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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 center

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ABSTRACT

Background: More recently, established systemic inflammation-based prognostic scores have been explored extensively, such as neutrophil-lymphocyte ratio (NLR) and serum C-reactive protein. 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.

Materials and Methods: In total, there were 150 patients with oral squamous cell carcinoma (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. **Conclusion:** Our findings reported herein demonstrated that pretreatment NLR is a potential biomarker for predicting the overall survival in OSCC patients. Combined with other markers, NLR may be used in decision-making and the selection of treatment modality in patients with oral SCC.

Key words: Disease-free survival, Neutrophil-to-lymphocyte ratio, Oral squamous cell carcinoma, Overall survival

Background

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 oral squamous cell carcinoma (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 neutrophil-lymphocyte ratio (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 non-specific change after treatment. NLR can be suggested as the balance between pro-tumor inflammatory status and antitumor 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]

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.

The aim of our present study is to determine whether NLR is a prognostic factor for the survival of patients with OSCC.

Materials and Methods

Clinical characteristics of the patients

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. Patients with factors that could influence the NLR such as concurrent infections, chronic inflammatory diseases, recent treatment with steroids, or previous treatment with chemo- or radiotherapy were excluded from the study. 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.

Methods

Blood samples were collected before the administration of pre-operative 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 pretreatment NLR status and the clinical and pathological variables. Patients were followed up for 3 years. 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 pretreatment NLR status on the DFS.

Results

Association of N/L ratio with patient parameters

A total of 150 patients were included in the study. 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 white blood cells 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).

Our data have 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, and differentiation of carcinoma and was observed [Table 1].

Relationships between the pretreatment NLR status and survival time

To assess the relationships between the pretreatment 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 ($P < 0.05$) [Figure 1]. The 3-year DFS rate in the NLR-high group was lower than that in the NLR-low group; however, there was no significant difference between the two groups [Figure 2].

Multivariate regression analysis for predicting the disease-free survival

To determine the independent prognostic value of the pretreatment NLR for OS, a multivariate analysis was

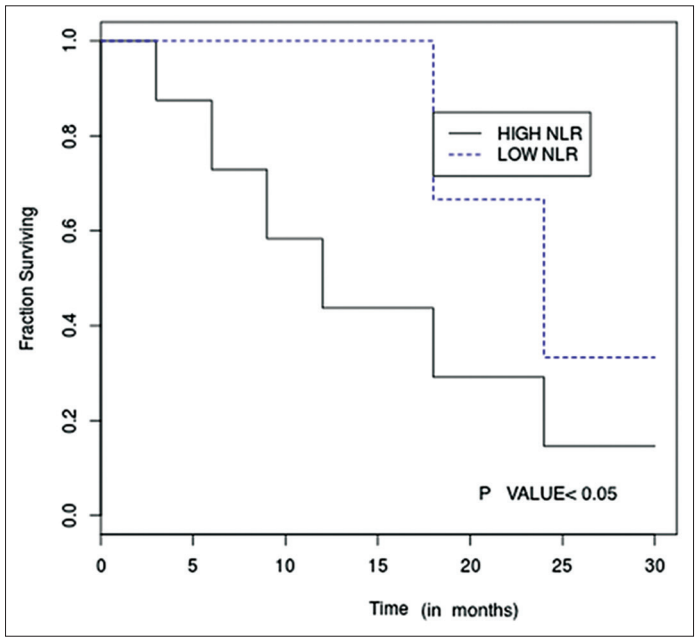

Figure 1: Kaplan–Meier survival by group

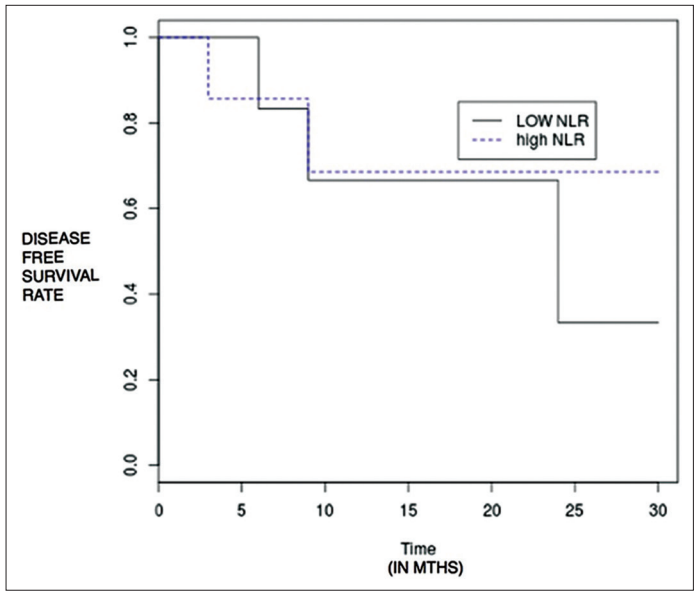

Figure 2: Disease-free survival

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				0.2373
<50 years	56 (37.33)	23	33	
>50 years	94 (62.66)	49	45	
Sex				0.0915
Male	96 (64)	41	55	
Female	54 (36)	31	23	
Clinical features				
Site				0.8041
Buccal mucosa	40 (26.66)	22	18	
Tongue	44 (29.33)	19	25	
Alveolus	36 (24)	17	19	
Hard palate	7 (4.6)	4	3	
Floor of mouth	23 (15.23)	10	13	
Tumor size				0.0305*
T1	48 (32)	15	33	
T2	37 (24.66)	19	18	
T3	40 (26.66)	22	18	
T4	25 (16.66)	16	9	
Lymph node status				0.0048*
N0	64 (42.66)	20	44	
N1	28 (18.66)	16	12	
N2	32 (21.33)	19	13	
N3	26 (17.33)	17	9	
Histological differentiation				0.2822
Well diff.	81 (54)	36	45	
Moderately diff.	28 (18.66)	12	16	
Poorly diff.	41 (27.33)	24	17	
Recurrence				0.5685
Yes	36 (24)	22	14	
No	114 (76)	63	51	

performed using a Cox proportional hazards regression model. Tumor size, 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).

Discussion

In our study, we have found that pretreatment NLR status is an independent prognostic factor of OS in OSCC patients together with recurrence of carcinoma. There are several explanations for the relationship between an elevated NLR and aggressive phenotypes in cases of cancer. In general, 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,[6] platelet-derived growth factor, fibroblast growth factor,[7] matrix metalloproteinase, and IL-6.[8] These molecules create a microenvironment for extracellular matrix remodeling, 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 coculture 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 the 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*.[11] demonstrated that elevated NLR at recurrence of NSCLC indicated poor prognosis and suggested it may be a significant independent prognostic factor in patients with recurrent NSCLC following curative resection. Nakano *et al*.[12] investigated the association between NLR and survival outcome in pre-operative 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.

Salim *et al*.[13] have studied the role of NLR in prognosis of head and neck SCC. 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*.[14] 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. Our study, however, 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 OS in oral SCC patients.

Conclusion

Our findings reported herein demonstrated that pretreatment NLR is a potential biomarker for predicting the OS 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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