	22 (15.7%)
	T4b	24 (17.1%)
	T4c	8 (5.6%)
	Tis	2 (1.4%)
	TX	2 (1.4%)

Nodal stage	N1	56 (40%)
	N2	39 (27.8%)
	N3	12 (8.5%)
	N0	22 (15.7%)
	NX	11 (7.9%)
Total stage		
Stage I		9 (6.4%)
Stage II		36 (25.7%)
Stage IIIA		59 (42.1%)
Stage IIIB		25 (18%)
Stage IIIC		11 (7.8%)
Molecular profiling		
Luminal A		56 (40%)
Luminal B/HER positive		33 (23.5%)
Luminal B/negative		29 (20.7%)
HER 2 positive		8 (5.8%)
Triple negative		14 (10%)

[Table/Fig-1]: Clinicopathological findings of the breast cancer patients (N=140).

Parameter	Minimum	Maximum	Mean±SD
Total leukocyte count (/cmm)	3800	15000	6496.29±2207.9
Absolute neutrophil count (/cmm)	1800	11850	4337.9±1949.1
Absolute lymphocyte count (/cmm)	750	3069	1659.07±472.7
Mean total NLR	0.91	7.0	2.75±1.36

[Table/Fig-2]: Peripheral blood analysis.

Relation of NLR with Other Prognostic Factors

In this study, most of the study subjects had their Neutrophil-Lymphocyte Ratio between 1.8-2.45 (31.4%) followed by between >2.45-3.33 (24.3%). NLR of 3.33 was used as the cut-off value to differentiate between high-NLR (≥3.33) and low-NLR (<3.33). The Chi-square test has been used to find the association between various clinicopathological parameters and NLR. The difference of proportion of high NLR between various groups was statistically significant (p<0.05) in the groups having skin, lymphovascular and perineural involvement [Table/Fig-3]. Whereas, when the median values of age and tumour size (46 years and 4.5 cm respectively) were considered as a cut-off level, no significant difference in the proportion of high NLR was found in those two parameters (p-value=0.089; p-value=0.095; respectively) [Table/Fig-3].

Parameters		NLR			p-value (Chi-square test)
		Low (<3.33)	High (≥3.33)	Total	
Age (years)	≤46	45 (73.8%)	16 (26.2%)	61	0.089
	>46	63 (79.8%)	16 (20.2%)	79	
	Total	108 (77.1%)	32 (22.9%)	140	
Tumour size (cm)	≤4.5	46 (76.7%)	14 (23.3%)	60	0.095
	>4.5	62 (77.5%)	18 (22.5%)	80	
	Total	108 (77.1%)	32 (22.9%)	140	
Skin involvement	Not involved	87.0 (87.0%)	13 (13.0%)	100	0.003
	Involved	21 (52.5%)	19 (47.5%)	40	
	Total	108 (77.1%)	32 (22.9%)	140	
Lymphovascular involvement	Not involved	73 (89.0%)	9 (11.0%)	82	0.029
	Involved	35 (60.3%)	23 (39.7%)	58	
	Total	108 (77.1%)	32 (22.9%)	140	
Perineural involvement	Not involved	104 (82.5%)	22 (17.5%)	126	0.002
	Involved	4 (28.6%)	10 (71.4%)	14	
	Total	108 (77.1%)	32 (22.9%)	140	

[Table/Fig-3]: Association between various clinicopathological parameters and NLR among study subjects (N=140).
p-value <0.05 considered significant

Most of the study subjects (17) presenting with T4 stage had NLR value of more than 3.33 while those with T1 stage (7) had NLR values within the range 1.8-2.45 as seen in [Table/Fig-4]. No significant distribution of the nodal stage can be associated to the value of NLR. The highest mean NLR (3.86±1.87) was seen in Stage IIIB patients followed by Stage IIIC (3.49±1.79). Patients who were at Stage IA had the lowest mean (2.26±0.39). The highest mean NLR (2.89±1.47) was found in the patients who were overall at Stage III followed by Stage II (2.50±1.13). Though the difference of mean NLR between various stages was not statistically significant (p-value=0.214) [Table/Fig-5]. The highest mean NLR (3.44±1.91) was found in the patients who had HER positive status followed by Luminal B/HER negative status (3.03±1.32) [Table/Fig-6].

Neutrophil-Lymphocyte ratio	T1	T2	T3	T4	Others	Total
<1.8	2 (16.6%)	18 (25.7%)	4 (18.2%)	6 (18.7%)	0	30 (21.4%)
1.8-2.45	7 (58.3%)	23 (32.8%)	5 (22.7%)	7 (21.8%)	2 (50%)	44 (31.4%)
>2.45-3.33	3 (25%)	20 (28.5%)	7 (31.8%)	2 (6.2%)	2 (50%)	34 (24.3%)
>3.33	0	9 (12.8%)	6 (27.2%)	17 (53.1%)	0	32 (22.8%)
Total	12 (8.5%)	70 (50%)	22 (15.7%)	32 (22.8%)	4 (2.8%)	140

[Table/Fig-4]: Neutrophil-Lymphocyte Ratio in various T-stages of the tumour.

Total stage	Number	NLR (Mean±SD)	p-value (ANOVA)
Stage I	9 (6.4%)	2.26±0.3	0.214
Stage II	36 (25.7%)	2.50±1.13	
Stage III	95 (67.8%)	2.89±1.47	
Total	140		

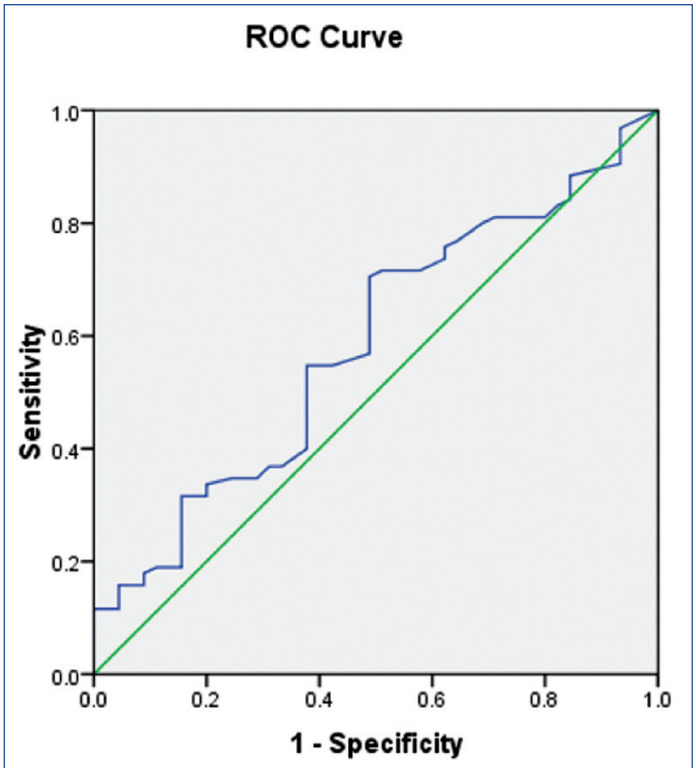
[Table/Fig-5]: Neutrophil-Lymphocyte ratio in various Total-stages of the tumour (N=140).

Molecular subclass	Number	NLR (Mean±SD)	p-value (ANOVA)
Luminal A	56 (40%)	2.60±1.37	0.076
Luminal B/HER positive	33 (23.5%)	2.83±1.25	
Luminal B/negative	29 (20.7%)	3.03±1.32	
HER positive	8 (5.7%)	3.44±1.91	
Triple negative	14 (10%)	2.49±1.87	
Total	140		

[Table/Fig-6]: NLR in the various molecular subclass of the tumour. Data is represented as a percentage (N=140).

In this study, a Receiver Operating Characteristic (ROC) curve has been plotted with the sensitivity values along the Y-axis and corresponding (1-specificity) values along the X-axis. Cancer category of total stage II and III were considered as an adverse diagnosis and corresponding NLR values were taken into account. An Area Under Curve (AUC) value of 0.6 signifies a poor predictive ability of high NLR and an adverse diagnosis [Table/Fig-7]. In this study majority of the study population (78) was present between the ranges of 1.8 to 3.33. A NLR cut-off value of 1.88 had 80% sensitivity and 31% specificity, whereas a NLR cut-off value of 3.33 had 80% specificity and 31% sensitivity.

In this study a cut-off value of 2.14 shows sensitivity of 71% and specificity of 48%. As Area Under the Curve (AUC) between 0.5 and 0.6 does not have any class separation capacity, in this study authors have not used this cut-off value. Instead we have used a range between 1.8 and 3.33 for NLR values with the higher cut-off value of 3.33 which has a sensitivity of 31% but specificity of 80%. A higher specificity will help reduce the false positive cases being included in the study.



[Table/Fig-7]: Receiver operator characteristics curve.

DISCUSSION

Inflammatory response plays an important role in tumourigenesis and tumour progression. Inflammatory cells like macrophages, mast cells and neutrophils act as tumour promoting cells whereas lymphocytes have tumour antagonising properties [2]. Many recent studies have put forward the evidence of systemic inflammatory response as a prognostic indicator in cancer patients [22]. In this study, NLR in breast cancer patients has been evaluated and its association to the already established prognostic factors of breast carcinoma has been evaluated. According to the present study findings, majority of our study population belonged to the age group of 40-49 years (50.7%). Clinical findings showed majority presented with upper outer quadrant mass (18.5%). Majority presented with breast mass in the left side (61.43%). The laterality of breast cancer depends on age. Right breast was found more common than left breast in younger patients (<40 years) in invasive carcinomas. In patients more than 40 years, invasive carcinomas are most commonly affect the left breast. Of all the histologic subtypes, IDC occurs more commonly in left breast. Ekbom A et al., also showed similar findings in patients above 45 years of age [23]. Amer M, in his study, also found predominance of left breast in all age groups except in patients <30 years [24].

As the mean TLC was within normal limits (6496.29±2207.9/cmm), authors can rule out the chances of neutrophilia caused due to infection in these patients. The mean NLR calculated was 2.75. Majority of the patients showed no skin involvement (87, 87%) and no lymphovascular invasion (73, 89%). Majority of the current study population presented with Tumour stage T2 (50%) followed by T4b (17.1%). Major study population presented with nodal N1 stage (40.0%) followed by N2 nodal stage (27.8%). Most of our study population belonged to stage III A (42.1%) followed by stage III B (18%). Most of the patients presented with Luminal A (40%) molecular subtype followed by Luminal B (HER + subtype) (23.5%). Of the patients presenting with T4 stage disease, majority (53.1%) showed higher NLR values of >3.33.

In those presenting with T3 stage, majority showed NLR values within the range of >2.45-3.33. In T1 stage majority patients presented with NLR values within the range (1.8-2.45). In T2 stage no significant difference was noted among the 4 quartiles of NLR. NLR of 3.33 was used as the cut-off value to differentiate between high-NLR (≥3.33) and low-NLR (<3.33). Chi-square test has been used to find the association between various clinicopathological parameters and NLR. The association of high NLR between various groups was found to be statistically significant (p-value <0.05) in the groups having skin, lymphovascular and perineural involvement. Whereas, when the median values of age and tumour size (46 years and 4.5cm respectively) were considered as a cut-off level, no significant difference in the proportion of high NLR was found in those two parameters (p-value >0.05) [25].

In the study by Noh H et al., median value of NLR was found to be 1.85. They took a cut-off value of 2.5 for NLR. According to Noh H et al., patients with values of NLR >2.5 showed increased association with higher T stage. In this study, it was observed that higher T stage (T4) shows increased association with NLR values >3.33. In this study however we fail to find any significant association between NLR and nodal status. Similar findings regarding NLR and nodal status is seen in the study by Noh H et al., [26]. In study by Ulas A et al, they found association between high NLR with larger tumour size and lower median age of presentation. However the findings were not statistically significant. Even in our study, we could not establish a statistically significant correlation of NLR with tumour size and age. Noh H et al., also could not find any statistical association of NLR with clinicopathological findings [27]. Another study with 1527 breast cancer patients took a cut-off of >4 for NLR. In this study increased NLR showed increased association of lymphnode involvement, tumour size, HER 2 positivity and advanced stage [28]. HER 2 positive tumours have poor prognosis compared to luminal A or luminal B molecular subtype. In our study, majority of study population fall under luminal A (40%) subtype. Highest mean NLR (3.44) was found in the patients who had HER postive status followed by Luminal B/HER 2 negative status (3.03). In the study by Ulas A et al., higher NLR was associated with HER 2+ and hormonal receptor. However, there was no significant correlation [27]. The findings of all the related studies have been summarised in [Table/Fig-8].

Variables	Present study (2022)	Varsha A et al., (2020) [21]	Ulas A et al., (2015) [27]	Noh H et al., (2013) [26]
Sample size	140	30	187	442
Study place	Kolkata, India	Karnataka, India	Turkey	Korea
Age	majority between 40-49 years (50.7%)	41-50 years	51±10.7	50±11.4
Tumour size (cm)	4.7±1.8	Mean size not mentioned	Mean size not mentioned	2.73±1.78
Nodal involvement	Majority in N1 stage {56 (40%)}	Majority in N3 stage {21 (70%)}	Majority in N0 stage {72 (38.5%)}	Majority in N0 stage {282 (63.8)}
T stage	Majority in T2 stage {70 (50%)}	Majority in T3 stage {21(70%)}	Majority in T2 stage {116 (62%)}	Majority in T2 stage {221 (50%)}
Lymphovascular involvement- skin involvement	Majority showed no involvement {82 (58.6%)}	Not mentioned in this study	Not mentioned in this study	Not mentioned in this study
Perineural involvement	Majority showed no involvement {126 (90%)}	Not mentioned in this study	Not mentioned in this study	Not mentioned in this study
Mean NLR	Divided into four quartile (NLR: <1.85, 1.85--2.45, >2.45-3.3, >3.3)	Divided into four quartile (NLR: <1.85, 1.85-2.4, 2.4-3.3, >3.3)	2.38±1.42	2.5

Molecular status	Majority in luminal A group {56 (40%)}	Not mentioned in the study	Majority were ER, PR negative {100 (53.5%)}	Majority in luminal A group {177 (48.7%)}
NLR associated with higher T stage	Higher NLR (>3.33) was seen in T4 stage	Higher NLR (>3.3) was seen in T3 stage	High NLR (>2.38) associated with T2 stage	Higher NLR (>2.5) was seen in T3 stage
NLR associated with higher N stage	No significant association was seen with N stage	Higher NLR (>3.3) was seen in N3 stage	Majority showed association with N0 stage {29 (42.6%)}	Majority showed association with N0 stage {68 (59.2%)}
NLR associated with molecular subtypes	Higher NLR showed higher association with HER 2 positive status	Not mentioned in the study	Higher NLR is high in both ER, PR positive patients	Higher NLR showed higher association with HER 2 status
Stage	Higher NLR was seen in stage IIIB	Higher NLR was seen in stage II	Higher NLR was seen in stage IIA	Not mentioned

[Table/Fig-8]: Comparison of the findings of different studies on NLR with this study.

Limitation(s)

The sample size was relatively small with a short observation period of one and a half years as it was an institution-based study, more number of patients with delayed presentation was selected. Thus, NLR could not be obtained at a uniform time for all patients. Also NLR is dependant on other conditions like inflammation and infection. Comparing NLR values with these markers would have thrown a better light on the study. The N stage depends on a number of factors like the type of specimen received as well as the number of axillary lymphnodes resected. Thus, the N stage may not always be accurately predicted.

CONCLUSION(S)

This study suggests that high NLR value is associated with poor prognosis in breast cancer patients. More prospective studies based on large population will help us to know more about NLR, so that it can be used as an early prognostic marker in breast cancer patients. NLR can be a marker of interest in long standing or higher T stage cases, as in the advanced stage, NLR tends to increase. So, careful assessment of NLR can be of utmost importance in breast carcinoma patients.

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