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Original Article

Role of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio as Prognostic Markers in Oral Cavity Cancers

Akshat Malik, Aseem Mishra, Manish Mair, Swagnik Chakrabarti, Apurva Garg, Hitesh Singhvi, Prashant Chopda, Burhanuddin Qayyumi, Nupoor Sawarkar, Yash Mathur, Rathan Shetty, Sudhir Nair, Deepa Nair, Pankaj Chaturvedi

Head and Neck Services, Department of Surgical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India

Abstract

Background: Various studies have associated inflammation with carcinogenesis. But still, the role of inflammatory markers in oral cancer has not been evaluated extensively. Most of the existing studies have been done on patients of varied sites, and their sample size is also scarce. In this study, we have evaluated the impact of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) on various clinicopathological factors and survival. **Methodology:** This was a retrospective analysis of prospectively collected data of 400 patients with oral squamous cell cancer. The pretreatment neutrophil and lymphocyte and platelet counts were recorded, and NLR and PLR were calculated for all patients. The NLR and PLR tertiles were correlated with the incidence of various clinicopathological factors and overall survival. **Results:** The median follow-up of the cohort was 36 months. The mean survival of the cohort was 41.7 months. PLR was associated with higher incidence of adverse clinicopathological factors. There was a trend of decreased overall survival with increasing NLR tertile. It was found to be significant only for the group which received adjuvant chemoradiotherapy (*P* 0.01). Patients with higher PLR values have been found to have a lower overall survival (*P* 0.006). **Conclusion:** NLR and PLR can be used to predict survival and outcomes in patients oral cavity cancer. PLR is a good predictor for adverse clinicopathological factors and survival. NLR can predict survival only in the subset of patients who have received chemotherapy.

Keywords: *Chemotherapy, head-and-neck cancers, inflammatory markers, neutrophil-to-lymphocyte ratio, oral cancer, platelet-to-lymphocyte ratio, prognosis*

Introduction

Oral cancers are among the common cancers in certain parts of the world. These have been found to be associated with various carcinogens such as chewable or nonchewable forms of tobacco and alcohol. Prognosis of these cancers can be predicted by the tumor, node, metastasis (TNM) stage and the presence or absence of various adverse histopathological factors such as poor differentiation, thickness, presence of nodes, extracapsular spread (ECS), perineural invasion (PNI), lymphovascular invasion, and presence of close or positive margins. Based on the presence of such factors, adjuvant therapy and prognosis is decided. Several studies have shown the role of inflammation on carcinogenesis. There have been studies which have tried to find hematological parameters which would predict survival in such patients. High neutrophil and platelet counts and low lymphocyte count have been shown to provide an environment conducive to growth of tumors. The use of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) has been explored in a few studies, but their results are equivocal. Few studies have found it to affect the survival and few have found contrary results. However, most of these studies have included patients of different subsites. Even when a single subsite has been studied, the sample size has been less. Hence, we decided to analyze the impact of NLR and PLR on survival in patients with oral cancer.

Methodology

This was a retrospective analysis of prospectively collected data of patients of oral cavity squamous cell carcinoma who underwent treatment at a tertiary care cancer center from January 2012 to October 2013. The study included

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Address for correspondence:
Dr. Aseem Mishra, Head and Neck Services, Department of Surgical Oncology, Tata Memorial Hospital, Mumbai - 400 012, Maharashtra, India.
E-mail: draseemmishra@gmail.com

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only *per primam* patients who underwent treatment with curative intent. All patients who had completed treatment were included in the analysis. Patients were followed up till March 2017. All patients in the study underwent either surgery alone or surgery followed by adjuvant radiotherapy or chemoradiotherapy. Adjuvant therapy was planned as per the NCCN guidelines. Adjuvant radiotherapy was administered for Stages III and IV tumors, depth of invasion >10 mm, and associated adverse prognostic factors such as PNI and lymphovascular emboli (LVE). Adjuvant chemoradiotherapy was administered to patients with involved margins and/or ECS. All the patients had performance status ECOG 0 or ECOG 1 and did not have any systemic illness. None of the patients had any associated infection or any signs of inflammation. Patients with histology other than squamous cancer, any associated infections or allergic disorders, those patients who had received any prior treatment or had recurrences or second primary, or who were being treated with palliative intent were excluded from the study. The demographic details and disease and treatment details were recorded from the electronic medical records. These included subsite, TNM stage, treatment received, adjuvant therapy received, and status at follow-up. The patients were followed up for a median of 38 months (8–49 months). The survival was updated based on the notes on electronic medical records. Those patients whose information was not available on electronic medical records were contacted telephonically and requested to visit the hospital. E-mails and postal letters requesting the patients to come for the follow-up were sent to the remaining patients. Nearly 91% of the patients had a follow-up of >24 months. At the time of analysis, 81 patients had died due to recurrence. Three patients had died due to causes other than the oral cavity carcinoma; however, they had completed treatment and did not have any signs of recurrence. As the study involved only retrospective analysis of the prospectively collected data with no intervention upon the patients, Institutional Review Board approval was not sought for. The study was in compliance with the Helsinki declaration.

Hematological investigations were conducted for all patients at initial presentation. Absolute values of neutrophil, platelets, and lymphocytes in the peripheral blood at initial presentation were recorded.

NLR and PLR for each patient were calculated. The NLR values consisted of ratios which ranged from 0.8 to 29.94. Similarly, for PLR, the ratio was calculated which ranged from 17 to 1432. The values were grouped into tertiles for ease of calculation and reference. Tertiles provided a uniform distribution of ratios and helped in assigning a risk group for survival calculations. For NLR, the first tertile had NLR value <2.5, the second had values from 2.5 to 5, and the third had >5. Similarly, for PLR, the first tertile had PLR <100, the second tertile had values between 100 and 200, and the third one had values >200. The association of age, gender, pT stage, pN stage, differentiation of the tumor, thickness, ECS, PNI, LVE, and the margin status was analyzed with different NLR and PLR tertiles using Chi-square test. Overall survival was calculated from the date of completion of treatment to the date of last follow-up. In case the patient developed recurrence or had a terminal event, the date of event was considered as the last date of follow-up. Association with overall survival was assessed using Kaplan–Meier test. In majority of the previous studies where the association of NLR value with survival was evaluated, patients had received chemotherapy. Hence, to evaluate the association of NLR and PLR with survival in patients receiving chemotherapy, we decided to stratify the cohort into three groups depending on adjuvant treatment received. The three patient groups were those who received surgery alone or surgery followed by adjuvant radiotherapy or chemoradiotherapy. Log rank test was used to compare distributions across NLR and PLR tertiles. Multivariate analysis was also done by Cox regression analysis to analyze the impact of various prognostic factors on survival. It was also done separately for the patients who received adjuvant chemoradiotherapy. All the statistical analyses were done using SPSS 21 software (SPSS Statistics for Windows, IBM Corp, Armonk, NY, USA).

Results

The study included 400 patients of carcinoma of oral cavity. Out of these, 308 were male and 92 were female. Classifying based on the subsite, 146 patients had carcinoma of tongue, 116 of lower alveolus, 104 of buccal mucosa, 16 of upper alveolus, 16 of lip, and 1 each of hard palate and retromolar trigone. Age ranged from 19 to 86 years. The median age was 52 years. When divided based on the pathological T stage, there were 105 patients of T1, 145 patients of T2, 31 patients of T3, and 119 patients of T4 disease. These patients were followed up for 1–49 months. The median follow-up was for 36 months. A total of 108 patients did not merit any adjuvant therapy, 199 received adjuvant radiotherapy, and 93 received adjuvant chemoradiotherapy. The median follow-up of the cohort was 38 months (8–49 months); 91% of the patients had follow-up of >24 months.

In the first group with NLR <2.5, there were 200 patients. In the second group with NLR between 2.5 and 5, there were 158 patients, and in the third group with NLR >5, there were 42 patients.

Chi-square test was done to look for association of various clinicopathological factors with different NLR tertiles. The results are depicted in Table 1. The factors assessed were age; gender; pT stage; pN stage; and differentiation of the tumor, thickness, ECS, PNI, LVE, and the margin status. Among these, pT stage ($P < 0.02$, linear by linear), thickness ($P < 0.00$, linear by linear), and margin status ($P <$ value 0.02, linear by linear) were found to be

Table 1: Association of neutrophil-to-lymphocyte ratio tertiles with various clinicopathological factors

Parameter	Neutrophil-to-lymphocyte ratio, number of patients (%)			*P*
	<2.5	2.5-5	>5	
Age (years)				
<50	96 (24)	61 (15.25)	16 (4)	0.15
>50	104 (26)	97 (24.25)	26 (6.5)	
Gender				
Male	147 (36.75)	125 (31.25)	36 (9)	0.02
Female	53 (13.25)	33 (13.25)	6 (1.5)	
T stage				
T1	57	42	6	0.02
T2	79	50	16	
T3	11	16	4	
T4	53	50	16	
Nodal status				
pN0	119 (29.75)	92 (23)	23 (5.75)	0.59
pN+	81 (20.25)	66 (16.5)	19 (4.75)	
Grade				
Well differentiated	34 (8.5)	23 (5.75)	5 (1.25)	0.14
Moderately differentiated	137 (34.25)	105 (26.25)	28 (7)	
Poorly differentiated	29 (7.25)	30 (7.5)	9 (2.25)	
Thickness (mm)				
0-4	51 (12.75)	20 (5)	4 (1)	0.00
5-10	84 (21)	68 (17)	10 (2.5)	
≥11	65 (16.25)	70 (17.5)	28 (7)	
ECS				
Yes	60 (15)	49 (12.25)	18 (4.5)	0.19
No	140 (35)	109 (27.25)	24 (6)	
Perineural invasion				
Yes	34 (8.5)	25 (6.25)	10 (2.5)	0.52
No	166 (41.5)	133 (33.25)	32 (8)	
Lymphovascular emboli				
Yes	1 (0.25)	1 (0.25)	1 (0.25)	0.306
No	199 (49.75)	157 (39.25)	41 (10.25)	
Margin status (mm)				
Free (≥5)	166 (41.5)	119 (29.75)	29 (7.25)	0.02
Close (1-4)	25 (6.25)	31 (7.75)	9 (2.25)	
Involved (≥10)	9 (2.25)	8 (2)	4 (1)	

ECS – Extracapsular spread

significantly associated with NLR. Higher NLR tertile was associated with higher pT stage, thicker tumors, and higher chances of having close or positive margins.

Based on PLR, the patients were grouped into three tertiles: <100, 100–200, and >200. A total of 111 patients had PLR <100, 212 patients had PLR between 100 and 200, and 77 patients had PLR above 200. Chi-square test was done to find the association between PLR and various clinicopathological factors [Table 2]. A statistically significant association was seen between PLR and gender ($P < 0.01$), pT stage ($P < 0.000$), nodal status ($P < 0.036$), grade of tumor ($P < 0.000$), thickness of tumor ($P = 0.00$), and presence of ECS ($P < 0.04$), PNI ($P < 0.001$), and margin status ($P < 0.001$). Higher PLR value was associated with higher T stage, nodal positivity, moderate or poorer differentiation, thicker tumors, ECS, PNI, and higher chances of close or positive margins.

The overall mean survival of the cohort was 41.7 months. It was 42.05 months for those with NLR <2.5 and 42.15 months for those with NLR between 2.5 and 5. Those with NLR >5 had a survival of 35.3 months. Though survival was lower in patients with high NLR >5, there was no statistically significant difference between the three groups.

We analyzed the impact of NLR on survival after stratifying the patients based on the adjuvant treatment received. Survival was lower for all the patients having NLR >5, but it affected survival significantly only in patients who received adjuvant chemoradiotherapy ($P < 0.015$) [Figure 1]. This was the case in all the groups when stratified based on the adjuvant therapy received, but it was statistically significant

Table 2: Association of platelet-to-lymphocyte ratio tertiles with various clinicopathological factors

Parameter	Platelet-to-lymphocyte ratio, number of patients (%)			*P*
	<100	100-200	>200	
Gender				
Male	96 (24)	157 (39.25)	55 (13.75)	0.01
Female	15 (3.75)	55 (13.75)	22 (5.5)	
Age (years)				
<50	59 (14.75)	85 (21.25)	29 (7.25)	0.04
>50	52 (13)	127 (31.75)	48 (12)	
pT stage				
T1	36 (9)	57 (14.25)	12 (3)	0.00
T2	43 (10.75)	78 (19.5)	24 (6)	
T3	9 (2.25)	15 (3.75)	7 (1.75)	
T4	23 (5.75)	62 (15.5)	34 (8.5)	
Nodal status				
pN0	73 (18.25)	122 (30.5)	39 (9.75)	0.036
pN+	38 (9.5)	90 (20.5)	38 (9.5)	
Grade				
Well differentiated	23 (5.75)	34 (8.5)	5 (1.25)	0.00
Moderately differentiated	75 (18.75)	145 (38.25)	50 (12.5)	
Poorly differentiated	13 (3.25)	33 (8.25)	22 (5.5)	
Thickness (mm)				
0-4	31 (7.75)	41 (10.25)	3 (0.75)	0.000
5-10	45 (11.25)	89 (22.25)	28 (7)	
≥11	35 (8.75)	82 (20.5)	46 (11.5)	
ECS				
Yes	31 (7.75)	63 (15.75)	33 (8.25)	0.044
No	80 (20)	149 (37.25)	44 (11)	
Perineural invasion				0.001
Yes	12 (3)	34 (8.5)	23 (5.75)	
No	99 (24.75)	178 (44.5)	54 (13.5)	
Lymphovascular emboli				
Yes	0	2 (0.5)	1 (0.25)	0.28
No	111 (27.75)	210 (52.5)	76 (19)	
Margin status (mm)				
Free (≥5)	95 (23.75)	168 (42)	51 (12.75)	0.001
Close (1-4)	12 (3)	36 (9)	17 (4.25)	
Involved (≤1)	4 (1)	8 (2)	9 (2.25)	

ECS – Extracapsular spread

only in those who received adjuvant chemoradiotherapy [Figure 2]. On comparing the NLR tertiles within the strata, NLR >5 had a significant effect on survival as compared to those with NLR <2.5 ($P < 0.016$) and also when compared to those with NLR between 2.5 and 5 ($P < 0.007$). No statistical significance was seen in survival when comparison was done between the groups having NLR between 2.5 and 5 and NLR <2.5.

Kaplan–Meier test was used to assess the impact of PLR on survival. For those with PLR <100, survival was 44.4 months, for those with PLR between 100 and 200, it was 41.7 months, and for those with PLR >200, survival was found to be 37.4 months. The association of high PLR with poor survival was found to be statistically significant ($P = 0.006$) [Figure 3]. On stratifying based on the adjuvant therapy received, lower survival was seen in the patients with PLR >200. However, this association was not found to be significant in any of the groups [Figure 4].

Multivariate analysis was done to see factors which affected survival independently. pT stage ($P < 0.038$, hazard ratio [HR]: 0.610, confidence interval [CI]: 0.382–0.972), grade of tumor ($P < 0.029$, HR: 1.600, CI: 1.050–2.439), thickness ($P < 0.015$, HR: 1.594, CI: 1.095–2.320), and PNI ($P < 0.019$, HR: 1.807, CI: 1.103–2.963) were found to be independently affecting the survival. NLR ($P < 0.315$) and PLR ($P < 0.363$) were not found to significantly affect survival on multivariate analysis. Multivariate analysis was done separately for patients who received adjuvant chemoradiotherapy. NLR ($P < 0.004$), grade of tumor ($P < 0.016$), and margin status ($P < 0.043$) were the other factors found to independently affect the survival in these patients.

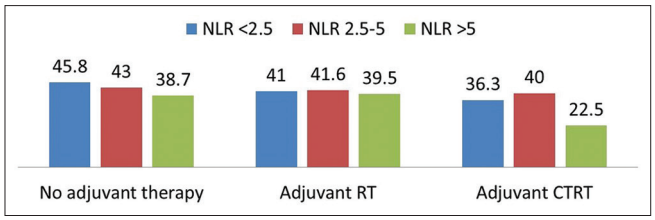

Figure 1: Association of mean overall survival and neutrophil-to-lymphocyte ratio stratified upon the adjuvant therapy received. RT – Radiotherapy; CTRT – Chemoradiotherapy

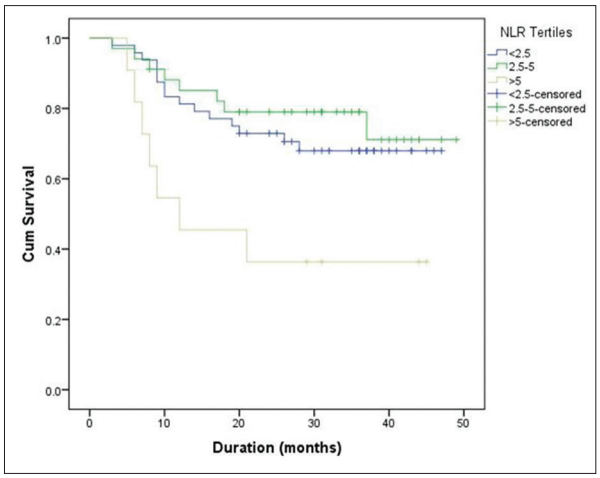

Figure 2: Overall survival in patients receiving chemoradiotherapy based on the neutrophil-to-lymphocyte ratio tertiles

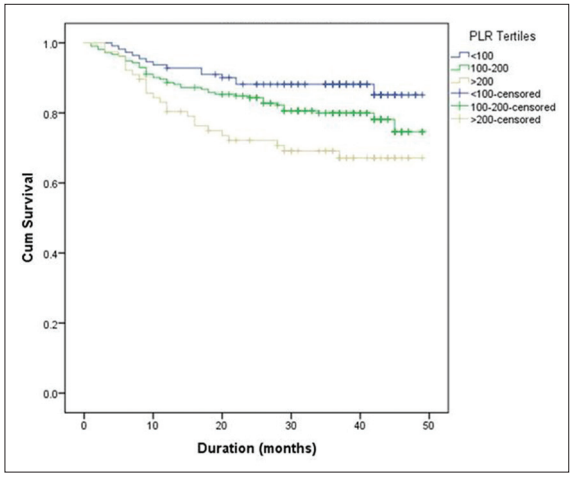

Figure 3: Overall survival based on the different platelet-to-lymphocyte ratio tertiles

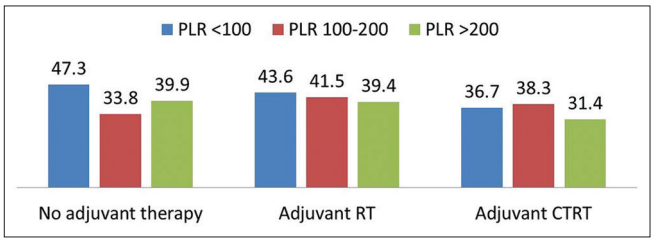

Figure 4: Association of mean overall survival and platelet-to-lymphocyte ratio stratified upon the adjuvant therapy received. RT – Radiotherapy, CTRT – Chemoradiotherapy

Discussion

In our analysis of 400 patients of oral cavity squamous cell carcinoma, higher NLR values were found to be associated with higher prevalence of pathological T stage ($P < 0.02$), thicker tumors ($P < 0.00$), and positive margins ($P < 0.02$). No association was seen with ECS and PNI. High PLR was associated with higher frequency of various clinicopathological factors such as higher pT stage ($P < 0.00$), nodal positivity ($P < 0.036$), poor grade of tumor ($P < 0.00$), thicker tumors ($P < 0.00$), presence of ECS ($P < 0.04$), PNI ($P < 0.001$), and positive margins (0.001). Thus, higher PLR values were associated with increased frequency of these adverse clinicopathological factors.

NLR >5 had a significant effect on survival as compared to those with NLR <2.5 ($P < 0.016$) and also when compared to those with NLR between 2.5 and 5 ($P < 0.007$). Higher NLR tertile showed a trend of decreased survival in the entire cohort as well as when stratified on the basis of adjuvant therapy in all the groups. However, it was found to be statistically significant only for the group which received adjuvant chemoradiotherapy. PLR was also found to have a significant impact on survival. PLR >200 was found to be associated with worst survival. Multivariate analysis was performed to confirm whether these hematological parameters had any independent impact on survival. We found that overall NLR and PLR were not independent predictors of survival. As majority of studies where NLR was found to be of significance for predicting survival had used chemotherapy, we did a separate multivariate analysis of 93 patients who had received adjuvant chemoradiotherapy. It showed that, in these patients, NLR was an independent predictor of survival ($P < 0.004$; HR: 0.137; 95% CI: 0.042–0.447).

Few other studies on oral cancer patients who received chemotherapy had similar findings and NLR was found to predict survival in them.[1,2] Ozturk *et al*. also tried to study the relationship of PLR with survival; however, there was no significant outcome in that analysis.[3] These studies do point toward the possible association of NLR and PLR with local recurrences, but there was no statistically significant association with survival.

The role of immunity in cancers has been analyzed in great details.[4] Cancers have been found to be associated with a chronic inflammatory state. It results in faster turnover of neutrophils as there are immature myeloid cells of granulocytic or monocytic lineages that are elevated in cancer. These reduce antitumor immune activity and help in the progression of cancer cells.[5] Neutrophils are considered to be pro-tumorigenic as they secrete pro-angiogenic substances such as vascular endothelial growth factor, platelet-derived growth factor, and several others such as cytokines and chemokines; these suppress the adaptive

immune system and produce environment for extracellular matrix remodeling.[1,6,7] Cancer cells themselves modify the behavior of the neutrophils by release of cytokines which cause chemotaxis and prevent their apoptosis.[8] Platelets support tumor growth by increased angiogenesis and increased capillary permeability, thereby causing extravasation of cancer cells. They decrease the release of lymphocytes and with the help of several receptors increase tumor growth and probability of metastasis.[8] In contrast, lymphocytic proliferation has been found to be associated with better prognosis in cancer patients.[9,10] These make NLR and PLR a good representation of the immunity status and also an indicator of prognosis of cancer patients.

NLR has been evaluated in head-and-neck cancers. It has been found to be a significant predictor of both survival and response to chemoradiotherapy in nasopharyngeal carcinomas. Studies have also shown it to predict survival in other head-and-neck sites.[2,11-18] Most of these studies involved multiple sites of head-and-neck region. Even when a single site was assessed, the patient numbers were not that large. In most of these studies, chemotherapy was used in neoadjuvant setting or as definitive treatment with radiotherapy.

It has been seen that there is a difference in the values of NLR and PLR between the patients having oral cancer and the control group.[3] Besides overall survival, NLR has also been found to predict disease-free survival in oral cancer patients.[4] However, in this study, all the patients were treated with definitive chemoradiotherapy. Another study has shown that NLR can help in predicting local recurrences, but it is not that useful in predicting survival. In this study, they also used PLR to predict local recurrence.[8] In a study on early-stage oral cancer patients, NLR, PLR, and NxPLR were found to be associated with local recurrences. They found that these parameters had limited role in predicting overall or disease-free survival.[3] Besides these, C-reactive protein, lymphocyte-to-monocyte ratio, and derived NLR have also been found useful as a prognostic markers in cases of oral cancers.[3,15]

PLR was also found to have a significant impact on survival. PLR >200 was found to be associated with worst survival. This is similar to what was seen in a study where they compared NLR and PLR. Only PLR was found to be associated with poor survival in that study,[8] although there are studies which have not shown any relationship of PLR with survival.[3] They found that NLR and PLR were both associated with local recurrences, but no statistically significant relationship was seen with survival. We then performed a multivariate analysis to confirm whether these hematological parameters had any independent impact on survival. We found that overall NLR and PLR were not independent predictors of survival. Separate multivariate analysis of 93 patients who had received adjuvant chemoradiotherapy showed that, in these patients, NLR was an independent predictor of survival. Even though not significant on multivariate analysis for survival, PLR may be used to predict poor outcomes in patients with oral cancer. NLR and PLR are both easy to calculate and do not require any additional tests. These can be used in addition to the already existing prognostic factors.

The study had few limitations due to its retrospective design. In spite of the drawback, the study had a large sample size of patients of single subsite (carcinoma of oral cavity). This was further supplemented with a robust follow-up of 91% at the end of 2 years. In this study, we have seen the impact of NLR and PLR on survival after stratifying the patients based on the adjuvant therapy. This aspect had not been evaluated so far in the previous studies and shows the importance of NLR in the setting of adjuvant chemoradiotherapy and that of PLR in predicting poor prognosis.

Conclusion

PLR is a good predictor for adverse clinicopathological factors and poor outcomes in oral cancer patients. NLR can be used to predict survival in a subset of patients of oral cavity cancer who have received adjuvant chemoradiotherapy.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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