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THE ROLE OF NEUTROPHIL TO LYMPHOCYTE RATIO IN TOXICITY AND RESPONSE OF HEAD AND NECK CANCER PATIENTS TREATED WITH CONCURRENT CHEMORADIATION

Oncology/Radiotherapy

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ABSTRACT

Background- Neutrophil to Lymphocyte Ratio (NLR) is a haematogical marker which signifies inflammatory burden and treatment outcome of a malignancy. We investigated prognostic value of NLR in Head and Neck Squamous Cell Carcinoma (HNSCC) patients treated with concurrent chemoradiotherapy. **Aims & Objective-** To compare acute toxicity, locoregional control, disease burden with patients with high (>4) and low (≤4) NLR groups. **Materials And Methods-** Head and neck squamous cell carcinoma patients treated with concurrent chemoradiotherapy were retrospectively selected from the records of Department of Radiation Oncology, Medical College Kolkata between 2018-2021. Baseline Neutrophil to Lymphocyte Ratio (NLR) was calculated using Differential Leucocyte Count (DLC) of Complete Blood Count (CBC) measured 10 days before the treatment initiation. An NLR value of greater than 4 has been considered as high. Data regarding stage at presentation, acute oral mucositis, acute dysphagia, anaemia, clinicoradiological response to treatment at 6 weeks after completion of chemoradiation were taken. **Results-** We analysed 150 patients between 2018-2021. Primary sites were oral cavity (37.3%), oropharynx (24%), hypopharynx (10.7%), larynx (28%). Our data suggests high baseline NLR correlates with poor prognosis because of more disease burden and poor treatment response. More numbers of locally advanced disease (T3 & T4) belong to high NLR group (P value= <0.0001). Grade II or more acute toxicities i.e oral mucositis, dysphagia was observed in high NLR group (P value <0.0001), which were statistically significant. Complete radiological response is lower in high NLR group, which was statistically significant (P Value = <0.0001). Mean Local Recurrence Free Survival (In Months) was less in high NLR group, this was also statistically significant. **Conclusion-** This study suggests that in head and neck squamous cell carcinoma, high NLR is correlated with higher stage of presentation, more acute locoregional toxicity during chemoradiotherapy, poor response to therapy and low local recurrence free survival (In Months)

KEYWORDS

Neutrophil Lymphocyte Ratio, Head and neck squamous cell carcinoma, Concurrent Chemoradiotherapy, Locoregional Control, Differential Leucocyte Count, Complete Blood Counts, Acute Toxicity.

BACKGROUND-

Cancer related inflammation correlates with survival, disease burden and therapeutic response in various solid tumours (1,2).Inflammation is the hallmark of malignancy (3). Cytokines released from tumour cells stimulate bone marrow to produce neutrophils (4-6). Neutrophil further releases cytokines which promote angiogenesis & metastasis (7-12). Haematological parameters may be used as a prognostic marker in malignancy (13-14). Neutrophil to Lymphocyte Ratio (NLR) is an emerging marker of host inflammation. NLR is one of the inexpensive, easily calculated and reproducible systemic inflammatory marker with prognostic significance in lung cancer, renal cell carcinoma, colon carcinoma (15-16).

This is easily calculated from Differential Leucocyte Count (DLC) of Complete Blood Count (CBC) simply by making ratio of neutrophil to lymphocyte. NLR has its prognostic significance in various solid tumour e.g – in Head & neck malignancy due to inflammatory burden (17-26). Impact of pre-treatment NLR on treatment related toxicity and outcome is limited. (17-28). Concurrent chemoradiation is the treatment approach for locally advanced head and neck squamous cell carcinoma. In post operative patients, we give concurrent chemoradiation whether in positive margin or extranodal extension is present.

In this study, we retrospectively evaluated the prognostic significance of pre-treatment NLR on treatment related toxicity and oncological outcome in head and neck squamous cell carcinoma patients treated with concurrent chemoradiation at Radiation Oncology department of Medical College Kolkata.

METHODS

Patient Selection

Patients were retrospectively selected from records of Radiation Oncology department of medical college Kolkata. Head and neck squamous cell carcinoma patients treated with primary of adjuvant concurrent chemoradtion were retrospectively analysed between January 2018 to December 2021. Patients with biopsy proven malignancy of oral cavity, oropharynx, hypopharynx and larynx were included in this study.

History of prior radiation to head and neck, non-squamous cell carcinoma histology, previous malignancy within five years, distant metastasis, lack of Differential Leucocyte Count (DLC) 10 days prior to RT start, early discontinuation from RT, elderly patient with impaired Renal Function Test (RFT) were defined as exclusion criteria.

Treatment and follow up

Biopsy proven head and neck squamous cell carcinomas were registered at Radiation Oncology department of Medical College Kolkata. History taking, physical examination, blood investigations, staging and metastatic workup were done. After proper TNM staging, treatment modalities were planned. The standard treatment approach in oral cavity cancer is surgery followed by adjuvant Radiotherapy (29-31).

For locally advanced oropharynx, hypopharynx, larynx cancer treatment of choice is definitive concurrent chemoradiaion. Gross tumour Volume (GTV), Clinical Target Volume (CTV), Planning target volume (PTV) all were delineated according to contouring guidelines (32-34) and planning was done using Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA.

Concurrent chemotherapy agent was Cisplatin, iv infusion @ 100/m^2 body surface area 3 weekly interval in normal renal function patients during radiation schedule. In few cases, induction chemotherapy consisting of cisplatin, docetaxel, 5 fluorouracil were used. Radiation dose was 66 Gy for inoperable locally advanced oral cavity, oropharynx, hypopharynx, larynx cancer @ 2 Gy/fraction, 5 days a week (mon-fri) over 6-7 weeks. Pretreatment CBC with Differential Leucocyte Count (DLC) was done 10 days prior to RT initiation for

calculating NLR. Deranged DLC due to infection was excluded from the study. Patients were followed up weekly and toxicities were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v 4.03.

Statistical Analysis

NLR was calculated by dividing absolute neutrophil count by absolute lymphocyte count measured in peripheral blood. Disease burden, treatment response, local control, acute toxicities were compared between high and low NLR groups.

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analysed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables.

Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.

The Kaplan–Meier estimator (Kaplan-Meier survival analysis) was a non-parametric statistic used to estimate the survival function from time data.

Once a *t* value is determined, a *p*-value can be found using a table of values from Student's t-distribution. If the calculated *p*-value is below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01 level), then the null hypothesis is rejected in favour of the alternative hypothesis. p-value ≤ 0.05 was considered for statistically significant.

RESULTS

Patient characteristics-

One hundred and fifty patients were included in this study. Majority of the patients were male and in good performance status (ECOG PS 1). Patient population was divided into two groups, one with NLR ≤ 4 was denoted as NLR_1 and the other with NLR > 4 was denoted as NLR_2. Majority of the patients were in the age group of 51-60 years, 32.5% for NLR_1 and 37% for NLR_2. Relation between age in group and NLR was not statistically significant (p= 0.79).

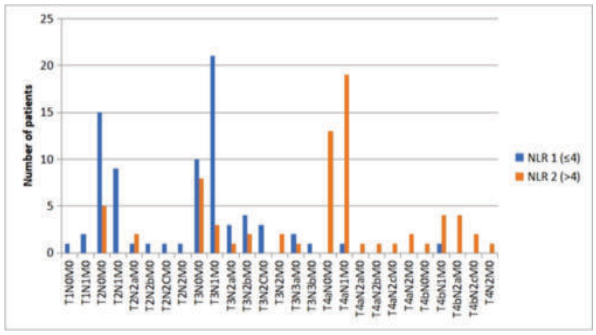
In NLR 1 (≤4), the mean Age (mean± s.d) of patients was 54.6234±11.2332. In NLR 2 (>4), the mean Age (mean± s.d) of patients was 55.6986±10.4266. Distribution of mean Age with NLR was not statistically significant (p=0.5449).

Majority of the patients in NLR_1(21.3%) and NLR_2(16%) had been suffering from oral cavity carcinoma but was not statistically significant (p=0.26). Majority of patients in NLR_1 were presented with $T_3N_1M_0$ stage (14%) and in NLR_2 were presented with $T_{4a}N_1M_0$(12.6%). It was statistically significant with NLR (p=<0.0001). Baseline NLR was not associated with gender, smoking status, subsite of tumour.

Table: Association between Subsite: NLR

NLR			
Subsite	NLR 1 (≤4)	NLR 2 (>4)	Total
Glottic Row % Col %	5 83.3 6.5	1 16.7 1.4	6 100.0 4.0
Hypo pharynx Row % Col %	6 37.5 7.8	10 62.5 13.7	16 100.0 10.7
Oral Cavity Row % Col %	32 58.2 41.6	24 41.8 31.5	55 100.0 36.7
Oropharynx Row % Col %	16 44.4 20.8	20 55.6 27.4	36 100.0 24.0
Supraglottis Row % Col %	18 50.0 23.4	18 50.0 24.7	36 100.0 24.0
Total Row % Col %	77 51.3 100.0	73 48.7 100.0	150 100.0 100.0

Association of Subsite with NLR was not statistically significant (p=0.2621).



Association of Stage with NLR was statistically significant (p=<0.0001).

Correlation between pre-treatment NLR and treatment related toxicities-

Acute toxicity oral mucositis Grade III was seen more in NLR_2 than NLR_1. Association of Acute Toxicity oral Mucositis with NLR was statistically significant (p=<0.0001). Acute toxicity dysphagia Grade II was seen more in NLR_2 than NLR_1. Association of Acute toxicity Dysphagia with NLR was statistically significant (p=<0.0001). Anaemia Grade III during concurrent chemoradiation was seen in NLR_2 than NLR_1. Association of Acute toxicity Anemia with NLR was statistically significant (p=<0.0001).

Table: Association between Acute Toxicity oral Mucositis: NLR

NLR			
Acute Toxicity Oral Mucositis	NLR 1 (≤4)	NLR 2 (>4)	TOTAL
Grade I Row % Col %	44 78.6 57.1	12 21.4 16.4	56 100.0 37.3
Grade II Row % Col %	8 38.1 10.4	13 61.9 17.8	21 100.0 14.0
Grade III Row % Col %	4 17.4 5.2	19 82.6 26.0	23 100.0 15.3
Grade II Row % Col %	13 38.2 16.9	21 61.8 28.8	34 100.0 22.7
Grade III Row % Col %	0 0.0 0.0	8 100.0 11.0	8 100.0 5.3
No Row % Col %	8 100.0 10.4	0 0.0 0.0	8 100.0 5.3
TOTAL Row % Col %	77 51.3 100.0	73 48.7 100.0	150 100.0 100.0

Association of Acute Toxicity Mucositis with NLR was statistically significant (p=<0.0001).

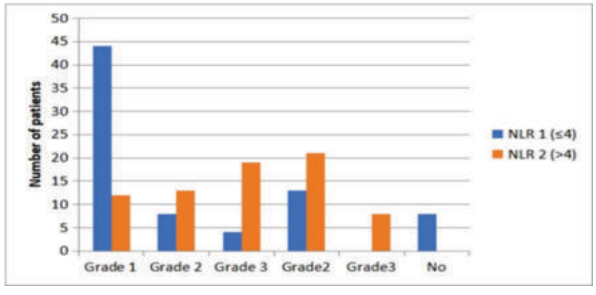


Table: Association between Acute toxicity Dysphagia: NLR

NLR			
Acute toxicity Dysphagia	NLR 1 (≤4)	NLR 2 (>4)	TOTAL
Grade I Row % Col %	18 43.9 23.4	23 56.1 31.5	41 100.0 27.3
Grade II Row % Col %	3 21.4 3.9	11 78.6 15.1	14 100.0 9.3

Grade III Row % Col %	2 8.7 2.6	21 91.3 28.8	23 100.0 15.3
Grade I Row % Col %	3 42.9 3.9	4 57.1 5.5	7 100.0 4.7
Grade II Row % Col %	3 50.0 3.9	3 50.0 4.1	6 100.0 4.0
No Row % Col %	48 81.4 62.3	11 18.6 15.1	59 100.0 39.3
TOTAL Row % Col %	77 51.3 100.0	73 48.7 100.0	150 100.0 100.0

Association of Acute toxicity Dysphagia with NLR was statistically significant (p=<0.0001).

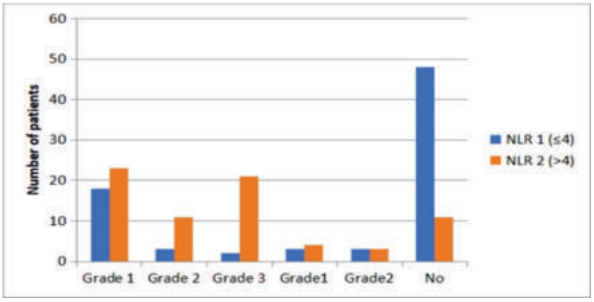
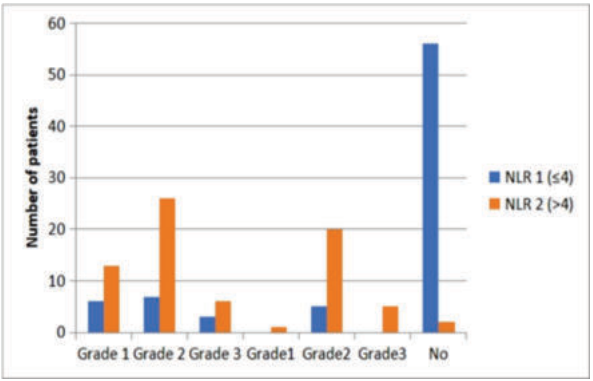


Table: Association between Acute toxicity Anaemia: NLR

NLR			
Acute toxicity Anaemia	NLR 1 (≤4)	NLR 2 (>4)	TOTAL
Grade I Row % Col %	6 31.6 7.8	13 68.4 17.8	19 100.0 12.7
Grade II Row % Col %	7 21.2 9.1	26 78.8 35.6	33 100.0 22.0
Grade III Row % Col %	3 33.3 3.9	6 66.7 8.2	9 100.0 6.0
Grade I Row % Col %	0 0.0 0.0	1 100.0 1.4	1 100.0 0.7
Grade II Row % Col %	5 20.0 6.5	20 80.0 27.4	25 100.0 16.7
Grade III Row % Col %	0 0.0 0.0	5 100.0 6.8	5 100.0 3.3
No Row % Col %	56 96.6 72.7	2 3.4 2.7	58 100.0 38.7
TOTAL Row % Col %	77 51.3 100.0	73 48.7 100.0	150 100.0 100.0

Association of Acute toxicity Anaemia with NLR was statistically significant (p=<0.0001).



Treatment outcomes-

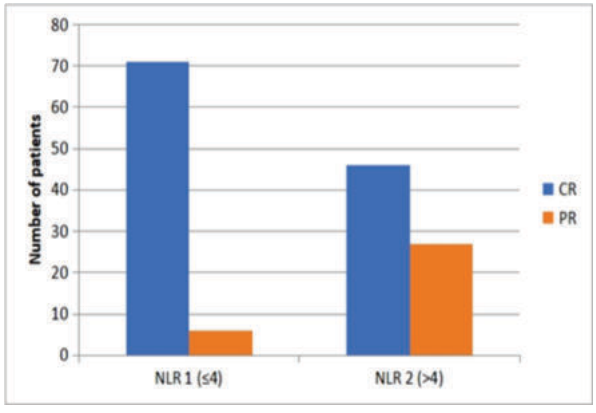
In NLR 1 (≤4) group, 71 (92.2%) patients had Complete Response (CR) after treatment and 6 (7.8%) patients had Partial Response (PR) after treatment.

In NLR 2 (>4) group, 46 (63.0%) patients had CR after treatment and 27 (37.0%) patients had PR after treatment.

Association of Treatment Outcome with NLR was statistically significant (p=<0.0001).

Table: Association between Treatment Outcome: NLR

NLR			
Treatment Outcome	NLR 1 (≤4)	NLR 2 (>4)	TOTAL
CR Row % Col %	71 60.7 92.2	46 39.3 63.0	117 100.0 78.0
PR Row % Col %	6 18.2 7.8	27 81.8 37.0	33 100.0 22.0
TOTAL Row % Col %	77 51.3 100.0	73 48.7 100.0	150 100.0 100.0



Association of Treatment Outcome with NLR was statistically significant (p=<0.0001).

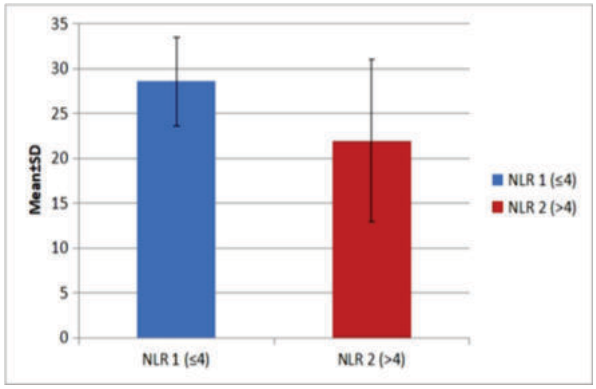
In NLR 1 (≤4), the mean Local Recurrence Free Survival (In Months) (mean± s.d) of patients was 28.5455±4.9085.

In NLR 2 (>4), the mean Local Recurrence Free Survival (In Months) (mean± s.d) of patients was 21.9452±9.0889.

Table: Distribution of mean Local Recurrence Free Survival (In Months): NLR

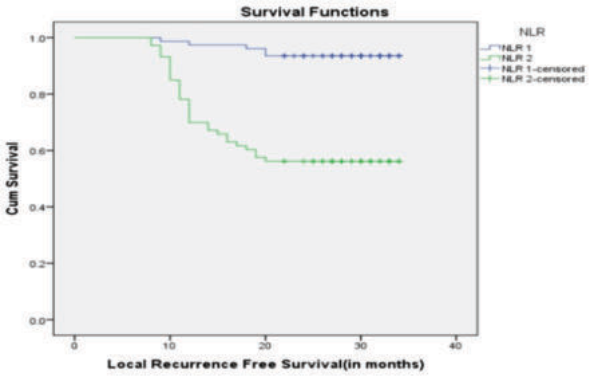
		Number	Mean	SD	Minimum	Maximum	Median	p-value
Local Recurrence Free Survival (In Months)	NLR 1 (≤4)	77	28.5455	4.9085	9.0000	34.0000	30.0000	<0.0001
	NLR 2 (>4)	73	21.9452	9.0889	8.0000	34.0000	25.0000	

Distribution of mean Local Recurrence Free Survival (In Months) with NLR was statistically significant (p=<0.0001).



NLR	Meana			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
NLR 1	32.818	.527	31.784	33.852
NLR 2	24.548	1.278	22.042	27.054
Overall	28.793	.758	27.308	30.279

Overall Comparisons			
	Chi-Square	df	p-value
Log Rank (Mantel-Cox)	29.423	1	<0.0001
Test of equality of survival distributions for the different levels of NLR.			



Prognostic significance of baseline NLR and other parameters

High baseline NLR was significantly correlated with higher T stage, poor treatment response and less Local Recurrence Free Survival (in Months) i.e- 21.9452±9.0889 months. Treatment interruption was more prominent in high NLR group (NLR_2) due to higher occurrence of Grade III toxicity oral mucositis, Grade II dysphagia, Grade III anaemia. That is why treatment response was suboptimal in NLR_2.

DISCUSSION

In this study we found that 1. high baseline NLR was correlated with advance T stage. 2. It is also correlated with poor treatment response after chemoradiation. 3. It is correlated with higher recurrence rate and lower Local Recurrence Free Survival (LRFS). NLR plays a major role in tumour microenvironment by secreting various growth factors i.e vascular endothelial growth factor, fibroblast growth factor, platelet derived growth factor, IL1, IL6. These cytokines create microenvironment for endothelial cell migration, angiogenesis, tumour progression (35). Neutrophils inhibits cytolytic activity of active T lymphocytes and natural killer cells, resulting in tumour growth (36). An early decrease in NLR is associated with favourable outcome and higher response rate, whereas an increase in NLR in the first week of treatment had the opposite effect (37). Chua et al. reported that high NLR correlated with poor OS in advanced colorectal cancer patients (38). Zhou et al. published that elevated NLR predicted poor PFS and OS in locally advanced oesophageal squamous cell carcinoma treated with definitive concurrent chemoradiation (39).

This study has several limitations. First, it is a retrospective study with confounding variables and selection bias. Second, we were unable to capture data on HPV status systemically. Third, it is a single institution study and study population was mostly Indian, extrapolation of this result to other Asian population should be done with care.

CONCLUSION

Our analysis suggests that NLR is an independent predictor of treatment response, disease burden, local recurrence free survival and acute toxicity in head and neck squamous cell carcinoma patients treated with concurrent chemoradiation.

Abbreviations- AJCC- American Joint Committee on Cancer, CBC- Complete Blood Count, CRT- Chemoradiotherapy, CTCAE-Common Terminology Criteria for Adverse Events DLC- Differential Leucocyte Count, HNSCC- Head and Neck Squamous Cell Carcinomas, NLR- Neutrophil to Lymphocyte Ratio, LRFS- Locoregional Recurrence Free Survival, RT- Radiotherapy.

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Availability of data and materials

The datasets used and analysed during the current study are available from the record section of Department of Radiation Oncology, Medical College & Hospital, Kolkata, West Bengal, India.

Authors' contributions

Dr. Kaustav Chatterjee and Prof Dr Subrata Chatterjee designed this study. Dr. Solanki Saha & Dr. Ansuman Bhattacharjee collected and analysed the data. Dr. Solanki Saha wrote the first draft. Dr. Ansuman Bhattacharjee edited and approved the final manuscript. All the authors hold all accountability for this study.

Consent for publication

All patients provided written consent for the publication of research performed with their medical data.

Competing interests

No potential conflicts of interests are to declare.

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