ORIGINAL RESEARCH

Significance of the neutrophil-to-lymphocyte ratio in young patients with oral squamous cell carcinoma

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Background: The main goal of this study was to evaluate the prognosis of young patients with oral squamous cell carcinoma (SCC) with a focus on the value of the pretreatment neutrophil-to-lymphocyte ratio (NLR).

Materials and methods: Young (≤40 years old) patients with oral SCC were retrospectively enrolled, and each young patient was matched with an old (≥60 years old) oral SCC patient. Associations between the NLR and clinicopathological variables were analyzed by the chi-square test, and the Kaplan–Meier method was used to analyze recurrence-free survival (RFS) and disease-specific survival (DSS) rates.

Results: A total of 103 young patients were enrolled, and compared to the old group, the young group had a significantly lower NLR value ($p=0.012$). In the young group, the 5-year RFS and DSS rates were 82% and 85%, respectively. In the old group, the 5-year RFS and DSS rates were 65% and 71%, respectively, and the differences between the groups were significant (both $p<0.05$). In the young patients with an NLR≤2.56, the 5-year DSS rate was 93%, while in the young patients with an NLR >2.56, the 5-year DSS rate was 76%. This difference was significant ($p=0.020$). A further Cox model analysis confirmed that the NLR was an independent prognostic factor for DSS.

Conclusion: Young patients with oral SCC have a better prognosis than old oral SCC patients, and the NLR is significantly associated with DSS in young patients.

Keywords: oral squamous cell carcinoma, young patient, head and neck cancer, neutrophil-to-lymphocyte ratio, survival analysis

Introduction

Oral squamous cell carcinoma (SCC) is a common and often lethal form of head and neck SCC; traditionally, it is thought to affect men older than 60 years old after extensive alcohol and tobacco use. However, an alarming increase in the incidence of oral SCC among young patients has been noted by other authors.[1,2] Generally, young patients are less likely to have a history of alcohol or tobacco exposure, and the common risk factors might act as inflammation promoters that upregulate the neutrophil-to-lymphocyte ratio (NLR).[3–7] The NLR is a well-known inflammatory marker, several cytokines, and angiogenic factors can be produced by neutrophils, and these agents play important roles in promoting tumor development, and lymphocytes are associated with immune surveillance and act by eliminating cancer cells, a decreased lymphocyte level is related to poorer ability to eliminate cancer cells. Increasingly stronger evidence has indicated the prognostic role of the NLR in traditional head and neck SCC,[3–8] but no researchers have analyzed whether there is a similar phenomenon in young patients. Moreover, the prognosis in young patients

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remains controversial, although many comparable outcomes have been reported in young and old patients. A recent study suggested that young patients may actually have worse recurrence rates and a worse prognosis,[8] which suggests that young oral SCC patients might be different from traditional oral SCC patients. Therefore, the current study evaluated the prognosis of young patients with oral SCC with a focus on the value of the pretreatment NLR.

Patients and methods

The Zhengzhou University institutional research committee approved our study, all participants provided written informed consent for medical research prior to their initial treatment, this study was conducted in accordance with the Declaration of Helsinki. All methods were performed in accordance with the relevant guidelines and regulations.

Consecutive patients from January 1995 to July 2018 surgically treated for primary oral SCC were retrospectively reviewed. Eligible patients were those who were ≤40 or ≥60 years old, of any sex, able to provide written informed consent, and not previously treated for oral SCC. Data regarding age, sex, TNM stage, the pretreatment NLR, pathological characteristics, surgical treatment, and follow-up were collected and analyzed. All pathological sections were re-reviewed, and all patients were routinely followed up by out-patient clinic, telephone, email, or we-chat.

In our cancer center, neck dissection was routinely suggested for any stage of oral SCC; in extreme cases, the wait-and-see approach was reserved only for patients with a very small primary lesion. Adjuvant treatments including radiotherapy or chemoradiotherapy were suggested if there was presence of high-risk factors including T3 to T4 or N2 to N3 disease, positive surgical margins, extracapsular extension, lymphovascular invasion, and perineural invasion. The regimens of chemotherapy were mainly platinum-based drugs.

Systematic examination was routinely performed with the help of ultrasound, CT, MRI, and/or PET-CT examinations. TNM staging was performed based on the AJCC 7th edition classification.

The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count measured within 2 weeks before the initial treatment.[3–9] The cutoff values calculated from the ROC curve, mean, tertiles, or median in previous studies varied from 1.98 to 5,[3–9] and the standard cutoff value remains undetermined. In the current study, the cutoff value was defined as the mean value of the NLR based on our previous studies.[8,9]

The patients ≤40 years old were enrolled as a young group. Matched patients ≥60 years old were selected. In this study, each young patient was matched to an old patient, and the patients were matched by sex, smoking status, drinking status, primary site, margin status, disease stage (stage I/II vs stage III/IV), and neck node status. The matched patients ≥60 years old were enrolled as the old group.[9,10] Drinkers were defined as patients who consumed at least one alcoholic drink per day for at least 1 year,[11,12] and smokers were defined as patients who smoked on a daily basis.[12]

The chi-square test was used to analyze the associations between the NLR and clinicopathological variables. Recurrence-free survival (RFS) and disease-specific survival (DSS) were calculated from the date of surgery to the date of the event or the last follow-up. The Kaplan–Meier approach was used to calculate the RFS and DSS rates. Factors that were significant in univariate analysis (log-rank method) were then analyzed by Cox model analysis to identify the independent risk factors for the RFS and DSS rates. All statistical analyses were performed by using SPSS 20.0, and $p<0.05$ was considered significant.

Results

A total of 103 (53 female and 50 male) young patients were enrolled, all patients underwent a neck dissection operation, a negative margin was achieved in all patients, and no patients had chronic steroid use or an autoimmune disease. The clinicopathological characteristics of the two groups are presented in Table 1. More patients received adjuvant therapy in young group, including radiotherapy and chemotherapy, than those in the old group ($p<0.001$), and the NLR value was significantly lower in the young patients than in the old patients ($p=0.012$). There was no apparent difference regarding adverse pathological characteristics (all $p>0.05$).

During our follow-up, which had a mean time of 89.9 (range: 7–205) months, recurrence occurred in 18 and 34 patients in the young and old groups, respectively. In the young group, there were 5 local recurrences, 7 regional recurrences, 3 locoregional recurrences, and 3 distant recurrences, while in the old group, there were 9 local recurrences, 10 regional recurrences, 12 locoregional recurrences, and 3 distant recurrences; the difference between the groups was not significant ($p=0.501$). The 5-year RFS rates in the young and old groups were 82% and 65%, respectively, and the difference was significant (Figure 1, $p=0.014$). Disease-related death occurred in 11 and 27 patients in the young

Table 1 Clinical pathologic information of the two groups

Variables	Young Group (n=103)	Old group (n=103)	p
Sex			
Female	53	53	
Male	50	50	1.000
Smoker			
Yes	10	10	
No	93	93	1.000
Drinker			
Yes	8	8	
No	95	95	1.000
Primary site			
Tongue	53	53	
Mouth floor	20	20	
Lower gingiva	20	20	
Buccal	10	10	1.000
Tumor stage			
T1+T2	83	83	
T3+T4	20	20	1.000
Node stage			
No	75	75	
N+	28	28	1.000
Disease stage			
I/II	66	66	
III/IV	37	37	1.000
Perineural invasion			
Yes	19	22	
No	84	81	0.601
Lymphovascular invasion			
Yes	15	18	
No	88	85	0.569
Differentiation			
Well	47	40	
Moderate	43	52	
Poor	13	11	0.453
NLR (mean)	2.56	2.81	0.012
Treatment			
S	6	26	
S+R	86	72	
S+R+C	11	5	<0.001

Abbreviations: S, surgery; R, radiotherapy; C, chemotherapy; NLR, neutrophil-to-lymphocyte ratio; NS, not significant.

and old groups, respectively. The 5-year DSS rates in the young and old groups were 85% and 71%, respectively, and the difference was significant (Figure 2, p=0.010).
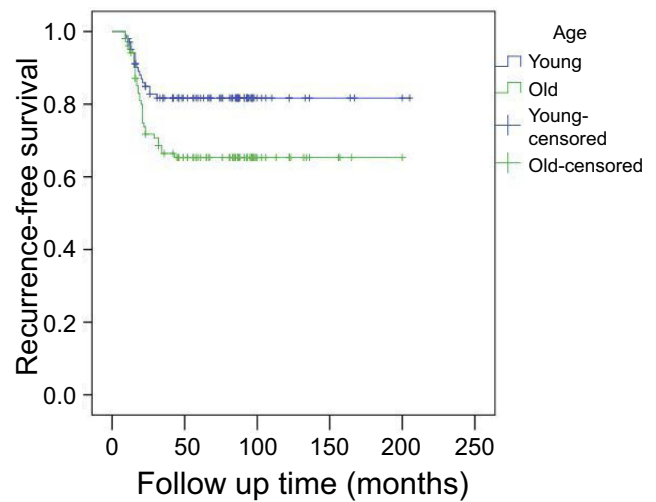

Figure 1 Comparison of recurrence-free survival between young and old groups (p=0.014).
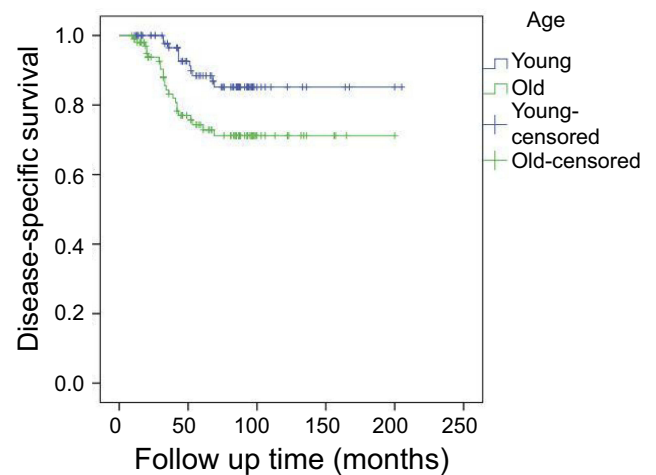

Figure 2 Comparison of disease-specific survival between young and old groups (p=0.010).

The associations between the NLR and clinicopathological variables are presented in Table 2. A high NLR was significantly related to advanced-stage disease and poor differentiation. There were no positive associations between the NLR and sex, tumor stage, node stage, perineural invasion, or lymphovascular invasion.

Univariate analysis (log-rank analysis) of RFS in the young group showed that in the patients with an NLR≤2.56, the 5-year RFS rate was 83%, while in the patients with an NLR >2.56, the 5-year RFS rate was 80%, and the difference was not significant (p=0.643). Other factors including the primary site, disease stage, tumor differentiation, radiotherapy use, and lymphovascular invasion status were significantly associated with RFS

Table 2 Association between neutrophil-to-lymphocyte ratio (NLR) and clinical pathologic characteristics in young patients with oral squamous cell carcinoma

Variables	NLR		P
	≤2.56 (n=55)	>2.56 (n=48)	
Sex			
Female	28	25	
Male	27	23	0.905
Smoker			
Yes	3	7	
No	52	41	0.182
Drinker			
Yes	2	6	
No	53	42	0.141
Tumor stage			
T1+T2	48	35	
T3+T4	7	13	0.066
Node stage			
N0	44	31	
N+	11	17	0.079
Disease stage			
I/II	45	21	
III/IV	10	27	<0.001
Perineural invasion			
Yes	7	12	
No	48	36	0.109
Lymphovascular invasion			
Yes	5	10	
No	50	38	0.092
Differentiation			
Well	32	15	
Moderate	18	25	
Poor	5	8	0.023

Abbreviation: NS, not significant.

(all $p<0.05$). In a further Cox model analysis, the primary site, disease stage, and lymphovascular invasion status were independent predictors of RFS (Table 3).

Univariate analysis (log-rank analysis) of DSS in the young group showed that in the patients with an NLR≤2.56, the 5-year DSS rate was 93%, while in the patients with an NLR >2.56, the 5-year DSS rate was 76%, and the difference was significant (Figure 3, p=0.020). Other factors including the primary site, disease stage, tumor differentiation, perineural invasion status, and radiotherapy use were also significantly associated with DSS

(all $p<0.05$). In a further Cox model analysis, a high NLR was also an independent predictor of worse DSS (Table 4).

Discussion

Oral SCC is uncommon in patients less than 40 years old, and no overall consensus concerning the difference in prognosis between old and young patients has been reached. One of the main findings in the current study was that the prognosis of young patients was significantly better than that of old patients, and this finding conflicted some with the findings of previous reports. Farquhar et al,[13] found that although there was no difference in overall mortality, young patients were more likely to recur within 3 years than old patients, and the authors concluded that oral SCC among young patients may be distinct from traditional oral SCC. Hilly et al,[14] described recurrence in similar proportions of patients in young and old groups (38% and 29.9%, respectively), and a Kaplan–Meier analysis yielded no between-group differences in disease-free or overall survival. Pitman et al,[15] noted that the 3-year disease-free survival rate of a group of patients older than 40 years old was 55.0%, while the 3-year disease-free survival rate was 53.3% in young groups, and the authors suggested that the outcomes of treatment for tongue SCC in young patients were similar to those in patients older than 40 with a similar extent of disease. Friedlander et al,[16] reported that younger patients with tongue SCC had a higher rate of locoregional recurrence than older patients, but this difference did not translate into a survival difference. However, the results of these reports were potentially influenced by one or more confounding factors that affected the interpretation of the outcomes. First, the definition of young patients was inconsistent, and the cutoff age varied from 30 years to 40 years. Second, the factors of smoking and alcohol use were never matched to prevent interference in previous studies;[13–16] the incidences of smokers and drinkers were usually higher in the older groups, and alcohol use and smoking have immunosuppressive effects and are associated with a worse prognosis,[17,18] which would lead to decreased disease control in the older, control groups. In the current study, as many confounding factors as possible were matched for increasing the study reliability, but there were still some differences regarding the baseline data of the two groups, which might partially explain the prognosis variation. Owing to the better toleration of side effects, more adjuvant treatments were performed in the young patients, and this increased treatment surely could improve patient prognosis. On the other hand, it was interesting to find that

Table 3 Predictors for recurrence-free survival in young patients with oral squamous cell carcinoma

Variables	Log-rank analysis	Cox model	
	p	HR(95% CI)	p
Sex	0.435		
Smoker	0.223		
Drinker	0.533		
Primary site (tongue vs other sites)	0.009	2.497(1.562–7.246)	<0.001
Tumor stage (T1+T2 vs T3+T4)	0.064		
Node stage (N0 vs N+)	0.111		
Disease stage (I/II vs III/IV)	0.008	3.458(1.597–9.335)	<0.001
Perineural invasion	0.099		
Lymphovascular invasion	0.006	2.002(1.346–4.886)	0.003
Differentiation (Well vs Moderate + Poor)	0.018	2.946(0.943–6.669)	0.099
NLR (≤2.56 vs >2.56)	0.643		
Radiotherapy	0.033	0.632(0.421–1.165)	0.154
Chemotherapy	0.875		

Abbreviation: NLR, neutrophil-to-lymphocyte ratio.
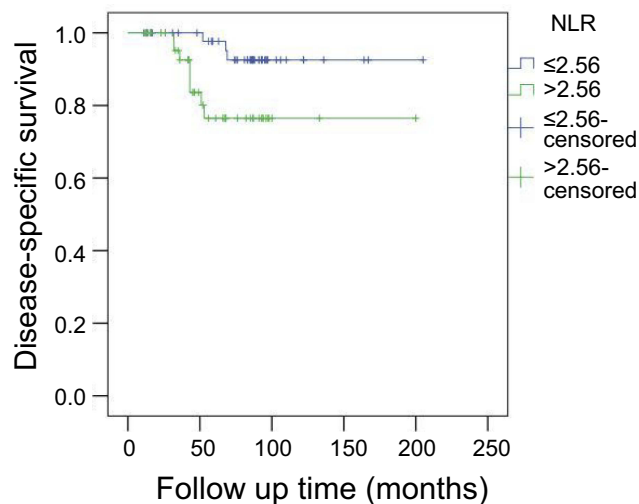

Figure 3 Disease-specific survival in patients with different neutrophil-to-lymphocyte ratio (NLR) (p=0.020).

the NLR value was significantly lower in the young patients than in the old patients, and previous strong evidence has shown that a high NLR value is a predictor of a worse prognosis in head and neck SCC.[3–7] Additionally, although we did not have the HPV status of the patients, because of the higher sexual activity in young patients, there might be higher rate of HPV infection in young patients, and several authors had shown the correlation between HPV + and better prognosis in young people.[19,20] Furthermore, other unassessed factors, including poor oral hygiene and poor dentures in the old patients, might also be responsible for this finding.

The significance of the NLR in traditional head and neck SCC has been widely analyzed. Yu et al,[21] described that head and neck cancer patients with an elevated pre-treatment NLR in the peripheral blood were prone to local invasion and distant recurrence and had a poor prognosis. Kano et al,[22] analyzed data from 285 patients with head and neck cancer treated with concurrent chemotherapy and found that there were significant relationships between a high NLR and hypopharyngeal or oropharyngeal cancer, N2b to N3 stages, T3 to T4 stages, and clinical stages III to IV and that in further survival assessments, a high NLR was significantly associated with decreases in disease-free survival and overall survival. However, whether there are similar findings in young oral SCC patients remains unknown. The current study is the first to report that a high NLR is related to adverse pathological characteristics and DSS but not RFS.

The exact mechanisms underlying the association between the NLR and the prognosis remain unknown, but some possible explanations can be inferred from previous evidence. On the one hand, an elevated neutrophil level is a sign of local and systemic inflammatory responses. Several cytokines and angiogenic factors can be produced by neutrophils, and these agents play important roles in promoting tumor development.[23] These hematological markers are also surrogate markers of cancer cachexia, which is related to poor survival.[24,25] On the other hand, lymphocytes are associated with immune surveillance and act by eliminating cancer cells,[26] a decreased lymphocyte level is related to poorer ability to eliminate

Table 4 Predictors for disease-specific survival in young patients with oral squamous cell carcinoma

Variables	Log-rank analysis	Cox model	
	p	HR(95% CI)	*p*
Sex	0.641		
Smoker	0.115		
Drinker	0.068		
Primary site (tongue vs other sites)	0.007	2.047(1.687–5.227)	0.004
Tumor stage (T1+T2 vs T3+T4)	0.245		
Node stage (N0 vs N+)	0.087		
Disease stage (I/II vs III/IV)	0.001	4.281(2.101–10.223)	<0.001
Perineural invasion	0.015	2.110(1.347–4.613)	0.009
Lymphovascular invasion	0.110		
Differentiation (Well vs Moderate + Poor)	0.003	2.348(1.612–6.759)	0.003
NLR (≤2.56 vs >2.56)	0.020	1.874(1.075–2.886)	0.037
Radiotherapy	0.031	0.845(0.431–1.221)	0.098
Chemotherapy	0.411		

Abbreviation: NLR, neutrophil-to-lymphocyte ratio.

cancer cells. Therefore, a high NLR is considered to predict a worse prognosis.

We failed to note there is a positive relationship between NLR and the RFS in young patients, the finding was conflicted with previous researchers,[9,21,22] possible explanation was our different subjects, only young patients were enrolled in the current study, young oral SCC patients might be a distinct entity from traditional oral SCC patients owing to different pathogenic factors, additionally, as our result described, lower NLR in young patients might mean relatively milder negative effect than higher NLR in old patients.

The limitations of the current study must be acknowledged. First, the number of events in the younger cohort was relatively small, which might decrease the statistical power of our research. A study with a larger sample size is needed to clarify some questions. Second, this is a retrospective study, and there is an inherent bias that might decease the statistical power. Third, it should be recognized that neutrophil and lymphocyte counts are nonspecific parameters because they can be influenced by concomitant conditions, such as infections or inflammation.

In summary, young patients with oral SCC have a better prognosis than old patients, and the NLR is significantly associated with DSS in young patients.

Availability of data and materials

All data generated or analyzed during this study are included in this published article. The primary data can be obtained from the corresponding author.

Ethics Statement

The Zhengzhou University institutional research committee approved our study, all participants provided written informed consent for medical research prior to their initial treatment, this study was conducted in accordance with the Declaration of Helsinki. All methods were performed in accordance with the relevant guidelines and regulations. All the material came from our cancer center, and the consent to publish was obtained from all patients.

Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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