

Original Research Article

Role of pretreatment neutrophil to lymphocyte ratio as an independent prognostic factor in oral squamous cell carcinoma patients: a prospective study in a tertiary care centre

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ABSTRACT

Background: More recently, established systemic inflammation-based prognostic scores have been explored extensively, such as NLR and serum C-reactive protein (CRP). We postulated that NLR might be a readily available and inexpensive objective prognostic index that could be used in daily oncologic clinical practice and could help to stratify patients in clinical trials.

Methods: In total, there were 150 patients with OSCC treated at GSVM medical college, Kanpur between October 2012 and January 2015 whose clinical information and laboratory parameters were obtained. The NLR was determined by dividing the absolute neutrophil count by the absolute lymphocyte count, and the NLR data were then dichotomized and divided into two groups as NLR-low and -high.

Results: The 3-year OS rate of the NLR-high group tended to be significantly lower than that of the NLR-low group, this relationship was found to be statistically significant (p value <0.05). The 3-year DFS rate in the NLR-high group was lower than that in the NLR-low group; however, there were no significant difference between the two groups.

Conclusions: Our findings reported herein demonstrated that pre-treatment NLR is a potential biomarker for predicting the overall survival in oral SCC patients. Combined with other markers, NLR may be used in decision-making and the selection of treatment modality in patients with oral SCC.

Keywords: Disease free survival, Neutrophil to lymphocyte ratio, Oral squamous cell carcinoma, Overall survival

INTRODUCTION

Oral cancer is one of the most common cancers. The survival rate of patients with oral cancer has not improved despite improvements and innovations in diagnostic techniques and treatments, and the prognosis of OSCC remains poor, with a 5-year survival rate of approximately 50%.¹

More recently, established systemic inflammation-based prognostic scores have been explored extensively, such as NLR and serum C-reactive protein (CRP). CRP is an

acute-phase response protein, which has been proven to be an independent prognostic factor for survival in malignancy. However, CRP is not routinely measured in many hospitals, and CRP level displays nonspecific change after treatment. NLR can be suggested as the balance between pro-tumor inflammatory status and anti-tumor immune status.² An increase in NLR has been shown to be associated with adverse overall survival (OS) in several solid tumors.³ A high NLR was associated with adverse outcomes of nasopharyngeal carcinoma, castration-resistant metastatic prostate carcinoma, breast cancer, non-small-cell lung cancer (NSCLC), local and

advanced esophageal squamous carcinoma and renal cell carcinoma.^{4,5} Authors postulated that NLR might be a readily available and inexpensive objective prognostic index that could be used in daily oncologic clinical practice and could help to stratify patients in clinical trials. Aim of our present study is to determine whether NLR is a prognostic factor for the survival of patients with oral squamous cell carcinoma.

METHODS

Clinical characteristics of the patients

In total, there were 150 patients with OSCC was selected whose clinical information and laboratory parameters were obtained. Patients with factors that could influence the NLR, such as con-current infections, chronic inflammatory diseases, recent treatment with steroids or previous treatment with chemo- or radiotherapy were excluded. All tumors were staged according to the TNM classification of the UICC (2002), and the degree of differentiation was determined based on the grade classification of the WHO. The nature and aims of the study were explained to all patients, who gave their written informed consent for the research.

NLR

NLR was calculated simply as the ratio of absolute neutrophil count to absolute lymphocyte count in blood samples.

Blood samples were collected before the administration of preoperative chemoradiotherapy for a routine laboratory analysis of the full blood count, neutrophil count and lymphocyte count. The NLR was determined by dividing the absolute neutrophil count by the absolute lymphocyte count, and the NLR data were then dichotomized and divided into two groups as NLR-low and -high. The chi-square test was used to determine the associations between the pre-treatment NLR status and the clinical and pathological variables. patients were followed up for 3 years. Overall survival (OS) and DFS were defined as the time from treatment initiation to the date of death from any cause and the date of recurrence of cancer or death from any cause, respectively. The Kaplan–Meier method was used to estimate the probability of OS and DFS as a function of time, and the statistical differences in the survival of the subgroups of patients were compared using the log-rank test. A multivariate survival analysis was performed using the Cox regression model to study the effects of the pre-treatment NLR status on the DFS.

RESULTS

Association of N/L ratio with patient parameters

Total 150 patients were included in the study. Out of which 96 were male and 64 females (M:F=3:2). The N/L

ratio of normal controls is generally <2.0 since the proportion of neutrophils and lymphocytes in WBCs is approximately 50-60 and 30-40%, respectively. Thus, compared with the normal controls, the N/L ratio values of patients with oral carcinoma exhibited a substantial upward shift. The median neutrophil count was 5150 per mm, the median lymphocyte count was 1970 per mm and the median NLR was 2.61. The subjects were dichotomized and the N/L ratio value of 2.6 to yield one group with N/L ratio >2.6 (high N/L ratio group, n=72) and another with N/L ratio ≤2.6 (low N/L ratio group, n=78).

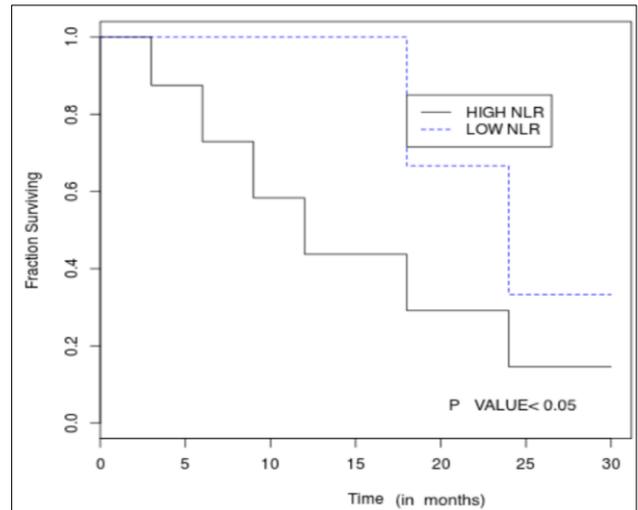


Figure 1: Kaplan-Meier survival by group.

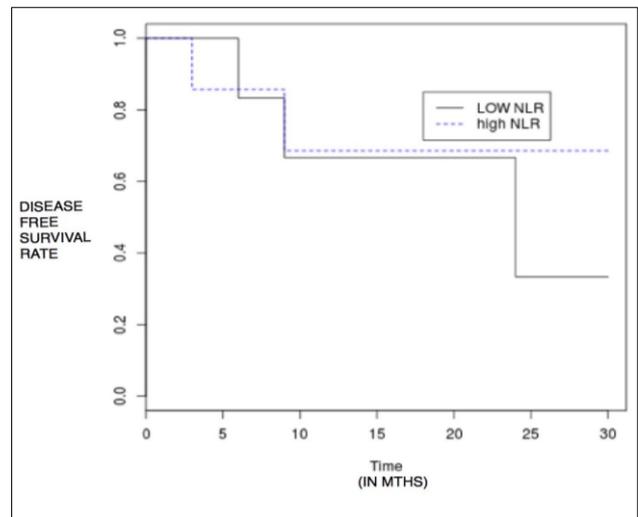


Figure 2: Disease free survival.

Our data has shown a significant correlation between high NLR status and advanced T stage and lymph node metastasis in OSCC patients (p<0.05). There was no correlation between High NLR status and age, gender, primary tumor site, recurrence, differentiation of carcinoma was observed (Table 1).

Relationships between the pre-treatment NLR status and survival time

In order to assess the relationships between the pre-treatment NLR status and survival time, the overall and disease-free survival of the 150 OSCC patients were analyzed using the Kaplan-Meier method. The 3-year OS rate of the NLR-high group tended to be significantly lower than that of the NLR-low group, this relationship was found to be statistically significant (p value <0.05) (Figure 1). The 3-year DFS rate in the NLR-high group was lower than that in the NLR-low group; however, there were no significant difference between the two groups (Figure 2).

Multivariate regression analysis for predicting the disease-free survival

In order to determine the independent prognostic value of the pre-treatment NLR for overall survival, a multivariate analysis was performed using a Cox proportional hazards regression model. tumor site, lymph node status, differentiation, recurrence and NLR were included in the multivariate analysis. Following Cox's regression analysis, only NLR and recurrence were found to be independent significant prognostic factors affecting OS (P=0.0412 and P=0.021, respectively).

Table 1: Correlation between the NLR status and clinicopathological factors in 150 OSCC patients.

Features	Number of cases	%	High NLR >2.6 (n=72)	Low NLR <2.6 (n=78)	P value
Demographic profile					
Age					
<50 years	56	37.33	23	33	0.2373
>50 years	94	62.66	49	45	
Sex					
Male	96	64	41	55	0.0915
Female	54	36	31	23	
Clinical feature Site					
Buccal mucosa	40	26.66	22	18	0.8041
Tongue	44	29.33	19	25	
Alveolus	36	24	17	19	
Hard palate	7	4.6	4	3	
Floor of mouth	23	15.33	10	13	
Tumor size					
T1	48	32	15	33	0.0305*
T2	37	24.66	19	18	
T3	40	26.66	22	18	
T4	25	16.66	16	9	
Lymph node status					
N0	64	42.66	20	44	0.0048*
N1	28	18.66	16	12	
N2	32	21.33	19	13	
N3	26	17.33	17	9	
Histological differentiation					
Well difference	81	54	36	45	0.2822
Moderately difference	28	18.66	12	16	
Poorly difference	41	27.33	24	17	
Recurrence					
Yes	36	24	22	14	0.5685
No	114	76	63	51	

* p value<0.05 is significant

DISCUSSION

In our study, we have found that pretreatment NLR status is a independent prognostic factor of overall survival in

oral SCC patients together with recurrence of carcinoma. There are several explanations for the relationship between an elevated NLR and aggressive phenotypes in cases of cancer. Generally, an elevated NLR reflects an

increased neutrophil count and/or decreased lymphocyte count. Circulating neutrophils contain and secrete various cytokines, chemokines, proteases and growth factors, including vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor, matrix metalloproteinase and IL-6.⁶⁻⁸

These molecules create a microenvironment for extracellular matrix remodelling, endothelial cell migration and tumor cell dissociation. Moreover, it has been shown that neutrophils may suppress the cytolytic activity of a variety of immune cells, such as lymphocytes, activated T cells and natural killer cells under the co-culture conditions of neutrophils and lymphocytes obtained from healthy donors, and the degree of suppression is closely associated with the number of neutrophils.^{9,10} Collectively, an elevated NLR may be associated with establishment of the tumor microenvironment and low immunocompetence in cancer patients with OSCC as well as subsequently induced tumor growth. These observations and hypothesis strongly support our results showing that an elevated NLR (i.e., elevated systemic inflammatory response) contributes to tumor progression in patients with OSCC.

Prognostic role of NLR has been studied in many solid tumors Wang et al, demonstrated that elevated NLR at recurrence of NSCLC indicates poor prognosis and suggested it may be a significant independent prognostic factor in patients with recurrent NSCLC following curative resection.¹¹ Nakano et al, investigated the association between NLR and survival outcome in preoperative local and locally advanced breast cancer and concluded that it may be an independent prognostic factor for disease-free survival and breast cancer-specific survival in patients with breast cancer.¹²

Salim et al, has studied role of NLR in prognosis of head and neck SCC.¹³ They concluded NLR as an independent prognostic factor. our results also identified NLR as an independent prognostic factor in patients with oral SCC. Tsai et al, in their study on oral cavity cancer patients, observed that NLR increased in parallel with the advancement of clinical stage and T stage, but it was not significantly associated with survival.¹⁴ However, our study shows positive correlation between Nodal metastasis and high NLR but no such significant association was seen with T stage. Our results also show high pretreatment NLR as an independent prognostic marker for overall survival in oral SCC patients.

CONCLUSION

Our findings reported herein demonstrated that pretreatment NLR is a potential biomarker for predicting the overall survival in oral SCC patients. Combined with other markers, NLR may be used in decision-making and the selection of treatment modality in patients with oral SCC.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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