Original Article

Neutrophil-to-lymphocyte ratio as a prognostic factor in oral squamous cell carcinoma – A single-institutional experience from a developing country

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Abstract

Background: Cell-mediated inflammatory response, neutrophils, lymphocytes and monocytes are being recognized as an important role in carcinogenesis. Neutrophil-to-lymphocyte ratio (NLR) has been used as an independent prognostic factor in varieties of cancers. NLR can be easily determined from complete blood count, and it could be considered as a simple and inexpensive prognostic marker.

Aim: In this study, we evaluate the prognostic significance of NLR in patients with oral squamous cell carcinoma (OSCC).

Materials and Methods: Clinical and epidemiological data of all biopsy-proven nonmetastatic OSCC treated between 2014 and 2018 were taken into consideration. Pretreatment absolute neutrophil and lymphocyte counts were used to get NLR. Using univariate and multivariate analysis, the impact of NLR on overall survival (OS) and progression-free survival (PFS) was investigated.

Results: A total of 50 patients of OSCC with median pretreatment NLR ratio of 2.52 were identified. Based on the median NLR as a cutoff, patients were classified into two groups, i.e., high NLR and low NLR. Elevated NLR was significantly associated with lymph node metastasis ($P = 0.01$). Four-year OS and PFS were significantly better for patients with low NLR when compared with high NLR group (51.4% vs. 100%, $P = 0.001$). Four-year PFS for high and low NLR groups was 38.8% and 87.8% ($P = 0.002$). Multivariate analysis confirmed that NLR is an independent prognostic factor ($P = 0.003$).

Conclusion: Pretreatment NLR provides a simple, cheap and early predictor of outcome in this group of patients. However, an optimal cutoff value of NLR should be determined, for which larger sample size and prospective studies are required.

Keywords: Neutrophil-to-lymphocyte ratio, oral squamous cell carcinoma, prognostic factor

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INTRODUCTION

Oral squamous cell carcinoma (OSCC) is one of the most common head and neck cancers worldwide.[1] Despite recent advances in the treatment of OSCC, 5-year survival rate is unsatisfactory because of treatment failure.[2] Recent studies have confirmed the role of host inflammatory response on tumor development and progression of

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cancer.[3] Neutrophil-to-lymphocyte ratio (NLR) has shown correlation with outcomes in several malignancies, such as breast cancer,[4] lung cancer,[5] nasopharyngeal cancer,[6] ovarian cancer[7] and renal cell cancer.[8]

NLR will be very much useful because it is an inexpensive, easily measured and reproducible marker. Till now, only very few studies have evaluated the prognostic role of NLR in OSCC. The aim is to evaluate the prognostic significance of pretreatment NLR in patients with OSCC.

MATERIALS AND METHODS

A total of 50 histologically diagnosed cases of OSCC treated radically during 2014–2018 were collected. Patients with nonsquamous histology, distant metastasis at the time of presentation, incomplete data, other inflammatory conditions or clinical evidence of infection and history of recent steroid intake were excluded from the study.

Demographic data and clinical characteristics were retrieved for all cases from medical records. Tumor-node-metastasis staging was done according to the 2010 American Joint Committee on Cancer system, and grading was done by Border's criteria and categorized as well, moderately and poorly differentiated. Information about pretreatment hematologic parameters was collected. NLR was calculated as the ratio of absolute neutrophil count to absolute lymphocyte count.

All patients were subjected to standard treatment protocols according to primary tumor site, stage and patient general conditions. After receiving primary treatment, patients were followed in the oncosurgery department in every 3 months for the 1st year, every 4 months in the 2nd year and every 6 months till completing 5 years, then annually. Clinical examination was performed at each visit. Radiological evaluation of response performed after the first posttreatment visit by computed tomography (CT), positron emission tomography-CT or magnetic resonance imaging. Local or regional recurrence was confirmed by pathological examination.

Statistical analysis

Survival times were calculated from the day of diagnosis. Overall survival (OS) was calculated at the date of death, and progression-free survival (PFS) was calculated at the date of relapse or the last date of follow-up. Survival rates were calculated by Kaplan–Meier method. The level of significance was set at $P \leq 0.05$. The Chi-square test was used to determine the associations between the pretreatment NLR and different variables. Statistical analysis was performed on SPSS Software version 23.

RESULTS

We identified 50 patients of OSCC with a median age of 45 years. Median pretreatment NLR ratio was 2.52. According to the median NLR as a cutoff value, patients were classified into two groups: high NLR group and low NLR group. The correlations between NLR and selected variables showed that elevated NLR (>2.52) was significantly associated with lymph node metastases ($P = 0.01$) [Table 1].

Survival analysis

In our patients, 4-year OS and PFS were significantly better for patients with low NLR when compared with high NLR group 51.4% versus 100% ($P = 0.001$) [Figure 1].

Four-year PFS for high and low NLR groups was 38.8% and 87.8% ($P = 0.002$) [Figure 2].

Table 2 shows the univariate analysis of the other prognostic factors. Multivariate analysis confirmed that NLR is an independent prognostic factor for PFS ($P = 0.003$) [Table 3].

DISCUSSION

Association between NLR and prognosis of cancer is not fully understood. Regarding the link between inflammation and cancer, till now, very few evidence is there. The neutrophils may act as tumor-promoting leukocytes as

Table 1: Correlation between neutrophil-to-lymphocyte ratio and different variables

No of cases	(*N*=50)	High NLR	Low NLR	*P*
Age				
≤45	26	11	15	0.25
>45	24	14	10	
Sex				
Female	14	6	8	0.52
Male	36	19	17	
Tobacco chewing				
No	9	4	5	0.71
Yes	41	21	20	
Smoking status				
Current smoker	20	12	8	0.24
Nonsmoker	30	13	17	
Alcohol consumption				
No	27	14	13	0.77
Yes	23	11	12	
LN status				
Negative	23	07	16	0.01
Positive	27	18	9	
Tumor classification				
T1-T2	33	16	9	0.76
T3-T4	17	9	8	
Tumor grade				
Grade 1	41	19	22	0.26
Grade 2	9	6	3	

Median NLR=2.52, High NLR(>2.52) and Low NLR(<2.52). NLR: Neutrophils-to-lymphocytes ratio, LN: Lymph node

Table 2: Univariate analysis for 4 years overall and progression-free survival in relation to different prognostic factors

Variables	4-year OS (%)	4-year PFS (%)
Age		
≤45	84.6	73.1
>45	79.2	70.8
P	0.52	0.95
Sex		
Female	85.7	78.6
Male	80.6	69.4
P	0.56	0.54
Tobacco chewing		
No	88.9	77.8
Yes	80.5	70.7
P	0.53	0.52
Alcohol consumption		
No	81.5	74.1
Yes	82.6	69.6
P	0.728	0.93
LN status		
Negative	87.0	69.6
Positive	77.8	74.1
P	0.382	0.96
Tumor classification		
T1-T2	84.8	75.8
T3-T4	76.5	64.7
P	0.425	0.29
Tumor grade		
Grade 1	85.4	73.2
Grade 2	66.7	66.7
P	0.327	0.86
NLR		
High NLR	64	52
Low NLR	100	92
P	0.001	0.002

OS: Overall survival, PFS: Progression-free survival, NLR: Neutrophil-to-lymphocyte ratio, LN: Lymph nodes

Table 3: Cox-regression multivariate analysis for overall and progression-free survivals

Covariate	OS		PFS	
	P	95% CI of Exp(B)	*P*	95% CI of Exp(B)
Age	0.972	0.232-4.095	0.444	0.479-5.358
LN status	0.651	0.328-5.956	0.170	0.692-8.120
T stage	0.402	0.106-2.460	0.465	0.192-2.126
Histological grade	0.178	0.067-1.657	0.816	0.067-1.651
NLR	0.933	0.000-3.616	0.003	2.225-54.749

OS: Overall survival, PFS: Progression-free survival, NLR: Neutrophil-to-lymphocyte ratio, LN: Lymph nodes, CI: Confidence interval

well as participate in metastatic cascade. Through the enzymatic actions, the tumor associated neutrophils promote remodelling of the extracellular matrix. It causes release of basic fibroblast growth factors, migration of endothelial cells and dissociation of tumor cells. This events result in enhanced angiogenesis, tumor growth and progression to metastatic cascade. Neutrophil also inhibit apoptosis or tumor cells by activation of nuclear factor kappa B (NF-kB).[9]

Inflammation can generate not only a cancer-prone microenvironment but also a systemic change in the host

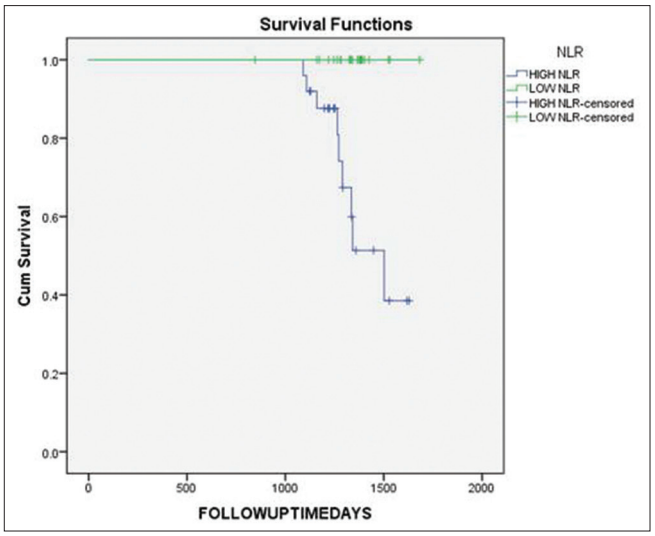

Figure 1: Overall survival according to neutrophil-to-lymphocyte ratio, high neutrophil-to-lymphocyte (>2.52) and low neutrophil-to-lymphocyte (<2.52). Mantel-Cox test, *P* = 0.001

that accelerates cancer growth. An elevated NLR can cause neutrophilia linked to tumor granulocyte colony-stimulating factor and can accelerate tumor development and increase plasma cytokine (such as interleukin-6 and tumor necrosis factor-α) level, while lymphopenia is associated with disease severity and immune escape of tumor cells from tumor-infiltrating lymphocytes.[10] In contrast, tumor infiltration by lymphocytes has been reported to indicate generation of an effective antitumor cellular immune response.[11] It also has role in cytotoxic cell death and cytokines production that inhibits tumor cell proliferation and metastasis.[6] The increased count of neutrophils and/or decreased count of lymphocytes may suppress lymphokine-activated killer cells. It may be a possible mechanism for decreased survival in cancer patients.[12] Depressed immune function due to lymphocytopenia may be the cause of decreased survival of the patient.[13]

In our present study, the cutoff value to define low and high NLR we used median NLR as 2.52. The way of choosing cutoff values differs among studies. Cutoff values on the basis of the median, higher quartile or values determined by the use of receiver operating characteristic curve analysis were used. As a result, different cutoff values are reported; however, the vast majority of cutoffs were in the ranges of 2–4. However, the optimal cutoff levels for NLR remain to be established. A study was done by Phulari *et al.* in 2019 found that mean value of NLR in OSCC cases and control was 2.8 and 1.95, respectively, where the value was statistically significant.[14]

In our work, high NLR was associated with the presence of LN metastases ($P = 0.01$). The association between

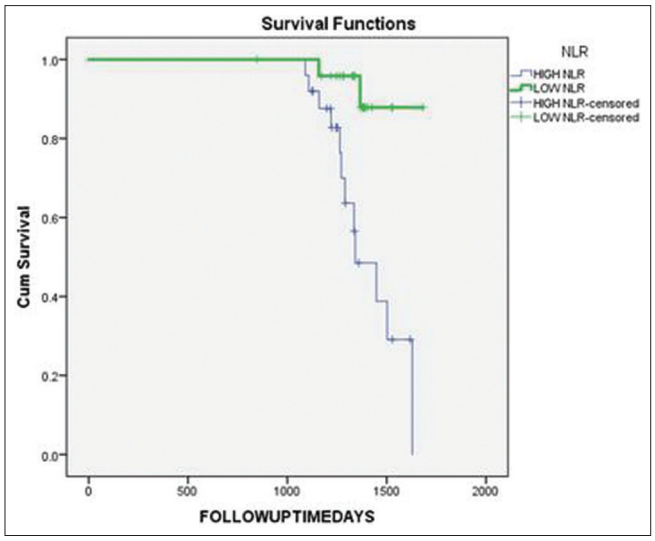

Figure 2: Progression-free survival according to neutrophil-to-lymphocyte ratio, high neutrophil-to-lymphocyte (>2.52) and low neutrophil-to-lymphocyte (<2.52). Mantel-Cox test, $P = 0.002$

high NLR with poor prognostic features such as positive nodal involvement has been observed in breast cancer patients.[15] We can speculate that our findings are due to similar reasons as described in other tumor types. Another study by Mattavelli *et al*. in 2019 that reviewed naive OSCC cases for a period of 14 years from 2000 to 2014 showed that median value of NLR was 2.5. In this study, association between NLR and clinical pathological variables is described. Patients with advanced T classification tend to show higher NLR values, while no correlation was demonstrated with tumor stage, number of positive nodes and perineural and lymphovascular invasion.[16]

Our present study demonstrates a positive correlation between low pretreatment NLR and survival outcome and PFS in patients with OSCC. These findings are consistent with study done by Nakashima *et al*. in 2016.[17] Malik *et al*. in 2019 told that decreased OS with increasing NLR was found to be significant only for the group which received adjuvant chemotherapy ($P = 0.01$).[18]

The limitations of our study are its retrospective nature and the limited number of patients. Prospective studies with larger number cases are needed to accurately define the cutoff value to discriminate the prognostic group.

CONCLUSION

Although evidences are there for the prognostic role of NLR, still the optimal cutoff levels for NLR remains to be established. Prospective studies are still needed for further evaluation of its benefit and clinical importance. Mechanism underlying high NLR and response to anticancer treatment should also be explored. It would also help the selection of patients who are more likely to be benefited from specific surgical approach or drugs. Whenever selecting a prognostic marker always, a cost-effective analysis and accessibility should be taken into consideration, NLR qualities an excellent one. In oral carcinoma, NLR can be potentially used as an independent prognostic marker for OS and PFS, and it should be assessed before any type of surgical and drug treatment.

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Conflicts of interest

There are no conflicts of interest.

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