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ORIGINAL RESEARCH

Development of a Prognostic Nomogram Incorporating the Naples Prognostic Score for Postoperative Oral Squamous Cell Carcinoma Patients

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Background: The Naples prognostic score (NPS) and its relation to the prognosis of oral squamous cell carcinoma (OSCC) have been inconclusive. This study aimed to investigate the correlation between NPS and the prognosis of postoperative OSCC patients. Additionally, the study sought to develop a new nomogram for predicting disease-free survival (DFS) and overall survival (OS).

Methods: The study included 576 OSCC patients who underwent surgical treatment at two hospitals between August 2008 and June 2018. Univariate and multivariate Cox regression analyses were conducted to identify independent prognostic factors. Subsequently, two nomograms were developed to predict DFS and OS based on these factors and underwent rigorous validation.

Results: The median DFS and OS were 31.5 months and 36.5 months, respectively. Significant differences in DFS and OS were observed among patients with different NPS scores. Adjuvant radiotherapy, age-adjusted Charlson comorbidity index (ACCI), extranodal extension (ENE), NPS, American Joint Committee on Cancer (AJCC) stage, surgical safety margin, eastern cooperative oncology group performance status (ECOG PS), and systemic inflammation score (SIS) were identified as independent predictors of DFS and OS. In the training cohort, the nomogram's concordance index (C-index) for predicting DFS and OS was 0.701 and 0.693, respectively. In the validation group, the corresponding values were 0.642 and 0.635, respectively. Calibration plots confirmed a high level of agreement between the model's predictions and actual outcomes. Decision curve analysis (DCA) demonstrated the nomogram's good clinical utility. Additionally, patients in the low-risk group did not benefit from adjuvant radiotherapy, while those in the medium-risk and high-risk group could benefit from adjuvant radiotherapy.

Conclusion: NPS significantly influences the prognosis of OSCC patients following surgery. The nomogram developed in this study holds significant clinical application potential. The low-risk subgroup of patients was not required to undergo postoperative radiotherapy.

Keywords: oral squamous cell carcinoma, naples prognostic score, nomogram, risk stratification, radiotherapy

Introduction

Oral carcinoma refers to malignant tumors that originate from various parts of the mouth, including the oral tongue, lips, oral mucosa, hard palate, gingiva, retromolar region, and floor of the mouth.[1] It accounts for 20–30% of head and neck cancers and is one of the most common subsites.[2] The most common type of oral carcinoma is squamous cell carcinoma, which makes up about 90% of all cases.[3,4] In China, there are approximately 52,000 new cases of oral squamous cell carcinoma (OSCC) each year.[5] The development of OSCC is linked to factors such as tobacco and alcohol consumption, betel nut chewing, human papillomavirus (HPV) infection, dietary habits, nutrition, and genetic predisposition.[6–11] Despite advances in treatment, the prognosis for OSCC patients has not substantially improved over the past 20 years, with current five-year survival rates remaining at around 50%.[12–14]

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The Tumor-Node-Metastasis (TNM) staging system, proposed by Pierre Denoix in 1953, is the standard for predicting tumor survival.[15] The most widely used tool to predict the survival of OSCC patients is the AJCC staging system.[16] Although the AJCC staging system provides general prognostic information for the patient population, its individualized evaluation accuracy is limited and does not fully consider other patient-specific factors.[17,18] The TNM staging system also has limitations, as it does not allow for the inclusion of tumor, lymph node, or metastatic tumor as continuous variables, and it overlooks important predictors such as age, comorbidities, tumor location, pathological type, grade, surgical margin, and treatment modalities. Therefore, a more comprehensive tool, such as a nomogram, is needed to integrate multiple variables and provide personalized prognostic information.[18–25]

The Naples prognostic score (NPS) was first proposed in 2017 and has been shown to be an independent prognostic factor for long-term survival rates of patients after colorectal surgery.[26] Recent research based on the National Health and Nutrition Examination Survey (NHANES) database in the United States also indicated that higher NPS is associated with significantly higher mortality rates.[27] NPS has been linked to the prognosis of various tumors, including lung cancer, esophageal cancer, colorectal cancer, ampullary tumors, and gynecological tumors.[28–32] NPS reflects the nutritional and inflammatory status of the body and is calculated based on serum albumin, total cholesterol (TC), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR). These test indicators are easily obtainable in clinical practice, yet their impact on prognosis is often overlooked. Currently, there is limited research on the relationship between NPS and the prognosis of OSCC patients following surgical intervention. This study aims to address this gap by constructing a predictive model, in the form of a nomogram, that integrates NPS and other clinical variables.

Materials and Methods

Materials

This retrospective study included cases from August 2008 to July 2018 from two medical institutions: the First Affiliated Hospital of Xinxiang Medical University and the Affiliated Cancer Hospital of Zhengzhou University. All cases included in the study involved patients who had undergone radical surgery for OSCC and met the following exclusion criteria: distant metastasis was present at initial diagnosis (N=114), radical surgery was not performed (N=120), age < 18 years (N=5), multiple primaries (N=35), AJCC stage unknown (N=67), incomplete clinical data (N=39), no follow-up data (N=60), perioperative death (N=10), neoadjuvant radiotherapy (N=24), adjuvant chemotherapy only (N=18), and immunotherapy (N=19). The flow chart for sample selection is presented in Figure 1. After the above procedure, a total of 576 postoperative patients with OSCC met the study criteria. The patients provided informed consent, and the study received approval from the ethics committee. The radiotherapy techniques used were conformal radiotherapy (CRT), intensity-modulated radiotherapy (IMRT), or volumetric-modulated arc therapy (VMAT). The total radiation dose ranged from 60.0 to 70.0 Gy, and the fractionated dose was 2.0–2.18 Gy, administered once a day, five days a week. The majority of concurrent chemotherapy with radiotherapy was predominantly observed in cases where ENE positivity and/or close resection margins were present. The staging system utilized in this study was based on the 8th edition of the AJCC staging system, while postoperative pathological staging was employed.

Variables Collection

As indicated in Table 1, a total of 29 variables were collected from the electronic medical record systems, including gender, age at diagnosis, eastern cooperative oncology group performance status (ECOG PS) score, grade, tobacco consumption, tumor location, AJCC stage, depth of invasion (DOI), surgical margin, vascular invasion (VI), perineural invasion, extranodal extension (ENE), TC, NPS, systemic immune-inflammation index (SII), prognostic nutrition index (PNI), platelet-to-albumin ratio (PAR), platelet-to-lymphocyte ratio (PLR), NLR, LMR, hemoglobin, albumin, body mass index (BMI), systemic inflammation score (SIS), age-adjusted Charlson comorbidity index (ACCI), adjuvant radiotherapy, adjuvant radiotherapy, disease-free survival (DFS), and overall survival (OS).

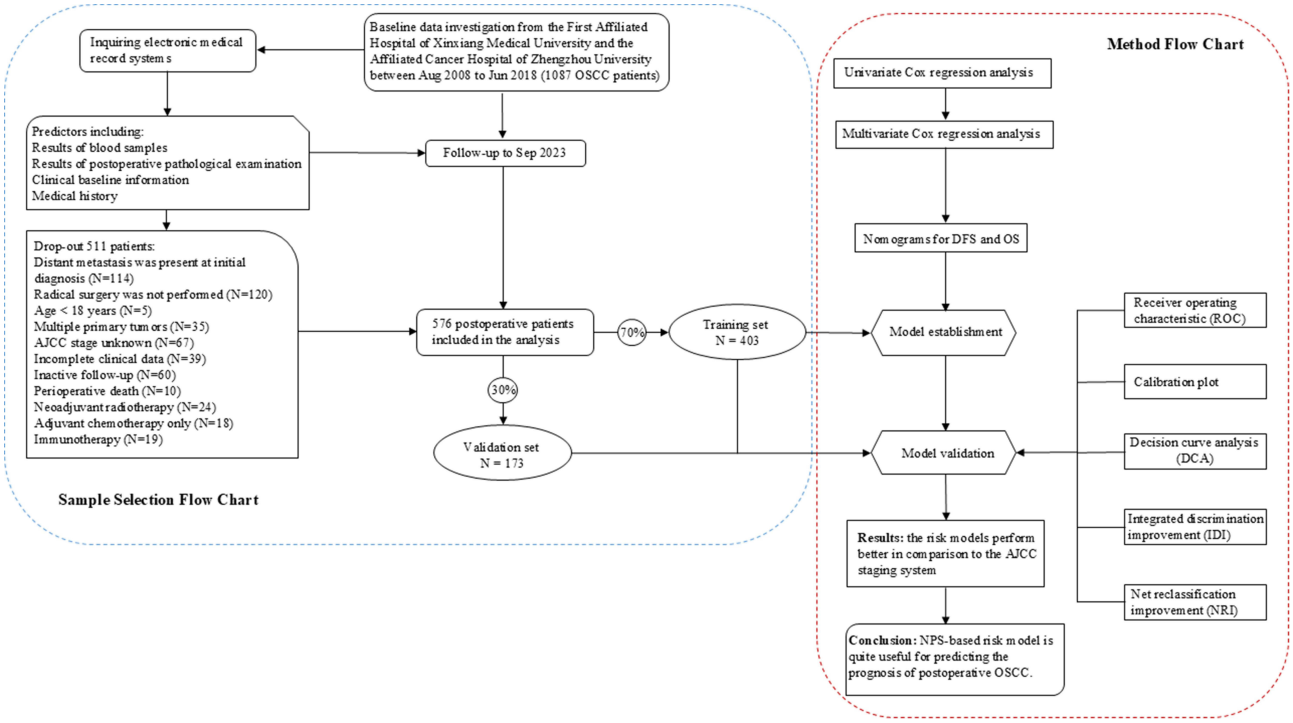

Figure 1 The flow chart of the study.
Abbreviations: AJCC, American Joint Committee on Cancer; DFS, disease-free survival; OS, overall survival; OSCC, oral squamous cell carcinoma.

Calculation Formula

The calculation formula and grouping process of NPS are clearly and comprehensively presented in Table S1 and Figure S1. The scoring methodology for ACCI is detailed in Table S2. Additionally, Table S2 presents the formulas for calculating various preoperative inflammation-nutrition indicators, including SIS, SII, LMR, PNI, NLR, PAR, PLR, and BMI.

Table 1 The Baseline Characteristics of Postoperative OSCC Patients and the Disparities Between the Two Cohorts

Characteristics	All Patients (n = 576) *N* (%)	Training cohort (n = 403) *N* (%)	Validation cohort (n = 173) *N* (%)	*P*
Gender				0.737
Female	237 (41.1%)	164 (40.7%)	73 (42.2%)	
Male	339 (58.9%)	239 (59.3%)	100 (57.8%)	
Age at diagnosis (years)				0.236
Median (Range)	51 (22–90)	51 (22–90)	52 (24–90)	
Tumor location				0.137
Oral tongue	194 (33.7%)	138 (34.2%)	56 (32.4%)	
Lip	166 (28.9%)	124 (30.8%)	42 (24.3%)	
Gingival	88 (15.3%)	63 (15.6%)	25 (14.5%)	
Oral mucosal	77 (13.4%)	47 (11.7%)	30 (17.3%)	
Others	51 (8.9%)	31 (7.7%)	20 (11.6%)	
Grade				0.848
I	178 (30.9%)	125 (31.0%)	53 (30.6%)	
II	191 (33.2%)	136 (33.7%)	55 (31.8%)	
III	207 (35.9%)	142 (35.2%)	65 (37.6%)	

(*Continued*)

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Table 1 (Continued).

Characteristics	All Patients (n = 576) *N* (%)	Training cohort (n = 403) *N* (%)	Validation cohort (n = 173) *N* (%)	*P*
ECOG PS score				0.734
0–1	451 (78.3%)	314 (77.9%)	137 (79.2%)	
2	125 (21.7%)	89 (22.1%)	36 (20.8%)	
Smoking				0.387
No	451 (78.3%)	351 (87.1%)	146 (84.4%)	
Yes	125 (21.7%)	52 (12.9%)	27 (15.6%)	
AJCC Stage				0.660
I	104 (18.1%)	73 (18.1%)	31 (17.9%)	
II	134 (23.3%)	96 (23.8%)	38 (22.0%)	
III	229 (39.8%)	154 (38.2%)	75 (43.4%)	
IVa / IVb	109 (18.9%)	80 (19.9%)	29 (16.8%)	
Surgical safety margin				0.982
≥ 5mm	513 (89.1%)	359 (89.1%)	154 (89.0%)	
< 5mm or positive	63 (10.9%)	44 (10.9%)	19 (11.0%)	
VI				0.590
No	525 (91.1%)	369 (89.3%)	146 (84.4%)	
Yes	51 (8.9%)	34 (8.4%)	17 (11.6%)	
Perineural invasion				0.477
No	511 (88.7%)	360 (89.3%)	151 (87.3%)	
Yes	65 (11.3%)	43 (10.7%)	22 (12.7%)	
ENE				0.572
Negative	534 (92.7%)	372 (92.3%)	162 (93.6%)	
Positive	42 (7.3%)	31 (7.7%)	11 (6.4%)	
DOI				0.068
<10mm	485 (84.2%)	332 (82.4%)	153 (86.9%)	
≥10mm	91 (15.8%)	71 (17.6%)	20 (13.1%)	
NPS				0.215
0 (Group I)	137 (23.8%)	88 (21.8%)	49 (28.3%)	
1–2 (Group II)	302 (52.4%)	219 (54.3%)	83 (48.0%)	
3–4 (Group III)	137 (23.8%)	96 (23.8%)	41 (23.7%)	
SIS				0.383
0	400 (69.4%)	279 (69.2%)	121 (69.9%)	
1	115 (20.0%)	85 (21.1%)	30 (17.3%)	
2	61 (10.6%)	39 (9.7%)	22 (12.7%)	
BMI (kg/m^2)				0.628
Median (range)	21.3 (15.8–32.9)	21.2 (16.4–32.9)	21.3 (15.8–31.8)	
SII				0.431
Median (IQR)	1150 (636–1581)	1198 (707–1590)	1084 (548–1558)	
PNI				0.130
Median (IQR)	72.0 (52.0–94.5)	74.5 (53.0–95.0)	71.0 (51.3–93.5)	
PLR				0.772
Median (IQR)	149.5 (93.0–212.5)	150.2 (92.4–213.5)	149.0 (89.5–214.0)	
NLR				0.119
Median (IQR)	2.40 (1.42–3.29)	2.46 (1.41–3.32)	2.26 (1.31–3.16)	
PAR				0.724
Median (IQR)	6.85 (3.69–9.79)	6.80 (3.53–9.96)	6.89 (4.16–9.52)	
TC				0.492
Median (IQR)	197.5 (129.2–253.8)	200.3 (130.1–256.7)	195.5 (127.2–246.0)	

(*Continued*)

Table 1 (Continued).

Characteristics	All Patients (n = 576) *N* (%)	Training cohort (n = 403) *N* (%)	Validation cohort (n = 173) *N* (%)	*P*
LMR				0.206
Median (IQR)	5.17 (2.56–7.89)	5.15 (2.52–7.46)	5.20 (2.65–8.11)	
Hemoglobin (g/L)				0.921
Median (IQR)	98.5 (89.1–119.0)	98.2 (91.0–118.5)	98.0 (89.0–119.2)	
Albumin (g/L)				0.356
Median (IQR)	42.2 (34.5–49.0)	41.9 (35.0–49.0)	43.0 (36.1–49.2)	
ACCI				0.970
2–3	242 (42.0%)	168 (41.7%)	74 (42.8%)	
4–5	195 (33.9%)	137 (34.0%)	58 (33.5%)	
≥6	139 (24.1%)	98 (24.3%)	41 (23.7%)	
Adjuvant radiotherapy				0.471
No	377 (65.5%)	260 (64.5%)	117 (67.6%)	
Yes	199 (34.5%)	143 (35.5%)	56 (32.4%)	
Adjuvant chemotherapy				0.062
No	436 (75.7%)	324 (80.4%)	127 (73.4%)	
Yes	140 (24.3%)	79 (19.6%)	46 (26.6%)	
DFS (months)				0.424
Median (range)	31.5 (1–130)	31.5 (2–130)	32.0 (1–123)	
OS (months)				0.504
Median (range)	36.5 (1–130)	36.0 (1–130)	37.0 (1–123)	

Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; BMI, body mass index; DFS, disease-free survival; DOI, depth of invasion; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; IQR, interquartile range; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPS, naples prognostic score; OS, overall survival; OSCC, oral squamous cell carcinoma; PAR, platelet-to-albumin ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; SII, systemic immune-inflammation index; SIS, systemic inflammation score; TC, total cholesterol; VI, vascular invasion.

Statistical Analysis

SPSS (version 20.0), X-tile (version 3.6.1), and R (version 4.22) software were utilized for data analysis. The study endpoints employed were DFS and OS. The observed differences were deemed to have statistical significance at a level of $P < 0.05$. The method flow chart is shown in Figure 1. Of all 576 patients included in the analysis, 70% were randomly selected for the training set, and the remaining 30% were included in the validation set. The baseline characteristics between the training set and the validation set were compared using SPSS software. The chi-square test was employed for categorical variables, while the independent sample *t*-test was utilized for continuous variables (refer to Table 1). The training set was utilized for identifying independent prognostic variables and establishing nomogram risk models, while the validation set was employed to validate the performance of the models.

In our investigation, we initially performed a univariate Cox regression analysis to discern potential prognostic factors among the 27 variables. Subsequently, the outcomes of this analysis were integrated into a multivariate Cox regression analysis to delineate the independent factors influencing DFS and OS. Two nomograms were then constructed utilizing the independent prognostic factors, with one designed to predict DFS and the other to predict OS. Finally, R software was used to perform statistical analyses including the calculation of the receiver operating characteristic (ROC) curve, integrated discrimination improvement (IDI), net reclassification improvement (NRI), calibration curve, and decision curve analysis (DCA) to validate the performance of the nomogram.

Risk Stratification

Each case has a corresponding prognostic risk score on the prognostic model. To establish a prognostic stratification system, we used the X-tile to find appropriate cut-off points and divided patients into three subgroups: high-, medium-,

and low-risk groups. The Log rank test and Kaplan-Meier curve were employed to compare the DFS and OS among different risk stratification subgroups. The Log rank test was used to assess the impact of adjuvant radiotherapy on DFS and OS in various risk subgroups.

Results

Clinical Characteristics

This study included a total of 576 OSCC patients who underwent radical surgery. The median age of the enrolled patients was 51 years, with a distribution of 339 males (58.9%) and 237 females (41.1%). The oral tongue (194 cases, 33.7%) was the predominant tumor location in all cases of OSCC included, with the lip (166 cases, 28.9%) being the second most common location. The comorbidities with the highest prevalence identified in this study included diabetes (79 cases, 13.7%), chronic pulmonary disease (61 cases, 10.6%), and cerebrovascular disease (40 cases, 6.9%). The breakdown of ACCI scores across all cases was as follows: 42.0% of cases scored 2–3, 33.9% scored 4–5, and 24.1% scored 6 or higher. This equated to 242 cases in the 2–3 category, 195 cases in the 4–5 category, and 139 cases in the 6 or higher category. There were 451 (78.3%) patients with an ECOG PS score of 0–1. The incidence rates of ENE, VI, and perineural invasion were 7.3%, 8.9%, and 11.3%, respectively. A surgical safety margin < 5 mm was found in 38 patients, with positive surgical margins observed in 25 patients, accounting for 10.9% of the total cases. The majority of patients (84.2%) had a DOI of less than 10mm, while a minority (15.8%) had a DOI of 10mm or more.

The median BMI was 21.3 kg/m^2 (Range: 15.8–32.9 kg/m^2). The SIS scores of 0, 1, and 2 correspond to the frequencies of 400 (69.4%), 115 (20.0%), and 61 (10.6%) respectively. Among the enrolled patients, 137 individuals, constituting 23.8% of the total, fell into group I with an NPS score of 0. Additionally, 302 individuals, making up 52.4% of the total, were categorized into group II with an NPS score of 1 or 2. Finally, 137 individuals, also accounting for 23.8% of the total, were placed in group III with an NPS score of 3 or 4.

The median DFS and OS were 31.5 and 37.0 months, respectively. Adjuvant radiotherapy was administered to 199 patients, comprising approximately one-third of the entire patient population. Adjuvant chemotherapy was given to 140 patients, constituting about a quarter of the total.

The clinicopathological characteristics of the 576 patients enrolled in this study are summarized in Table 1. Meanwhile, Table 1 also presents the disparities in baseline characteristics between the training set and the validation set, indicating that there were no statistically significant differences observed across all 29 variables between the two groups (all $P > 0.05$).

Nomogram Risk Models Establishing

The independent prognostic factors were identified using both univariate and multivariate Cox regression analysis, as shown in Table 2 and Table 3. These significant predictors were then used to create a nomogram for predicting Disease-Free Survival (DFS) and Overall Survival (OS). The variables used to build the nomogram for predicting DFS included NPS, ENE, ACCI, stage, postoperative safety margin, ECOG PS score, SIS, and adjuvant radiotherapy (Figure 2A). Similarly, the predictors for constructing a nomogram to predict OS included tumor location, NPS, ENE, ACCI, stage, postoperative safety margin, ECOG PS score, SIS, and adjuvant radiotherapy (Figure 2B). In addition, dynamic web-based calculators were developed for predicting OS and DFS, which can be utilized in different scenarios or conditions. The dynamic web-based calculator for predicting OS and DFS can be found at the following URLs: https://chengh.shinyapps.io/OSCC-NPS-OS/; https://chengh.shinyapps.io/OSCC-NPS-DFS/.

Validation

After using a nomogram for risk prediction, it is necessary to verify its accuracy and efficiency through a series of indicators and charts. Our calibration curves (Figure 3) closely adhered to the 45-degree diagonal, suggesting a high degree of consistency between the risk probabilities predicted by the model and the actual observations. The DCA curve is depicted in Figure 4, revealing that the new nomogram risk models exhibit superior clinical benefit compared to AJCC staging across various thresholds. The training set demonstrated a substantial area under the curve (AUC) values for 3-year DFS (0.766),

Table 2 Univariate and Multivariate Analyses of Clinicopathologic Data in Postoperative OSCC Patients for DFS

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
Age at diagnosis (years)	1.009 (1.002–1.017)	**0.015***	1.004 (0.994–1.014)	0.481
Gender				
Male	Reference			
Female	1.026 (0.784–1.343)	0.852		
Tumor location				
Oral tongue	Reference		Reference	
Lip	0.689 (0.488–0.971)	**0.034***	0.738 (0.521–1.047)	0.088
Gingival	1.241 (0.836–1.841)	0.284	1.060 (0.704–1.597)	0.779
Oral mucosal	1.053 (0.682–1.627)	0.815	0.959 (0.613–1.499)	0.853
Others	1.546 (0.941–2.541)	0.085	1.475 (0.886–2.453)	0.135
Grade				
I	Reference		Reference	
II	1.205 (0.861–1.686)	0.277	1.117 (0.776–1.606)	0.552
III & IV	1.547 (1.117–2.142)	**0.009****	1.202 (0.825–1.753)	0.338
ECOG PS score				
0–1	Reference		Reference	
2	1.436 (1.057–1.950)	**0.021***	1.413 (1.030–1.938)	**0.032***
Smoking				
No	Reference			
Yes	1.392 (0.956–2.028)	0.085		
BMI (kg/m^2)	0.978 (0.944–1.013)	0.213		
AJCC stage				
I	Reference		Reference	
II	1.143 (0.748–1.747)	0.537	1.449 (0.732–1.741)	0.584
III	1.716 (1.177–2.502)	**0.005****	1.409 (0.947–2.097)	0.091
IVa&b	2.207 (1.435–3.395)	**<0.001*****	1.902 (1.213–2.982)	**0.019***
DOI				
< 10mm	Reference		Reference	
≥ 10mm	1.533 (1.069–2.199)	**0.020***	1.335 (0.917–1.945)	0.132
Surgical safety margin				
≥ 5mm	Reference		Reference	
< 5mm or Positive	1.689 (1.165–2.447)	**0.006****	1.565 (1.044–2.346)	**0.030***
VI				
No	Reference		Reference	
Yes	1.696 (1.099–2.616)	**0.017***	1.060 (0.589–1.908)	0.846
Perineural invasion				
No	Reference		Reference	
Yes	1.535 (1.057–2.230)	**0.024***	1.132 (0.647–1.981)	0.664
ENE				
Negative	Reference		Reference	
Positive	2.032 (1.318–3.133)	**0.001****	1.783 (1.089–2.920)	**0.021***
NPS				
0 (Group I)	Reference		Reference	
1–2 (Group II)	1.384 (0.983–1.949)	0.063	1.457 (1.021–2.080)	**0.038***
3–4 (Group III)	2.592 (1.749–3.843)	**0.021***	2.338 (1.552–3.523)	**<0.001*****
SIS				
0	Reference		Reference	
1	1.384 (0.983–1.949)	0.063	1.418 (1.014–1.984)	**0.041***
2	2.592 (1.749–3.843)	**0.005****	2.338 (1.552–3.523)	**0.018***

(*Continued*)

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Table 2 (Continued).

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		**HR (95% CI)**	
SII	1.013 (1.001–1.030)	**0.032***	1.019 (1.003–1.038)	0.563
PNI	0.721 (0.540–0.963)	**0.027***	0.998 (0.996–1.000)	0.466
PAR	0.983 (0.947–1.020)	0.356		
PLR	1.265 (0.956–1.675)	0.100		
NLR	1.137 (1.007–1.310)	0.098		
LMR	0.990 (0.946–1.035)	0.649		
TC	0.998 (0.996–1.000)	**0.039***	0.998 (0.997–1.000)	0.054
Hemoglobin (g/L)	0.999 (0.992–1.005)	0.669		
Albumin (g/L)	0.988 (0.973–1.004)	0.149		
ACCI				
2–3	Reference		Reference	
4–5	1.298 (0.953–1.768)	0.259	1.229 (0.888–1.701)	0.213
≥ 6	1.775 (1.256–2.508)	**0.001****	1.722 (1.204–2.461)	**0.002****
Adjuvant chemotherapy				
No	Reference			
Chemotherapy	0.766 (0.551–1.066)	0.114		
Adjuvant radiotherapy				
No	Reference		Reference	
Yes	0.677 (0.510–0.898)	**0.007****	0.583 (0.506–0.907)	**0.009****

Note: *P < 0.05, **P < 0.01, ***P < 0.001. All the data in bold indicates statistical significance.

Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; BMI, body mass index; CI, confidence interval; DFS, disease-free survival; DOI, depth of invasion; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPS, naples prognostic score; OSCC, oral squamous cell carcinoma; PAR, platelet-to-albumin ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; SII, systemic immune-inflammation index; SIS, systemic inflammation score; TC, total cholesterol; VI, vascular invasion.

Table 3 Univariate and Multivariate Analyses of Clinicopathologic Data in Postoperative OSCC Patients for OS

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		**HR (95% CI)**	
Age at diagnosis (years)	1.010 (1.002–1.018)	**0.015***	1.006 (0.995–1.017)	0.283
Gender				
Male	Reference			
Female	1.026 (0.782–1.387)	0.780		
Tumor location				
Oral tongue	Reference		Reference	
Lip	0.591 (0.410–0.853)	**0.005****	0.630 (0.434–1.913)	**0.015***
Gingival	1.160 (0.769–1.748)	0.479	1.001 (0.650–1.542)	0.998
Oral mucosal	0.903 (0.564–1.447)	0.672	0.814 (0.501–1.321)	0.404
Others	1.418 (0.842–2.387)	0.189	1.257 (0.733–2.154)	0.406
Grade				
I	Reference		Reference	
II	1.156 (0.808–1.655)	0.427	1.193 (0.814–1.748)	0.366
III & IV	1.649 (1.170–2.325)	**0.004****	1.424 (0.959–2.114)	0.080
ECOG PS score				
0–1	Reference		Reference	
2	1.496 (1.083–2.064)	**0.014***	1.448 (1.031–2.032)	**0.033***

(*Continued*)

Table 3 (Continued).

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
Smoking				
No	Reference		Reference	
Yes	1.519 (1.034–2.233)	**0.033***	1.479 (0.988–2.213)	0.056
BMI (kg/m^2)	0.990 (0.956–1.026)	0.596		
AJCC stage				
I	Reference		Reference	
II	1.266 (0.822–2.054)	0.263	1.417 (0.887–2.264)	0.145
III	2.011 (1.341–3.013)	**0.001****	1.639 (1.054–2.550)	**0.028***
IVa&b	2.510 (1.581–3.985)	**<0.001*****	2.282 (1.400–3.720)	**0.001****
DOI				
< 10mm	Reference			
≥ 10mm	1.285 (0.863–1.912)	0.217		
Surgical safety margin				
≥ 5mm	Reference		Reference	
< 5mm or Positive	1.862 (1.274–2.722)	**0.001****	1.909 (1.255–2.903)	**0.003****
VI				
No	Reference			
Yes	1.606 (1.010–2.544)	0.046		
Perineural invasion				
No	Reference		Reference	
Yes	1.529 (1.034–2.261)	**0.033***	0.959 (0.553–1.664)	0.883
ENE				
Negative	Reference		Reference	
Positive	2.661 (1.718–4.123)	**<0.001*****	2.178 (1.295–3.665)	**0.003****
NPS				
0 (Group I)	Reference		Reference	
1–2 (Group II)	1.328 (0.926–1.904)	0.123	1.334 (0.917–1.940)	0.132
3–4 (Group III)	2.650 (1.754–4.002)	**0.001****	2.200 (1.412–3.428)	**<0.001*****
SIS				
0	Reference		Reference	
1	1.490 (1.063–2.089)	**0.021***	1.351 (0.940–1.941)	0.104
2	1.838 (1.155–2.924)	**0.010***	1.771 (1.094–2.868)	**0.020***
SII	1.003 (1.001–1.012)	**0.014***	1.007 (1.001–1.018)	0.611
PNI	0.973 (0.958–0.997)	**0.028***	0.998 (0.992–1.004)	0.507
PAR	0.991 (0.952–1.031)	0.643		
PLR	1.001 (0.999–1.002)	0.293		
NLR	1.072 (0.944–1.217)	0.286		
LMR	1.002 (0.955–1.051)	0.939		
TC	0.998 (0.996–0.999)	**0.013***	0.998 (0.996–1.000)	0.051
Hemoglobin (g/L)	0.993 (0.986–1.000)	0.057		
Albumin (g/L)	0.981 (0.975–1.007)	0.284		
ACCI				
2–3	Reference		Reference	
4–5	0.991 (0.710–1.382)	0.956	0.956 (0.669–1.366)	0.806
≥ 6	1.809 (1.270–2.578)	**0.001****	1.768 (1.213–2.577)	**0.003****
Adjuvant chemotherapy				
No	Reference			
Chemotherapy	0.804 (0.573–1.139)	0.224		

(*Continued*)

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Table 3 (Continued).

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
Adjuvant radiotherapy				
No	Reference		Reference	
Yes	0.596 (0.439–0.808)	**0.001****	0.623 (0.450–0.862)	**0.004****

Note: *P < 0.05, **P < 0.01, ***P < 0.001. All the data in bold indicates statistical significance.
Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; BMI, body mass index; CI, confidence interval; DOI, depth of invasion; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPS, naples prognostic score; OS, overall survival; OSCC, oral squamous cell carcinoma; PAR, platelet-to-albumin ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; SII, systemic immune-inflammation index; SIS, systemic inflammation score; TC, total cholesterol; VI, vascular invasion.

5-year DFS (0.770), 3-year OS (0.769), and 5-year OS (0.772) in Figure S2A & S2C, indicating strong predictive performance. Similarly, the validation group exhibited promising AUC values for 3-year DFS (0.809), 5-year DFS (0.767), 3-year OS (0.808), and 5-year OS (0.771) as shown in Figure S2B & S2D. All AUCs were > 0.7, which proved the excellent discrimination ability of the model.

The concordance index (C-index) of the models for DFS and OS in the training group are 0.701 and 0.693, respectively, while the C-index of the models for DFS and OS in the validation group are 0.642 and 0.635, respectively. The C-index values mentioned above all surpass the corresponding C-index values for AJCC staging. All the INI values were > 0 in both the training and validation groups, providing evidence of the enhanced discriminatory ability of the new models compared to the AJCC staging system. Similarly, all NRI values were > 0, which proved that our nomogram models had stronger reclassification performance than the traditional AJCC staging. The detailed results above are illustrated in Table 4.

Prognostic Risk Stratification

According to the prognostic risk points, we categorized the patients into three subgroups: low-, medium-, and high-risk. Prognostic risk points for DFS prediction: low-risk (≤ 131.3), medium-risk (131.6–225.1), and high-risk (≥ 225.3). Prognostic risk points for OS prediction: low-risk (≤ 150.3), medium-risk (150.1–230.0), and high-risk (≥ 230.4). The Kaplan-Meier curves demonstrated significant differences in DFS and OS among the three subgroups, both in the training and validation sets (Figure 5). In addition, adjuvant radiotherapy did not significantly improve DFS and OS in the low-risk subgroup. Conversely, patients in the medium-risk subgroup and high-risk subgroup demonstrated a significant survival benefit from adjuvant radiotherapy (Figure 6 and Table S3).

Discussion

The recent report indicates that the global incidence of oral cancer accounted for approximately 2.0% of all reported cancer cases, while its mortality rate constituted 1.9% of all recorded cancer deaths.[33] The incidence and mortality of oral cancer in developing countries and regions are notably higher, typically 2–3 times greater than those in developed regions.[34] As one of the world's largest developing countries, China has experienced a significant rise in oral cancer cases and deaths. Between 1990 and 2017, the number of oral cancer cases increased by 289%, while the number of deaths rose by 79%.[35] The vast majority of oral cancers are squamous cell carcinomas, accounting for about 90% of the total, and the oral tongue is the most common site of disease.[35,36] Previous studies have shown different survival rates in different subclinical sites of OSCC, and the prognosis of lip cancer is better than that of other subclinical sites,[37–39] which is consistent with the results of the present study. Based on the treatment guidelines, surgical resection is considered the primary therapeutic approach for OSCC.[40,41] The TNM staging, which has been updated to the 8th edition of the AJCC staging system, currently serves as the predominant tool for predicting the survival of OSCC patients.[16,17] To identify additional prognostic factors beyond TNM staging, a series of ongoing studies are currently being conducted to investigate the determinants influencing the prognosis of OSCC.[11,42–44] However, the relationship between NPS and the prognosis of OSCC remains ambiguous.

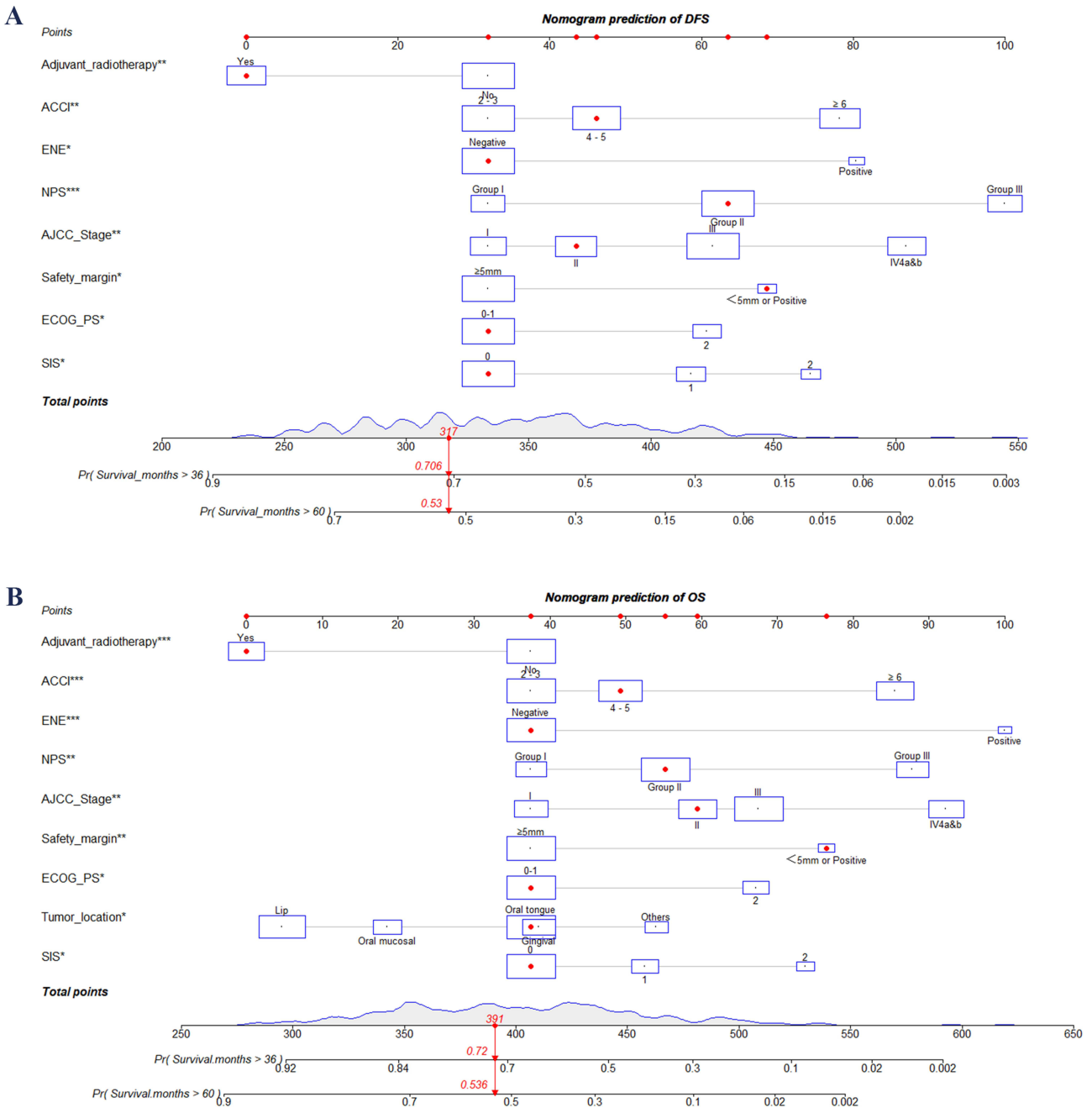

Figure 2 Nomogram risk models for prediction of DFS (**A**) and OS (**B**) for postoperative OSCC patients. The figure demonstrates an instance of a patient utilizing the new model for computing the overall risk score and forecasting prognosis. The size of the rectangle corresponds to the number of cases for each situation.
Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; DFS, disease-free survival; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; NPS, Naples prognostic score; OSCC, oral squamous cell cancer; OS, overall survival, SIS, systemic inflammation score.

The nutritional- and inflammatory-based prognostic score (NPS) is a comprehensive index calculated from a series of inflammatory and nutritional markers, including LMR, NLR, serum albumin, and TC.[26] The systemic inflammatory response and nutritional status play crucial roles in treatment efficacy and prognosis. Inflammatory factors produced by cancer cells have significant effects on vascular permeability, microvasculature integrity, and lymphangiogenesis, as well as the process of tumor metastasis.[45] Previous studies have shown that the preoperative inflammatory state is significantly linked to a poor prognosis in oral squamous cell carcinoma (OSCC).[46–48] Additionally, nutritional status significantly affects the prognosis of postoperative patients, with low serum albumin predicting a higher postoperative complication

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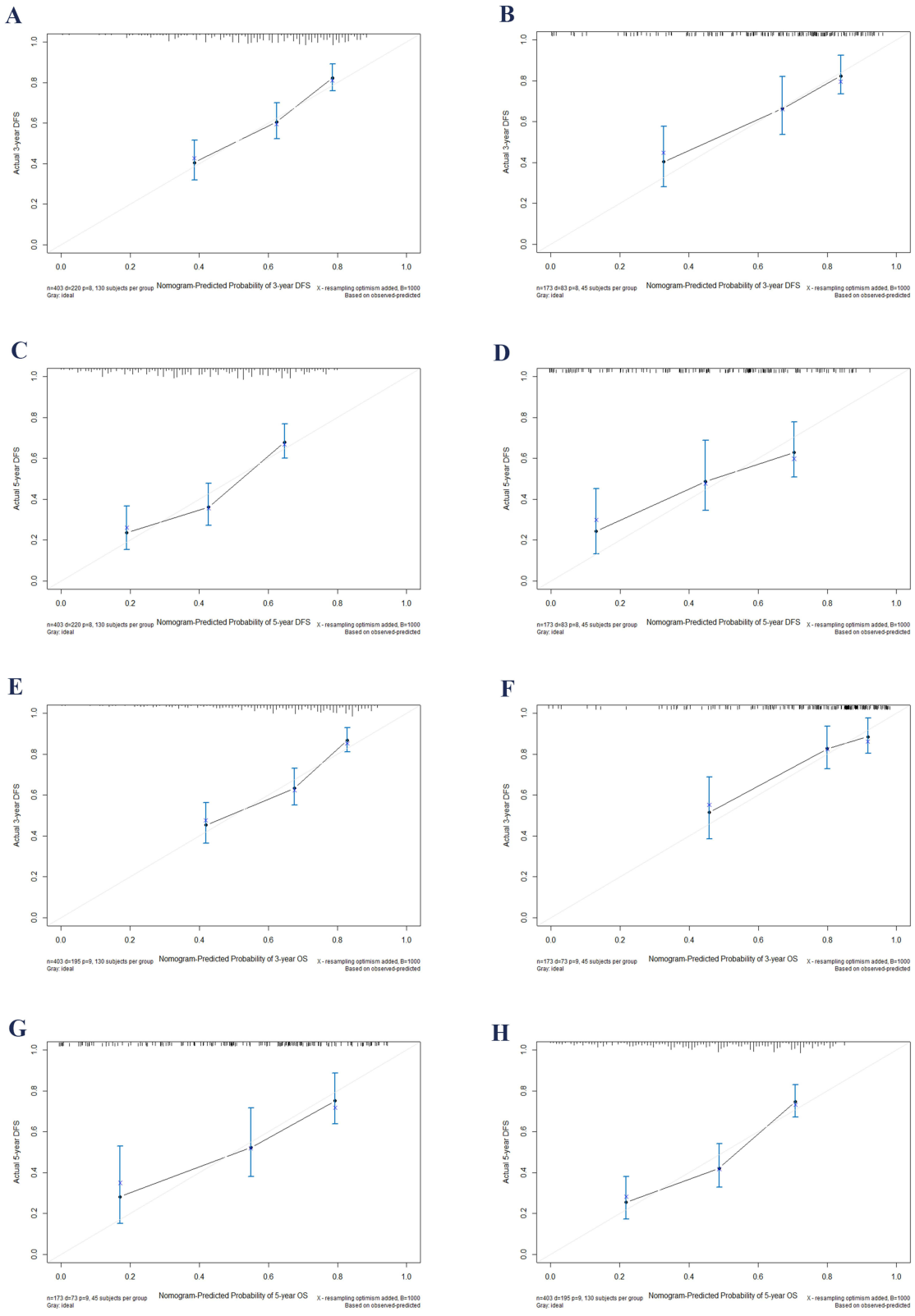

Figure 3 Calibration plots to assess 3-, and 5-year survival for postoperative OSCC patients. Calibration plots for 3-, and 5-year DFS (**A** and **C**), and OS (**E** and **G**) in the training set. Calibration plots for 3-, and 5-year DFS (**B** and **D**), and OS (**F** and **H**) in the validation set. The X-axis represents the model-predicted survival outcome, while the Y-axis represents the actual observed survival. The bar line illustrates the 95% confidence interval measured through Kaplan-Meier analysis, whereas the diagonal line serves as an ideal reference line.

Abbreviations: OS, overall survival; CI, confidence interval; DFS, disease-free survival; OSCC, oral squamous cell cancer.

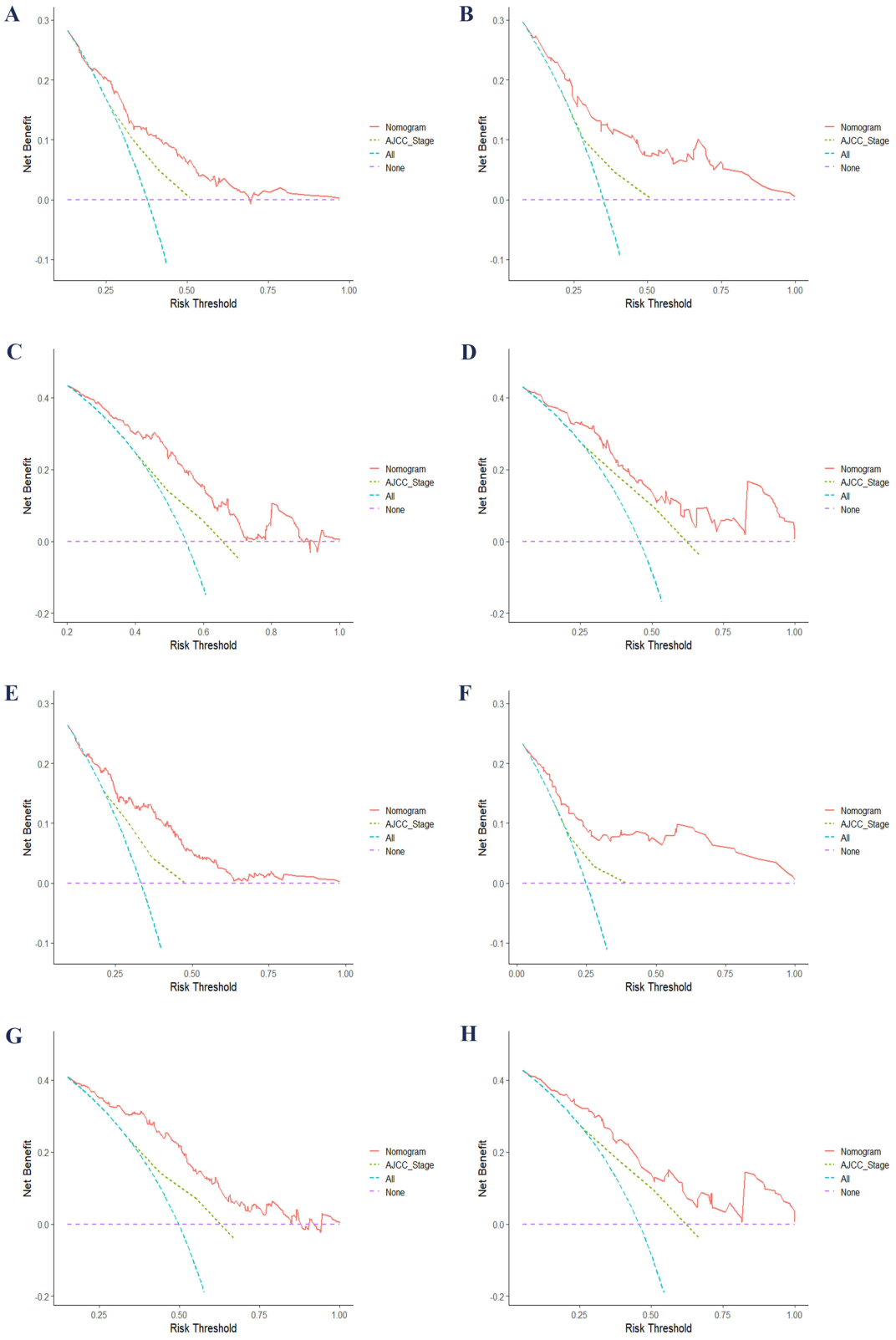

Figure 4 The DCA curves of the nomograms and AJCC stage to assess DFS and OS. DCA curves of 3-, and 5-year DFS in the training (**A** and **C**) and validation (**B** and **D**) set. DCA curves of 3- and 5-year OS in the training (**E** and **G**) and validation (**F** and **H**) set. X-axis: risk threshold. Y-axis: net benefit, which measures the effectiveness of the model under different thresholds. The higher the net benefit, the greater the benefit of the model in practical application.
Abbreviations: AJCC, American Joint Committee on Cancer; DCA, decision curve analysis; DFS, disease-free survival; OS, overall survival.

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Table 4 The NRI, IDI, and C-Index of the Nomograms and AJCC Stage System for DFS and OS Prediction

	Training Cohort			Validation Cohort		
	Estimate	**95% CI**	***P***	**Estimate**	**95% CI**	***P***
IDI (vs AJCC Stage system)						
For 3-year DFS	0.121	0.080–0.182	**<0.001*****	0.219	0.147–0.366	**<0.001*****
For 5-year DFS	0.118	0.067–0.187	**<0.001*****	0.176	0.112–0.310	**<0.001*****
For 3-year OS	0.135	0.090–0.213	**<0.001*****	0.261	0.160–0.385	**<0.001*****
For 5-year OS	0.137	0.081–0.205	**<0.001*****	0.194	0.107–0.329	**<0.001*****
NRI (vs AJCC Stage system)						
For 3-year DFS	0.317	0.231–0.444	**<0.001*****	0.422	0.221–0.577	**<0.001*****
For 5-year DFS	0.311	0.193–0.473	**<0.001*****	0.283	0.072–0.482	**<0.001*****
For 3-year OS	0.348	0.177–0.439	**<0.001*****	0.443	0.233–0.613	**<0.001*****
For 5-year OS	0.369	0.228–0.497	**<0.001*****	0.293	0.119–0.551	**<0.001*****
C-index						
The nomogram (DFS)	0.701	0.660–0.742		0.642	0.569–0.715	
The nomogram (OS)	0.693	0.654–0.732		0.635	0.572–0.698	
The AJCC Stage (DFS)	0.628	0.583–0.673		0.577	0.512–0.642	
The AJCC Stage (OS)	0.624	0.581–0.667		0.550	0.487–0.613	

Note: ***P < 0.001. All the data in bold indicates statistical significance.
Abbreviations: AJCC, American joint committee on cancer; CI, confidence interval; C-index, concordance index; DFS, disease-free survival; IDI, integrated discrimination improvement; NRI, net reclassification index; OS, overall survival.

rate and a poor prognosis in patients with head and neck cancer.[49–51] Total cholesterol levels may exert intricate effects on the nutritional status and prognosis of cancer patients.[52–54]

The NPS is an innovative prognostic factor that effectively integrates inflammatory and nutritional markers. The impact of NPS on the prognosis of various malignant tumors is currently a prominent research focus. The study conducted by Benjie Xu et al involving 232 patients with resectable cholangiocarcinoma revealed that NPS was identified as a significant prognostic risk factor.[55] Li Qing et al conducted a retrospective analysis of the clinical data from 1038 patients diagnosed with operable endometrial cancer, and the findings indicated that elevated NPS levels were significantly associated with unfavorable progression-free survival (PFS) and OS, thus highlighting its significance as an independent prognostic factor for operable endometrial cancer patients.[31] Another retrospective study showed that NPS serves as an independent prognostic factor for the survival of 404 patients with ampullary carcinoma following surgery, and it is significantly correlated with the occurrence of postoperative complications.[30] Various studies have shown that NPS is a significant prognostic factor in various malignant tumors, including gastric cancer,[56] colorectal cancer,[57] esophageal cancer,[58] upper tract urothelial cancer,[59] pancreatic cancer,[60] and hepatocellular carcinoma.[61] However, there is a lack of research exploring the association between NPS and the prognosis of OSCC. In this study, we discovered that NPS was a significant independent prognostic factor for OSCC. A higher NPS score was associated with worse DFS and OS in postoperative OSCC patients, consistent with previous studies.

SIS is an inflammatory and nutritional marker, which is based on serum albumin and the LMR. The association between SIS and the prognosis of various tumors has been confirmed by multiple studies, with high SIS indicating a poor survival outcome.[62–65] SIS has also been implicated in the prognosis of OSCC. In a study involving 613 patients with OSCC, Eltohami YI et al found that higher SIS was significantly associated with advanced age, DOI, stage, ENE, and the presence of neural invasion, and it was an independent factor for poor prognosis.[66] Our study identified SIS as an independent predictor of postoperative OSCC, with a high SIS being significantly associated with an unfavorable prognosis, which was consistent with the results of previous studies.

The postoperative safety margins and ENE status were obtained from the pathology reports. Numerous previous studies have consistently demonstrated that both safety margins and ENE status serve as crucial prognostic indicators for

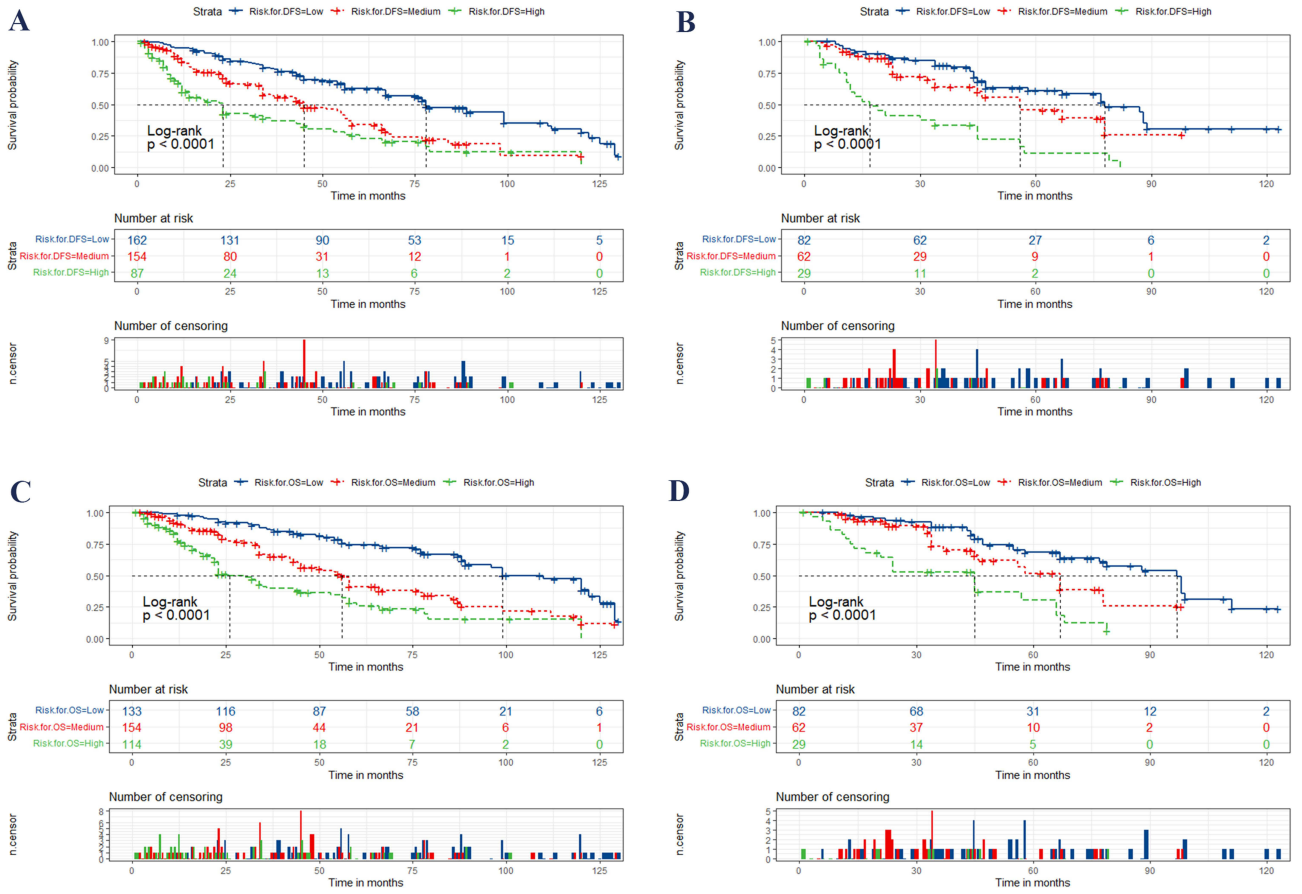

Figure 5 Kaplan-Meier curves for postoperative patients with OSCC in training and validation cohort according to the new risk stratification system. The Kaplan-Meier curves predicting DFS in the training and validation sets are presented for (**A** and **B**), respectively. Similarly, (**C** and **D**) display the Kaplan-Meier curves predicting OS in the training and validation sets. The blue, red, and green curves represent high -, medium-, and low-risk groups, respectively.
Abbreviations: DFS, disease-free survival; OS, overall survival; OSCC, oral squamous cell cancer.

OSCC. The study conducted by Patel Vishaal et al demonstrated that patients who exhibited positive surgical margins following early oral cavity squamous cell carcinoma surgery experienced significantly poorer OS.[67] Another study initiated by Brinkman David et al suggested that postoperative margin < 3 mm was an independent prognostic factor in patients with OSCC.[68] The existing studies also indicate that the optimal safe margin for OSCC should exceed 5mm, and cases with a safety margin < 5mm exhibit significantly poorer prognosis.[69,70] The ENE has been incorporated into the most recent AJCC staging system.[17,71] ENE is an important factor affecting the staging of locally advanced oral squamous cell carcinoma as it indicates a higher risk of metastasis and more aggressive behavior. The presence of ENE implies that the cancer has invaded the lymph node to a greater extent than its surrounding capsule. Previous research has found that the presence of ENE on postoperative histopathology in head and neck squamous cell carcinoma is indicative of an unfavorable prognosis.[72] Similarly, there is substantial evidence supporting the impact of ENE on the prognosis of OSCC.[73–77] In this study, we also found that ENE and safety margin are independent prognostic factors for DFS and OS in postoperative OSCC patients, which is consistent with previous studies.

The impact of age[78,79] and comorbidities[80–82] on the prognosis of OSCC has been substantiated by prior research. The Charlson comorbidity index (CCI) was developed by Donald R. Charlson et al in 1987.[83] CCI was further combined with age to compose ACCI. Based on the hypothesis that the presence of specific medical conditions is correlated with an elevated mortality risk, ACCI evaluates 19 distinct comorbidities individually and incorporates age as a contributing factor. A retrospective analysis of 607 cases of oral cavity squamous cell carcinoma revealed that ACCI serves as an independent prognostic indicator for DFS and OS.[46] In our study, ACCI is also identified as a significant predictor for prognosis prediction. Additionally, the ECOG PS reflects a patient's physical condition and an elevated score exerts

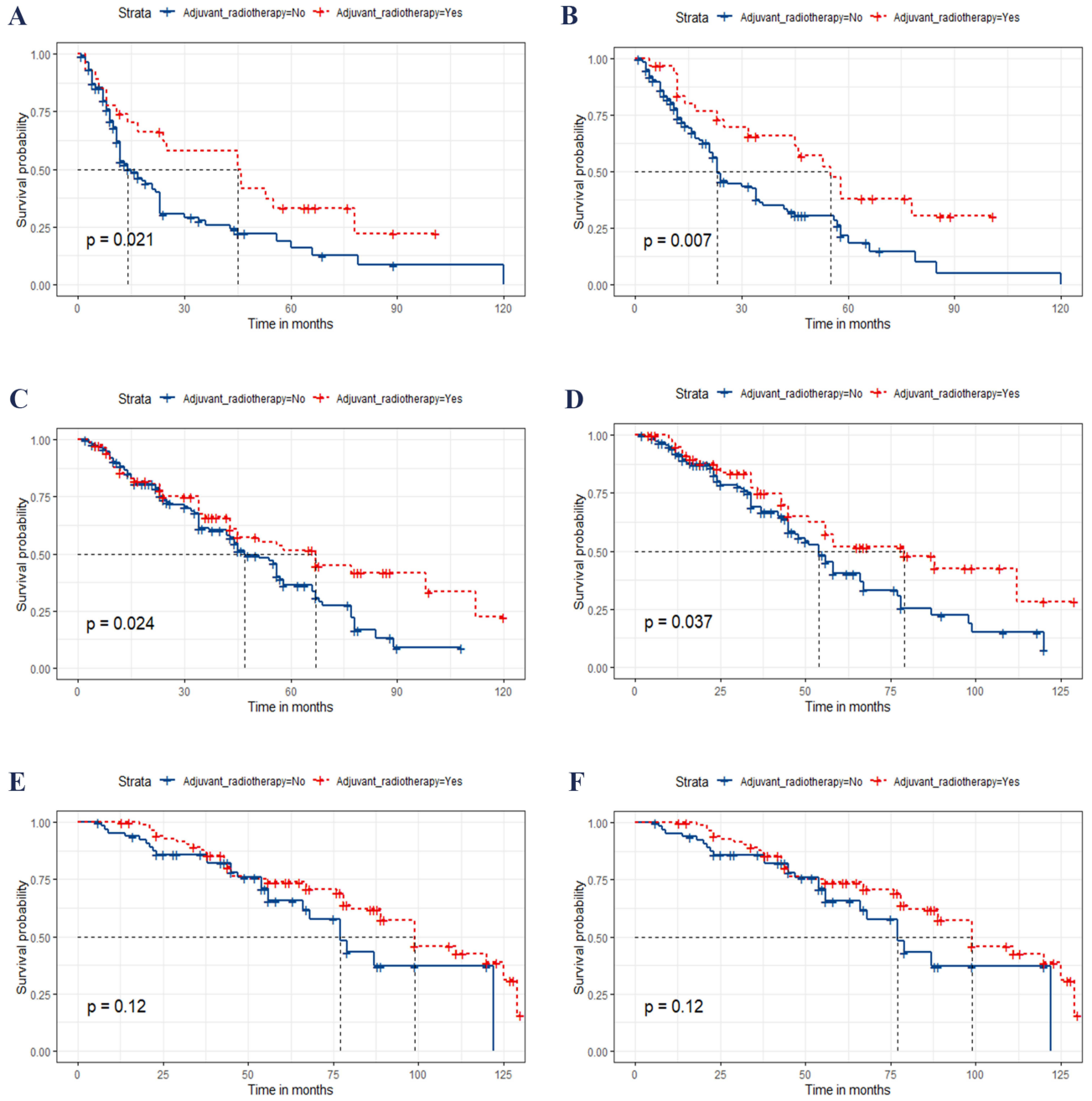

Figure 6 The Kaplan-Meier curves derived from new risk stratification to predict the impact of adjuvant radiotherapy on DFS and OS in various subgroups. Curves (**A, C**, and **E**) illustrate the impact of adjuvant radiotherapy on DFS in the low-, medium-, and high-risk groups, respectively. Similarly, curves (**B, D**, and **F**) depict the impact of adjuvant radiotherapy on OS in the low-, medium-, and high-risk groups, respectively. Red and blue curves represent Kaplan-Meier curves for patients who received adjuvant radiotherapy and those who did not, respectively.
Abbreviations: DFS, disease-free survival; OS, overall survival.

a direct impact on cancer progression, significantly influencing treatment decisions. A study conducted by Yamada SI et al on elderly patients diagnosed with oral squamous cell carcinoma demonstrated that individuals with an ECOG PS score ≥ 2 exhibited a poorer prognosis.[84] The inclusion criteria for our study were limited to OSCC patients with ECOG PS scores of 0, 1, and 2. Notably, patients with a score of 2 exhibited a significantly worse prognosis compared to those with a score of 0–1, which is consistent with previous studies.

Previously, many researchers had developed various nomograms for OSCC patients. Timothy P J Liu et al compiled a comprehensive nomogram based on data from 2508 patients with OSCC across four medical centers.[85] This nomogram

incorporates prognostic factors such as adjuvant radiotherapy, age, stage, surgical margin status, neural invasion, and vascular invasion. Another study involving 432 patients with OSCC from Peking University School and Hospital of Stomatology utilized variables such as gender, BMI, oral premalignant disorders, pain score, grade, and N-stage to construct a nomogram for predicting both 3-year and 5-year survival probabilities.[86] Zhiliang Nie et al constructed a survival prediction nomogram consisting of 269 patients with OSCC, including variables such as age, the Kaplan-Feinstein index, T-stage, the number of positive nodes, and the SII.[87] Although various prognostic factors have been identified and numerous nomograms have been built for OSCC patients, the association between NPS and the prognosis of OSCC patients is still unclear. In this study, the NPS was first identified as an important independent prognostic factor for OSCC patients. Then, the nomogram model for postoperative OSCC patients was constructed based on the NPS and other independent prognostic indicators, including NPS, ENE, ACCI, stage, surgical margin, ECOG PS score, SIS, adjuvant radiotherapy, and tumor location. It is the first time that the NPS has been incorporated into the prognosis model, which is different from previous studies.

The decision to give adjuvant radiotherapy to OSCC patients currently depends on treatment guidelines.[40,41] However, there is a need for better tools to accurately assess the benefits and risks of treatment for these patients. In this study, patients were grouped into three categories based on their risk scores from the nomogram: low-risk, medium-risk, and high-risk. The analysis showed that low-risk patients did not benefit from adjuvant radiotherapy and may not need it, while medium-risk and high-risk patients would benefit from it to improve their prognosis. This discovery can help clinicians make more personalized treatment decisions.

Our study also has several limitations: Firstly, the statistical models underlying the nomogram can be intricate and challenging to comprehend. Oncologists and patients may require specialized statistical knowledge for accurate interpretation of the nomogram. Secondly, our study was retrospective and could not encompass all clinicopathological variables that influence the prognosis of OSCC. Lastly, our nomogram was primarily developed within this specific population of postoperative OSCC and its applicability to other populations or settings may be limited. Therefore, a larger multicenter and prospective study is needed to verify our findings.

Conclusion

The NPS emerged as an independent prognostic factor for DFS and OS among patients with OSCC following surgical treatment. The nomogram risk models, which incorporated NPS along with other clinicopathological variables, demonstrated excellent predictive ability, outperforming the traditional TNM staging system. The risk stratification system was developed using the risk scores derived from the nomograms. There were significant differences in DFS and OS between patients in different risk subgroups. Patients in the low-risk subgroup can be spared from adjuvant radiotherapy, while those in the medium-risk and high-risk subgroups may benefit from it.

Abbreviations

ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; AUC, area under the curve; BMI, body mass index; C-index, concordance index; CCI, Charlson comorbidity index; CCL2, Chemokine (C-C motif) ligand 2; CI, confidence interval; CSF1, colony-stimulating factor 1; CSF2, colony-stimulating factor 2; CRT, conformal radiotherapy; DFS, disease-free survival; DCA, decision curve analysis; DOI, depth of invasion; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; HPV, human papillomavirus; IL-6, interleukin-6; LMR, lymphocyte-to-monocyte ratio; IMRT, intensity-modulated radiotherapy; IDI, integrated discrimination improvement; IQR, interquartile range; NHANES, National Health and Nutrition Examination Survey; NLR, neutrophil-to-lymphocyte ratio; NPS, Naples prognostic score; NRI, net reclassification improvement; OS, overall survival; OSCC, oral squamous cell carcinoma; PAR, platelet-to-albumin ratio; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; ROC, receiver operating characteristic; SII, systemic immune-inflammation index; SIS, systemic inflammation score; TC, total cholesterol; TNM, Tumor-Node-Metastasis; VI, vascular invasion; VMAT, volumetric-modulated arc therapy.

Data Sharing Statement

Data can be obtained from the corresponding author upon reasonable request.

Ethics Statement

This study followed the Declaration of Helsinki guidelines and was approved by the Ethics Committees of the First Affiliated Hospital of Xinxiang Medical University and the Affiliated Cancer Hospital of Zhengzhou University. All participants provided informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest, financial or otherwise, related to this work.

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