Research article

Role of systemic inflammatory markers (biomarkers) as important prognostic factors for survival in head and neck cancerSumana Maiti Das¹, Dharmendra Singh², Anjana Bose (Ghosh Dastidar)³, Siddhartha Das⁴, Neena Prasad S.⁵, Aloke Ghosh Dastidar⁶¹Assistant Professor, ⁵Junior Resident, ⁶Professor, Dept. of Radio-Therapy, Institute of Post-Graduate Medical Education and Research, Kolkata, 700020, West Bengal, India²Senior Resident, All India Institute of Medical Sciences, Patna, Bihar, India³Associate Professor, Dept. of Anesthesiology, ⁴Professor, Dept. of Physiology, Diamond Harbour Govt. Medical College Hospital, Diamond Harbour, South 24 Parganas, West Bengal, 743331, India

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Corresponding author: **Siddhartha Das**. Email: das.siddhartha01@gmail.com**ABSTRACT**

Introduction and Aim: Cancer related inflammation is recognized as a critical multifaceted player in tumour initiation and progression. The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are important markers of systemic inflammatory burden in malignancy. The present retrospective study aimed to evaluate the prognostic value of pre-treatment baseline (NLR) and (PLR) for survival in HNC patients.

Materials and Methods: Analysis of data of 257 patients with head and neck cancer treated with definitive therapy over 3.5 yrs. Neutrophil, lymphocyte and platelet counts before treatment of all patients were collected and NLR and PLR were calculated.

Results: Median value of NLR and PLR were 3.7 and 170.63 respectively. Receiver operator characteristics (ROC) curve analysis showed the predictive cut-off value of NLR and PLR as 3.9 and 158.3. Univariate analysis using Cox-regression model showed NLR ($p < 0.001$) and PLR ($p = 0.001$) significantly influenced the locoregional recurrence free survival (LRRFS) and overall survival (OS). The multivariate analysis showed NLR is the independent prognostic factors influencing LRRFS ($p = 0.007$) and OS ($p = 0.002$). Kaplan-Meier survival curve (Log rank test; Chi-square (χ^2) value) showed OS is significantly influenced by NLR group (LRRFS; $\chi^2 = 23.9$ and OS; $\chi^2 = 33.7$) and PLR group (LRRFS; $\chi^2 = 11.2$ and OS; $\chi^2 = 19.3$) in contrast to LRRFS.

Conclusion: NLR can be strongly used as biomarker for prognostication for outcome and survival in head neck cancer. However, a well-designed, larger studies with longer follow-up is warranted.

Keywords: NLR; PLR; prognostic factors; head neck cancer (HNC).

INTRODUCTION

Head and neck cancers (HNCs) affect the upper aerodigestive tract and are one of the most common cancers worldwide (1). Nearly 60% of the population presents with locally advanced but non-metastatic disease. Radiotherapy along with concurrent chemotherapy has long been the standard nonsurgical therapy for locally advanced disease. Definitive chemo-radiotherapy is the main modality of treatment in locally advanced cancer but response varied depending upon both tumour characteristics and host related factors like age, sex, performance status etc., (2).

Inflammation is considered to have role in tumour development and progression (3). In the 19th century, Rudolf Virchow showed leukocytes were present in tumours and suggested a possible link between inflammation and cancer and chronic inflammation together with the tissue injury enhance cell proliferation (4). Various studies have also showed close associations of systemic inflammation as an independent prognostic factor for treatment outcomes for many types of cancers, including colorectal

cancer, renal cell cancer, pancreatic cancer, and head and neck squamous cell carcinoma (5). Neutrophil to lymphocyte ratio (NLR) may also predict the survival in HNCs (6). Host response to malignant tumours involved in systemic alterations, not only changes in the tumour microenvironment. An elevation of circulating neutrophil count is thought to be the result of tumour cells releasing cytokines, which stimulate the bone marrow to produce neutrophils (7).

Malignant tumours may also influence the number of platelets and alter their functioning. Several hypotheses have been suggested on pathophysiological relation between tumour progression and thrombocytosis (8). Platelets may also support tumour progression through facilitation of neo-angiogenesis, generation of adhesion molecules and rise of early metastatic niches. For this reason, platelet to lymphocyte ratio (PLR) has been proposed as an independent prognostic factor in different solid tumours (9). Although various clinical and molecular biomarkers of treatment outcomes after definitive radiotherapy (RT) for HNC have been investigated, no clear consensus regarding reliable

predictive indicators has been reached. This study aimed to prove NLR and PLR as a predictive biomarker for survival in HNCs.

MATERIALS AND METHODS

The clinical data of 257 patients treated either by definitive radiotherapy or by adjuvant radiotherapy at Institute of Post Graduate Medical Education and Research (IPGME&R), Kolkata, from February 2015 to August 2018 were collected. Staging was done based on the American Joint Committee on Cancer (AJCC) TNM staging system (7th edition, 2010) (10). 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) without any haematological disorders or any treatment within one month before radiotherapy leading to elevated NLR and PLR, like administration of hematopoietic drugs such as G-CSF, (v) no autoimmune disease or usage of steroids. The performance status of patients was categorised using Eastern cooperative oncology group (ECOG) (11). Routine blood counts were done within seven days prior to starting RT. NLR and PLR were calculated as the absolute neutrophil or platelet counts, respectively, divided by the absolute lymphocyte counts. After treatment completion, patients were followed up every 3 months. Local recurrence of the disease was referred as locoregional recurrence (LRR). The locoregional recurrence free survival (LRRFS) was defined as interval between completion of treatment (adjuvant radiation or definitive radiation) and locoregional recurrence. The

overall survival (OS) was calculated as the interval between the completion of treatment to the date of death or the last visit.

Statistical analysis

The Statistical Package for the Social Sciences (IBM SPSS for Windows, version 25.0) was used for the statistical analysis. Descriptive statistics were used to characterize the patient population. Continuous variables were analysed using Student's t-test. Receiver operator characteristics (ROC) curve analysed using the NLR and PLR for locoregional recurrence and event at last follow-up to find out the predictive cut-off value of NLR and PLR. The assessment of the accuracy of NLR and PLR cut-off value is done by calculation of area under curve (AUC) and 95% confidence interval (CI). The Kaplan-Meier method was used to compute LRRFS and OS. Comparison of variables influencing LRRFS and OS were done using Logrank test. Univariate and multivariate analysis were performed using Cox regression model. The factors found statistically significant on univariate analysis were included in multivariate analysis for survival outcomes. A p-value less than 0.05 considered statistically significant in all performed analysis.

RESULTS

Clinicopathological characteristics

Two hundred and fifty-seven patients were included in this study. The epidemiological, clinical, pathological and therapeutic data have been mentioned in Table- 1.

Table 1: Clinicopathological characteristics features of patients with head and neck carcinoma

		Count	Table N %
Sex	Male	214	83.3%
	Female	43	16.7%
Age group	< 30 years	2	0.8%
	31 - 40 years	21	8.2%
	41 - 50 years	49	19.1%
	51 - 60 years	87	33.9%
	61 - 70 years	73	28.4%
	> 70 years	25	9.7%
Primary site	CUP	6	2.3%
	Hypopharynx	21	8.2%
	Larynx	97	37.7%
	Nasopharynx	6	2.3%
	Oral cavity	71	27.6%
	Oropharynx	50	19.5%
	Sinonasal cavity	6	2.3%
Symptoms	Cough	10	3.9%
	Dysphagia	44	17.1%
	Epistaxis	6	2.3%
	Hoarseness of voice	54	21.0%
	Sensation of lump in throat	9	3.5%
	Non healing ulcer	34	13.2%
	Pain oral cavity	51	19.8%
	Swelling	49	19.1%

ECOG PS	ECOG 0	39	15.2%
	ECOG 1	80	31.1%
	ECOG 2	109	42.4%
	ECOG 3	29	11.3%
Smoking	No	54	21.0%
	Yes	203	79.0%
Co-morbidity	COPD	6	2.3%
	DM	14	5.4%
	HTN	32	12.5%
	Hypothyroidism	3	1.2%
	Seizure disorder	2	0.8%
	None	200	77.8%
Surgery	Yes	45	17.5%
	No	212	82.5%
Stage group	Stage I	5	1.9%
	Stage II	10	3.9%
	Stage III	85	33.1%
	Stage IVA	114	44.4%
	Stage IVB	43	16.7%
Histopathology grade	Well differentiated	60	23.3%
	Moderately differentiated	166	64.6%
	Poorly differentiated	31	12.1%
Post-operative Surgical Margin	Positive	24	53.3%
	Negative	21	46.6%
NLR group	Low risk NLR group.	136	52.9%
	High risk NLR group.	121	47.1%
PLR group	Low risk PLR group	111	43.2%
	High risk PLR group	146	56.8%
Locoregional recurrence (LRR)	Yes	116	45.1%
	No	141	54.9%
Distant metastasis	Yes	16	6.2%
	No	241	93.8%
CUP-carcinoma unknown primary; ECOG PS- Eastern Co-operative Oncology Group performance status; COPD-chronic obstructive pulmonary disease; HTN-hypertension, DM-diabetes mellitus; TB-tuberculosis; NLR-neutrophil lymphocyte ratio; PLR-platelet lymphocyte ratio; LRR-loco-regional recurrence.			

Different parameters including bio-markers with prognostic values have been mentioned in table 2.

Table 2: Different parameters with prognostic values

	Median	Maximum	Minimum	Standard Deviation
Age (years)	58	85	27	11
Duration of symptoms (months)	5	36	1	6
Addiction duration (years)	20	50	0	13
Hemoglobin (Hb) (g/dl)	12.10	17.00	6.40	1.79
NLR	3.70	9.44	.49	1.76
Platelet count (lakhs/dl)	3.00	9.10	.90	1.32
PLR	170.63	827.17	26.14	146.56
EBRT dose (Gy)	66.0	66.0	4.0	11.61
Follow up duration (months)	14	39	2	8

ROC curve and optimal cut-off value of NLR and PLR

The optimal cut-off points of NLR was calculated for events (including locoregional recurrence and status at last follow-up) using ROC curve. The results showed that the optimal predictive cut-off value of NLR is 3.9 (area under ROC curve = 68.2%, $p < 0.001$), at which most significant difference was

observed in events. The sensitivity and specificity was 66.4% and 69.5% respectively (fig 1). The patients were divided into two groups based on NLR cut-off points into low risk NLR group ($NLR \leq 3.9$) and high risk NLR group ($NLR > 3.9$). The frequency of distribution of NLR risk group i.e., low risk NLR and high risk NLR were 52.9% and 47.1% respectively.

Diagonal segments are produced by ties.

Fig. 1: The receiver operator characteristics curve of the cut-off point for NLR (blue curve); area under ROC curve = 68.2%. The receiver operator characteristics curve of the cut-off point for PLR (red curve); area under ROC curve = 64.4%.

The optimal predictive cut-off value of PLR was 158.3 (area under ROC curve = 64.4%, $p < 0.001$), at which most significant difference was observed in events. The sensitivity and specificity were 69.8% and 54.6% respectively (fig 1). The patients were divided into two groups based on PLR cut-off points into low-risk PLR group ($PLR \leq 158.3$) and high-risk PLR group ($PLR > 158.3$). The frequency of distribution of PLR risk group i.e., low risk PLR and high-risk PLR were 43.2% and 56.8% respectively.

Prognostic factors affecting locoregional recurrence and overall survival

The univariate analysis using the Cox-regression model showed that ECOG PS ($p < 0.001$), smoking ($p = 0.006$), stage of the disease ($p = 0.007$), grade of the tumour ($p = 0.041$), NLR group ($p < 0.001$) and PLR group ($p = 0.001$) were statistically significantly influencing the LRR. The ECOG PS ($p < 0.001$), smoking status ($p = 0.020$), stage of the disease ($p = 0.019$), NLR ($p < 0.001$), PLR ($p < 0.001$) were statistically significantly influencing the OS (table 3a).

Table 3a: Univariate and multivariate analysis of factors associated with locoregional recurrence (LRR) in head and neck cancer

Characteristics	Univariate analysis (LRR)			Multivariate analysis (LRR)		
	HR	95% CI	p-value	HR	95% CI	p-value
Age < 45	1.058	0.652 – 1.715	0.819			
ECOG	1.903	1.526 – 2.373	< 0.001	1.640	1.310 – 2.054	< 0.001
Smoking	2.094	1.231 – 3.561	0.006	1.873	1.091 – 3.216	0.023
Stage	1.338	1.083 – 1.652	0.007	1.217	0.970 – 1.528	0.090
Grade	0.720	0.525 – 0.987	0.041	0.747	0.542 – 1.030	0.075
Margin	0.951	0.510 – 1.771	0.874			
NLR group	2.496	1.698 – 3.670	< 0.001	2.010	1.205 – 3.350	0.007
PLR group	1.936	1.297 – 2.889	0.001	1.030	0.604 – 1.759	0.931

The multivariate analysis showed that ECOG PS ($p < 0.001$), smoking ($p = 0.023$), and NLR group ($p = 0.007$) are the independent prognostic factors influencing LRR. The ECOG PS ($p < 0.001$), and

NLR ($p = 0.002$) are the independent prognostic factors influencing OS (table 3b).

Table 3b: Univariate and multivariate analysis of factors associated with overall survival (OS) in head and neck cancer

Characteristics	Univariate analysis (OS)			Multivariate analysis (OS)		
	HR	95% CI	p-value	HR	95% CI	p-value
Age ≤ 45 years	0.916	0.554 – 1.515	0.733			
ECOG	1.993	1.557 – 2.550	< 0.001	1.716	1.336 – 2.205	< 0.001
Smoking	1.969	1.114 – 3.479	0.020	1.753	0.964 – 3.023	0.056
Stage	1.316	1.046 – 1.656	0.019	1.139	0.890 – 1.458	0.301
Grade	0.735	0.522 – 1.034	0.077			
Margin	0.773	0.413 – 1.449	0.423			
NLR group	3.443	2.192 – 5.376	< 0.001	2.443	1.372 – 4.347	0.002
PLR group	2.474	1.708 – 4.419	< 0.001	1.309	0.710 – 2.416	0.389

Survival analysis

The average follow-up duration of the study was 14 (2-39) months. A total of 116 patients had LRR and 16 patients developed distant metastasis and 98 patients died. The median LRRFS was 21 months

(95% CI; 19.691 – 25.309; fig. 2). The median OS was 26 months (95% CI; 19.453 – 32.547; fig. 3). 1-year and 3-year LRRFS was 67.6% and 28.5% respectively and 1-year and 3-year OS was 77% and 33% respectively.

Fig. 2: The Kaplan Meier survival curve of locoregional recurrence free survival (LRRFS) **Fig. 3:** The Kaplan Meier survival curve of overall survival (OS)

Fig. 4: The Kaplan Meier survival curve of OS according to NLR group; Log rank; $p < 0.001$ and Chi-square value is 33.7

Fig. 5: The Kaplan Meier survival curve of OS according to PLR group; Log rank; $p < 0.001$ and Chi-square value is 19.3

The LRRFS (Logrank test; $p < 0.001$) and OS (Logrank test; $p < 0.001$) curves of NLR risk groups differed significantly. The median LRRFS and OS of low risk NLR group were not reached, while for high-risk group the median LRRFS and OS was 20.6 and 22.4 months respectively. The LRRFS (Logrank test; $p < 0.001$) and OS (Logrank test; $p < 0.001$) curves of PLR risk groups were differing significantly. The median LRRFS and OS of low-risk PLR group were not reached, while for high-risk group the median LRRFS and OS was 18 months and 21 months respectively.

The Chi-square test value of NLR group for LRRFS (Log rank $\chi^2 = 23.9$; $p < 0.001$) and OS (Log rank $\chi^2 = 33.7$; $p < 0.001$; fig. 4). LRRFS and OS influenced by NLR risk group as per Logrank test, but the Chi-square value of NLR risk group is more for OS compared to LRRFS. Therefore, it can be concluded that NLR risk group is influencing OS more than LRRFS. The Chi-square test value of PLR group for LRRFS (Log rank $\chi^2 = 11.2$; $p < 0.001$) and OS (Log rank $\chi^2 = 19.3$; $p < 0.001$; fig. 5). LRRFS and OS influenced by PLR risk group as per Logrank test, but the Chi-square value of PLR risk group is more for OS compared to LRRFS. Therefore, it can be

concluded that PLR risk group is influencing OS more than LRRFS.

DISCUSSION

Inflammatory responses play major decisive roles at different stages of tumour development, including initiation, promotion, malignant conversion, invasion, and metastasis. Inflammation also affects immune surveillance and responses to therapy and elevated inflammatory mediators are related to poor prognosis in patients with cancer (12).

HNC occurs more frequently in older patients. The incidence of these tumours is low among the persons younger than 40 years. 9% of our patients were less than 40 years. This rate matches with results of other studies around the world. Most of the patients (33.9%) in our study were aged between 51 to 60 years and 80% patients were between 41 to 70 years of age which approximates with other study (13). Most patients (83.3%) in current study were male. Large scale epidemiological studies and national cancer registries showed that male to female ratio varied depending of site of tumour from 2:1 to 15:1 (14). HNC in women has been increased significantly in recent days, probably due to changes in

environmental exposure (15). In the present study, the most common involved site was larynx (37.7%) followed by oral cavity ca (27.6%). This finding is in agreement with other reports (16) but it is not matched with studies where oral cavity is the most affected site (17).

In the current study, the median duration of symptoms in most cases were 5 months. Delay in diagnosis may be due to illiteracy or poor financial status, or tendency of most patients to resort to home remedies before seeking medical help. A comparable time span has been reported by Sheno *et al.*, in their study (18). In the present study, microscopically, Grade II (moderately differentiated) tumours were the most common (64.4%) followed by Grade I (well differentiated) tumours (23.3%).

In present study, ECOG PS ($p < 0.001$), smoking ($p = 0.006$), stage ($p = 0.007$), tumour grade ($p = 0.041$), NLR ($p < 0.001$) and PLR ($p = 0.001$) are the most important factor for the LRR and ECOG PS ($p < 0.001$), smoking ($p = 0.020$), stage ($p = 0.019$), NLR ($p < 0.001$), and PLR ($p < 0.001$) influencing the OS. This is supported by another study from India where 400 patients of oral cavity squamous cell carcinoma were analysed and showed advanced T stage ($P < 0.02$), thicker tumours ($P < 0.00$) as important factor for LRR (19).

Normal NLR values are in the range of 0.78-3.53 in the general and NLR and PLR cut-off levels deployed in numerous studies varied in a wide range of PLR: 105.3-170 and NLR: 2.0 to 4.2 (20). In our study, the optimal threshold value, determined with the statistical method detailed above, was 3.9 for NLR and 158.3 for PLR. The frequency of distribution of NLR risk group i.e., low risk NLR and high risk NLR were 52.9% and 47.1% respectively.

In the present study, we found NLR as one of the important prognostic factors for LRR and OS. Our findings matched with other studies (19, 20). Cho *et al.*, analysed 621 patients and found the 5-year PFS and OS rates for all patients were 63.8% and 72.9%, respectively. Both PFS and OS were significantly worse in high NLR patients receiving any type of treatment (PFS: 39.2% vs. 75.8%, $p < 0.001$; OS: 50.9% vs. 83.8%, $p < 0.001$). In survival analyses, a high NLR remained significantly associated with a poor PFS and OS. The multivariate analysis revealed significant associations of a high NLR with poor PFS, an older age, and an advanced T classification. An elevated PLR was also found to be associated with a poor PFS (20). The patients with higher NLR showed more than 2.5 times higher risk of mortality compared to normal NLR (HR 2.62; 95% CI 1.19–5.81; $p = 0.02$). NLR > 5 had a significant effect on survival as compared to those with NLR < 2.5 ($P < 0.016$) for the group which received adjuvant chemoradiotherapy shown by Malik *et al.* (19). Bojaxhiu *et al.*, analysed 186 patients treated from

2007 to 2010 with a result of higher NLR related with poor Overall Survival (21). In another study it has been shown that NLR values higher than the threshold i.e., 3.9 represented an enhanced risk regarding OS (22). Tazeen *et al.* showed a statistically significant association of PLR ($P = .001$) and NLR ($P = .002$) with shorter disease-free survival (DFS) (23). Sano *et al.* analysed 94 patients of locally advanced oral squamous cell carcinoma which demonstrated that high NLR and high PLR were associated with significantly worse OS and CSS (24). But our study result is not matched with their other results where they showed no association with high NLR with LRFS (HR, 1.49 (0.83–2.68), $p = 0.182$), DRFS (HR, 1.38 (0.65–3.22), $p = 0.4$), or acute toxicity grade ≥ 2 (24).

PLR also came out as important negative prognostic factor for survival in this study as also supported by other studies (19, 23). Malik *et al.* associated high PLR with higher frequency of various adverse clinicopathological factors such as higher pT stage ($P < 0.00$), nodal positivity ($P < 0.036$), poor grade of tumour ($P < 0.00$), thicker tumours ($P < 0.00$), presence of extra capsular extension (ECE) ($P < 0.04$), perineural invasion (PNI) ($P < 0.001$), and positive margins ($p < 0.001$). Thus, higher PLR values were associated with increased frequency of these adverse clinicopathological factors. PLR was also found to have a significant negative impact on survival (19). Tazeen *et al.* showed in a multivariate analysis that a high PLR (HR, 2.998; 95% CI, 1.128 to 7.968; $P = 0.028$) was independent factors for determining DFS and OS in oral cavity cancer (23). Ninety-two patients with locally advanced oropharyngeal cancer with a median follow-up was 39 months. Median NLR was 3 and median PLR was 153. The 3-year DFS was 82.9%. Univariate analysis showed that PLR were statistically significant factors in determining 3-year DFS ($p = 0.01$). High NLR and high PLR were correlated with lower DFS, patients with NLR > 4 had a 3-years DFS of 50% versus 75% in the group with NLR ≤ 4 ($p = 0.04$) and patients with PLR > 150 had a 3-years DFS of 65% versus 82% in the group with PLR ≤ 150 ($p = 0.04$) (25).

In contrast to this, there were many studies which were not matched with our result where PLR was not associated with outcome with no significant correlation between baseline PLR and OS or the association between PLR and OS or DFS was not statistically significant (21).

Our results are therefore consistent with the concept that a high NLR contributes to poor disease control by suppressing the cytolytic activities of activated effector T cells and the peritumoral infiltration of immunosuppressive cells such as macrophages (26).

We further demonstrated that a higher PLR was associated with PFS in our multivariate analysis. Again, the significance of interactions between

platelets and the tumour microenvironment remains somewhat unclear. The platelet count provides an additional index of systemic inflammation elicited by the tumour and degranulation. This inflammation with consequent release of platelet-derived proangiogenic mediators within the microvasculature of tumour serve as important factor for tumour growth (27).

CONCLUSION

Overall, the findings of the present study support that NLR and PLR are the potential biomarkers for host response to tumour aggressiveness, therapeutic response to chemo-radiotherapy and survival in HNC patients. NLR can be strongly used as biomarker for prognostication for outcome and survival of patients with head neck cancer. However, a well-designed, larger studies with longer follow-up is warranted.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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