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ORIGINAL RESEARCH

A Novel Survival Prediction Nomogram Based on the Naples Prognostic Score and Clinicopathological Factors for Postoperative Hypopharyngeal Squamous Cell Carcinoma Patients

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Background: Hypopharyngeal squamous cell carcinoma (HSCC) is a rare yet highly aggressive malignant tumor of the head and neck. This study aims to investigate the clinical factors influencing the prognosis of HSCC and develop a prognostic prediction model combining inflammation-nutrition indicators, such as the Naples Prognostic Score (NPS).

Methods: A retrospective analysis was conducted on clinical data from 292 hSCC patients who underwent radical surgery between 2007 and 2019. Univariate and multivariate Cox regression analyses were used to identify the independent prognostic factors affecting disease-free survival (DFS) and overall survival (OS). Finally, the nomogram models for predicting 3-year and 5-year DFS and OS were constructed and validated based on these factors.

Results: This study included 292 hSCC patients, with a median age of 51 years. The nomograms were developed using Cox regression to predict 3- and 5-year DFS and OS, incorporating factors such as adjuvant radiotherapy, age-adjusted Charlson comorbidity index (ACCI), Naples prognostic score (NPS), and surgical safety margin. The nomograms demonstrated strong predictive performance with area under the curve (AUC) values >0.78 in both training and validation sets. It outperformed the American Joint Committee on Cancer (AJCC) staging system in terms of discriminative power, clinical utility, and reclassification, as confirmed by decision curve analysis (DCA), concordance index (C-indices), integrated discrimination improvement (IDI), and net reclassification improvement (NRI). Patients were categorized into high-, medium-, and low-risk groups based on total risk points, with significant differences in DFS and OS observed across these groups. Furthermore, the study found that adjuvant radiotherapy significantly improved survival in high-risk and medium-risk patients, while low-risk patients did not benefit.

Conclusion: The results suggest that NPS is an independent prognostic factor for HSCC, and the nomogram model incorporating NPS can provide important references for individualized treatment decisions and offer new perspectives for clinical prognostic assessment.

Keywords: naples prognostic score, hypopharyngeal squamous cell carcinoma, disease-free survival, overall survival, nomogram

Introduction

Hypopharyngeal carcinoma accounts for approximately 3% to 5% of all head and neck malignancies, making it a relatively uncommon but aggressive neoplasm in clinical settings.[1,2] Squamous cell carcinoma represents the predominant histopathological type of hypopharyngeal cancer, comprising approximately 95% of all diagnosed cases,[3] and is predominantly observed in male patients.[4,5] The anatomical features of hypopharyngeal squamous cell carcinoma (HSCC) result in early symptoms that are frequently nonspecific. Consequently, approximately 80% of patients present with stage III–IV disease at the time of diagnosis,[3,6] and vocal cord dysfunction is not an uncommon finding.[7]

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Multidisciplinary treatment, with surgery serving as the cornerstone, remains the preferred approach for managing hypopharyngeal cancer.[8–10] Nonetheless, the therapeutic outcomes for hypopharyngeal cancer remain suboptimal, with a 5-year survival rate ranging from 25% to 45%.[1,11–13] Therefore, it is imperative to investigate the clinical factors that influence the prognosis of HSCC.

Currently, the predominant tool utilized for predicting the prognosis of hypopharyngeal cancer is the Tumor-Node-Metastasis (TNM) staging system, which aims to provide a comprehensive assessment of cancer prognosis based on anatomical classification.[14,15] The most recent edition of the TNM staging system is the 8th edition of the American Joint Committee on Cancer (AJCC) guidelines.[14] However, numerous clinically relevant variables, including comorbidities, age, histologic type, adverse lifestyle factors, and various inflammatory and nutritional indicators, are not accounted for in the current staging system. Therefore, it is essential to develop a prognostic model that incorporates a wider range of clinical variables rather than focusing primarily on anatomical structure.[16]

The Naples Prognostic Score (NPS) is an innovative inflammation-nutrition marker initially developed to assess the long-term postoperative survival of patients with colorectal cancer.[17] It is calculated based on a panel of routine clinical blood tests that include the neutrophil count, lymphocyte count, monocyte count, total cholesterol (TC), and serum albumin concentration. Due to its considerable prognostic value, further research has extensively explored the NPS as a critical predictor of survival outcomes in various malignancies, including lung cancer,[18,19] gastric cancer,[20] esophagus cancer,[21] breast cancer,[22] gallbladder cancer,[23] and oral cancer.[24] However, while some studies have investigated the effects of inflammation-nutrition marker in HSCC patients,[25–27] no study has specifically examined the relationship between NPS and the prognosis of HSCC. Furthermore, although several prognostic models for HSCC have been developed,[28–30] the integration of NPS into these models represents a highly innovative strategy, thereby offering a novel perspective on the clinical evaluation of disease prognosis.

Methods

Materials

This retrospective study analyzed clinical data from patients diagnosed with postoperative HSCC treated at the First Affiliated Hospital of Xinxiang Medical University and the Affiliated Cancer Hospital of Zhengzhou University between January 2007 and December 2019. The follow-up protocol was based on domestic clinical practice guidelines.[31] Inclusion criteria comprised imaging confirmation of hypopharyngeal origin, histologically confirmed squamous cell carcinoma, and age ≥18. Exclusion criteria encompassed no surgical treatment (N=71), Eastern Cooperative Oncology Group performance status (ECOG PS) >2 (N=62), lack of necessary imaging examinations (N=17), histological type unknown (N=24), distant metastasis at diagnosis (N=102), AJCC stage unknown (N=30), multiple primary tumors (N=20), inactive follow-up (N=55), perioperative death (N=5), neoadjuvant chemoradiotherapy (N=15), and immunotherapy (N=18). After applying these criteria, 292 postoperative HSCC patients were in the analysis. Treatment protocols involved advanced radiotherapy techniques such as intensity-modulated radiation therapy (IMRT), conformal radiation therapy (CRT), and volumetric modulated arc therapy (VMAT), with a total radiation dose ranging from 60.0 to 70.0 Gy, administered in daily fractions of 2.0 to 2.2 Gy, five days per week. Concurrent chemoradiotherapy was primarily used for cases that exhibit extranodal extension (ENE) and/or have close surgical margins. Chemotherapy regimens included fluorouracil, platinum-based agents, and taxanes. The staging was conducted by the 8th edition of the AJCC staging system, utilizing pathological staging criteria. Figure 1 illustrates the flowchart of the study, whereas Table 1 summarizes the baseline characteristics of the patients enrolled in the study.

Variables

Data were derived from the electronic medical record system and retrieved from follow-up records, including 23 variables: age at diagnosis, gender, grade, ECOG PS, smoking history, AJCC stage, surgical safety margin, ENE, Naples prognostic score (NPS), geriatric nutritional risk index (GNRI), prognostic nutrition index (PNI), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-albumin ratio (PAR), TC, lymphocyte-to-monocyte ratio (LMR), hemoglobin levels, systemic inflammation score (SIS), age-adjusted Charlson comorbidity index

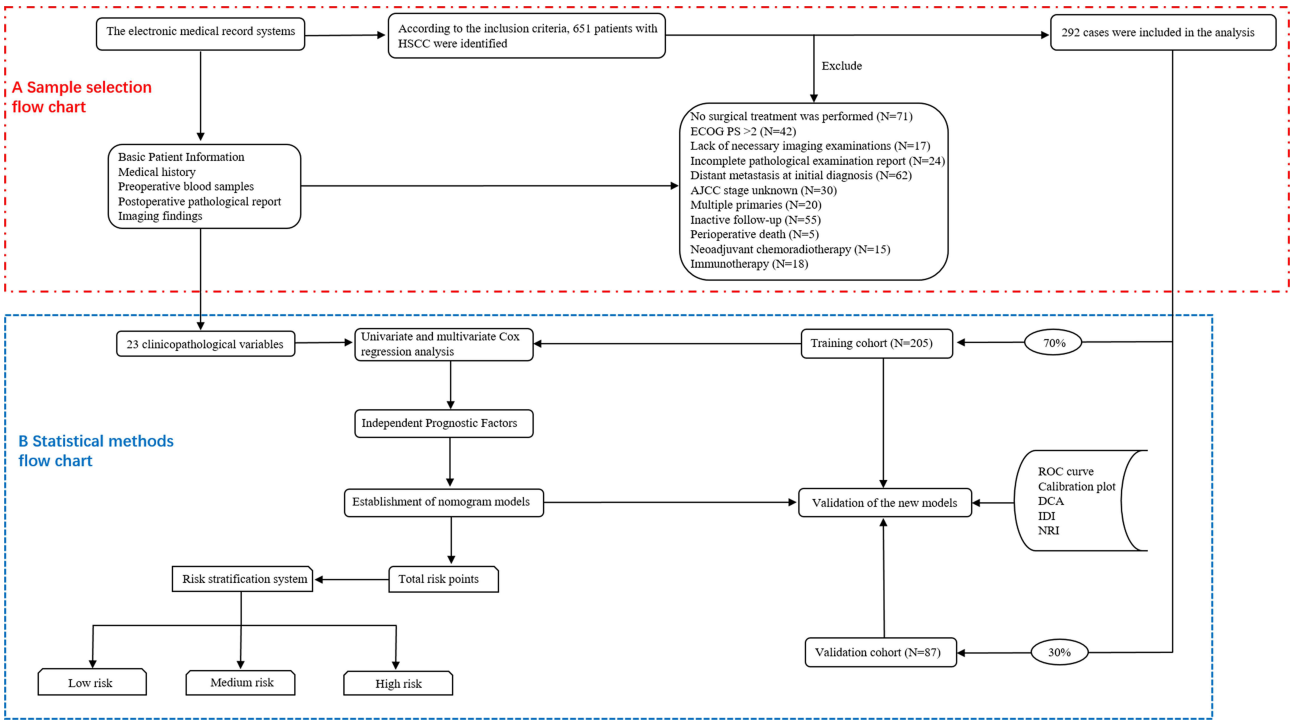

Figure 1 Flowchart of the Enrollment and Exclusion Process: Panel A illustrates the Sample Selection, and Panel B details the Statistical Methods Applied.
Abbreviations: AJCC, American Joint Committee on Cancer; ECOG PS, eastern cooperative oncology group performance status; HSCC, hypopharyngeal squamous cell carcinoma. DCA, decision curve analysis; IDI, integrated discrimination improvement; NRI, net reclassification index; ROC, receiver operating characteristic.

(ACCI), adjuvant chemotherapy, adjuvant radiotherapy, disease-free survival (DFS), and overall survival (OS). The endpoints of this study were DFS and OS. The surgical safety margin and GNRI were converted into binary variables using the X-tile software, with cut-off values of 5.0 mm and 96.8, respectively. Continuous variables were assessed for normality using the Shapiro–Wilk test, and the results are presented in Table S1. PAR, BMI, DFS, and OS. With the exception of PAR, BMI, DFS, and OS, all other continuous variables were normally distributed.

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

Characteristics	All Patients (n = 292) *N* (%)	Training Cohort (n = 205) *N* (%)	Validation Cohort (n = 87) *N* (%)	*P*
Gender				0.893
Female	72 (24.7%)	51 (24.9%)	21 (24.1%)	
Male	220 (75.3%)	154 (75.1%)	66 (75.9%)	
Age at diagnosis (years)				0.637
Median (Range)	51 (22–89)	51 (23–89)	50 (22–88)	
Grade				0.375
I	47 (16.1%)	32 (15.6%)	15 (29.9%)	
II-III	245 (83.9%)	173 (84.4%)	72 (70.1%)	
ECOG PS score				0.441
0–1	223 (76.4%)	154 (75.1%)	69 (79.3%)	
2	69 (23.6%)	51 (24.9%)	18 (20.7%)	

(*Continued*)

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Table 1 (Continued).

Characteristics	All Patients (n = 292) *N* (%)	Training Cohort (n = 205) *N* (%)	Validation Cohort (n = 87) *N* (%)	*P*
Smoking				0.159
No	257 (88.0%)	184 (89.8%)	73 (83.9%)	
Yes	35 (12.0%)	21 (10.2%)	14 (16.1%)	
AJCC Stage				0.101
I	33 (11.3%)	24 (11.7%)	9 (10.3%)	
II	41 (14.0%)	23 (11.2%)	18 (20.7%)	
III	141 (48.3%)	98 (47.8%)	43 (49.4%)	
IVa / IVb	77 (26.4%)	60 (29.3%)	17 (19.5%)	
Surgical safety margin				0.687
≥ 5mm	252 (86.3%)	178 (86.8%)	74 (85.1%)	
< 5mm or positive	40 (13.7%)	27 (13.2%)	13 (14.9%)	
ENE				0.309
Negative	264 (90.4%)	183 (89.3%)	81 (93.1%)	
Positive	28 (9.6%)	22 (10.7%)	6 (6.9%)	
NPS				0.157
0 (Group I)	62 (21.2%)	38 (18.5%)	24 (27.6%)	
1–2 (Group II)	163 (55.8%)	121 (59.0%)	42 (48.3%)	
3–4 (Group III)	67 (22.9%)	46 (22.4%)	21 (24.1%)	
SIS				0.892
0	200 (68.5%)	142 (69.3%)	58 (66.7%)	
1	59 (20.2%)	40 (19.5%)	19 (21.8%)	
2	33 (11.3%)	23 (11.2%)	10 (11.5%)	
GNRI				0.100
≥ 96.8	123 (42.1%)	80 (39.0%)	43 (49.4%)	
< 96.8	169 (57.9%)	125 (61.0%)	44 (50.6%)	
BMI (kg/m^2)				0.952
Median (range)	21.4 (16.0–32.9)	21.3 (16.0–32.9)	21.4 (16.0–31.8)	
PNI				0.264
Median (IQR)	75.0 (54.3–96.0)	76.0 (55.0–96.0)	72.0 (47.0–93.0)	
PLR				0.905
Median (IQR)	149.0 (94.0–220.0)	149.0 (92.0–220.0)	149.0 (102.0–214.0)	
NLR				0.921
Median (IQR)	2.35 (1.37–3.19)	2.35 (1.33–3.30)	2.45 (1.66–3.06)	
PAR				0.710
Median (IQR)	7.06 (3.60–9.97)	6.92 (3.72–10.12)	7.26 (3.27–9.55)	
TC				0.787
Median (IQR)	199.2 (126.5–256.2)	202.5 (125.5–257.14)	198.2 (133.44–252.15)	
LMR				0.843
Median (IQR)	5.33 (2.53–8.12)	5.41 (2.66–7.94)	4.85 (2.06–8.38)	
Hemoglobin (g/L)				0.607
Median (IQR)	98.0 (90.0–115.5)	100.0 (91.0–115.0)	97.0 (89.0–119.0)	
Albumin (g/L)				0.709
Median (IQR)	41.0 (35.0–48.0)	41.0 (34.5–49.0)	43.0 (36.0–48.0)	
ACCI				0.731
< 6	221 (75.7%)	154 (75.1%)	67 (77.0%)	
≥ 6	71 (24.3%)	51 (24.9%)	20 (23.0%)	

(*Continued*)

Table 1 (Continued).

Characteristics	All Patients (n = 292) *N* (%)	Training Cohort (n = 205) *N* (%)	Validation Cohort (n = 87) *N* (%)	*P*
Adjuvant radiotherapy				0.647
No	105 (36.0%)	72 (35.1%)	33 (37.9%)	
Yes	187 (64.0%)	133 (64.9%)	54 (62.1%)	
Adjuvant chemotherapy				0.096
No	214 (73.3%)	156 (76.1%)	58 (66.7%)	
Yes	78 (26.7%)	49 (23.9%)	29 (33.36%)	
DFS (months)				0.610
Median (range)	22.0 (1–127)	22.0 (1–127)	20.0 (3–110)	
OS (months)				0.316
Median (range)	33.0 (1–128)	34.0 (1–127)	32.0 (3–128)	

Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; BMI, body mass index; DFS, disease-free survival; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; GNRI, geriatric nutritional risk index; HSCC, hypopharyngeal squamous cell carcinoma; IQR, interquartile range; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPS, Naples prognostic score; OS, overall survival; PAR, platelet-to-albumin ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; SIS, systemic inflammation score; TC, total cholesterol.

Calculation

Table S2 provides the formulas for calculating various preoperative inflammatory and nutritional indicators, including NPS, GNRI, SIS, LMR, PNI, NLR, PAR, PLR, and BMI. The methodology for scoring the ACCI is detailed in Table S3.

Analysis

Data analysis was performed using X-tile (version 3.6.1), SPSS (version 20.0), and R (version 4.22) software. A P-value less than 0.05 was considered statistically significant. The flowchart outlining the sample selection process and statistical methods is presented in Figure 1. Tolerance and variance inflation factor (VIF) values were computed using linear regression analysis, as detailed in Table S4. A total of 292 patients were included in this study, with participants randomly allocated to a training set and a validation set at a ratio of 7:3. SPSS software was utilized to compare the baseline characteristics between the two groups. The chi-square test was employed for categorical variables. For continuous variables, an independent samples *t*-test was conducted for those conforming to a normal distribution, while the Mann–Whitney *U*-test was applied for non-normally distributed samples (see Table 1). The training set was utilized to identify independent prognostic factors and develop a nomogram risk prediction model, whereas the validation set served to evaluate the model's performance.

In this study, we initially conducted univariate Cox regression analysis to identify potential prognostic factors among the 21 explanatory variables. We screened for variables associated with DFS and OS through univariate analysis. Subsequently, using these pre-selected variables, we performed multivariate Cox regression analysis with a stepwise backward elimination method to further confirm the independent prognostic factors influencing DFS and OS. This approach allows us to isolate the significant prognostic factors after adjusting for the effects of other variables. After identifying the independent prognostic factors, we developed two nomograms: one for predicting DFS and another for predicting OS. These nomograms, based on their respective independent prognostic factors, are designed to provide clinicians with simple yet effective tools for individualized risk assessment in clinical settings. To validate the predictive performance of these nomograms, we utilized R software to conduct comprehensive evaluations, including constructing receiver operating characteristic (ROC) curves, calculating integrated discrimination improvement (IDI) and net reclassification improvement (NRI), generating calibration curves, and performing decision curve analysis (DCA).

Furthermore, each case was assigned a corresponding prognostic risk score based on the established prognostic model. To further investigate the prognosis of different patients, we utilized X-tile software to determine the optimal cut-off points, thereby dividing all patients into three distinct subgroups according to their risk scores: high-risk, medium-

risk, and low-risk groups. Consequently, an effective prognostic stratification system was established. To validate the efficacy of this stratification system, we employed the Log rank test and Kaplan-Meier curves to analyze differences in DFS and OS among patients across the various risk subgroups. Additionally, we assessed the impact of adjuvant radiotherapy on DFS and OS within these risk subgroups using the Log rank test, to elucidate the role and effectiveness of adjuvant radiotherapy in different prognostic risk categories.

Results

Clinical Characteristics

This study encompassed 292 hSCC patients who underwent radical surgery. The participants' ages ranged from 22 to 89 years, with a median age of 51 years. Among the participants, 220 were male (75.3%) and 72 were female (24.7%). A significant majority of the patients showed moderate to poor differentiation, with 245 patients (83.9%) falling into this category. The distribution of patients across different stages of disease was as follows: Stage I accounted for 11.3%, Stage II for 14.0%, Stage III for 48.3%, and Stage IVa-b for 26.4%. Notably, 223 patients (76.4%) had an ECOG PS score of 0–1. Regarding the ACCI, 75.7% of patients had a score of less than 6, while 24.3% scored 6 or higher. The incidence of ENE was noted in 9.6% of the patients (28 patients), and 40 patients (13.7%) had a surgical margin of less than 5 mm. For NPS, 62 patients (21.2%) were classified in Group I (score 0), 163 patients (55.8%) in Group II (score 1–2), and 67 patients (22.9%) in Group III (score 3–4). In terms of the GNRI, 123 patients (42.1%) had a score ≥96.8, while 169 patients (57.9%) had a score <96.8. Furthermore, 187 patients (64%) received adjuvant radiotherapy, and 78 patients (26.7%) received adjuvant chemotherapy. The median DFS was 22 months, and the median OS was 33 months. Table 1 illustrates the baseline characteristics of patients in both the training and validation sets. Statistical analysis revealed that there were no significant differences in these characteristics between the two sets (all $P > 0.05$).

Nomogram Construction

Univariate and multivariate Cox regression analyses were initially conducted to identify independent prognostic factors for DFS and OS, as detailed in Tables 2 and 3. Based on these findings, a nomogram was developed to predict 3-year and 5-year DFS and OS. The nomogram incorporated several independent prognostic variables: adjuvant radiotherapy, ACCI, AJCC stage, NPS, ECOG PS, ENE, surgical margin status, and gender for DFS prediction (Figure 2A and Table 2). For OS prediction, the nomogram included adjuvant radiotherapy, ACCI, AJCC stage, NPS, GNRI, ENE, and surgical margin status (Figure 2B and Table 3). Figure 2 also illustrates an example of how this predictive model can be applied to estimate DFS and OS for individual patients.

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

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		**HR (95% CI)**	
Age at diagnosis (years)	0.994 (0.983–1.005)	0.278		
Gender				
Female	Reference			
Male	1.609 (1.047–2.472)	**0.030**	1.589 (1.045–2.416)	**0.030**
Grade				
I	Reference			
II-III	1.204 (0.814–1.781)	0.352		

(*Continued*)

Table 2 (Continued).

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
ECOG PS score				
0–1	Reference		Reference	
2	1.586 (1.097–2.293)	**0.014**	1.569 (1.085–2.269)	**0.017**
Smoking				
No	Reference			
Yes	1.347 (0.840–2.161)	0.216		
AJCC stage				
I	Reference		Reference	
II	1.616 (0.754–3.465)	0.217	1.674 (0.796–3.520)	0.175
III	2.416 (1.289–4.531)	**0.006**	2.800 (1.542–5.084)	**0.001**
IVa&b	3.261 (1.655–6.424)	**0.001**	3.710 (1.945–7.074)	**<0.001**
Surgical safety margin				
≥ 5mm	Reference		Reference	
< 5mm or Positive	2.687 (1.697–4.254)	**<0.001**	2.814 (1.796–4.409)	**<0.001**
ENE				
Negative	Reference		Reference	
Positive	1.784 (1.077–2.955)	**0.025**	1.779 (1.083–2.924)	**0.023**
NPS				
0 (Group I)	Reference		Reference	
1–2 (Group II)	1.305 (0.832–2.047)	0.246	1.474 (0.954–2.279)	0.081
3–4 (Group III)	2.079 (1.251–3.453)	**0.005**	2.253 (1.367–3.713)	**0.001**
GNRI				
≥ 96.8	Reference			
< 96.8	1.380 (0.963–1.978)	0.079		
PNI	0.996 (0.988–1.004)	0.289		
PLR	1.001 (0.999–1.003)	0.202		
NLR	1.129 (0.951–1.341)	0.166		
PAR	0.989 (0.938–1.043)	0.698		
TC	0.998 (0.996–1.001)	0.205		
LMR	0.994 (0.936–1.057)	0.854		
Hemoglobin	0.994 (0.984–1.004)	0.259		
SIS				
0	Reference			
1	1.355 (0.840–2.186)	0.212		
2	1.759 (1.006–3.076)	0.047		
ACCI				
< 6	Reference		Reference	
≥ 6	1.954 (1.249–3.057)	**0.003**	1.706 (1.181–2.464)	**0.004**
Adjuvant chemotherapy				
No	Reference			
Yes	1.022 (0.711–1.468)	0.906		
Adjuvant radiotherapy				
No	Reference		Reference	
Yes	0.629 (0.439–0.901)	**0.011**	0.603 (0.426–0.854)	**0.004**

Notes: P value in bold means statistically significant.

Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; BMI, body mass index; CI, confidence interval; DFS, disease-free survival; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; GNRI, geriatric nutritional risk index; HSCC, hypopharyngeal squamous cell carcinoma; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; NPS, Naples prognostic score; PAR, platelet-to-albumin ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; SIS, systemic inflammation score; TC, total cholesterol.

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

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
Age at diagnosis (years)	0.992 (0.981–1.004)	0.189		
Gender				
Female	Reference			
Male	1.577 (1.013–2.454)	**0.043**	1.497 (0.974–2.302)	0.066
Grade				
I	Reference			
II-III	1.257 (0.836–1.891)	0.271		
ECOG PS score				
0–1	Reference		Reference	
2	1.501 (1.023–2.203)	**0.038**	1.465 (1.000–2.148)	0.050
Smoking				
No	Reference			
Yes	1.365 (0.826–2.255)	0.224		
AJCC stage				
I	Reference		Reference	
II	1.747 (0.788–3.873)	0.169	1.961 (0.896–4.289)	0.092
III	2.263 (1.180–4.337)	**0.014**	2.553 (1.366–4.770)	0.003
IVa&b	3.219 (1.591–6.511)	**0.001**	3.571 (1.810–7.045)	**<0.001**
Surgical safety margin				
≥ 5mm	Reference		Reference	
< 5mm or Positive	2.758 (1.728–4.399)	**<0.001**	2.648 (1.666–4.211)	**<0.001**
ENE				
Negative	Reference		Reference	
Positive	2.298 (1.382–3.820)	**0.001**	2.290 (1.391–3.772)	**0.001**
NPS				
0 (Group I)	Reference		Reference	
1–2 (Group II)	1.267 (0.790–2.031)	0.327	1.360 (0.854–2.167)	0.195
3–4 (Group III)	2.308 (1.346–3.958)	**0.002**	2.314 (1.351–3.963)	**0.002**
GNRI				
≥ 96.8	Reference			
< 96.8	1.476 (1.014–2.149)	**0.042**	1.532(1.059–2.217)	**0.023**
PNI	0.997 (0.989–1.005)	0.485		
PLR	1.002 (1.000–1.004)	0.138		
NLR	1.188 (0.993–1.421)	0.060		
PAR	0.988 (0.935–1.045)	0.682		
TC	0.997 (0.994–1.000)	0.061		
LMR	1.002 (0.940–1.067)	0.960		
Hemoglobin	0.990 (0.979–1.001)	0.073		
SIS				
0	Reference			
1	1.353 (0.820–2.231)	0.237		
2	1.610 (0.887–2.924)	0.118		
ACCI				
< 6	Reference		Reference	
≥ 6	2.240 (1.404–3.575)	**0.001**	1.849 (1.255–2.723)	**0.002**

(*Continued*)

Table 3 (Continued).

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
Adjuvant chemotherapy				
No	Reference			
Yes	1.084 (0.745–1.578)	0.674		
Adjuvant radiotherapy				
No	Reference		Reference	
Yes	0.582 (0.400–0.848)	**0.005**	0.597 (0.413–0.863)	**0.006**

Notes: P value in bold means statistically significant.
Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; BMI, body mass index; CI, confidence interval; DFS, disease-free survival; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; GNRI, geriatric nutritional risk index; LMR, lymphocyte-to-monocyte ratio; HSCC, hypopharyngeal squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; NPS, Naples prognostic score; PAR, platelet-to-albumin ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; SIS, systemic inflammation score; TC, total cholesterol.

Validation

Following the construction of the risk prediction nomogram, we conducted extensive validations. The calibration curve closely approximates the 45-degree diagonal line, indicating a high degree of concordance between predicted risk probabilities and actual outcomes (Figure 3). The area under the curve (AUC) for the training set demonstrated robust predictive performance: AUC values were 0.814 for 3-year DFS, 0.786 for 5-year DFS, 0.832 for 3-year OS, and 0.811 for 5-year OS (Figure 4A–C). Similarly, the validation set exhibited strong AUC values: 0.804 for 3-year DFS, 0.839 for 5-year DFS, 0.797 for 3-year OS, and 0.791 for 5-year OS (Figure 4B–D). These results underscore the model's excellent discriminative power. Furthermore, DCA confirmed the clinical utility of the new nomogram, demonstrating that it provided greater clinical benefits compared to the AJCC staging system across various threshold probabilities (Figure 5). The C-indices for the training set were 0.701 (DFS) and 0.693 (OS), and for the validation set, they were 0.642 (DFS) and 0.635 (OS), all surpassing those of the traditional AJCC staging system (Table 4). Finally, the IDI and NRI values in both the training and validation sets were consistently positive, further substantiating the superior discrimination and reclassification performance of the nomogram over the traditional AJCC staging system (Table 4).

Prognostic Risk Stratification System

Patients were stratified into three subgroups based on their total risk points: high-risk, medium-risk, and low-risk. For DFS prediction, patients with total risk points ≥230.3 were categorized as high-risk, those with scores between 103.6 and 230.0 as medium-risk, and those with total risk points ≤109.1 as low-risk. Similarly, for OS prediction, patients with total risk points ≥201.5 were classified as high-risk, those with total risk points between 103.3 and 200.2 as medium-risk, and those with total risk points ≤102.5 as low-risk. Kaplan-Meier survival curves were subsequently plotted, demonstrating significant differences in DFS and OS across the three subgroups (Figure 6), which indicated a clear distinction in survival outcomes between the training and validation sets. Additionally, we investigated the impact of adjuvant radiotherapy on survival outcomes within these subgroups. Results showed that adjuvant radiotherapy was associated with improved prognosis in the high- and medium-risk subgroups, whereas patients in the low-risk group did not derive any survival benefit from adjuvant radiotherapy in terms of DFS or OS (Figure 7 and Table S5).

Discussion

HSCC is considered one of the most prognostically unfavorable malignancies in the head and neck region.[32] This poor prognosis is primarily attributed to its deep anatomical location in the pharynx, which makes early detection extremely challenging. As a result, the majority of patients present with symptoms only when the tumor has already reached an advanced stage.[2] HSCC exhibits significant local invasiveness, often extending to adjacent structures such as the larynx, trachea, and esophagus. Furthermore, this cancer has a high propensity for lymph node metastasis even at an early

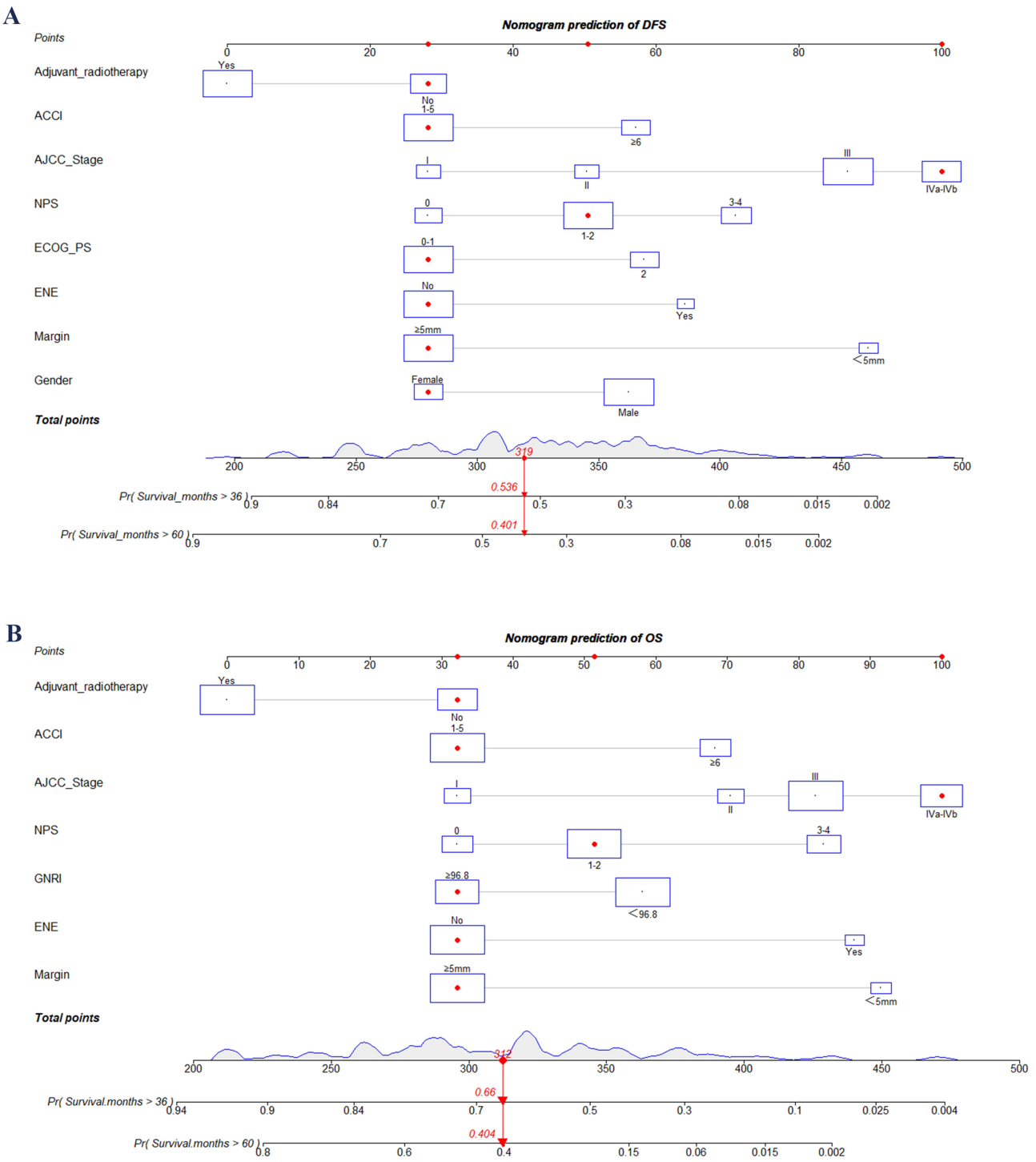

Figure 2 Nomogram-Based Prediction of DFS (**A**) and OS (**B**) in Postoperative HSCC Patients.
Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; DFS, disease-free survival; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; GNRI, geriatric nutritional risk index; HSCC, hypopharyngeal squamous cell carcinoma; NPS, Naples prognostic score; OS, overall survival.

stage.[33,34] A substantial body of research indicates that surgery combined with postoperative radiotherapy or chemoradiotherapy significantly improves survival outcomes compared to radical chemoradiotherapy alone.[11,35–37] However, despite some advancements in treatment, the prognosis for HSCC patients remains poor, and survival rates are relatively

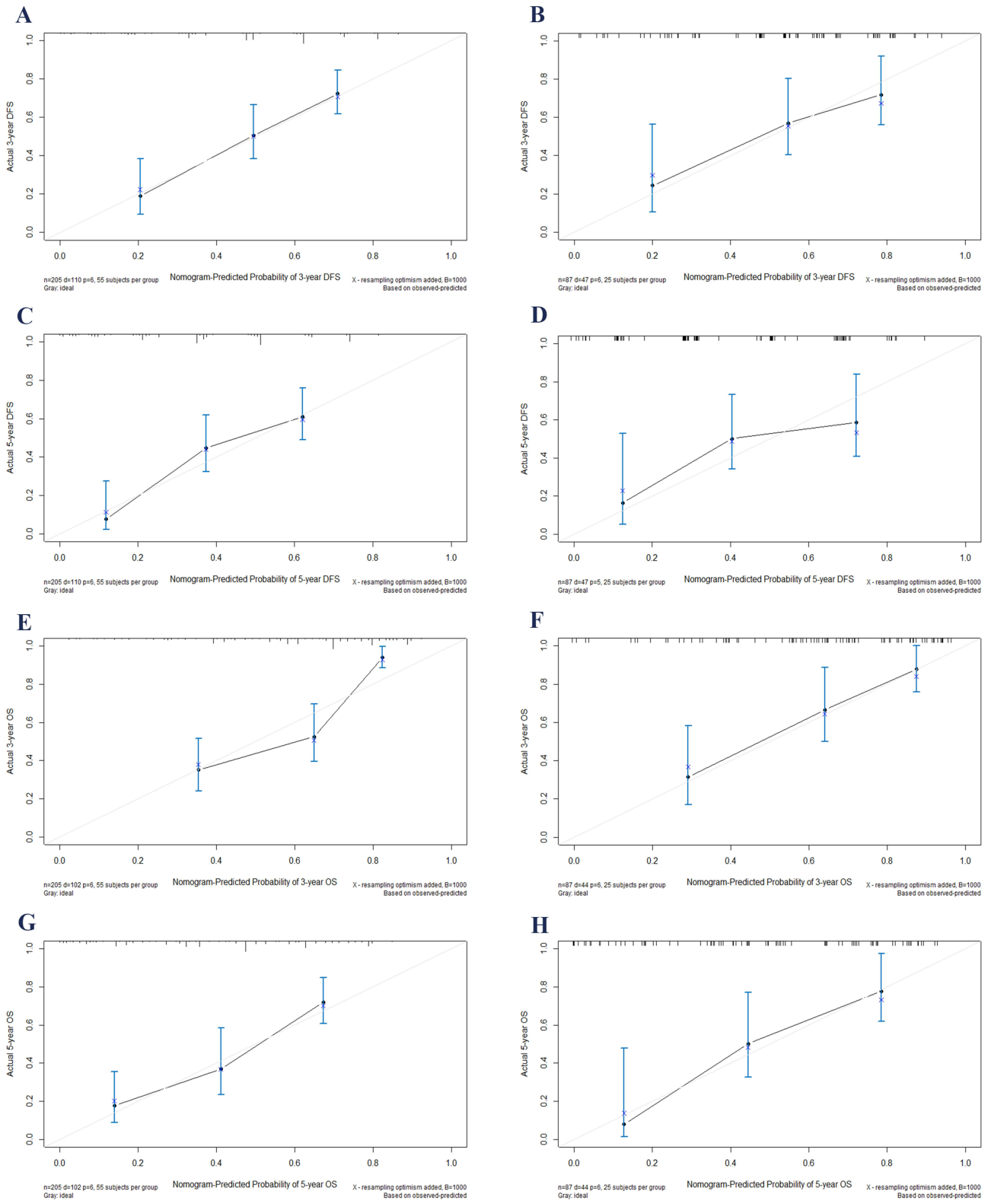

Figure 3 Calibration Plots for 3- and 5-Year DFS and OS in Postoperative HSCC Patients. Calibration plots of 3-year DFS in the training and validation cohorts (**A** and **B**), as well as 5-year DFS (**C** and **D**). Calibration plots of 3-year OS in the training and validation cohorts (**E** and **F**), as well as 5-year OS (**G** and **H**).
Abbreviations: HSCC, hypopharyngeal squamous cell carcinoma; OS, overall survival; DFS, disease-free survival.

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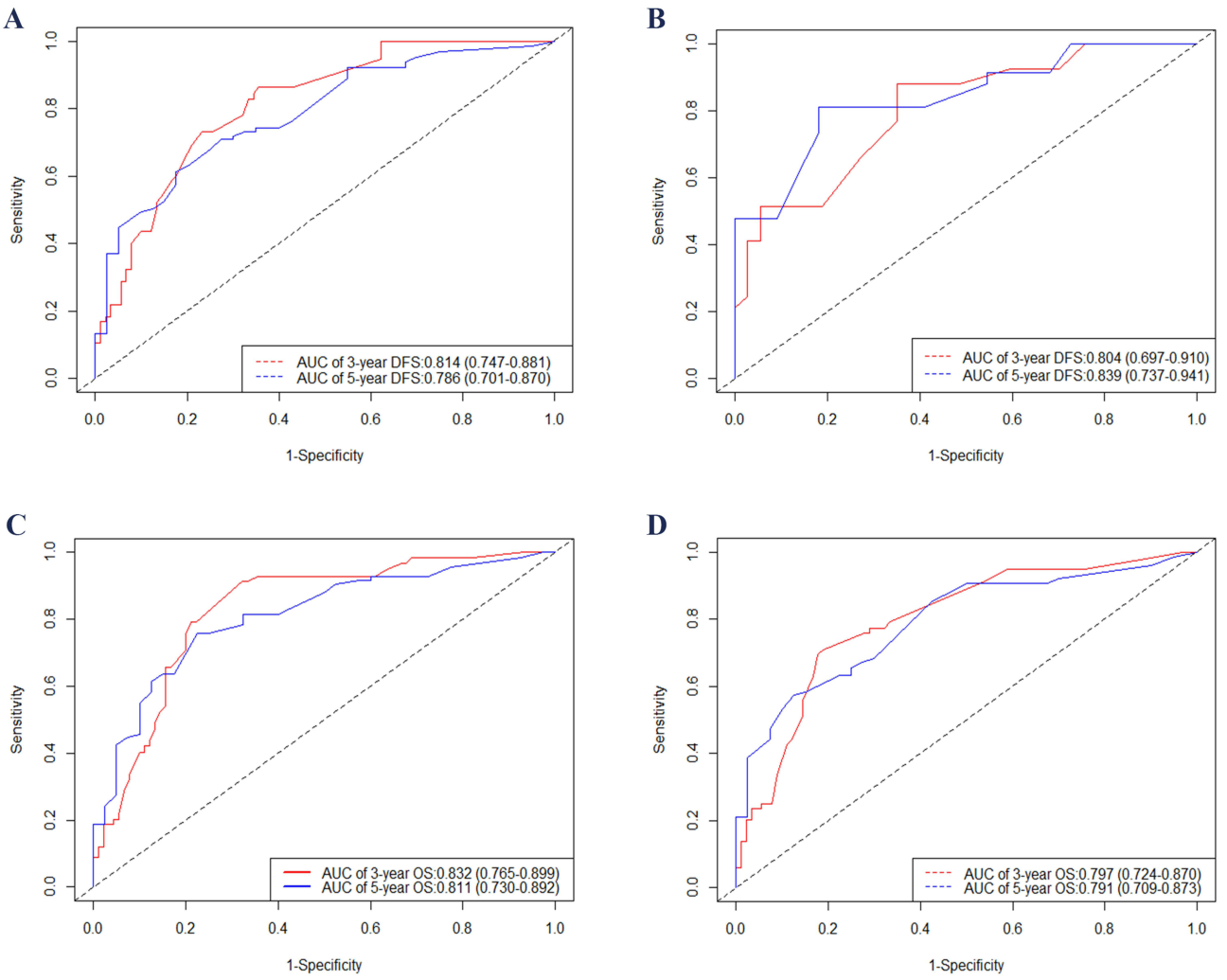

Figure 4 Time-dependent ROC Curves of the Nomograms: AUC for predicting 3- and 5-year DFS in the training (**A**) and validation (**B**) cohorts, and AUC for 3- and 5-year OS in the training (**C**) and validation (**D**) cohorts.
Abbreviations: AUC, area under curve; OS, overall survival; DFS, disease-free survival; ROC, receiver operating characteristic.

low. Given the unfavorable prognosis associated with HSCC, this study aimed to identify several independent factors influencing DFS and OS among a range of clinical variables, including NPS, a relatively novel biomarker.

Among the various prognostic factors, tumor characteristics, patient comorbidities, inflammatory markers, and nutritional status have become key research focuses.[38–41] Imbalances in inflammation and nutrition were closely associated with the prognosis of multiple malignancies. In recent years, the NPS, a marker reflecting inflammation and nutritional status, has attracted increasing attention in clinical research. The NPS integrates inflammatory and nutritional indicators commonly used in clinical practice, such as neutrophil, lymphocyte, monocyte, total cholesterol, and albumin levels. It has been proven to be of significant value in prognostic assessment for various cancers. Therefore, this study aims to incorporate the NPS into the prognostic predictive models for HSCC, to provide new insights into risk prediction for postoperative patients.

The NPS, derived from routine blood tests, has been validated as a strong predictor of prognosis in various cancers, including colorectal,[42–44] gastric,[20,45–47] and lung cancers,[18,48–50] but its application in HSCC had not been previously explored. Our study demonstrated that NPS, along with other independent factors like AJCC stage, ENE, and surgical margin status, significantly influences both DFS and OS in HSCC patients. These findings are consistent with previous research showing that systemic inflammation and nutritional status are closely linked with cancer prognosis.[51] Specifically, the inflammatory markers (eg, neutrophil, lymphocyte, monocyte counts) and nutritional indicators (eg, total cholesterol, albumin

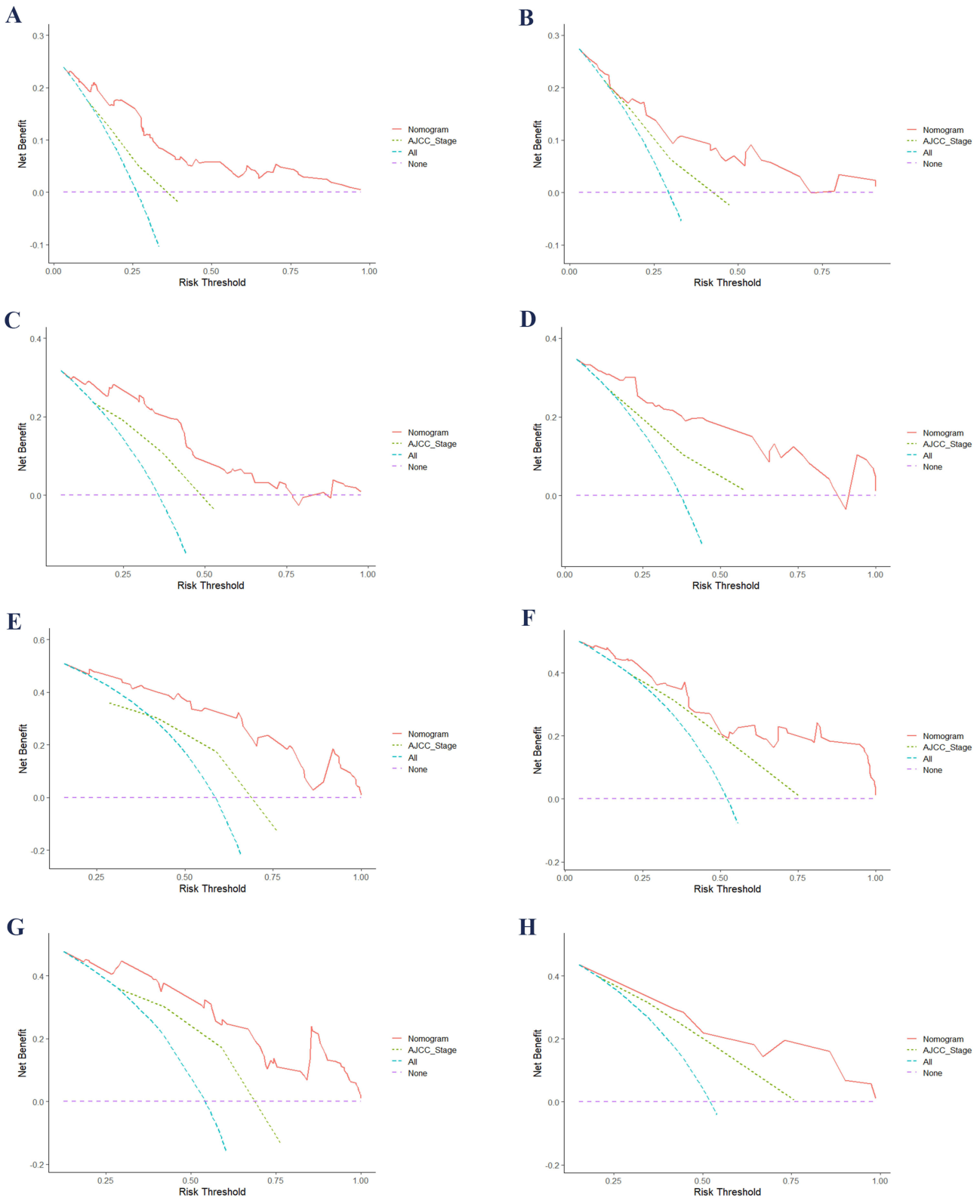

Figure 5 DCA of Nomograms and AJCC Stage for DFS and OS: DCA curves for 3-year DFS (**A** and **B**) as well as 3-year OS (**C** and **D**) in the training and validation groups; DCA curves for 5-year DFS (**E** and **F**) as well as 5-year OS (**G** and **H**) in the training and validation cohorts.
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		
	Value	**95% CI**	***P***	**Value**	**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	

Notes: P value in bold means statistically significant.
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.

levels) included in the NPS provide a comprehensive assessment of the patient's overall health status, which can predict both treatment response and long-term survival.[52,53] The incorporation of NPS into our model significantly improved predictive accuracy compared to the AJCC staging system alone, as demonstrated by the higher C-indices, ROC curve analysis, and DCA. This suggests that NPS can help identify patients at higher risk who might benefit from more aggressive treatment strategies, such as intensified chemoradiotherapy or closer postoperative monitoring.

ENE refers to the spread of cancer beyond the lymph nodes and serves as a critical prognostic factor in HSCC.[43,44] In our study, positive ENE was observed in 9.6% of patients, and multivariate Cox regression analysis revealed that it was independently associated with poorer DFS and OS, consistent with previous studies.[54,55] Surgical safety margins represent a critical factor influencing the prognosis of head and neck tumors. Despite variations in the definition of "close margins" across different studies, the general trend indicates that larger safety margins are typically associated with improved prognosis,[56–59] which is consistent with our findings. In this study, we established a safety margin threshold of 5mm using X-tile software analysis. Subsequent analyses revealed that surgical margin < 5 mm constitute an independent prognostic factor for poorer outcomes. Patients presenting with ENE or close surgical margins may benefit from more aggressive postoperative adjuvant therapy,[60] aligning with recommendations from several clinical practice guidelines.[31,61]

The ACCI is a widely used tool that helps assess the overall health status of cancer patients by factoring in both age and the presence of other comorbidities and provides a measure of a patient's ability to tolerate aggressive cancer treatments.[62–65] In this study, the ACCI was identified as a significant prognostic factor for HSCC, influencing both DFS and OS (all $p < 0.05$), which is consistent with previous studies.[66] Further analysis revealed that patients with lower ACCI scores (ACCI < 6), indicating fewer comorbidities, had significantly better survival outcomes, while those with higher ACCI scores (ACCI≥6), reflecting multiple comorbidities or advanced age, faced poorer prognoses. The ACCI's integration into the nomogram, alongside other factors like ENE and the NPS, allows for a more personalized treatment approach, helping clinicians balance aggressive therapies with the patient's ability to tolerate them.

Several studies have consistently demonstrated that male patients constitute over 80% of hypopharyngeal cancer cases, with a significantly higher incidence compared to females.[28,67,68] This gender disparity in incidence has been

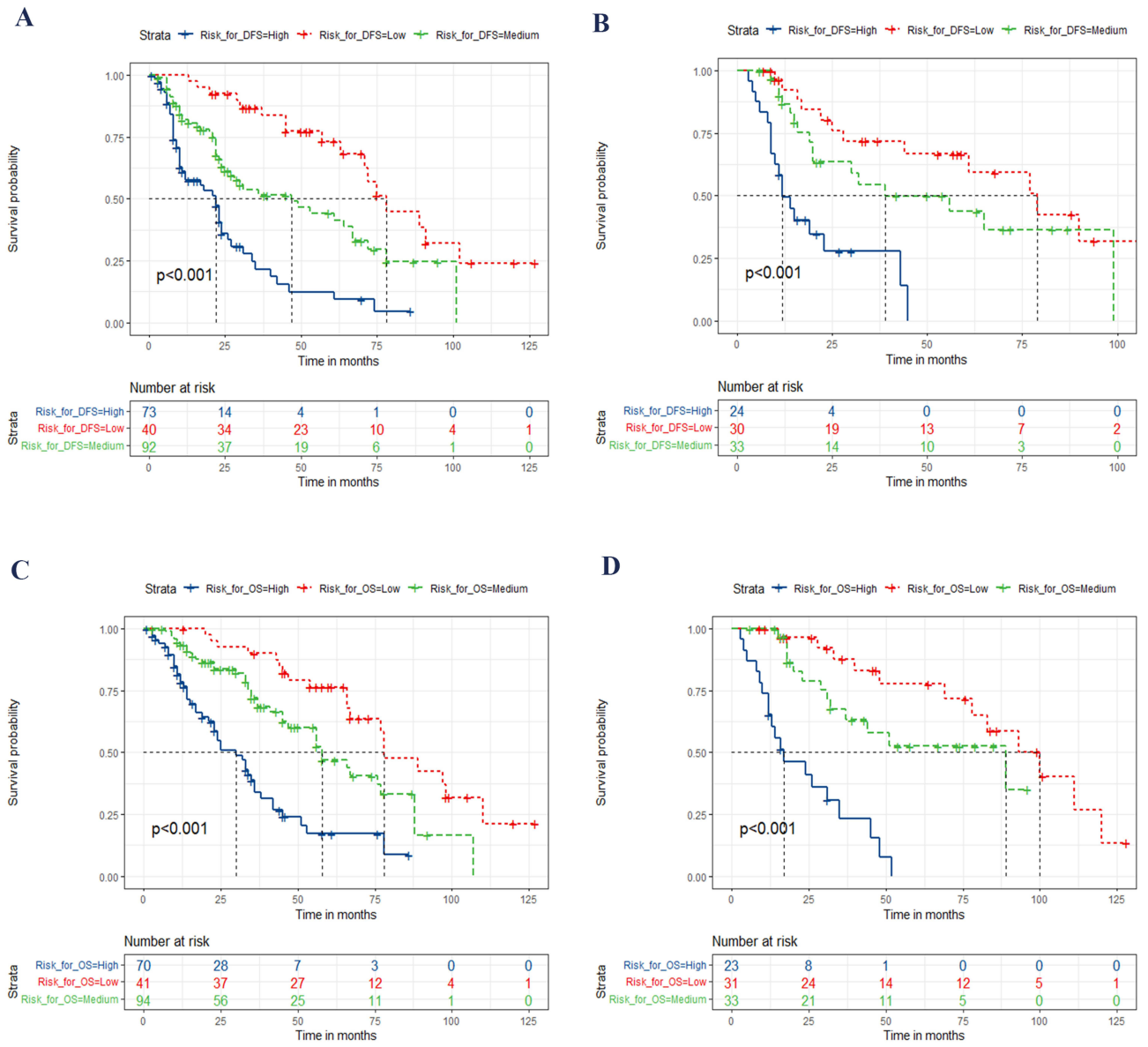

Figure 6 Kaplan-Meier Curves for Postoperative HSCC Patients Based on the New Risk Stratification System. Prediction of DFS (**A** and **B**) and OS (**C** and **D**) in Training and Validation Cohorts Using the New Risk Stratification System.

Abbreviations: AJCC, American Joint Committee on Cancer; DFS, disease-free survival; HSCC, hypopharyngeal squamous cell carcinoma; OS, overall survival.

attributed to various factors, including higher rates of tobacco use, alcohol consumption, and occupational exposures, which are more prevalent among men. Moreover, male patients exhibit a higher incidence of lymph-node metastases at the time of diagnosis.[67] The spread to regional lymph nodes is frequently associated with more advanced disease stages, thereby complicating favorable treatment outcomes. Consequently, male patients with hypopharyngeal cancer tend to present with more aggressive disease and lower survival rates, findings that are corroborated by several studies.[12,69–71] Despite the differences in the study population compared to the aforementioned study, the current investigation also yielded comparable outcomes, indicating that male patients with HSCC exhibited poorer DFS.

Our study also highlighted the critical role of adjuvant therapies, particularly radiotherapy, in improving survival outcomes for high-risk patients. Adjuvant radiotherapy was associated with better DFS and OS in patients stratified as medium- or high-risk based on their prognostic scores. This finding aligns with prior studies that emphasize the importance of postoperative adjuvant therapy in improving local control and reducing the likelihood of recurrence in hypopharyngeal cancers.[72,73] However, our results also suggest that low-risk patients may not experience the same

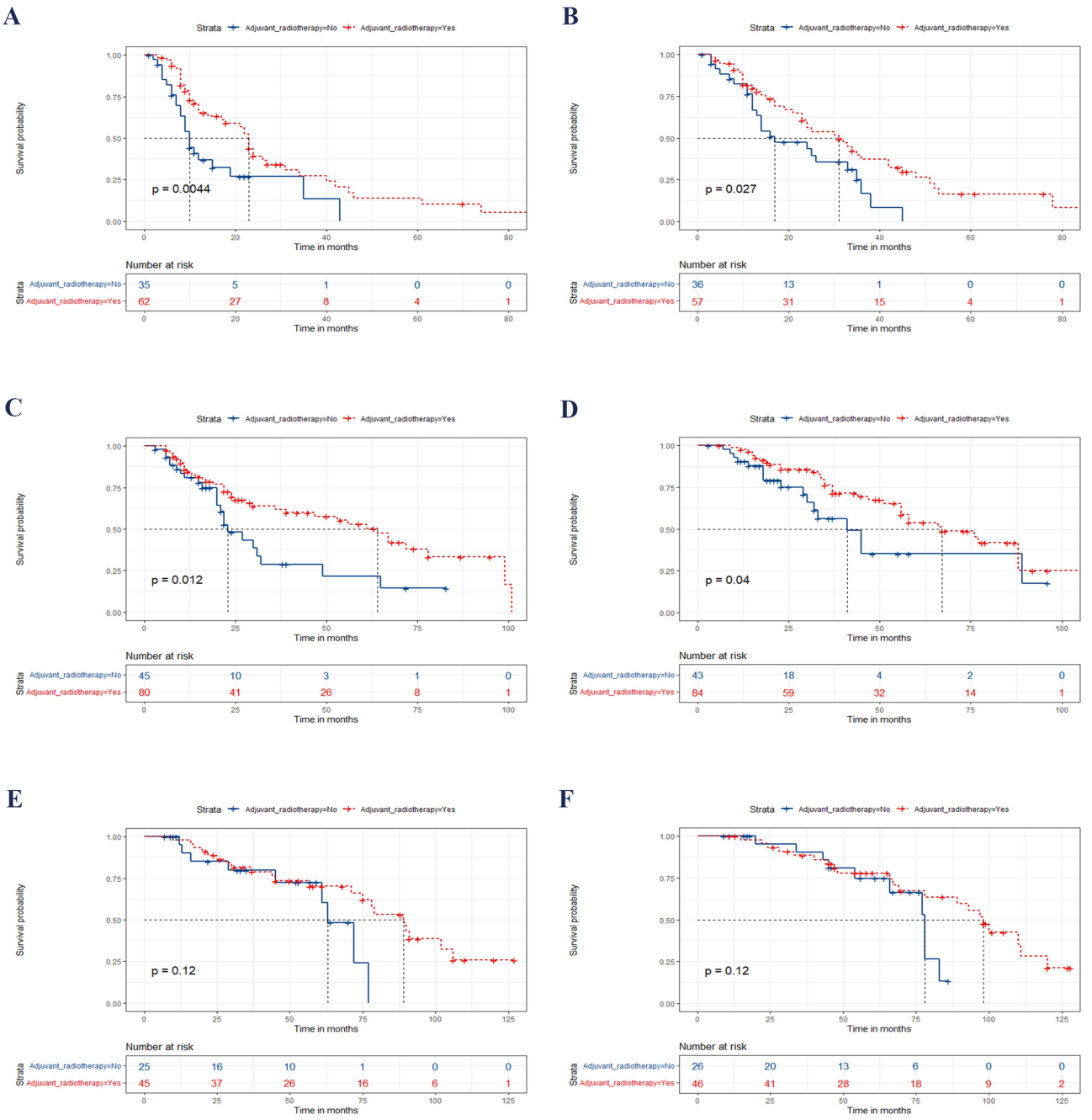

Figure 7 Kaplan-Meier curves based on the new risk stratification system to predict the impact of adjuvant radiotherapy on DFS and OS across different subgroups. Kaplan-Meier curves (**A** and **B**) show the impact of adjuvant radiotherapy on DFS and OS in the high-risk group; Kaplan-Meier curves (**C** and **D**) demonstrate the impact of adjuvant radiotherapy on DFS and OS in the medium-risk group; Kaplan-Meier curves (**E** and **F**) illustrate the effect of adjuvant radiotherapy on DFS and OS in the low-risk group, respectively.

Abbreviations: DFS, disease-free survival; OS, overall survival.

survival benefits from adjuvant radiotherapy, which could indicate that unnecessary aggressive treatments might be spared in this group. Specifically, these patients may not see significant improvements in DFS or OS, while being exposed to the side effects of treatment. This highlights the potential for the prognostic model, which incorporates the NPS, to guide clinicians in making more tailored treatment decisions, such as sparing low-risk patients from unnecessary aggressive therapies and focusing on supportive care.

The AJCC staging system remains a cornerstone in cancer prognosis, however, its limitations in accurately predicting outcomes for HSCC patients are evident in our findings. The system is primarily based on anatomical features, such as

tumor size, nodal involvement, and distant metastasis, which are crucial but fail to capture the broader physiological factors that influence survival.[14,16,74] Our study demonstrated that the prognostic predictive accuracy could be substantially improved by incorporating biomarkers of inflammation and nutritional status together with the AJCC staging system, particularly in patients with HSCC.

The primary finding of this study is that NPS scores of 3–4 represent an independent prognostic factor for both DFS and OS. Furthermore, we developed two nomograms based on NPS to predict DFS and OS, respectively. Following rigorous validation through multiple methods, the new model demonstrates excellent performance and surpasses the traditional AJCC staging system. Additionally, the potential benefits of adjuvant radiotherapy across different risk subgroups were thoroughly evaluated. In terms of research significance, this study constitutes the first investigation into the association between NPS and the prognosis of HSCC, thereby providing a critical addition to the existing body of literature.

Although this study provides valuable insights into prognostic factors in HSCC, several limitations should be acknowledged. First, a potential selection bias may have arisen due to the retrospective nature of our study and the use of direct deletion as a method for handling missing data. Second, although we validated the predictive nomograms using both training and validation datasets, further prospective studies are warranted to confirm the robustness of these models across diverse patient populations and treatment modalities. Additionally, while NPS has been identified as an important prognostic factor, future models could incorporate other biomarkers, such as genetic and molecular markers, to enhance risk stratification. Lastly, the relatively small sample size may compromise the accuracy of our results and hinder their replicability due to substantial random variation. In future research, we aim to collaborate with multiple centers to increase the sample size and investigate the prognostic impact of additional biomarkers in HSCC.

Conclusion

NPS serves as an independent prognostic factor for both DFS and OS in postoperative HSCC patients. Moreover, an NPS score of 3–4 indicates a poorer prognosis. The nomogram model constructed based on NPS and other independent prognostic factors demonstrates high predictive accuracy and can provide limited reference for adjuvant treatment decisions.

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; CI, confidence interval; CRT, conformal radiotherapy; DFS, disease-free survival; DCA, decision curve analysis; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; GNRI, geriatric nutritional risk index;HSCC, Hypopharyngeal squamous cell carcinoma; IMRT, intensity-modulated radiotherapy; IDI, integrated discrimination improvement; IQR, interquartile range; LMR, lymphocyte-to-monocyte ratio;NLR, neutrophil-to-lymphocyte ratio; NPS, Naples prognostic score; NRI, net reclassification improvement; OS, overall survival; PAR, platelet-to-albumin ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; ROC, receiver operating characteristic; SIS, systemic inflammation score; TC, total cholesterol; TNM, Tumor-Node-Metastasis; VIF, variance inflation factor; VMAT, volumetric-modulated arc therapy.

Data Sharing Statement

All clinical data are available 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 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 that they have no conflicts of interest, whether financial or otherwise, pertaining to this work.

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