Biomedicine: 2024; 44(2):204-215 *April-June 2024*
Research Article

Impact of Neutrophil Lymphocyte Ratio on Tumour Parameters and Overall Survival in patients of Breast Cancer: A Single Institutional Retrospective Audit

Sumana Maiti Das[1], Krishnangshu Bhanja Choudhury[2], Oona Chakrabarty[3], Sanskriti Poddar[4], Partha Dasgupta[5], Siddhartha Das[6]

[1]Associate Professor, Department of Radiotherapy, R.G.Kar Medical College & Hospital
[2]Associate Professor, Department of Radiotherapy, Malda Medical College and Hospital, Malda, West Bengal, India
[3]Associate Professor, Department of Physiology, Diamond Harbour Govt. Medical College and Hospital, South 24 PGS., West Bengal, India
[4]Senior Resident, Dept of radiotherapy,Serampore walsh SDH, Hooghly, West Bengal
[5]Professor and Head, Department of Radiotherapy, R.G.Kar Medical College & Hospital
[6]Professor and Head, Department of Physiology, Diamond Harbour Govt. Medical College and Hospital, South 24 PGS., West Bengal, India

(Received : 07.05.2024 Revised : 13.06.2024 Accepted : 18.06.2024)

Corresponding author: **Sanskriti Poddar[4],** Email : sanskritipoddar@gmail.com

ABSTRACT

INTRODUCTION: Inflammation is recognized as a triggering factor of the initiation and progression of neoplastic processes. Neutrophilia and lymphopenia are hallmarks of inflammation. The aim of this study is to correlate pretreatment value of neutrophil lymphocyte ratio [NLR] as prognostic factor in breast cancer.

MATERIALS AND METHODS: Data of biopsy proven cases of breast cancer were analysed retrospectively. Pearson correlation test was used to correlate NLR with stage, luminal subtypes and IHC markers of breast cancer. The cut off values of NLR were calculated using median and ROC curve analysis.

RESULTS: 742 patients out of 1275 patients were eligible for study. Median age was 47 years (mean ± sd 47.67 ± 10.63 years). 43.1% patients are of Luminal A type, 7.1 % are Luminal B type, 11.9% are HER 2 neu enriched and 37.9% are TNBC. Median follow up time for study was 53 months.NLR median value is 2.14 (0.52 to 15). Median value of NLR 2.14 was used as cutoff into high (>2.14) and low (< 2.14)arms. Statistically significant association was found in high NLR and HER 2 neu positive patients and patients with high ki67%. The median DFS in high NLR (> 2.1) was 82 months (95% CI 79.143, 84.847). Median DFS was not reached in the low NLR arm.

CONCLUSION: High neutrophil count and high NLR is strongly associated with poor survival of breast cancer patients.This can be used as predictive and prognostic factor.

KEYWORDS: Breast cancer, NLR, overall survival, DFS

INTRODUCTION

Female breast cancer has surpassed the lung cancer as the most commonly diagnosed cancer since 2020 and was estimated to 2.3million new cases[1]. Data suggests a slow increase of female breast cancer cases (by 0.5% per year)during 2014 through 2018[2]. In India 178361 (13.5%) new breast cancer cases along with 90408 (10.6%) deaths have been reported as per the Globocan data 2020[3]. Tumor microenvironment is the key factor for tumorigenesis and host's inflammatory response is directly correlated with cancer progression and prognosis[4]. Hanahan and Weinberg defined the hallmark of cancer as sustained proliferative signalling, evasion of growth suppressors, development of resistance against cell death,and activation of evasion and metastasis. So inflammation plays for all these through different pathways.

Inflammation has direct correlation with development, upstaging and metastasis of cancer as both extrinsic and intrinsic inflammations can cause immunosuppression in human body that leads to favourable background for tumour development[5]. There are three major components of systemic inflammatory response such as Neutrophils, Lymphocytes and Platelets which plays an important role in carcinogenesis and tumor progression[6]. Neutrophils act as tumour promoting leucocytes,inhibits the immune system by supressing the cytolytic activity of lymphocytes.A high neutrophil

count is a surrogate marker of highly proliferative tumor and provide insight into a cancer with a high chance of recurrence and metastasis[7]. Many studies have evaluated the systemic inflammatory responses with help of some biochemical tests and also some haematological tests. Neutrophil to Lymphocyte ratio (NLR), Platelet to Lymphocyte ratio (PLR) derived from simple hematological test used to project simple inflammation based prognostic markers in cancer[8]. Increased NLR, PLR has inversely proportional to the survival in case of colorectal and gastrointestinal , head neck and cervical cancers[9-11]. In case of breast cancer higher NLR ratio shows lower survival and increased PLR ratio is adverse prognostic marker[12]. This study was conducted to detect NLR value on disease free survival and overall survival in breast cancer patients in tertiary care cancer hospital.

2.0 MATERIAL AND METHOD

2.1 The clinical data of breast cancer patients treated at Institute of Post Graduate Medical Education and Research (IPGMER), Kolkata, from February 2015 to August 2020 were collected. Staging was done based on the American Joint Committee on Cancer (AJCC) TNM staging system (7th edition, 2010). The diagnosis had been validated by histopathological examination. The inclusion criteria for the patients were as follows: (i) age more than 18 years; (ii) complete clinical, laboratory, imaging, and follow-up data, (iii) no chronic infectious diseases, (iv) no haematological disorders or treatment that can result in an elevated NLR, for example, administration of hematopoietic drugs such as granulocyte-colony stimulating factor (G-CSF) within one month , (v) no autoimmune disease or usage of steroids. The performance status of patients were categorised using Eastern cooperative oncology group (ECOG). Routine blood tests were done within seven days prior to the start of treatment. NLR were calculated as the absolute neutrophil counts divided by the absolute lymphocyte counts[13]. Patients were followed up every 3 months after treatment completion. Local recurrence of the disease was referred to as locoregional recurrence (LRR). The locoregional recurrence free survival (LRRFS) was defined as the interval between completion of treatment (adjuvant radiation or definitive radiation) and locoregional recurrence. The overall survival (OS) was calculated from the diagnosis to the date of death or the last visit.

2.2 Statistical Analysis:

IBM SPSS (Statistical Package for the Social Sciences) version 20, Armonk and R statistical software were used for statistical analysis. The major study endpoints were to determine a cutoff value for NLR and to determine the impact of high vs low NLR on disease free survival (DFS) and overall survival (OS). The minor endpoints of the study were to determine the Pearson correlation of NLR with different immunohistochemistry (IHC) parameters like ER, PR, Her 2 neu and Ki67%, TNM parameters, and in multivariate Cox proportional hazards (coxph regression mode) analysis impact of NLR with other covariates on DFS and OS.

The cutoff values can be determined by several methods in statistics which includes the Mean±2SD method, Logistic Regression Analysis, Receivers Operating Characteristics (ROC) curve analysis and Discriminant Analysis (DA)[14,15]. In another study by Ayala de la Peña et.al, median NLR value was used as cutoff while calculating the impact of high vs low NLR as prognostic marker among metastatic breast cancer patients[16]. For our study, first median value of NLR was calculated. In the second step cutoff value (median) was used to calculate coxph hazards ratio using overall survival parameters.

Lastly Receiver operating characteristic (ROC) curve analysis was used for internal validation to determine the optimal cut off value NLR.

3.0 RESULTS:

3.1A Demographic parameters

Total of 1275 patients were diagnosed with breast cancer and were recruited for this non interventional retrospective study. Out of which due to paucity of data, only 742 patients were eligible for study.

Table 1. Patient and tumour characteristics:

Age in years						
Gender	N	Median	Mean	Std. Deviation	Minimum	Maximum
Female	734	47.00	47.68	10.622	21	83
Male	8	45.50	46.63	11.563	24	66
Total	742	47.00	47.67	10.625	21	83
P VALUE:0.779						

Table 2 : Presentation of Disease

		Count	Column N %
Gender	Female	734	98.9%
	Male	8	1.1%
Site	Left breast	398	53.6%
	Right breast	340	45.8%
	Bilateral synchronous breast	4	0.5%
Symptoms of presentation	Breast lump	729	98.2%
	Pain	94	1.2%
	Nipple discharge	38	0.5%
Family history of malignancy	Yes	70	5.1%
	No	43	94.9%
Menopause	Yes	60	48.5%
	No	37	50.4%
	Not eligible	48	1.1%

Table 3. IHC and luminal parameters

IHC parameters		Count	Column N %
ER	Negative	396	53.4%
	Positive	346	46.6%
PR	Negative	454	61.2%
	Positive	288	38.8%
Her 2 neu	Negative	508	68.5%
	Positive	234	31.5%
Ki67	<14%	501	67.5%
	>14%	241	32.5%
LUMINAL	LA	320	43.1%
	LB	53	7.1%
	Her 2 neu enriched	88	11.9%
	TNBC	281	37.9%

Table 4. Treatment parameters

Different treatment modalities		Count	Column N %
Surgery type	Only biopsy	46	6.2%
	MRM	501	67.5%
	Simple Mastectomy with Axillary Dissection	135	18.2%
	Simple Mastectomy without Axillary Dissection	48	6.5%
	Toilet Mastectomy	12	1.6%
Chemotherapy	Neoadjuvant	387	52.2%
	Adjuvant	309	41.6%
	Palliative	46	6.2%
Radiation	No radiation	385	59.1%
	Locoregional radiation	140	21.5%
	Palliative radiation	53	8.1%
	Both	73	11.2%

Table 5. Total leucocyte count, differential count and NLR

	Total leucocyte count (/cmm)	NEUTROPHIL ABSOLUTE	LYMPHOCYTE_ABSOLUTE	NLR
Mean	7732.92	4945.18	2257.17	2.4229
Median	7500.00	4623.00	2157.00	2.1400
Std. Deviation	2502.091	2089.908]	834.559	1.25843
Minimum	3100	1394	702	.52
Maximum	25600	23040	6875	15.00

The mean absolute count of Neutrophil is 4945.18 (Thousand per cmm), Lymphocyte is 2257.17(thousand per cmm) and the NLR median value is 2.14(0.52 to 15). (Table 5)

Table 6. NLR correlation with IHC parameters and luminal classification

IHC parameters / luminal classification		NLR		Pearson correlation (p value)
		Mean	S.D	
ER	Negative	2.46	1.35	- 0.30 (0.422)
	Positive	2.38	1.14	
PR	Negative	2.44	1.32	- 0.015 (0.693)
	Positive	2.40	1.16	
Her 2 neu	Negative	2.35	1.26	+ 0.090 (0.014)**
	Positive	2.59	1.23	
Ki67	<14%	2.18	1.04	+ 0.279 (0.000)**
	>14%	2.93	1.51	
LUMINAL	LA	2.27	1.07	+ 0.039 (0.284)
	LB	3.01	1.27	
	Her 2 neu enriched	2.77	1.44	
	TNBC	2.37	1.34	
**statistically significant correlation.				

High NLR statistically significant with Her 2 neu positive patients (p value 0.014) and patients with > 14% Ki67%(p value 0.00). (Table 6) Higher pretreatment N stage was showing positive correlation with higher NLR. Patients with LABC and MBC also had statistically significant positive correlation with high NLR.(Table 7)

Table 7. NLR correlation with TNM staging

TNM parameters – pretreatment parameters		NLR				Pearson correlation (p value)
		Count	Median	Mean	S.D	
T	1	43	1.88	2.03	1.01	+ 0.201** (0.000)
	2	345	2.06	2.24	0.99	
	3	205	2.34	2.50	1.00	
	4	149	2.42	2.86	1.90	
N	0	197	2.1300	2.3630	1.26	+ 0.055 (0.131)
	1	291	2.1300	2.3660	1.15	
	2	178	2.3300	2.5344	1.18	
	3	76	2.1150	2.5345	1.70	
cM	No	696	2.13	2.42	1.27	+ 0.014 (0.712)
	Yes	46	2.34	2.49	1.01	
STAGE*	EBC	275	1.97	2.20	1.00	+ 0.117** (0.001)
	LABC	421	2.23	2.56	1.41	
	MBC	46	2.34	2.49	1.01	
*Early Breast Cancer (EBC), Locally Advanced Breast Cancer (LABC), Metastatic Breast Cancer (MBC)						

3.2 Tumour parameters and NLR cutoff value

Table 8. Tumour characteristics according to NLR cutoff value

Tumour parameters		NLRcutoff				P value
		High (>2.14)		Low (<2.14)		
		Mean	S.D	S.D	S.D	
Grade	Grade 1	14	42.4%	19	57.6%	0.606
	Grade 2	270	49.5%	275	50.5%	
	Grade 3	85	51.8%	79	48.2%	
ER	Negative	199	50.3%	197	49.7%	0.761
	Positive	170	49.1%	176	50.9%	
PR	Negative	227	50.0%	227	50.0%	0.854
	Positive	142	49.3%	146	50.7%	
Her 2 neu	Negative	231	45.5%	277	54.5%	0.001*
	Positive	138	59.0%	96	41.0%	
Ki67	<14%	203	40.5%	298	59.5%	0.000*
	>14%	166	68.9%	75	31.1%	
LUMINAL	LA	143	44.7%	177	55.3%	0.000*
	LB	40	75.5%	13	24.5%	
	Her 2 neu enriched	60	68.2%	28	31.8%	
	TNBC	126	44.8%	155	55.2%	
**statistically significant correlation.						

Table 9. TNM staging parameters according to NLR cutoff value

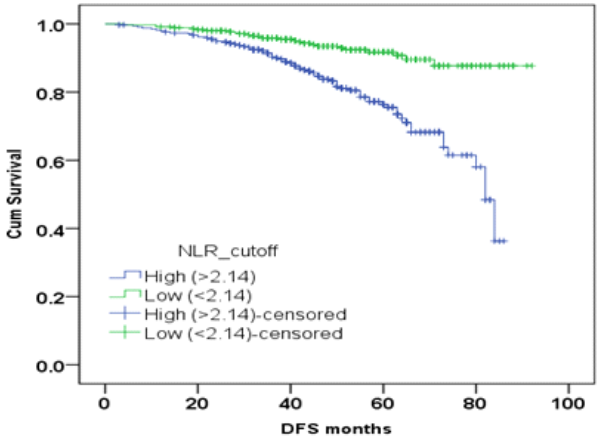
TNM staging parameters		NLRcutoff				P value
		High (>2.14)		Low (<2.14)		
		Count	Row N %	Count	Row N %	
cT	1	15	34.9%	28	65.1%	0.007*
	2	156	45.2%	189	54.8%	
	3	114	55.6%	91	44.4%	
	4	84	56.4%	65	43.6%	
cN	0	94	25.5%	103	27.6%	0.634
	1	142	38.5%	149	39.9%	
	2	96	26.0%	82	22.0%	
	3	37	10.0%	39	10.5%	
cM	No	341	49.0%	355	51.0%	0.119
	Yes	28	60.9%	18	39.1%	
STAGE	EBC	117	42.5%	158	57.5%	0.007*
	LABC	224	53.2%	197	46.8%	
	MBC	28	60.9%	18	39.1%	
*Statistically significant p value, Chi Square test.						

3.3 Survival analysis and NLR cutoff

The median follow up time for study was 53 months, using Reverse Kaplan Meier Survival analysis with overall survival parameters.

3.31 DFS vs NLRcutoff

The median DFS in high NLR (> 2.1) was 82 months (95% CI 79.143, 84.847). Median DFS was not reached in the low NLR arm. 73 out of 341 patients (21.4%) in high NLR arm had disease progression. Among the patients below the cut off value, with lower NLR, the events accounted for 26 out of 355 patients. Only local recurrence was documented in 28 patients, only distant metastases in 56 individuals and both in 15 patients. Most common sites for distant metastases were only liver (n=22) and only bone(n=14). Multiple organs involvements were documented in 22 patients.



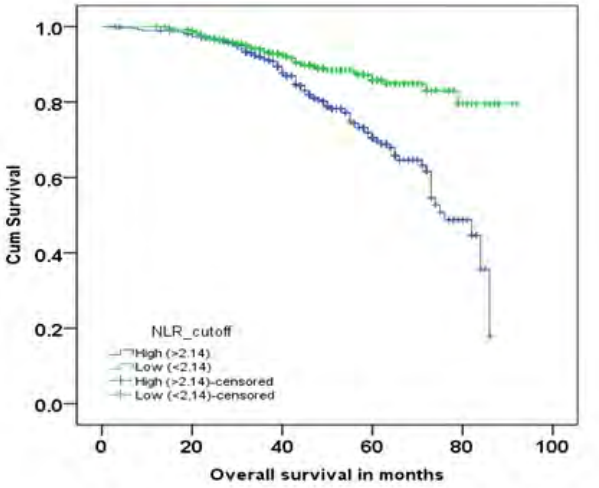
	1 month	20 month	40 month	60 month	80 month	90 month
High (> 2.14)	0/341** (1.000)	13/324 (0.962)	23/233 (0.885)	23/97 (0.764)	11/18 (0.581)	NA
Low (< 2.14)	0/355 (1.000)	6/343 (0.983)	9/254 (0.955)	8/120 (0.917)	3/20 (0.877)	0/2 (0.877)

**No of events / No at risk (survival Probability)
*49 patients who presented with metastasis at presentation never achieved complete response.

Figure 1. DFS in months according to NLR cut off value, with log rank test chi square 29.405, df 1, p value <0.001.

3.32 Overall survival (OS) vs NLR cutoff

The median overall survival for the study was reached. The median OS in the high NLR arm was 76.0 months (95% C.I 69.77, 82.23) with the number of events being 95/369 (25.7%). In the low NLR arm, median OS was not reached with the number of events being 43/373 (11.5%). The log rank comparison shows that individuals in high NLR arm had higher death events with p value < 0.001.(figure 2) Among all patients whose death due to cancer was documented with verification of death certificates, multiple organ involvements were in 62/138 patients, with lung, liver and brain being commonly affected. Local recurrence or progression were chestwall only (n= 21), lymph nodes (n= 37) and both in 34 patients..



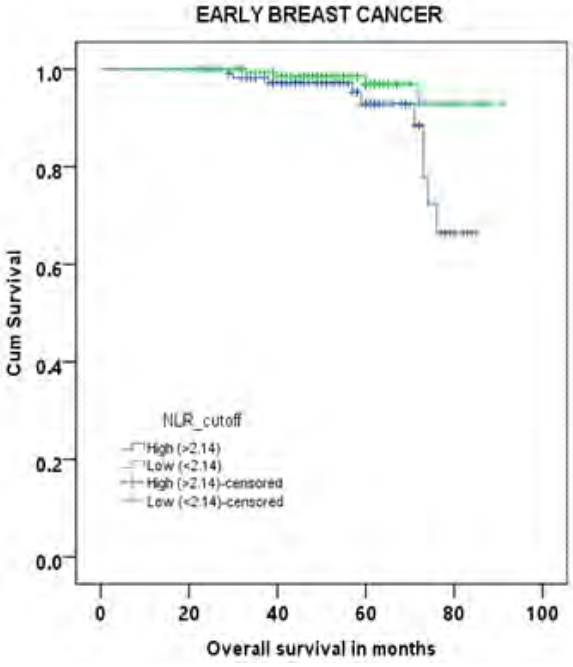
	1 month	20 month	40 month	60 month	80 month
High (> 2.14)	0/369** (1.000)	10/356 (0.973)	31/258 (0.876)	36/105 (0.705)	15/18 (0.487)
Low (< 2.14)	0/373 (1.000)	4/363 (0.989)	22/262 (0.924)	14/122 (0.858)	3/20 (0.796)

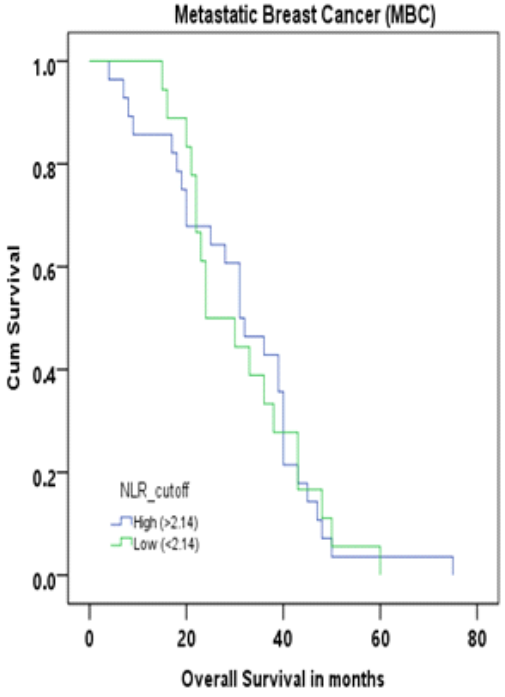
**No of events / No at risk (survival Probability)

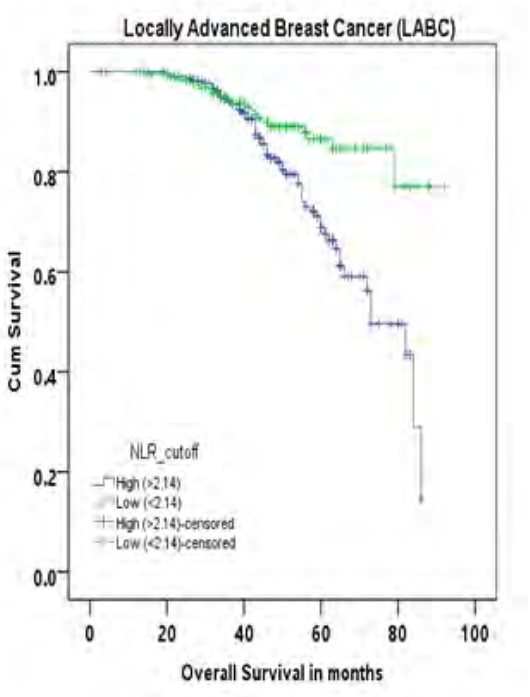
Figure 2. OS in months according to NLR cut off value, with log rank test chi square 24.066, df 1, p value <0.001.

Table 10:Overall survival according to stage in NLR arms

STAGE	NLR_cutoff	Total N	N of Events	Censored	
				N	Percent
Early Breast Cancer (EBC)	High (>2.14)	117	10	107	91.5%
	Low (<2.14)	158	4	154	97.5%
	Overall	275	14	261	94.9%
Locally Advanced Breast Cancer (LABC	High (>2.14)	224	57	167	74.6%
	Low (<2.14)	197	21	176	89.3%
	Overall	421	78	343	81.5%
Metastatic Breast Cancer (MBC)	High (>2.14)	28	28	0	0.0%
	Low (<2.14)	18	18	0	0.0%
	Overall	46	46	0	0.0%







Second-order Controls		First-order Controls		Median OS months
STAGE	Early Breast Cancer (EBC)	NLR_cutoff	High (>2.14)	84.00
			Low (<2.14)	84.00
	Locally Advanced Breast Cancer (LABC)	NLR_cutoff	High (>2.14)	78.60
			Low (<2.14)	84.00
	Metastatic Breast Cancer (MBC)	NLR_cutoff	High (>2.14)	34.00
			Low (<2.14)	30.00

Figure 3. Kaplan Meier survival curve with stratification by Stage between low and high NLR arms, Log rank test 0.001.

3.4 Determination of NLR cutoff value using Coxph regression model and ROC

The median value of NLR 2.14 was used as cutoff in our study. Coxph regression model showed that individuals with low pretreatment NLR (< 2.14) had reduced hazards rate by 59% and improved OS, [HR 1 in high NLR (> 2.14) vs 0.41 in low NLR, p value < 0.001].

Table 11.Cox ph regression models with effect of different covariates and NLR cutoff on Disease Free Survival (DFS)

Immunohistochemistry markers					
	Coef	exp(coef)	se(coef)	95%C.I	P value
NLR_cutoff	-1.22	0.29	0.24	0.18, 0.47	<0.001
ER	-0.16	0.85	0.29	0.47, 1.52	*0.589
PR	0.09	1.10	0.29	0.63, 1.94	0.734
her_2_neu	-0.04	0.96	0.21	0.63, 1.47	0.857
Ki67	-0.15	0.85	0.24	0.54, 1.35	0.499
TNM parameters					
NLR_cutoff	-1.02	0.36	0.23	0.23, 0.56	< 0.001*
T	0.52	1.69	0.16	1.24, 2.30	< 0.001*
N	0.19	1.22	0.12	0.95, 1.55	0.114
M	NA	NA	NA	NA	NA
STAGE	0.5593	1.75	3.89	0.82, 3.75	0.15

*statistically significant p value.
**total number of patients eligible for DFS calculation, n= 696, number of events =99, 46
observations deleted – presented with metastases at presentation and never achieved complete response.

Table 12. Cox ph regression models with effect of different co variates and NLR cutoff on Overall Survival

Immunohistochemistry markers					
	Coef	exp(coef)	se(coef)	95%C.I	P value
NLR_cutoff	-0.888200	0.411396	0.193435	0.28, 0.60	< 0.001 *
ER	-0.148371	0.862112	0.248254	0.53, 1.40	0.550
PR	0.035667	1.0363310	0.245819	0.64, 1.68	0.885
her_2_neu	-0.008961	0.991079	0.184692	0.69, 1.42	0.961
Ki67	-0.031752	0.968747	0.198323	0.66, 1.43	0.873
TNM parameters					
NLR_cutoff	-0.5990	0.5493	0.1863	0.38, 0.97	0.00130*
T	0.4468	1.5633	0.1247	1.22, 1.99	0.00034 *
N	0.1218	1.1295	0.1038	0.92, 1.38	0.24062
M	1.9142	6.7813	0.4418	2.85, 16.11	< 0.001
STAGE	0.7603	2.1388	0.3522	1.07, 4.27	*0.03088 *

*statistically significant p value.

3.5 Receiver Operating Characteristic curve (ROC)

ROC was calculated using NLR against overall survival outcome, death as an event. The Area Under Curve (AUC) was 0.639(95% C.I 0.587,0.691) with the Youden index calculated as sensitivity + specificity -1. The Youden index was maximum for 2.17. This value is subsequently used for coxph regression model. Patients with low NLR (≤ 2.17) had reduced HR by 59% (coefficient -0.8685, 95%C.I 0.29, 0.59) from high NLR cutoff (> 2.17) , p value < 0.001. The concordance index (C index) was 0.575. The table 12 highlights the sensitivity analysis of different cut off values of NLR..

Table 13. Different cutoff values used to calculate Hazard Ratio for overall survival parameters.

Different values	Sensitivity	Specificity	Cutoff	HR	95% C.I	P value
Median (2.14)	68.8%	54.1%	High >2.14	1	0.289, 0.597	< 0.001
			Low≤2.14	0.4159		
ROC (Youden index, 2.17)	67.4%	56.1%	High >2.17	1	0.294, 0.599	< 0.001
			Low≤2.17	0.4196		
Mean (2.42)	58.0%	62.7%	High >2.17	1	0.303, 0.611	<0.001
			Low ≤ 2.17	0.43		

4.0 DISCUSSION:

This retrospective study was conducted to understand the impact of NLR in breast cancer patients in terms of survival .Both Neutrophil and lymphocytes play an important triggering role in inflammation and immunity in the human body. Inflammation has direct correlation with cancer occurrence, development, progression, transformation and metastasis. NLR is described by relative increase in the neutrophil count and relative decrease in the lymphocyte count which leads to breakdown of balance in the tumour microenvironment[17].

Median age of our study population was 47 years (47.67±10.63) which matched with other Indian study[18]. The Median age of menarche was 13 years and menopause ranges from 41 to 53 years. Similar findings were also found in another Indian study by Tripathi p et al. Who also showed similar age distribution[19].

Our study showed significant correlation between high NLR (>2.14) with large tumour size (p value 0.007) and positive estrogen receptor and HER 2 neu receptor status. A similar finding was observed by Elyasinia F et.al however they showed no correlation between receptor status with high NLR[20]. We also found a high proliferative index (Ki 67%) is significantly correlated with higher NLR (p value 0.000) which was supported by Arora R et. al. [21].Among all subtypes luminal A was predominant which was around 43.1%(n=320) and triple negative breast cancer[TNBC] was 37.9%(n=281). Maximum patients (67.5%) underwent modified radical mastectomy after neoadjuvant chemotherapy followed by radiation where indicated.

Azab B et al. performed a study with 316 patients and concluded that high NLR >3.3 was an independent predictor of short and long-term mortality in breast cancer patients[22]. Our study showed correlation between pretreatment NLR and overall survival. We found the cutoff value for higher NLR is >2.14, which is similar to other studies where median cutoff value of NLR was 2.0 to 5.0 [23].However NLR cut off values varied. A meta-analysis from fifteen studies including 8563 patients showed high NLR cutoffs ranged from 1.9 to 5. All studies showed a worse OS with high NLR in patients irrespective of early and metastatic disease.

The median followup time for our study was 53 months. Coxph regression model showed that individuals with low pretreatment NLR (< 2.14) had reduced hazard rate by 59% and improved OS, [HR 1 in high NLR (> 2.14) vs 0.41 in low NLR, p value < 0.001]. The median OS in the high NLR arm was 76.0 months (95% C.I 69.77, 82.23) with the number of events being 95/369 (25.7%).

The log rank comparison showed that individuals in high NLR arm had higher death events with p value < 0.001, which was same as other pooled analysis[24]. The median DFS in high NLR (> 2.1) was 82 months (95% CI 79.143, 84.847). High NLR arm had disease progression, with lower NLR the events were less. Shao et.al showed that NLR has prognostic correlation of OS in HER 2 neu positive metastatic cancer and in our study,we found direct association between the tumour with higher expression of HER 2 neu receptor and NLR values above 2.14[25].

5.0 CONCLUSION

There is limited data available on use of NLR as prognostic marker in breast cancer from eastern India. Even though our single institutional retrospective study is limited with deficiencies in data, it goes on to show that elevated neutrophil count and high NLR inhibits the immune system which in turn aids in rapid disease progression.This high NLR is strongly associated with poor survival of breast cancer patients and can be used as predictive and prognostic factor.

6.0 LIMITATION

Due to lack of appropriate data,the association of NLR and other clinical parameters such as mean platelet volume, red cell dispersion width was not explored.

Prior publication ……NIL

Funding……This research received no external funding

Conflicts of interest……...The authors declare no conflict of interest in this work

Informed consent statement ……Informed consent was waived due to the retrospective nature of this study and analysis used anonymous clinical data.

Acknowledgement .....This study was not supported by any company or institution.

Ethical clearance.....As treatment already completed according to standard protocol and no new intervention will be done, so ethical committee waived it of.

REFERENCES:

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338]
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022 Jan;72(1):7-33. doi: 10.3322/caac.21708. Epub 2022 Jan 12. PMID: 35020204.].
3. Mehrotra R, Yadav K. Breast cancer in India: Present scenario and the challenges ahead. World J Clin Oncol. 2022;13(3):209-218. doi: 10.5306/wjco.v13.i3.209. PMID: 35433294; PMCID: PMC8966510.

   linkhttps://gco.iarc.fr/today/data/ factsheets/ populations/356-india-fact-sheets.pdf] .
4. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144: 646–674. [PubMed] [Google Scholar]
5. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. Ann Afr Med. 2019;18(3):121-126. doi: 10.4103/aam.aam_56_18. PMID: 31417011; PMCID: PMC6704802.]
6. DeNardo DG, Coussens LM. Inflammation and breast cancer. Balancing immune response: crosstalk between adaptive and innate immune cells during breast cancer progression. Breast Cancer Res. 2007;9(4):212. doi: 10.1186/bcr1746. PMID: 17705880; PMCID: PMC2206719.]
7. Xiong S, Cheng L. Neutrophils in cancer carcinogenesis and metastasis. J Hematol Oncol 2021;14(01):173.
8. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010;6(1):149-63. doi: 10.2217/fon.09.136. PMID: 20021215.]

9. Koh CH, Bhoo-Pathy N, Ng KL, Jabir RS, Tan GH, See MH, et.al. Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. Br J Cancer. 2015;113(1):150-8. doi: 10.1038/bjc.2015.183. Epub 2015 May 28. PMID: 26022929; PMCID: PMC4647546.]

10. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, et.al Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23: 1204–1212. [PubMed] [Google Scholar]

11. Sarkar S, Mirza B, Das SM, et al. Pretreatment Systemic Inflammatory Markers, Neutrophil Lymphocyte Ratio, and Platelet Lymphocyte Ratio as a Prognostic Factor in Cervical Cancer: A Retrospective Study. South Asian J Cancer 2023;00(00):00–00. 10.1055/s-0043-1768682.

12. Azab B, Shah N, Radbel J, Tan P, Bhatt V, Vonfrolio S, et.al. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. Med Oncol 2013;30: 432. [PubMed] [Google Scholar]

13. Kim, JY., Jung, E.J., Kim, JM. et al. Dynamic changes of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio predicts breast cancer prognosis. BMC Cancer 2020;20:1206. https://doi.org/10.1186/s12885-020-07700-9.

14. Sharma, Balkishan and Ravi Kant Jain. "Right choice of a method for determination of cut-off values: A statistical tool for a diagnostic test." Asian Journal of Medical Sciences 2014; 5:30-34.

15. Habibzadeh F, Habibzadeh P, Yadollahie M. On determining the most appropriate test cut-off value: the case of tests with continuous results. Biochem Med (Zagreb). 2016;26(3):297-307. doi: 10.11613/BM.2016.034. PMID: 27812299; PMCID: PMC5082211.

16. Ayala de la Peña, F. et al. Neutrophil-lymphocyte ratio (NLR) as a prognostic factor in metastatic breast cancer. Annals of Oncology. 2017;28,v94. DOI:https://doi.org/10.1093/annonc/mdx365.046.

17. Shilpa, M., Kalyani, R., & Sreeramulu, P. N.Prognostic value of pre-treatment routine hematological parameters in breast carcinoma: Advantageous or deleterious?. Biomedical Research and Therapy. 2020;7(8):3916-3920.

18. Rao JS, Hanumappa HK, Joseph EP, Chowdappa RG, Ramesh R. Elevated Neutrophil-Lymphocyte Ratio in Luminal-Type Locally Advanced Breast Cancer to Circumvent Neo-Adjuvant Chemotherapy. Indian J Surg Oncol. 2019 Sep;10(3):454-459. doi: 10.1007/s13193-019-00944-3. Epub 2019 Jun 15. PMID: 31496590; PMCID: PMC6708037.

19. Tripathi P, Nigoskar S, Singh R, Kala S, Yadav GD, Athar M, et.al. Role of peripheral blood parameters (neutrophil-to-lymphocyte, lymphocyte-to-monocyte and neutrophil-to-monocyte ratios) in breast cancer. Curr Med Res Pract 2022;12:67-72.

20. Elyasinia F, Keramati MR, Ahmadi F, Rezaei S, Ashouri M, Parsaei R, Yaghoubi M, Elyasinia F, Aboutorabi A, Kaviani A. Neutrophil-Lymphocyte Ratio in Different Stages of Breast Cancer. Acta Med Iran. 2017;55(4):228-232.

21. R. Arora, F. Alam, A. Zaka-Ur-Rab, V. Maheshwari, K. Alam. 32P Neutrophil to lymphocyte ratio (NLR) as a surrogate clinical marker for Ki-67 in breast cancer,Annals of Oncology 2022;3:S137. DOI:https://doi.org/10.1016/j.annonc.2022.03.047

22. Azab B, Bhatt VR, Phookan J, Murukutla S, Kohn N, Terjanian T, Widmann WD. Usefulness of the

neutrophil-to-lymphocyte ratio in predicting short- and long-term mortality in breast cancer patients. Ann Surg Oncol. 2012;19(1):217-24.

23. Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. Breast Cancer Res. 2017;19(1):2.

24. Chen J, Deng Q, Pan Y, He B, Ying H, Sun H, et.al. Prognostic value of neutrophil-to-lymphocyte ratio in breast cancer. FEBS Open Bio. 2015;12;5:502-7. doi: 10.1016/j.fob.2015.05.003. PMID: 26137435; PMCID: PMC4483486.

25. Shao B, Liu X, Li H, Song G, Di L, Jiang H, et.al. Value of Pretreatment Neutrophil-to-Lymphocyte Ratio in HER2-Positive Metastatic Breast Cancer. Curr Oncol. 2022;29(9):6154-6166. doi: 10.3390/curroncol29090483. PMID: 36135052; PMCID: PMC9498194.