



OPEN Prognostic value of positive lymph node ratio in oral cavity squamous cell carcinoma after neoadjuvant treatment: a retrospective real-world study

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This study aimed to address the prognostic value of positive lymph node ratio for oral cavity squamous cell carcinoma (OCSCC) patients after neoadjuvant treatment, and build a prediction nomogram model. Patients with OCSCC with neoadjuvant treatment were retrieved from the Surveillance, Epidemiology, and End Results database from 2004 to 2021. The primary outcome was overall survival (OS), and the second outcome was disease-specific survival (DSS). Kaplan–Meier and log-rank tests were used to analyze the survival outcomes. Univariable and multivariable analyses were conducted, and then a nomogram was constructed. A total of 419 were included in this study. The optimal cutoff value of the positive lymph node ratio (LNR) was 7.0%. The 5-year OS of patients with low LNR was significantly improved over those with high LNR ($p < 0.0001$). LNR $> 7.0\%$ (HR 50.7, 95% CI 19.7–130.5), and unmarried status (HR 1.33, 95% CI 1.03–1.70) were the independent risk factors for OS (all $p < 0.05$). LNR $> 7.0\%$ (HR 35.8, 95% CI 9.63–132.7), gum primary site (HR 0.330, 95% CI 0.132–0.827), and preoperative chemotherapy and radiotherapy (HR 2.91, 95% CI 1.78–4.73) were the independent risk factors for DSS (all $p < 0.05$). According to the nomogram, patients were stratified into the high-risk group and the low-risk group for OS and DSS. Patients in the low-risk group were predicted with superior survival (both $p < 0.05$). The LNR was an independent prognostic factor of the OS and DSS for OCSCC patients after neoadjuvant treatment. The tools may be valuable to guide multidisciplinary teams in making treatment decisions.

Keywords Oral cavity squamous cell carcinoma, Neoadjuvant treatment, Lymph node ratio, Overall survival, Nomogram

As the most common subtype of head and neck carcinoma, oral cavity carcinoma is reported with nearly 36,620 new cases and 7930 deaths annually in the United States¹. Oral cavity squamous cell carcinoma (OCSCC) accounts for approximately 90% of oral cavity carcinoma, and despite the worldwide decline in smoking and alcohol consumption, the incidence of OCSCC has remained annually increasing in the United States¹. There has been no significant improvement in the overall survival of patients with OCSCC over the past few decades in spite of the continuous advancements in drugs and technologies^{2,3}. Approximately 60% of patients with OCSCCs presenting with advanced disease at diagnosis may make some contribution to this unsatisfied survival⁴.

According to National Comprehensive Cancer Network (NCCN) guidelines, surgery is the preferred initial treatment for OCSCC, including the advanced (T3, T4a) primary oral tongue cancers⁵. However, for patients with advanced disease, radical dissection of the primary tumor often impacts the speech and swallowing functions, markedly affecting their postoperative quality of life⁶. As such, for those patients who are not suitable for primary resection, neoadjuvant treatment is suggested, including preoperative chemotherapy, preoperative

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radiotherapy, or concurrent chemoradiotherapy. For now, the common consensus on how to utilize neoadjuvant treatment regimens preoperatively is less well-defined, and existing research findings suggested that the impacts of the introduction treatment on survival outcomes of patients with OCSCC were heterogeneous^{7–9}.

Several prior studies have suggested that the positive lymph node ratio (LNR), defined as the ratio of positive lymph nodes to the total number of dissected cervical lymph nodes, serves as an additional prognostic indicator for various carcinomas^{10–13}. These studies observed that the survival outcomes varied according to different LNR levels even when patients shared the same pathological node stage. These findings indicated that a more precise prediction might contribute to an accurate evaluation of patients' survival prospects and more suitable follow-up strategies. Till now, few studies reported the prognostic factors of patients who underwent introduction treatment¹⁴. To address this issue, we utilized data from the Surveillance, Epidemiology, and End Results (SEER) database to assess the prognostic value of LNR in patients with OCSCC. Additionally, this study aimed to determine an optimal LNR threshold and build a nomogram model to improve the accuracy of survival predictions for OCSCC patients.

Method

Ethics statement

Signed permission was required to access the SEER database. On account of excluding individual identity information, it was unnecessary to get the ethical authorization of the Institutional Review Board to extract data from the SEER database.

Data source

For this study, data on patients diagnosed with OCSCC between 2004 and 2021 were extracted from the Surveillance, Epidemiology, and End Results (SEER) database (SEER Research Data, 17 Registries, 2023 Sub (2000–2021)). Sponsored by the National Cancer Institute, the SEER program collects demographic, clinicopathologic, and survival data across the United States. Representing 27.8% of the U.S. population with a typical demographic distribution, SEER is considered reflective of the overall U.S. population. Retrieved patient information included age at diagnosis, gender, race, marital status, primary tumor site, survival duration, time to treatment, vital status, grade, pTNM staging, the number of lymph nodes dissected, the number of positive lymph nodes, receipt of surgery and neoadjuvant therapy (including radiotherapy, chemotherapy, and concurrent chemoradiotherapy).

Patient cohort

The patient selection process is illustrated in Fig. 1. Patients were identified based on the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), using topography codes for the oral cavity (tongue: C02.0–C02.9, gum: C03.0–C03.9, floor of mouth: C04.0–C04.9, palate: C05.0–C05.9, other parts of the mouth: C06.0–C06.9) and morphology codes 8052, 8070–8076, 8083–8084, 8094, and 8560 for squamous cell carcinoma. Patients who had adjuvant treatment before surgery were included. A total of 42,706 cases were retrieved from the SEER database. Ineligible cases were excluded based on the following criteria: (1) surgery was not performed; (2) with <10 lymph nodes dissected; (3) age was below 18 years; (4) not primary only; (5) no neoadjuvant treatment was taken; (6) pathological status of the lymph nodes was unknown. Ultimately, 419 patients were enrolled in the study. Patients who were eligible for this cohort study were pathologically confirmed stage I–IV according to the 7th edition of the American Joint Committee on Cancer Staging Manual. For cases before 2010 and after 2018, the AJCC stage was determined using collaborative stage and extent-of-disease codes for tumor size, tumor extension, and lymph node involvement¹⁵. The primary outcome of the analysis was overall survival (OS), defined as the duration of time from diagnosis to the time of death from any causes. Patients still alive by the end of the follow-up period were considered censored. Another outcome was disease-specific survival (DSS), defined as the time from diagnosis until death specifically attributed to oral cavity squamous cell carcinoma, and deaths from other causes are censored in the analysis. The follow-up information on the SEER database was updated in November 2023.

Statistical analysis

We summarized patient characteristics for categorical variables using frequencies and proportions. The Kaplan–Meier method, along with the log-rank test, was employed to assess the impact of treatment on the survival of OCSCC patients. Univariable and multivariable Cox regression analyses were applied to identify the independent risk factors for OCSCC patients. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated through these regression analyses. All statistical tests were two-sided, with a significance level set at 0.05. Analyses were performed using SPSS Statistics 25.0 software (IBM SPSS, Inc., Chicago, IL, USA), GraphPad Prism, and R4.0.3 software. The data was analyzed in October 2024.

Results

Patient characteristics

According to the inclusions and exclusions, 419 patients were enrolled in this study from January 2004 to December 2021. The median age at diagnosis was 59 years (range, 20–85 + years) with a male-to-female ratio of about 1.87, and the median follow-up was 20 months (range, 1–196 months). Most tumor arises from the epithelial tissue of the tongue (194 patients, 46.3%), with floor of the mouth being the second most common site (85 patients, 20.3%). Of the whole cohort, 80.2% were white people, and 53.0% were married. A total of 121 patients (28.9%) were pathologically diagnosed with IV-stage disease, and 63 patients (15.0%) were pathologically diagnosed with I to III-stage disease, with 235 patients (56.1%) being unknown status. As for

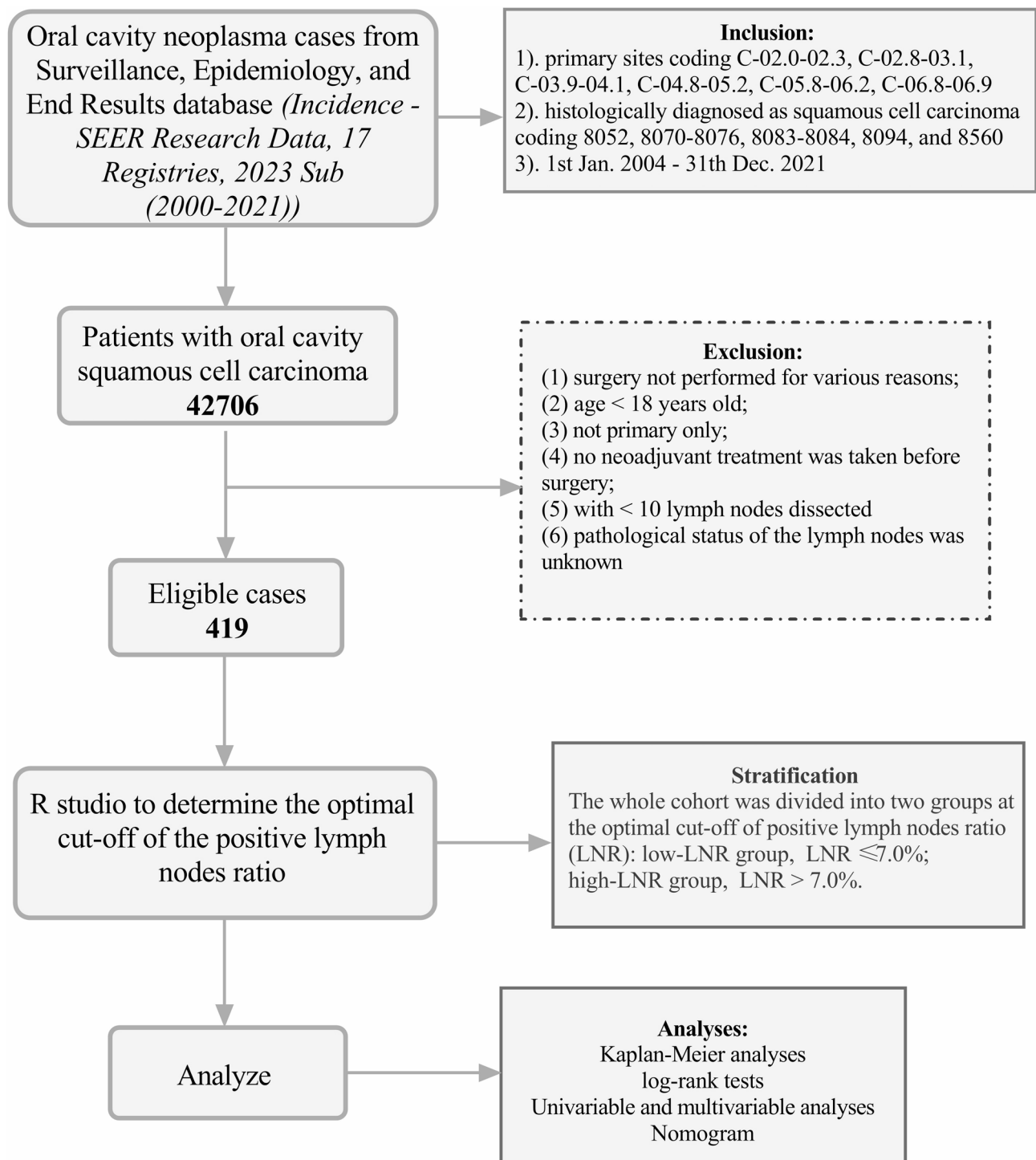


Fig. 1. Flowchart of patient selection.

the histological grade, over half of the patients (212 patients, 50.6%) presented well or moderately at diagnosis, and 63 patients (15.0%) presented poorly differentiated or undifferentiated. The majority of patients received treatment within 60 days. Before surgery treatment, 112 patients (26.7%) undertook radiotherapy alone, and 219 patients (52.3%) undertook chemotherapy alone, with 144 patients (34.4%) undertaking chemoradiotherapy. After the introduction of therapy, 146 patients (34.8%) received wide excision, and 273 patients (65.2%) received radical excision of the primary tumor. All patients received neck dissection. Grade and the primary site were statistically related with lymph nodes ratio (all $p < 0.05$). The demographic and clinicopathologic characteristics are listed in Table 1.

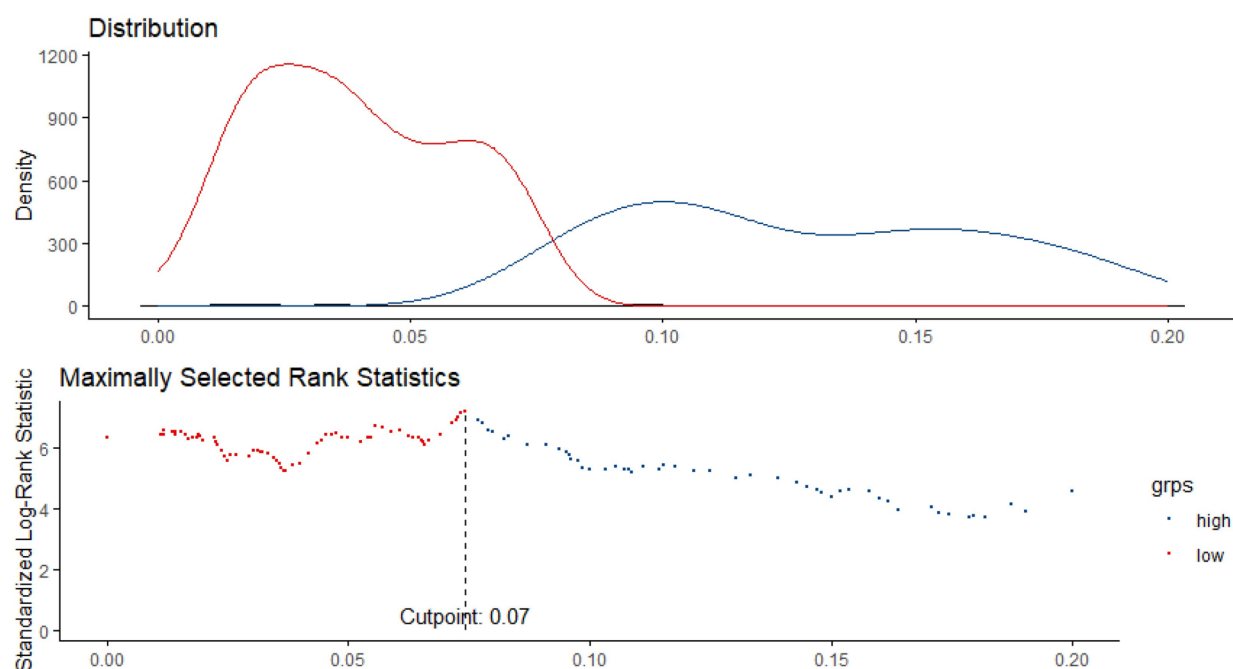
Characteristics	Lymph node ratio (LNR)			p-value
	Overall (N = 419)	Low (N = 283)	High (N = 136)	
Age				0.123
< = 65 years	308 (73.5%)	201 (71.0%)	107 (78.7%)	
> 65 years	111 (26.5%)	82 (29.0%)	29 (21.3%)	
Sex				0.981
Male	273 (65.2%)	185 (65.4%)	88 (64.7%)	
Female	146 (34.8%)	98 (34.6%)	48 (35.3%)	
Race				0.523
White	336 (80.2%)	224 (79.2%)	112 (82.4%)	
Others/Unknown	83 (19.8%)	59 (20.8%)	24 (17.6%)	
Marital status				0.457
Married	222 (53.0%)	154 (54.4%)	68 (50.0%)	
Others/Unknown	197 (47.0%)	129 (45.6%)	68 (50.0%)	
Preoperative treatment				0.376
Preoperative radiotherapy	112 (26.7%)	77 (27.2%)	35 (25.7%)	
Preoperative chemotherapy	219 (52.3%)	152 (53.7%)	67 (49.3%)	
Both	88 (21.0%)	54 (19.1%)	34 (25.0%)	
Grade				0.006
I/II	212 (50.6%)	142 (50.2%)	70 (51.5%)	
III/IV	63 (15.0%)	33 (11.7%)	30 (22.1%)	
Unknown	144 (34.4%)	108 (38.2%)	36 (26.5%)	
Stage				0.131
I/II/III	63 (15.0%)	45 (15.9%)	18 (13.2%)	
IV	121 (28.9%)	73 (25.8%)	48 (35.3%)	
Unknown	235 (56.1%)	165 (58.3%)	70 (51.5%)	
Surgery				0.527
Wide excision	146 (34.8%)	102 (36.0%)	44 (32.4%)	
Radical excision	273 (65.2%)	181 (64.0%)	92 (67.6%)	
Site				0.032
Tongue	194 (46.3%)	126 (44.5%)	68 (50.0%)	
Floor of mouth	85 (20.3%)	59 (20.8%)	26 (19.1%)	
Gum	42 (10.0%)	35 (12.4%)	7 (5.15%)	
Hard palate	14 (3.34%)	13 (4.59%)	1 (0.74%)	
Cheek mucosa	55 (13.1%)	32 (11.3%)	23 (16.9%)	
Retromolar area	29 (6.92%)	18 (6.36%)	11 (8.09%)	
Time to treatment				0.765
< = 30 days	144 (34.4%)	94 (33.2%)	50 (36.8%)	
> 30, < = 60 days	180 (43.0%)	125 (44.2%)	55 (40.4%)	
> 60 days	80 (19.1%)	55 (19.4%)	25 (18.4%)	
Unknown	15 (3.58%)	9 (3.18%)	6 (4.41%)	

Table 1. Patient characteristics in surveillance epidemiology and end results database. Significant values are in [bold].

Univariable and multivariable analyses

We figured out the best cutoff value on the LNR by R studio, which turned out to be 7.0% (Fig. 2A). Based on the optimal LNR value, patients were divided into the LNR-high group (136 patients, 32.5%) and the LNR-low group (283 patients, 67.5%), detailed in Table 1. The 5-year OS of OCSCC patients with low LNR is significantly improved over those with high LNR by Kaplan–Meier analysis ($p < 0.0001$, Fig. 2B). We performed univariable Cox regression analyses and found that marital status, grade, stage, time to treatment, and LNR were closely associated with OS (all $p < 0.05$, Table 2). Then the factors were included in multivariable Cox regression analyses, indicating that LNR $> 7.0\%$ (HR 50.7, 95% CI 19.7–130.5), and unmarried status (HR 1.33, 95% CI 1.03–1.70) were the independent risk factors for OS in patients with OCSCC (all $p < 0.05$, Table 2). The predictive performance of the multivariable Cox regression model achieved a C-index of 0.67 with a standard error (SE) of 0.019, indicating a high level of discriminatory power in predicting the order of event occurrences (Table 2). Preoperative treatment, primary site, and LNR were closely associated with DSS (all $p < 0.05$), further multivariable Cox regression analyses indicated that LNR $> 7.0\%$ (HR 35.8, 95% CI 9.63–132.7), gum primary site (HR 0.330, 95% CI 0.132–0.827), and preoperative chemoradiotherapy (HR 2.91, 95% CI 1.78–4.73) were

A



B

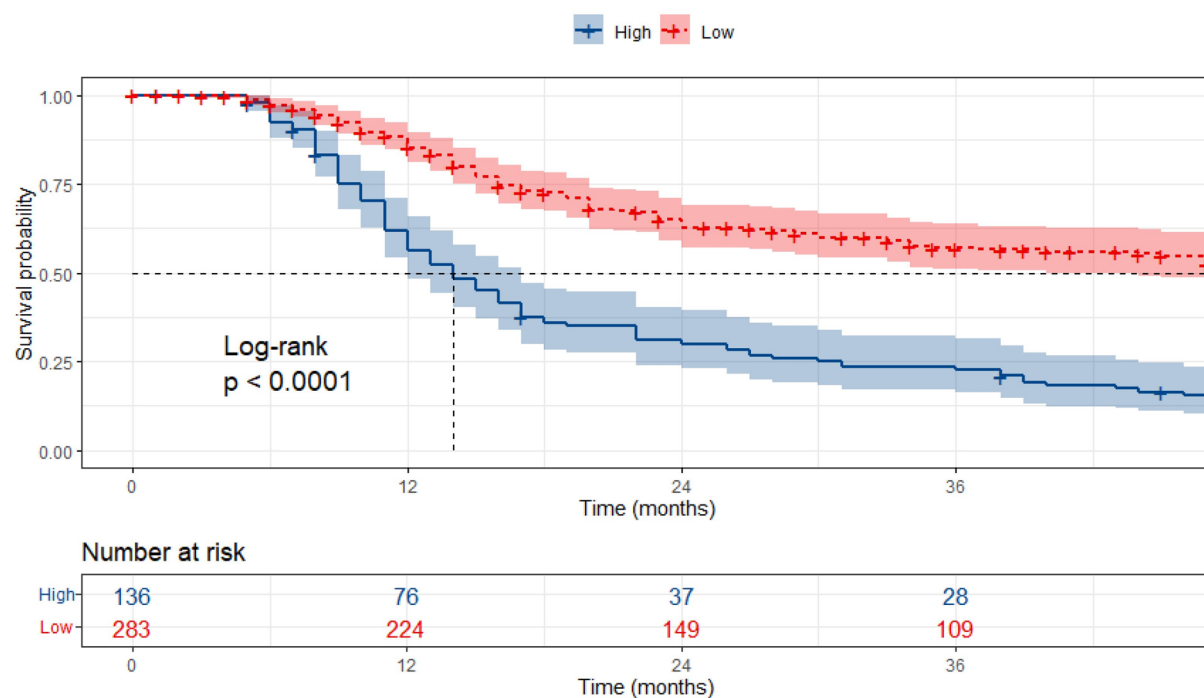


Fig. 2. (A) The processing of cutoff value of the positive lymph node ratio; (B) The Kaplan–Meier analysis of the positive lymph node ratio for overall survival.

the independent risk factors for DSS (all $p < 0.05$, Table 3). The predictive performance of the multivariable Cox regression model achieved a C-index of 0.722 with a standard error (SE) of 0.023.

The construction of the nomogram prediction model

Furthermore, we constructed a nomogram for OS based on the independent risk factors mentioned above along with two common clinical factors, which were age and sex, to build a prognostic model for OCSCC patients with neoadjuvant treatment. Each covariate is assigned a score ranging from 1 to 100, reflecting its predictive

Variables		Univariable Cox analysis		Multivariable Cox analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	< = 65 years	1 [Reference]		1 [Reference]	
	> 65 years	1.04 (0.79–1.38)	0.762	1.08 (0.796–1.46)	0.628
Sex	Male	1 [Reference]		1 [Reference]	
	Female	1.03 (0.79–1.33)	0.846	1.00 (0.756–1.32)	0.998
Race	White	1 [Reference]			
	Others/Unknown	1.15 (0.846–1.55)	0.381		
Marital status	Married	1 [Reference]		1 [Reference]	
	Others/Unknown	1.34 (1.05–1.71)	<0.05	1.33 (1.03–1.70)	<0.05
Preoperative treatment	Preoperative radiotherapy	1 [Reference]			
	Preoperative chemotherapy	0.78 (0.586–1.04)	0.088		
	Both	1.39 (0.998–1.93)	0.051		
Grade	I/II	1 [Reference]		1 [Reference]	
	III/IV	1.5 (1.09–2.05)	<0.05	1.33 (0.966–1.84)	0.080
	Unknown	0.795 (0.57–1.11)	0.177	0.896 (0.606–1.33)	0.583
Stage	I/II/III	1 [Reference]		1 [Reference]	
	IV	0.76 (0.589–0.982)	<0.05	1.36 (0.958–1.93)	0.086
	Unknown	0.979 (0.69–1.39)	0.905	0.936 (0.628–1.39)	0.745
Surgery	Wide excision	1 [Reference]			
	Radical excision	1.15 (0.886–1.49)	0.295		
Site	Tongue	1 [Reference]			
	Floor of mouth	0.975 (0.71–1.34)	0.878		
	Gum	0.87 (0.572–1.32)	0.516		
	Hard palate	0.757 (0.333–1.72)	0.506		
	Cheek mucosa	0.764 (0.508–1.15)	0.196		
	Retromolar area	1.12 (0.697–1.78)	0.649		
Time to treatment	< = 30 days	1 [Reference]		1 [Reference]	
	> 30, < = 60 days	0.871 (0.655–1.16)	0.34	0.953 (0.712–1.28)	0.744
	> 60 days	1.13 (0.802–1.6)	0.48	1.27 (0.894–1.81)	0.181
	Unknown	2.24 (1.25–4.03)	<0.05	2.63 (1.43–4.84)	<0.05
LNR		38.8 (16.1–93.8)	<0.05	50.7 (19.7–130.5)	<0.05
C-index (SE)				0.67 (0.019)	

Table 2. Univariable and multivariable Cox proportional hazard regression analyses for overall survival in oral cavity squamous cell carcinoma patients from Surveillance Epidemiology and End Results database. Significant values are in [bold].

contribution to the model. In summary, the variable with the strongest prognostic effect receives 100 points, which is LNR, while all others are assigned proportionally smaller values based on their effect size. The total score for an individual case correlates with the survival probability of patients (Fig. 3A,B). The best cutoff value of the total scores was identified as 23 (Fig. 3C), according to which patients were divided into the high-risk group and the low-risk group. It turned out that patients in the low-risk group had superior survival outcomes than those in the high-risk group, indicating the excellent prediction efficiency of the model ($p < 0.0001$, Fig. 3D). The prediction model for DSS was constructed in the same way (Fig. 4A,B), and the low-risk group had superior survival outcomes than the high-risk group ($p < 0.0001$, Fig. 4C,D).

Discussion

In this study, the LNR was an independent prognostic factor for OS and DSS in OCSCC patients with neoadjuvant treatment, and patients with high LNR showed over 50 times higher risk of death compared to those with low LNR in OS and over 35 times higher risk in DSS. Based on the multivariable Cox regression analyses, we constructed the nomogram to build a prediction system for OCSCC patients with adjuvant treatment. It turned out that patients in the low-risk group had superior survival outcomes than those in the high-risk group, indicating the excellent prediction efficiency of the model.

The mainstay treatment for OCSCC is surgery, according to NCCN, including the advanced (T3, T4a) primary oral tongue cancers⁵. For patients who are not suitable for primary resection, neoadjuvant treatment is considerable, including preoperative chemotherapy, preoperative radiotherapy, or concurrent chemoradiotherapy, to achieve the preservation of functions and elevation of quality of life. However, the common consensus on how to utilize neoadjuvant treatment regimens preoperatively is less well-defined, and existing research findings suggested that the impacts of the neoadjuvant or introduction treatment on survival outcomes of patients with OCSCC were heterogeneous^{7–9}. Previous research suggested that the potential

Variables		Univariable Cox analysis		Multivariable Cox analysis	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age	< = 65 years	1 [Reference]		1 [Reference]	
	> 65 years	0.69 (0.438–1.09)	0.097	0.935 (0.578–1.51)	0.783
Sex	Male	1 [Reference]		1 [Reference]	
	Female	0.872 (0.591–1.29)	0.486	0.844 (0.565–1.26)	0.408
Race	White	1 [Reference]			
	Others/Unknown	1.09 (0.705–1.7)	0.688		
Marital status	Married	1 [Reference]			
	Others/Unknown	1.18 (0.827–1.69)	0.361		
Preoperative treatment	Preoperative radiotherapy	1 [Reference]		1 [Reference]	
	Preoperative chemotherapy	0.993 (0.632–1.56)	0.975	1.15 (0.721–1.84)	0.553
	Both	2.49 (1.56–3.98)	< 0.05	2.91 (1.78–4.73)	< 0.05
Grade	I/II	1 [Reference]			
	III/IV	1.43 (0.906–2.26)	0.125		
	Unknown	0.781 (0.492–1.24)	0.295		
Stage	I/II/III	1 [Reference]			
	IV	1.1 (0.672–1.8)	0.703		
	Unknown	0.83 (0.513–1.34)	0.447		
Surgery	Wide excision	1 [Reference]			
	Radical excision	0.987 (0.682–1.43)	0.944		
Site	Tongue	1 [Reference]		1 [Reference]	
	Floor of mouth	0.704 (0.446–1.11)	0.131	0.769 (0.486–1.22)	0.262
	Gum	0.26 (0.105–0.645)	< 0.05	0.330 (0.132–0.827)	< 0.05
	Hard palate	0.193 (0.027–1.39)	0.102	0.143 (0.02–1.04)	0.055
	Cheek mucosa	0.485 (0.257–0.916)	< 0.05	0.570 (0.296–1.10)	0.093
	Retromolar area	0.73 (0.352–1.52)	0.4	0.930 (0.442–1.96)	0.848
Time to treatment	< = 30 days	1 [Reference]			
	> 30, < = 60 days	0.859 (0.569–1.3)	0.468		
	> 60 days	1.12 (0.691–1.81)	0.647		
	Unknown	1.24 (0.443–3.46)	0.683		
LNR		39.9 (11.7–136)	< 0.05	35.8 (9.63–132.7)	< 0.05
C-index (SE)				0.722 (0.023)	

Table 3. Univariable and multivariable Cox proportional hazard regression analyses for disease-specific survival in oral cavity squamous cell carcinoma patients from Surveillance Epidemiology and End Results database. Significant values are in [bold].

advantage of induction or neoadjuvant chemotherapy lies in organ preservation rather than a significant survival benefit^{7,8,16–18}. Neoadjuvant radiotherapy has been reported to achieve downstaging and facilitate radical tumor resection¹⁹, but was associated with a statistically significant increased risk of flap complications, failure and fistula²⁰.

Lymph node involvement is known as a significant prognostic factor for oral cavity carcinoma²¹, and the presence of extra-nodal extension, larger nodal deposit, high LNR correlated with worse survival outcomes²². The American Joint Committee on Cancer (AJCC) staging system considers multiple factors to assess nodal disease, such as the size, laterality, and number of malignant lymph nodes, as well as the extra-nodal extension. Emerging studies have noticed the number of lymph nodes examined or positive nodes may have a better prediction efficacy in head and neck carcinomas^{23,24}. In the previous study, we found that the LNR was an independent prognostic factor for cancer-specific survival of patients with parotid gland cancer, and patients with LNR > 0.32 turned out with inferior survival outcomes¹⁰. Similarly, a lymph node density exceeding 0.06 was associated with poorer overall survival for OCSCC patients²⁵. Since the staging system for malignancies of the head and neck encompasses cancers originating from multiple subsites, there may be heterogeneity in the staging outcomes. A comparable analysis of the National Cancer Database revealed that patients with clinically node-negative OCSCC who had less than 16 lymph nodes removed were closely related to inferior survival²⁴. In a published study, we found that for patients with T1-2N1M0 OCSCC, those with lymph nodes examined ≤ 16 were more likely to benefit from postoperative radiotherapy²⁶, indicating that the number of lymph nodes examined might be a factor to consider when developing therapeutic plans for early-stage OCSCC patients. Despite these findings, lymph node density has not yet been incorporated into NCCN guidelines.

Previous studies have found that psychosocial factors, such as gender, marital status, and medical insurance status, can also affect the prognosis of cancer patients²⁷. Qiu et al.²⁸ found that married lung cancer patients had a better prognosis and longer survival time than non-married patients. In this study, we found a similar

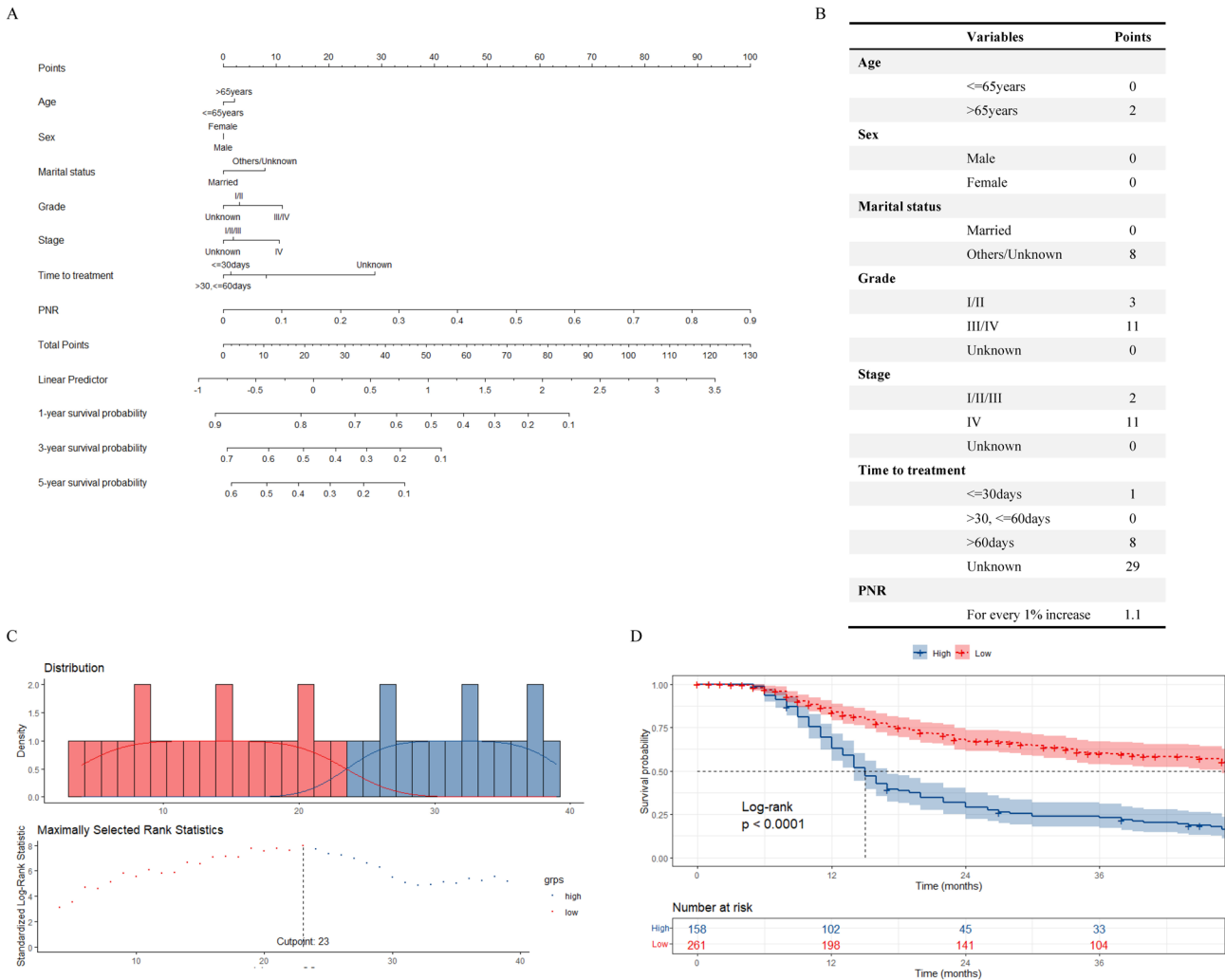


Fig. 3. (A) Prognostic nomogram based on the positive lymph node ratio for overall survival; (B) The score of each variable; (C) The processing of cutoff value of the risk score; (D) The Kaplan–Meier analysis of the risk score.

phenomenon in patients with oral squamous cell carcinoma who received neoadjuvant therapy and had a better prognosis for married than for non-married patients. The reason for these phenomena may be that married patients will be diagnosed and treated earlier in the company of their families, and may be more confident in facing the disease.

There are several limitations in this study. First, our prediction model was developed using the SEER database but lacked an external validation cohort, which is inherent to many SEER-based studies due to the difficulty in acquiring compatible multicenter datasets. Further external validation would help to strengthen clinical applicability of this prediction model. Second, the well-established prognostic factors such as extra-nodal extension, depth of invasion, HPV status, comorbidities, perineural invasion, lymphovascular invasion, and margin status were notably missing, which compromised the accuracy of patient staging might impact the prediction accuracy. Third, the study lacks detailed information on chemotherapy regimens, preventing analysis of their potential impact on patient outcomes. Despite these limitations, the large sample size and the extensive range of covariates in the SEER data provide a valuable foundation for addressing the research question.

Conclusions

In summary, the lymph node ratio was identified as an independent prognostic factor for overall survival and disease-specific survival in OCSCC patients with neoadjuvant treatment. The prediction model developed in our study may assist clinicians in assessing the prognosis of OCSCC.

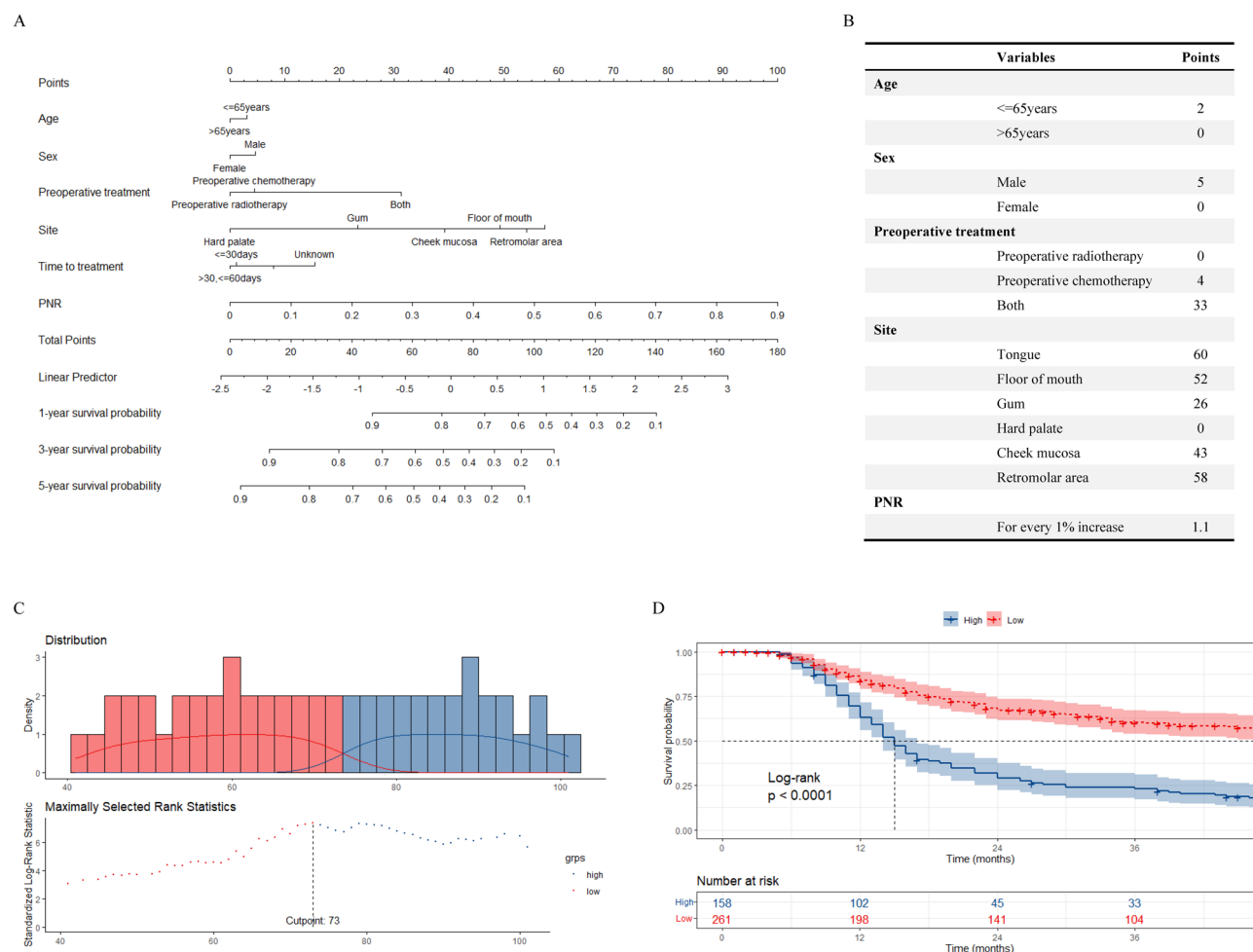


Fig. 4. (A) Prognostic nomogram based on the positive lymph node ratio for disease-specific survival; (B) The score of each variable; (C) The processing of cutoff value of the risk score; (D) The Kaplan–Meier analysis of the risk score.

Data availability

All data of patients performed in this study was based on the SEER database (<https://seer.cancer.gov/>), which is a public database.

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Author contributions

F. S., C. Y., C. S., W. Y., and J. W. conceived and designed the research study; W. Y. and J. W. analyzed the data and visualized the results. F. S. and J. W. wrote the manuscript. F. S., C. Y., C. S., W. Y., and J. W. reviewed and revised the manuscript. All authors contributed to the final approval of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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