Chung Shan Medical Journal 2023; 34:1-10

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Original Article

A scoring system to predict early oral cavity squamous cell carcinoma without long-term survival

Hsueh-Ju Lu[1, 2*], Yu-Wei Chiu[3, 4], Wen-San Lan[1,5], Wei-Shiou Huang[1,2]

[1] *Division of Hematology and Oncology, Department of Internal Medicine, Chung Shan Medical University Hospital, Taichung City, Taiwan*

[2] *School of Medicine, Chung Shan Medical University, Taichung City, Taiwan*

[3] *Department of Dentistry, Chung Shan Medical University Hospital, Taichung City, Taiwan*

[4] *School of Dentistry, Chung Shan Medical University, Taichung City, Taiwan*

[5] *Department of Nursing, Chung Shan Medical University Hospital, Taichung City, Taiwan*

Purpose: Oral cavity squamous cell carcinomas (OCSCCs) are the largest subgroup of head and neck squamous cell carcinoma (HNSCC), up to 50% of all. More than half of them are early OCSCCs (pT1-2N0M0). Despite higher curative rates of these early OCSCCs, nearly one-fifth of early OCSCCs patients did not have long-term survival and rare biomarkers are available to predict these events.

Method: A total of 376 early OCSCC diagnosed at Chung Shan Medical University Hospital were enrolled. All of them were divided into training (225 patients, from 2010 to 2013) and validation (151 patients, from 2014-2016) cohorts. The clinical–pathological variables were compared using the χ^2 test. Cox proportional-hazards analyses were performed for overall survival (OS). A scoring system was established to predict the death occurring within five years after diagnosis.

Results: The 5-year locoregional-free survival (LFS) and OS were 70.6% and 81.6%, respectively. Each of the training cohort's independent factors for the OS, including age, surgical margin, and lymphocyte-monocyte ratio, was scored one point to establish a scoring system. The sensitivity, specificity, and area under the curve for the training and validation cohorts were 83.3%, 41.7%, and 0.694, and 70.0%, 50.0%, and 0.645, respectively.

Conclusions: A scoring system to predict long-term survival was established for early OCSCC.

Keywords: early staging, oral cavity squamous cell carcinoma, long-term survival, predictive markers

1. Introduction

Oral cavity squamous cell carcinomas (OCSCCs) are the largest subgroup of head and neck squamous cell carcinoma (HNSCC), which is the sixth most common cancer globally, and 50% of HNSCCs are OCSCCs in Taiwan(1, 2). Among these OCSCC patients, more than half of all (59.6%, 2889/4845) belonged to early staging OCSCC without pathologically regional lymph node involvement (pT1-2N0)(3) and curative surgical resection is recommended for them (4, 5). The five-year overall survival (OS) of these early OCSCC patients was at least 80% or more (6, 7), and one-fifth of patients with early OCSCC would dead within 5 years after initial diagnosis.

In the era of precision medicine, predicting the major events, such as disease recurrence or death, was important in clinical managements. However, these major events were difficult be identified based

* Corresponding author: Hsueh-Ju Lu
Address: No. 110, Sec. 1, Jianguo N. Rd., Taichung City, 40201, Taiwan
Tel: +886-4-2473-9595 ext. 34711
E-mail: hsuehju0311@gmail.com

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on clinical-pathologic factors. Genetic sequencing and classifications might be the way to characterize the molecular determinants driving OCSCC, a heterogeneous and complex disease (8). However, due to long wait times for genetic services and uncertain utility of sequencing results, it is a major issue to discuss the cost-effectiveness of gene sequencing for clinical implementation (9). In spite of being challenged in cost-effectiveness for gene sequencing, early detecting major events and prompt treatment are still the best means to prolong survival. However, there are rare biomarkers to predict long-term survival of early OCSCC.

In this study, we enrolled early OCSCC patients (pT1-2N0M0), who were diagnosed at Chung Shan Medical University Hospital, from 2010 to 2016. All of them were treated with curative surgical resection. The patients were divided into training and validation groups according to the date of diagnosis (patients diagnosed from 2010 to 2013 as training cohort and those from 2014-2016 as validation cohort). A scoring system for predicting the events of death happening within five years after diagnosis was established and tested with the training and validation cohorts. Based on the results, it is helpful for clinicians to identify the deaths of early OCSCC patients and provide effective treatments as soon as possible.

2. Materials and methods

2.1. Study design and patient selection

This was a single-institute, retrospective cohort study. Patients with newly diagnosed OCSCC at Chung Shan Medical University Hospital from January 2010 to December 2016 were selected. All of these patients were treated with curative surgical resection according to the guideline of multidisciplinary head and neck cancer conference system in Chung Shan Medical University. Only patients diagnosed with early staging OCSCC (pT1-2N0M0) were enrolled for analysis. The following patients were excluded: patients previously diagnosed as having or treated for HNSCC, those who did not undergo curative surgery, and those with secondary malignancies, those with advanced OCSCC.

2.2. Data collection

The baseline clinicopathological parameters were recorded according to the medical records and included age, sex, primary tumor location, pathologic staging, and pathologic features (e.g., histological grade, primary tumor size, depth of invasion, lymphovascular invasion, and perineural invasion, and surgical margin).

2.3. Clinical outcomes

Locoregional-free survival (LRS) was calculated from the date of disease diagnosis to the date of disease progression to locoregional recurrence. OS was calculated from the date of disease diagnosis to the date of death or last follow-up. The last follow-up date was July 31, 2019.

2.4. Statistical analysis

The correlations between the clinicopathological variables were analyzed using the χ^2 test or Fisher's exact test. Cox proportional-hazards analyses were performed for univariate and multivariate analyses to identify the independent prognostic factors for the OS. Variables with P values of <0.05 in the univariate analyses were entered into the backward multivariate analysis. A two-sided P value of <0.05 was considered statistically significant. Survival was estimated using the Kaplan–Meier method, and the log-rank test was used to compare the survival curves. SPSS (version 21.0, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

3. Results

3.1. Baseline characteristics of early OCSCC patients

A total of 1109 patients diagnosed HNSCC at Chung Shan Medical University Hospital from Jan 2010 to Dec 2016. Most of patients (71.6%, 794/1109) belonged to OCSCC and 76.3% (606/794) of these OCSCC patients were operable. After excluding patients with synchronous secondary primary tumors and advanced staging, a total of 376 early staging OCSCC patients (pT1-2N0M0), more than half of all OCSCC patients (63.2%, 376/595), were enrolled for analysis. Based on the date of diagnosis, patients were divided into training (from 2010-2013) and validation (2014-2016) cohorts. And all of these

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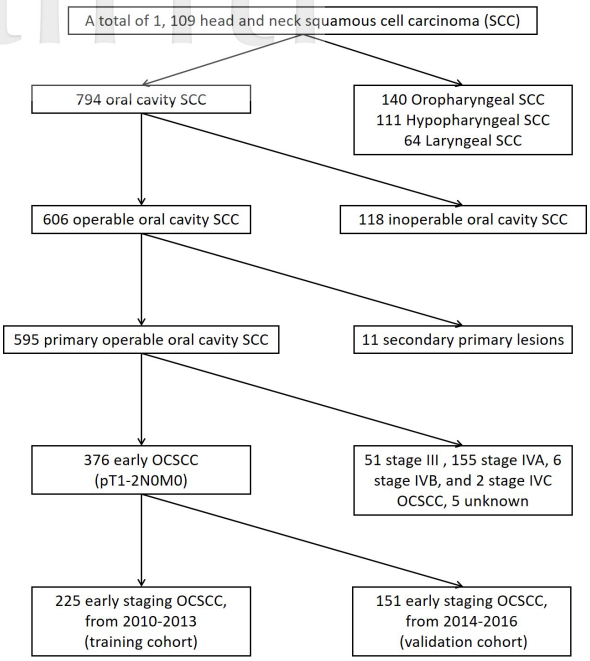


Figure 1. The flowchart of patients enrolled in our study. A total of 1109 patients diagnosed HNSCC at Chung Shan Medical University Hospital from Jan 2010 to Dec 2016. Most of patients (71.6%, 794/1109) belonged to OCSCC and 76.3% (606/794) of these OCSCC patients were operable. After excluding patients with synchronous secondary primary tumors and advanced staging, a total of 376 early staging OCSCC patients (pT1-2N0M0) were enrolled and separated into training and validation cohorts.

patients were treated according to the guideline of multidisciplinary head and neck cancer conference system in Chung Shan Medical University. The flowchart of patients' selection was shown as Figure 1.

Cheek mucosa (39.6%, 149/376) and oral tongue (31.4%, 118/376) were the most common primary tumor sites in our institute [cheek mucosa and oral tongue, 42.7% (96/225) and 28.4% (64/225) in training cohort, and 35.1% (53/151) and 35.8% (54/151) in validation cohort, respectively]. In addition, more than half OCSCC patients (63.1%, 226/358) could not get surgical free margin [60.8% (129/212) and 77.4% (97/146) in training and validation cohorts, respectively]. And the depth of invasion was more than 5mm for nearly forty percentage (39.7%, 138/348) of all samples [43.4% (89/205) and 34.3% (49/143) in training and validation cohorts, respectively] (Table 1).

3.2. Clinical outcomes

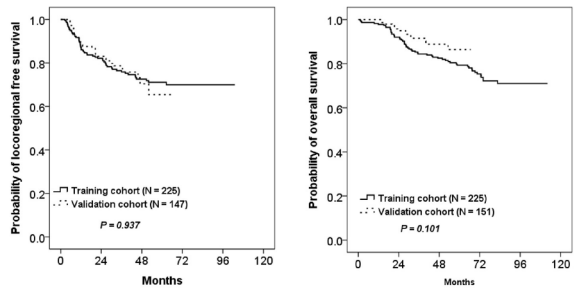


Figure 2. Clinical outcomes of early OCSCC patients. The 5-year LRS and OS of all patients were 70.6% and 81.6%, respectively. There were no differences in (a) LRS (5-year LRS, 71.1% vs. 65.4%, *P = 0.937*), and (b) OS (5-year OS, 79.3% vs. 86.4%, *P = 0.101*) in training and validation cohorts, respectively.

The 5-year LRS and OS of all patients were 70.6% and 81.6%, respectively. And the clinical outcomes between training and validation cohorts were no significant (5-year LRS, 71.1% vs. 65.4%, *P = 0.937*; 5y- OS, 79.3% vs. 86.4%, *P = 0.101*, respectively). The median follow-up time was 53.3 months (68.7 months and 36.8 months for training and validation cohorts, respectively) (Figure 2).

3.3. Prognostic factors for the locoregional free survival and overall survival

Cox regression was used to identify the independent prognostic factors for the LRS and OS. In training cohort, primary tumor site [cheek mucosa, hazard ratio (HR) (95% confidence index (CI)), 2.155(1.230-3.778), *P* = 0.007], poorly differentiated [HR (95% CI), 2.473 (1.036-5.906), *P* = 0.041] , surgical margin [HR (95% CI), 2.200 (1.170-4.137), *P* = 0.041], and neutrophil-lymphocyte ratio [HR (95% CI), 1.655(0.952-2.876), *P* = 0.074] were the independent factors for LRS. And age [HR (95% CI), 2.342 (1.218-4.504), *P* = 0.011] , surgical margin [HR (95% CI), 2.821 (1.438-5.534), *P* = 0.003], and lymphocyte-monocyte ratio(LMR) [HR (95% CI), 4.160(2.002-8.640), *P* < 0.001] were independent for OS (Table 2). Other factors were also important, such as alcoholism (*P* = 0.006), oral tongue (*P* = 0.020), and LMR (*P* = 0.014) for LRS, and LMR (P = 0.042) for OS, in training cohort.

Similarly, these factors which were significant in training cohort were also independent for LRS and OS in validation cohort by univariate and multivariate

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Table 1. Basic characteristics of pT1-2N0 OCSCC patients

	Training cohort (2010-2013) N = 225	Validation cohort (2014-2016) N = 151	P value
Age > 65	32(14.2)	22(14.6)	0.519
Male	208(92.4)	136(90.1)	0.265
Smoking	135/223(60.5)	119/150(79.3)	<0.001*
Alcohol	124/221(56.1)	98/149(65.8)	0.039*
Betel nut	137/223(61.4)	113/150(75.3)	0.003*
Primary tumor site			0.135
Cheek mucosa	96(42.7)	53(35.1)	
Oral tongue	64(28.4)	54(35.8)	
Lip	27(12.0)	13(8.6)	
Gum	27(12.0)	23(15.2)	
Mouth floor	6(2.7)	4(2.6)	
Hard palate	1(0.4)	2(1.3)	
Retromolar trigone	4(1.8)	0(0.0)	
Others	0(0.0)	2(1.3)	
Histological grade			0.517
Well	79(35.1)	49(32.5)	
Moderately	124(55.1)	86(57.0)	
Poorly	14(6.2)	14(9.3)	
Undifferentiated	1(0.4)	0(0.0)	
Unknown	7(3.1)	2(1.3)	
Pathologic feature			
Primary tumor size ≥ 2cm	84/225(37.3)	50/150(33.3)	0.248
Depth of invasion ≥ 5mm	89/205(43.4)	49/143(34.3)	0.054
10mm	36/205(17.6)	11/143(7.7)	0.005*
Lymphovascular invasion	1/208(0.5)	8/142(5.6)	0.004*
Perineural invasion	34/208(16.3)	32/142(22.5)	0.095
Surgical margin < 5mm	129/212(60.8)	97/146(66.4)	0.167
Preoperative biochemistry data			
Elevated WBC ≥ 10000 /μl	21/206(10.2)	10/138(7.2)	0.230
HgB ≤ 10 g/dl	2/206(1.0)	4/138(2.9)	0.179
Elevated Platelet ≥ 450K μl	1/206(0.5)	1/138(0.7)	0.642
Neutro/Lymph ratio ≥ 2.6	87/203(42.9)	43/114(37.7)	0.220
Lymph/Mono ratio < 2.5	12/203(5.9)	6/114(5.3)	0.514

*P value < 0.05

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Table 2. Univariate and multivariate Cox regression analysis for locoregional free survival and overall survival in training cohort.

	Locoregional free survival		Overall survival	
	Univariant P value, HR (95 CI %)	Multivariant P value, HR (95 CI %)	Univariant P value, HR (95 CI %)	Multivariant P value, HR (95 CI %)
Age ≥ 65	0.729, 0.861 (0.369-2.008)		0.010, 2.274 (1.221-4.234)*	0.011, 2.342 (1.218-4.504)*
Male	0.789, 1.148 (0.416-3.174)		0.956, 1.029 (0.372-2.848)	
Smoking	0.568, 1.160 (0.680-1.978)		0.862, 0.954 (0.561-1.622)	
Alcohol	0.014, 2.017 (1.154-3.534)*		0.326, 1.308 (0.765-2.235)	
Betel nut	0.314, 1.327 (0.765-2.303)		0.625, 0.876 (0.515-1.489)	
Primary tumor site				
Cheek mucosa vs. non-cheek mucosa	0.003, 2.208 (1.300-3.749)*	0.007, 2.155 (1.230-3.778)*	0.368, 1.273 (0.752-2.153)	
Oral tongue vs. non-oral tongue	0.020, 0.429 (0.210-0.874)*		0.088, 0.563 (0.291-1.089)	
Poorly differentiated	0.021, 2.550 (1.153-5.642)*	0.041, 2.473 (1.036-5.906)*	0.209, 1.722 (0.737-4.023)	
Pathologic feature				
Primary tumor size ≥ 2cm	0.510, 1.196 (0.702-2.040)		0.502, 1.202 (0.703-2.055)	
Depth of invasion ≥ 5mm	0.175, 1.452 (0.847-2.489)		0.667, 1.128 (0.652-1.950)	
Lymphovascular invasion	0.689, 0.049 (0.000-)		0.689, 0.048 (0.000-)	
Perineural invasion	0.239, 0.601 (0.257-1.403)		0.197, 1.547 (0.797-3.001)	
Surgical margin < 5mm	0.014, 2.106 (1.162-3.818)*	0.014, 2.200 (1.170-4.137)*	0.001, 2.873 (1.512-5.460)*	0.003, 2.821 (1.438-5.534)*
Preoperative biochemistry data				
Elevated WBC ≥ 10000 /μl	0.409, 1.397 (0.631-3.092)		0.724, 0.847 (0.337-2.128)	
Neutro/Lymph ratio ≥ 2.6	0.023, 1.860 (1.087-3.182)*	0.074, 1.655 (0.952-2.876)	0.042, 1.767 (1.022-3.055)*	
Lymph/Mono ratio < 2.5	0.014, 2.916 (1.246-6.826)*		<0.001, 4.924 (2.39-10.14)*	<0.001, 4.160 (2.002-8.64)*

*P value < 0.05

Cox regression (Table 3).

3.4. Predictive scoring system for the overall survival

In order to forecast patients who have long-term survival, the events in predictive model was defined

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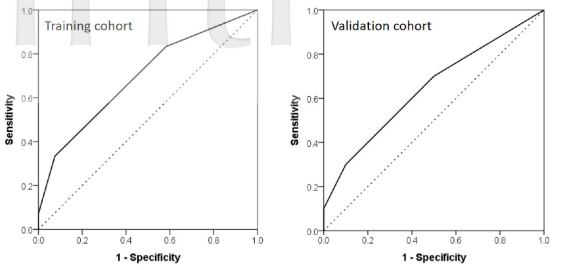
Table 3. Univariate and multivariate Cox regression analysis for locoregional free survival and overall survival in validation cohort.

	Locoregional free survival		Overall survival	
	Univariate P value, HR (95 CI %)	Multivariate P value, HR (95 CI %)	Univariate P value, HR (95 CI %)	Multivariate P value, HR (95 CI %)
Age ≥ 65	0.443, 0.627 (0.190-2.067)		0.019, 3.716 (1.242-11.116)*	
Male	0.552, 1.545 (0.368-6.476)		0.414, 23.711 (0.012-)	
Smoking	0.325, 1.695 (0.592-4.851)		0.942, 1.049 (0.292-3.760)	
Alcohol	0.732, 0.879 (0.421-1.837)		0.191, 0.496 (0.174-1.417)	
Betel nut	0.131, 0.549 (0.252-1.196)		0.456, 0.643 (0.201-2.054)	
Primary tumor site				
Cheek mucosa vs. non-cheek mucosa	0.528, 1.258 (0.616-2.568)		0.117, 2.331 (0.809-6.722)	
Oral tongue vs. non-oral tongue	0.185, 0.566 (0.244-1.313)		0.060, 0.142 (0.019-1.089)	
Poorly differentiated	0.883, 0.915 (0.278-3.010)		0.641, 1.429 (0.319-6.394)	
Pathologic feature				
Primary tumor size ≥ 2cm	0.323, 0.666 (0.298-1.491)		0.782, 1.167 (0.391-3.484)	
Depth of invasion ≥ 5mm	0.031, 2.173 (1.072-4.402)*	0.023, 2.356 (1.125-4.934)*	0.474, 1.473 (0.511-4.248)	
Lymphovascular invasion	0.630, 1.426 (0.337-6.037)		0.678, 1.539 (0.201-11.791)	
Perineural invasion	0.058, 2.058 (0.977-4.333)		0.970, 0.976 (0.272-3.503)	
Surgical margin < 5mm	0.173, 1.756 (0.781-3.946)		0.504, 1.486 (0.464-4.760)	
Preoperative biochemistry data				
Elevated WBC ≥ 10000 /μl	0.035, 2.825 (1.076-7.416)*		0.537, 0.045 (0.000-871.79)	
Neutro/Lymph ratio ≥ 2.6	0.614, 0.786 (0.309-2.001)	0.043, 2.728 (1.030-7.222)*	0.190, 2.332 (0.657-8.271)	
Lymph/Mono ratio < 2.5	0.573, 0.046 (0.000-)		0.034, 5.368 (1.133-25.435)*	0.034, 5.368 (1.113-25.435)

*P value < 0.05

that patients dead within five years from initial diagnosis. And the scoring system was established, included age, surgical margin, and LMR, that each of the training cohort's independent factors for OS was scored one point. The areas under the curve (AUCs) were 0.693 and 0.645 in the training and

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	Sensitivity	Specificity	AUC		Sensitivity	Specificity	AUC
Training cohort	83.3%	41.7%	0.694	Validation cohort	70.0%	50.0%	0.645

Figure 3. Predictive scoring system for long-term survival in early OCSCC. In training cohort, age > 65, surgical margin, and lymphocyte-monocyte ratio were the independent factors for OS. Then, each of these independent factors for OS was scored one point to establish a scoring system in order to predict the events that patients dead within five years from initial diagnosis. The areas under the curve (AUCs) of the score were 0.693 and 0.645 in the training and validation cohorts, respectively. If the cutoff level was ≥1 or not, the sensitivity and specificity were 82.4% and 43.2% in training cohort, and 70.0% and 50.0% in the validation cohort, respectively. Positive predictive value (PPV) and negative predictive value (NPV) were 40% and 84.2% in training cohort, and 58.3% and 62.5% in validation cohort, respectively.

validation cohorts, respectively. If the cutoff level was ≥1 or not, the sensitivity and specificity were 82.4% and 43.2% in training cohort, and 70.0% and 50.0% in the validation cohort, respectively (Figure 3). The accuracy of all predicted were 41.8% and 81.5% in positive predictive value (PPV) and negative predictive value (NPV), respectively. Individually, PPV and NPV were 40% and 84.2% in training cohort, and 58.3% and 62.5% in validation cohort, respectively.

4. Discussion

Up to seventy percentage of HNSCC belong to OCSCC in our institute, and more than half of them were operable early OCSCC. Nevertheless, one-fifth of these early OCSCC patients were no long-term survival. In this study, we enrolled 376 OCSCC patients and divided them into training (from 2010-2013) and validation (2014-2016) cohorts. The independent factors for OS in training cohort, such as age, surgical margin, and LMR, were selected to establish a predictive scoring system. The AUCs were 0.694 and 0.645 in both cohorts, respectively. If the cutoff level was ≥1 or not, the sensitivity and specificity were 83.3% and 41.7% in training cohort, and 70.0% and 50.0% in the validation cohort, respectively. It was an effective predictive scoring system in clinical managements.

In spite to high curative rate of early OCSCC, up to twenty percentages of them still progress to dead within5 years after diagnosis (4, 5). In the era of precision medicine, exactly predicting the major events during follow-up is significant for clinical managements. Previous studies had been published to predict local recurrence and regional lymph node metastasis (10-12), but rare parameters were established to predict death. Furthermore, although gene sequencing provided more information to identify the prognosis of OCSCC, which were helpful to classify the molecular subgroups (13, 14), the cost-effectiveness was still the major challenge to implement sequencing in real world. Consequently, we established a scoring system, based on clinical-pathological factors, to predict long-term survival for early OCSCC patients.

The status of the resected surgical margin is an important and valuable tool to predict the treatment outcome. It is necessary to get optimal surgical margin to avoid local recurrence and improve OS (15). In our study, the surgical margin was also independent for both LRS and OS in our training cohort. Notwithstanding, surgical margin was not significant in validation cohort, it might be because the duration of following up was too short. However, the controversies of clear surgical margin exist, such as > 1mm and > 5mm. In a meta-analysis study, the surgical margin, which was defined as clear by more than 5mm, would reduce the local recurrent rate up to 21% (95% CI 12-30%, $P < 0.001$) (16). So, a 5mm pathological margin is the minimum acceptable margin size in OSCC. And adjuvant therapies were recommended for patients with either positive (<1mm) or close margin (<5mm)(17).

Previous studies showed lymphocyte-to-monocyte (LMR) ratio was significant in clinical outcome for HNSCC (18-20). The relationships between pretreatment inflammatory markers and the prognosis of cancer patients were consistently important issues for clinical managements because of easily approaching. In Kano study, a high LMR was

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significantly associated with a decreased survival rate for HNSCC (18). And a meta-analysis study, enrolled 4260 patients pooled from seven cohorts, showed that an elevated LMR was an indicator of favorable prognosis that significantly improved OS (HR 0.5; 95% CI 0.44-0.57) and DFS (HR 0.70; 95% CI 0.62-0.80) (19). Elevated LMR was also an favorable factor in OS for other cancer types but the mechanism of relationship between tumor microenviroment, lymphocyte, and monocyte was unknown. Based on current evidences, lymphopenia might decrease the efficacy of the immune system and be associated with worse prognosis in cancers (21) and circulating monocytes may contribute to both tumor growth and reduced immunosurveillance through differentiating into macrophages after infiltrating a tumor and then respond to the wide spectrum of chemokines and growth or differentiation factors(21). In our study, patients with lower LMR were worsening in OS than those without, which was comparable with previous studies.Advanced studies were warranted.

There were some limitations in our study. First, although it was only a single-institute study, the patients enrolled were divided into training and validation cohorts to test the scoring system. Future large studies are warranted. Additionally, the independent factors for LRS or OS between training and validation cohorts were not similar might be due to the short follow-up timing for validation cohort. Third, although the scoring system predicts the patients who would not have long-term survival, there are no recommended treatments for them.

In conclusion, age, surgical margin, and LMR were the independent factors for OS in early OCSCCs. Based on these three factors, an established scoring system could be applied to predict long-term survival for early OCSCC patients. Even through the accuracy should improve, the scoring system still provide effective information for clinicians. Advanced studies are warranted.

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