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ORIGINAL RESEARCH

A CRP-Albumin-Lymphocyte (CALLY) Index–Based Nomogram for Predicting Survival After Radical Surgery for Hypopharyngeal Squamous Cell Carcinoma

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Background: Hypopharyngeal squamous cell carcinoma (HSCC) is an aggressive malignancy associated with a notably poor prognosis. This study assessed the prognostic significance of the CRP-albumin-lymphocyte (CALLY) index for disease-free survival (DFS) and overall survival (OS) in postoperative HSCC patients, and constructed nomograms integrating the CALLY index and other independent predictors to enhance clinical applicability of individualized survival prediction.

Methods: This multicenter retrospective study of 278 postoperative HSCC patients had a 3:1 training/validation split. Multivariate Cox regression analyses were performed to identify clinicopathological variables independently associated with DFS and OS. A predictive nomogram incorporating these significant prognostic factors was subsequently developed. Following a series of validations, a risk stratification system was established based on the risk scores within the model.

Results: Multivariate Cox regression analysis identified the CALLY index, eastern cooperative oncology group performance status (ECOG PS), stage, surgical margin, extranodal extension (ENE), and the age-adjusted Charlson comorbidity index (ACCI) as independent prognostic predictors of both DFS and OS. Using these predictors, two clinicopathological nomograms were developed—one to estimate DFS, and another for OS. Validations demonstrated robust discriminative ability, with area under the curve (AUC) values consistently exceeding those of the conventional AJCC staging system. Furthermore, a risk stratification system was established based on the integrated nomogram-derived total risk score, categorizing patients into different subgroups. Notably, subgroup analysis revealed that adjuvant radiotherapy was associated with statistically significant survival benefits exclusively among high- and medium-risk patients; no clinically meaningful improvement in DFS or OS was observed in the low-risk group.

Conclusion: For postoperative HSCC patients, CALLY index serves as a significant independent prognostic factor for DFS and OS. The nomograms developed by CALLY index and other clinicopathological variables outperforms the staging system. Adjuvant radiotherapy warrants caution in low-risk patients.

Keywords: CRP-albumin-lymphocyte index, hypopharyngeal squamous cell carcinoma, nomogram, survival, risk stratification system

Introduction

Hypopharyngeal squamous cell carcinoma (HSCC) is a rare neoplasm, accounting for approximately 3% of all head and neck malignant tumors,[1] with a markedly higher incidence in male patients.[2,3] In recent years, several studies have indicated a potential increase in the incidence of HSCC.[4,5] Recommending surgery as the standard treatment for HSCC, Chinese clinical guidelines also specify postoperative adjuvant radiotherapy for patients with adverse features including

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positive margins, extranodal extension (ENE), advanced stage, or lymphovascular invasion.[6] The anatomical structure of the hypopharynx is deep and relatively concealed, which makes early detection of tumors challenging. The initial clinical manifestations of HSCC are often non-specific,[7] and patients typically do not exhibit noticeable symptoms until the disease has advanced, leading to delayed medical intervention.[8] Consequently, the majority of HSCC patients are diagnosed at a locally advanced or advanced stage, with approximately 80% of cases classified as stage III–IV at the time of initial diagnosis.[9,10] The advanced disease stage at diagnosis may represent one of the key factors contributing to the low overall survival rate. Prior studies have demonstrated that, compared to radical chemoradiotherapy alone, surgical intervention followed by postoperative radiotherapy or concurrent chemoradiotherapy offers certain survival benefits.[11–14] Nevertheless, overall survival (OS) remains unsatisfactory, with previous reports indicating a 5-year OS rate of only 25% to 45%.[5,15,16]

To date, the Tumor-Node-Metastasis (TNM) staging system remains the primary method for assessing survival prognosis in patients with HSCC, with its stratification primarily based on tumor anatomical characteristics.[17,18] However, this system has limitations in capturing individual patient variability and does not incorporate important clinical factors such as age,[19] marital status,[20] race,[20,21] comorbidities,[7] and inflammatory or nutritional status.[22] Consequently, the development of prognostic models that integrate multidimensional clinical variables has emerged as a key area of research interest.[23,24]

In recent years, increasing attention has been paid to the role of inflammation and nutritional status in tumor initiation, progression, and prognosis assessment.[22,25–27] The CRP-albumin-lymphocyte (CALLY) index, a recently proposed comprehensive inflammation-nutrition biomarker, is calculated based on C-reactive protein (CRP) levels, serum albumin concentrations, and peripheral blood lymphocyte count, enabling an integrated assessment of the body's immune-inflammatory response and nutritional reserves.[28] Emerging evidence indicates that the CALLY index demonstrates robust prognostic predictive value across various solid tumors.[28–32] The crucial role of immune function in shaping the microenvironment of head and neck tumors and affecting prognosis.[33] However, research on inflammation-nutrition scoring systems in patients with HSCC remains limited, and evidence supporting the integration of the CALLY index into prognostic assessment models for HSCC is still insufficient. Most existing models have not comprehensively incorporated indicators that reflect the host's inflammatory and nutritional status. Therefore, this study aims to systematically evaluate the impact of multiple clinical variables, including the CALLY index, on disease-free survival (DFS) and OS in postoperative HSCC patients. Based on these analyses, we seek to develop a more clinically applicable prognostic assessment model, with the goal of providing a reliable reference for individualized treatment strategies in HSCC management.

Method

Materials

This study was a retrospective study. The clinical data of patients with HSCC who underwent radical surgery were collected from the First Affiliated Hospital of Xinxiang Medical University, the Affiliated Cancer Hospital of Zhengzhou University and the First People's Hospital of Shangqiu from August 2009 to November 2020 were included. The inclusion criteria included: imaging examination confirmed that the primary tumor was in the hypopharynx; squamous cell carcinoma confirmed by pathology. Exclusion criteria included: ECOG performance status > 2 (n = 36), distant metastasis (n = 40), age < 18 years (n = 1), no radical surgery (n = 50), multiple primary tumors (n = 13), only postoperative adjuvant chemotherapy (n = 13), and incomplete clinical data (n = 22, only when the missing rate of a variable was < 5%) and loss to follow-up or inactive follow-up (n = 27). The follow-up program was carried out according to the domestic clinical practice guidelines.[6] After screening in accordance with the criteria above, a total of 278 postoperative patients with HSCC were incorporated into the analysis. All patients were staged in accordance with the 8th edition of AJCC staging system. Figure 1 depicts the overall research process of this study. Table 1 presents a summary of the baseline clinicopathological characteristics of the finally included patients. Radiotherapy was conducted using conformal radiotherapy (CRT), intensity - modulated radiotherapy (IMRT), and volumetric - modulated arc therapy (VMAT). The total radiotherapy dose ranged from 60.0 to 70.0 Gy, with a single - fraction dose of 2.0 to 2.18

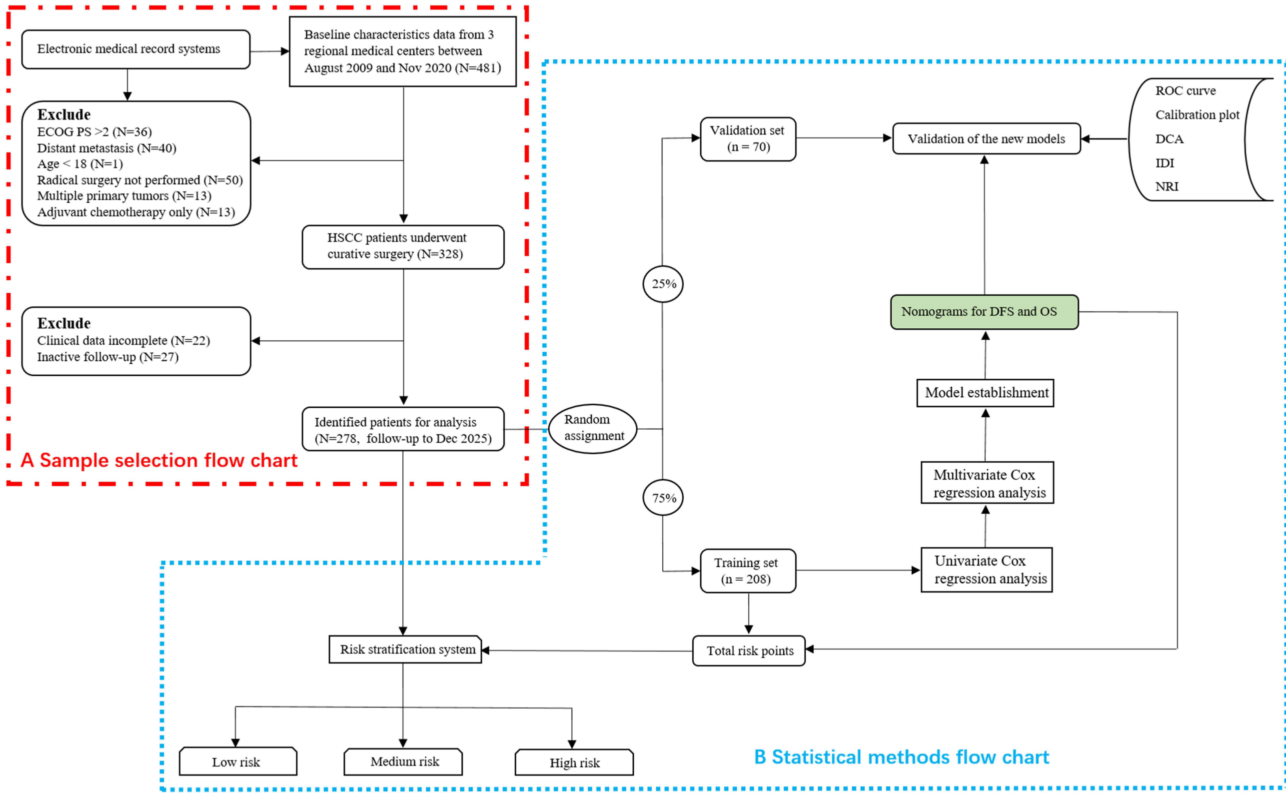

Figure 1 Flow chart of the study. (**A**) depicts the screening and final inclusion process of the study sample, while (**B**) illustrates the statistical analysis process employed in this study.

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.

Gy, administered 5 times per week. For patients without surgical margin proximity and ENE, postoperative radiotherapy alone was primarily administered as adjuvant therapy. Once any of the aforementioned risk factors were present, concurrent chemoradiotherapy was employed, and fluorouracil, platinum, and taxane were the principal chemotherapeutic drugs.

Table 1 Baseline Characteristics of Patients with HSCC Following Curative Surgery and a Comparison Between the Two Cohorts

Characteristics	All Patients N (%)	Training Cohort N (%)	Validation Cohort N (%)	*P*
Age at diagnosis (years)				0.740
Median (Range)	51 (22–88)	51 (23–87)	50 (22–88)	
ECOG PS score				0.657
0–1	187 (75.7%)	138 (75.0%)	49 (75.7%)	
2	60 (24.3%)	46 (25.0%)	14 (24.3%)	
Smoking				0.891
No	249 (89.4%)	186 (89.4%)	63 (90.0%)	
Yes	29 (10.4%)	22 (10.6%)	7 (10.0%)	
Gender				0.375
Female	76 (27.3%)	54 (26.0%)	22 (31.4%)	
Male	202 (72.7%)	154 (74.0%)	48 (68.6%)	

(*Continued*)

Table 1 (Continued).

Characteristics	All Patients N (%)	Training Cohort N (%)	Validation Cohort N (%)	*P*
Grade				0.421
I	61 (25.3%)	44 (24.0%)	17 (29.3%)	
II–III	180 (74.7%)	139 (76.0%)	41 (70.7%)	
AJCC Stage				0.965
I	30 (12.2%)	23 (12.5%)	7 (11.5%)	
II	28 (11.4%)	20 (10.9%)	8 (13.1%)	
III	112 (45.7%)	84 (45.7%)	28 (45.9%)	
IVa/IVb	75 (30.6%)	57 (31.0%)	18 (29.5%)	
Surgical safety margin				0.325
≥ 5mm	212 (84.8%)	161 (86.1%)	51 (81.0%)	
< 5mm or positive	38 (15.2%)	26 (13.9%)	12 (19.0%)	
ENE				0.235
Negative	224 (80.6%)	171 (82.2%)	53 (75.7%)	
Positive	54 (19.4%)	37 (17.8%)	17 (24.3%)	
VI				0.833
No	209 (83.3%)	156 (83.0%)	53 (83.3%)	
Yes	42 (16.7%)	32 (17.0%)	10 (16.7%)	
Perineural invasion				0.835
No	224 (80.6%)	167 (80.3%)	57 (81.4%)	
Yes	54 (19.4%)	41 (19.7%)	13 (18.6%)	
BMI				0.868
Median (range)	22.5 (15.8–32.9)	22.3 (15.8–32.9)	22.9 (16.0–32.5)	
Hemoglobin (g/L)				0.780
Median (IQR)	111.0 (103.5–121.4)	108.4 (103.8–121.0)	112.1 (102.6–122.2)	
TC (mg/dL)				0.712
Median (IQR)	199.6 (125.1–256.2)	202.0 (125.0–256.4)	198.3 (124.4–252.2)	
Albumin (g/dL)				
Median (IQR)	4.21 (3.90–4.65)	4.20 (3.88–4.63)	4.25 (3.92–4.68)	0.805
Lymphocyte count (/μL)				
Median (IQR)	2.22 (1.49–2.61)	2.20 (1.50–2.60)	2.26 (1.45–2.62)	0.856
CRP (mg/dL)				
Median (IQR)	0.40 (0.15–1.67)	0.38 (0.18–1.60)	0.42 (0.13–1.70)	
CALLY index				0.678
Median (IQR)	1.98 (0.40–8.25)	1.95 (0.50–8.30)	2.04 (0.45–8.50)	
ACCI				0.869
2–5	186 (73.8%)	139 (73.5%)	47 (74.6%)	
≥ 6	66 (26.2%)	50 (26.5%)	16 (25.4%)	
Adjuvant radiotherapy				0.789
No	99 (35.6%)	75 (36.1%)	24 (34.3%)	
Yes	179 (64.4%)	133 (63.9%)	46 (65.7%)	

Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; BMI, body mass index; CALLY, CRP-albumin-lymphocyte; CRP, C-reactive protein; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; HSCC, hypopharyngeal squamous cell carcinoma; IQR, interquartile range; TC, total cholesterol; VI, vascular invasion.

Variables

The subjects of this study were HSCC patients who underwent radical surgery. The primary endpoints of this study were DFS and OS. Multiple clinicopathological and treatment - related variables were included as independent variables: age, gender, eastern cooperative oncology group performance status (ECOG PS), smoking history, tumor differentiation, AJCC pathological stage (8th edition), vascular invasion (VI), perineural invasion, surgical margin status, ENE, CALLY index, age - adjusted Charlson comorbidity index (ACCI), and whether postoperative adjuvant radiotherapy was received. Clinical data were obtained from the electronic medical record system and follow - up records.

Calculation

The CALLY index was calculated as [albumin (g/dL) × lymphocyte count (/μL)]/C-reactive protein (CRP, mg/dL) × 10^4.[28] The optimal cut-off value was 2.38, which was calculated using X-tile software. The BMI was calculated using the formula: weight (kg)/height^2 (m^2). The ACCI was calculated based on a series of comorbidities and age, as detailed in Table S1. All of the indicators above were derived from clinical test data obtained from patients within one week prior to surgery.

Analysis

Statistical analyses were conducted using SPSS software, version 24.0, and R software, version 4.2.2. A P - value of less than 0.05 was deemed to be statistically significant. Initially, the Shapiro–Wilk test was employed to assess the normality of the baseline continuous variables, and the results are presented in Table S2. The subjects were randomly partitioned into a training cohort and a validation cohort, which constituted 75% and 25% of the total sample size, respectively. The disparities in baseline clinical characteristics between the two groups are presented in Table 1. Categorical variables were compared via the $\chi 2$ test. Statistical methods for continuous variables were chosen based on their distribution characteristics. The Mann–Whitney *U*-test was utilized for non - normally distributed data, and the independent sample *t* - test was utilized for normally distributed data. To evaluate the existence of multicollinearity among the independent variables incorporated in the analysis, linear regression analysis was employed to compute the tolerance and variance inflation factor (VIF), and the outcomes are presented in Table S3. A VIF value of 5 or greater was regarded as indicating significant multicollinearity.

Variable screening and the construction of a prediction model were accomplished within the training cohort. Meanwhile, the validation cohort was primarily employed to assess the external validation performance of the model, aiming to test its generalization ability across different datasets. Missing data were managed through various approaches, as detailed in Table S4. Corresponding treatments were implemented based on the missing ratio of each variable. For variables with a missing rate of less than 5%, the complete - case analysis method was utilized to exclude individuals with a small number of missing values, given the limited amount of missing data. Variables with missing rates ranging from 5% to 20% were imputed using predictive mean matching. Upon completion of the imputation process, appropriate regression models were selected for processing according to the variable type: Logistic regression for dichotomous variables and multinomial Logistic regression for multinomial variables, yielding a total of 10 imputed datasets. Subsequently, Cox proportional hazards regression analysis was conducted on each imputed dataset, and the estimated results of each dataset were combined in accordance with Rubin's rule to obtain the combined hazard ratio (HR) and 95% confidence interval (CI), thereby ensuring the stability and reliability of the analysis results.

On this basis, a univariate Cox regression analysis was initially conducted on 14 candidate explanatory variables to screen for potential prognostic factors associated with DFS and OS. Subsequently, a multivariate Cox regression model employing the stepwise backward elimination method was utilized to further identify the independent prognostic factors influencing DFS and OS. Based on the screening of independent prognostic factors, nomograms were constructed to respectively predict DFS and OS.

After the nomogram models were constructed, its prediction performance was comprehensively verified in a systematic manner. The receiver operating characteristic (ROC) curve and calibration curve were plotted to assess the discriminatory ability of the model and the consistency of the prediction results. Simultaneously, decision curve analysis (DCA) was employed to further evaluate the potential net benefit and practicality of the nomogram model in clinical applications. Additionally, integrated discrimination improvement (IDI) and net reclassification improvement (NRI) were computed, and the enhancement of the model's prediction performance compared with the AJCC staging was quantified.

In each nomogram model, each variable is associated with a specific risk score. Patients can calculate their individualized total risk score using the nomogram. The X-tile software was employed to determine the optimal cut -

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off value. Subsequently, patients were classified into different risk subgroups based on this cut-off value to establish an effective prognostic stratification system. The DFS and OS among different risk subgroups were compared using the Kaplan - Meier survival curve and Log rank test. Simultaneously, the benefits of adjuvant radiotherapy for patients in different risk subgroups were investigated.

This study was reported in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines.[34]

Results

Clinical Characteristics

A total of 278 patients diagnosed with HSCC who underwent radical surgical treatment were included in this study. The median age at the time of diagnosis was 51 years (ranging from 22 to 88 years). According to the AJCC staging system, stage I, II, III, and IVA - B accounted for 12.2%, 11.4%, 45.7%, and 30.6% respectively. The median serum albumin level was 4.21 g/dL (interquartile range [IQR]: 3.90–4.65), the median lymphocyte count was $2.22\times10^3/\mu L$ (IQR: 1.49–2.61), and the median CRP level was 0.40 mg/dL (IQR: 0.15–1.67). The median CALLY index was 1.98 (IQR: 0.40–8.25). 64.4% of the patients received postoperative adjuvant radiotherapy. The median DFS and OS were 45.5 months and 57 months, respectively. All patients were randomly allocated into a training cohort (n = 208) and a validation cohort (n = 70) at a ratio of 3:1. As presented in Table 1, there were no significant disparities in the baseline clinicopathological characteristics between the two groups (all P > 0.05), indicating that the two cohorts were highly comparable.

Nomogram Models Development

First, univariate and multivariate Cox proportional hazards regression analyses were conducted to identify independent prognostic factors associated with DFS and OS, respectively. The results are presented in Tables 2 and 3. Multivariate analysis revealed that ECOG performance status score, AJCC stage, surgical margin status, ENE, CALLY index, and

Table 2 Univariate and Multivariate Cox Regression Analysis of Clinicopathologic Factors for DFS in Postoperative HSCC Patients

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
Age at diagnosis (years)	1.008 (0.997–1.019)	0.147		
Gender				
Female	Reference		Reference	
Male	1.657 (1.046–2.626)	**0.031**	1.256 (0.766–2.062)	0.366
ECOG PS score				
0–1	Reference		Reference	
2	1.808 (1.195–2.736)	**0.005**	1.598 (1.038–2.462)	**0.033**
Smoking				
No	Reference			
Yes	1.504 (0.841–2.689)	0.168		
Grade				
I	Reference			
II–III	1.534 (0.999–2.356)	0.048		
AJCC stage				
I	Reference		Reference	
II	1.195 (0.536–2.668)	0.663	1.493 (0.658–3.390)	0.338
III	2.485 (1.345–4.590)	**0.004**	2.221 (1.161–4.247)	**0.016**
IV a&b	2.818 (1.462–5.431)	**0.002**	2.485 (1.252–4.932)	**0.009**

(*Continued*)

Table 2 (Continued).

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
VI				
No	Reference		Reference	
Yes	1.727 (1.062–2.808)	**0.028**	1.006 (0.568–1.782)	0.985
Perineural invasion				
No	Reference		Reference	
Yes	1.854 (1.213–2.834)	**0.004**	1.510 (0.927–2.460)	0.098
Surgical safety margin				
≥ 5mm	Reference		Reference	
< 5mm or Positive	2.409 (1.478–3.926)	**<0.001**	1.864 (1.083–3.208)	**0.025**
ENE				
Negative	Reference		Reference	
Positive	2.540 (1.647–3.916)	**<0.001**	2.209 (1.415–3.449)	**<0.001**
CALLY index				
< 2.38	Reference		Reference	
≥ 2.38	0.578 (0.385–0.867)	**0.008**	0.530 (0.346–0.809)	**0.003**
ACCI				
2–5	Reference		Reference	
≥ 6	2.088 (1.398–3.118)	**<0.001**	1.622 (1.057–2.489)	**0.027**
Adjuvant radiotherapy				
No	Reference			
Yes	0.708 (0.476–1.054)	0.089		

Note: Bold values indicate statistical significance at p<0.05.
Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; BMI, body mass index; CALLY, CRP-albumin-lymphocyte; CRP, C-reactive protein; DFS, disease-free survival; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; HSCC, hypopharyngeal squamous cell carcinoma; IQR, interquartile range; VI, vascular invasion.

Table 3 Univariate and Multivariate Cox Regression Analysis of Clinicopathologic Factors for OS in Postoperative HSCC Patients

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
Age at diagnosis (years)	1.012 (1.001–1.023)	**0.039**	0.996 (0.983–1.009)	0.517
Gender				
Female	Reference			
Male	1.618 (1.008–2.597)	0.046		
ECOG PS score				
0–1	Reference		Reference	
2	1.799 (1.174–2.757)	**0.007**	1.666 (1.068–2.599)	**0.024**
Smoking				
No	Reference			
Yes	1.588 (0.868–2.905)	0.134		
Grade				
I	Reference			
II–III	1.531 (0.985–2.379)	0.059		

(*Continued*)

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Table 3 (Continued).

Characteristics	Univariate Analysis	*P*	Multivariate Analysis	*P*
	HR (95% CI)		HR (95% CI)	
AJCC stage				
I	Reference		Reference	
II	1.177 (0.511–2.713)	0.701	1.629 (0.692–3.833)	0.264
III	2.436 (1.291–4.597)	**0.004**	2.211 (1.149–4.253)	**0.017**
IV a&b	2.839 (1.445–5.579)	**0.002**	2.304 (1.144–4.639)	**0.019**
VI				
No	Reference		Reference	
Yes	1.829 (1.108–3.017)	**0.018**	1.119 (0.621–2.017)	0.707
Perineural invasion				
No	Reference		Reference	
Yes	1.784 (1.149–2.769)	**0.010**	1.433 (0.848–2.422)	0.179
Surgical safety margin				
≥ 5mm	Reference		Reference	
< 5mm or Positive	2.448 (1.496–4.004)	**<0.001**	2.116 (1.256–3.565)	**0.005**
ENE				
Negative	Reference		Reference	
Positive	2.816 (1.797–4.413)	**<0.001**	2.448 (1.540–3.891)	**<0.001**
CALLY index				
< 2.38	Reference		Reference	
≥ 2.38	0.637 (0.421–0.963)	**0.032**	0.578 (0.376–0.890)	**0.013**
ACCI				
2–5	Reference		Reference	
≥ 6	2.513 (1.666–3.790)	**<0.001**	2.002 (1.297–3.092)	**0.002**
Adjuvant radiotherapy				
No	Reference			
Yes	0.676 (0.446–1.025)	0.065		

Note: Bold values indicate statistical significance at p<0.05.
Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; BMI, body mass index; CALLY, CRP-albumin-lymphocyte; CRP, C-reactive protein; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; HSCC, hypopharyngeal squamous cell carcinoma; IQR, interquartile range; OS, overall survival; VI, vascular invasion.

ACCI were independently associated with both DFS and OS. Based on these significant prognostic factors, a nomogram was developed to predict 3-year and 5-year probabilities of DFS (Figure 2A) and OS (Figure 2B) for postoperative HSCC patients. In this nomogram, each variable is assigned a point value corresponding to its relative contribution to the outcomes. A total score can be calculated by summing the points for individual patient characteristics, enabling a quantitative and intuitive estimation of predicted survival probabilities. Figure 2 includes an illustrative example demonstrating the practical application of the nomogram in a clinical context.

Nomogram Models Validation

Based on the ROC curve analysis, the prediction model demonstrated excellent discriminative ability in both the training set and the validation set (Figure 3). As shown in Figure 3A and B, the AUCs for predicting 3-year and 5-year DFS were 0.801 and 0.783 in the training set, and 0.812 and 0.803 in the validation cohort, respectively. Furthermore, for OS prediction, the model achieved AUCs of 0.811 and 0.781 in the training set, and 0.819 and 0.804 in the validation set, as presented in Figure 3C and D, respectively. The trend of the calibration plot exhibits a relatively high degree of consistency with the diagonal line, which suggests a favorable alignment between the predicted risk probability and the actual observed results (see Figure 4). In decision curve analysis, the model was compared with the reference strategies of "treating all patients" and "treating no patients". The findings indicated that the decision curve of the model

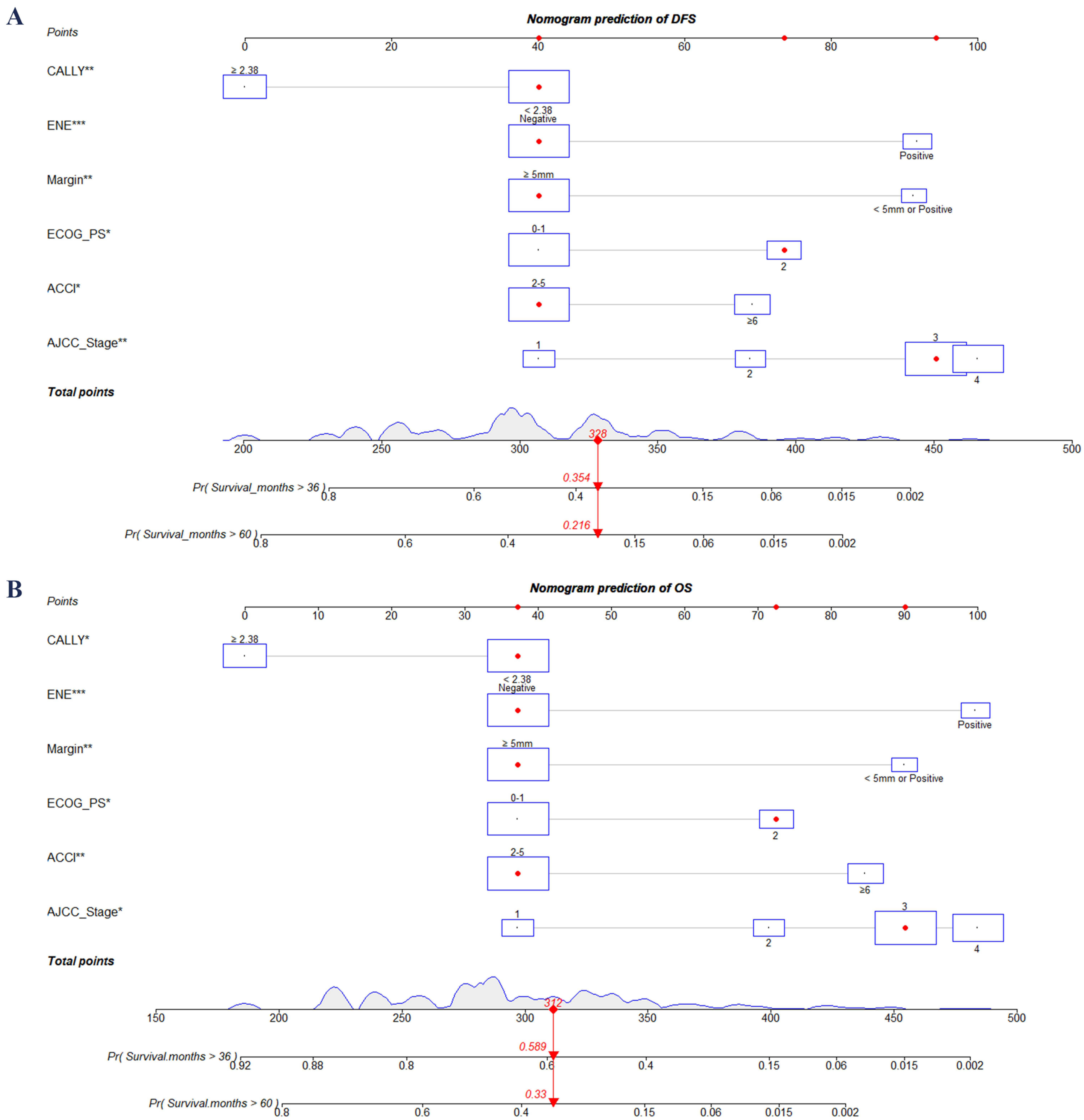

Figure 2 Nomogram prediction models for DFS and overall survival OS in patients with postoperative HSCC. (**A**) depicts the predictive nomogram for DFS, while (**B**) depicts the predictive nomogram for OS. *P < 0.05; **P < 0.01; ***P < 0.001.
Abbreviations: ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; CALLY, CRP-albumin-lymphocyte; CRP, C-reactive protein; DFS, disease-free survival; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; HSCC, hypopharyngeal squamous cell carcinoma; OS, overall survival.

was above the aforementioned reference lines across most threshold probability ranges, implying its potential practical application value in diverse clinical decision - making scenarios. More significantly, within the vast majority of threshold probability intervals, the newly developed nomogram model attained higher net benefits than the AJCC staging system, further substantiating its advantages in clinical risk assessment (Figure 5). To assess the predictive superiority of the nomogram compared to the AJCC staging system, we computed the IDI and NRI. The findings indicated that in both the training dataset and the validation dataset, the IDI and NRI values of the nomogram for forecasting 3-year and 5-year

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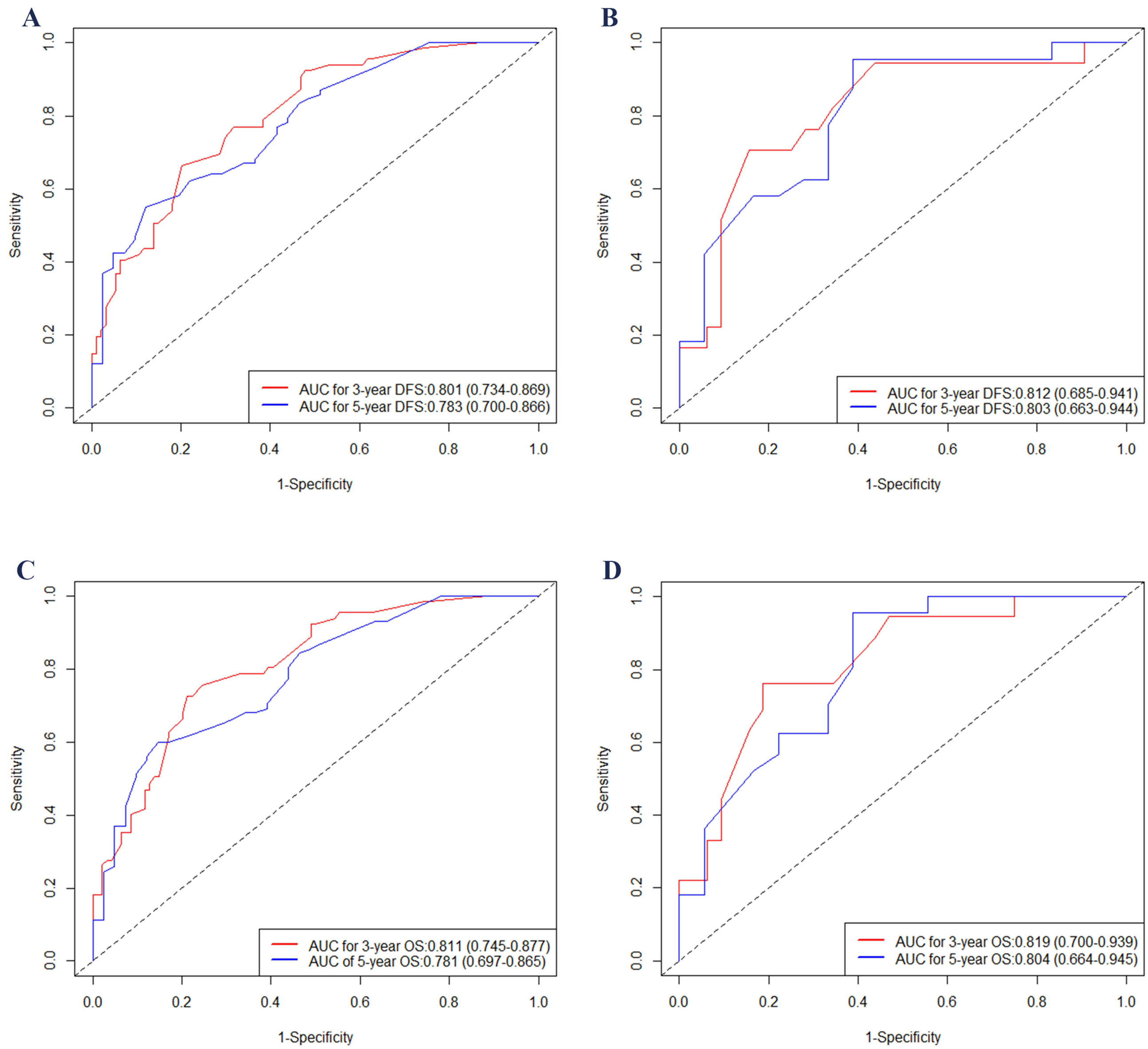

Figure 3 The time-dependent ROC analysis of the nomograms for DFS and OS in the training and validation cohorts. (**A** and **B**) illustrate the AUC for 3-year and 5-year DFS, while (**C** and **D**) depict the AUC for 3-year and 5-year OS.
Abbreviations: AUC, area under curve; OS, overall survival; DFS, disease-free survival; ROC, receiver operating characteristic.

DFS and OS were positive and statistically significant (all P < 0.001), suggesting that its predictive performance was markedly superior to that of the conventional AJCC staging system (Table 4).

Risk Stratification System

Patients were categorized into high-, medium-, and low-risk groups according to the total risk score using X-tile software (Table S5). Specifically, for DFS, the high-risk group had a score of ≥ 170.5 points, the medium-risk group had a score ranging from 100.5 to 165.4 points, and the low-risk group had a score of ≤ 98.4 points. For OS, the high-risk group had a score of ≥ 173.5 points, the medium-risk group had a score ranging from 91.2 to 169.2 points, and the low-risk group had a score of ≤ 90.1 points. Kaplan - Meier curves indicated significant disparities in DFS and OS among different risk groups (Figure 6), which implies that risk stratification can effectively differentiate survival outcomes. Moreover, patients in the high - and medium - risk groups who underwent adjuvant radiotherapy experienced an improved prognosis, whereas no benefit was detected in the low - risk group (detailed in Table S5 and Figure 7).

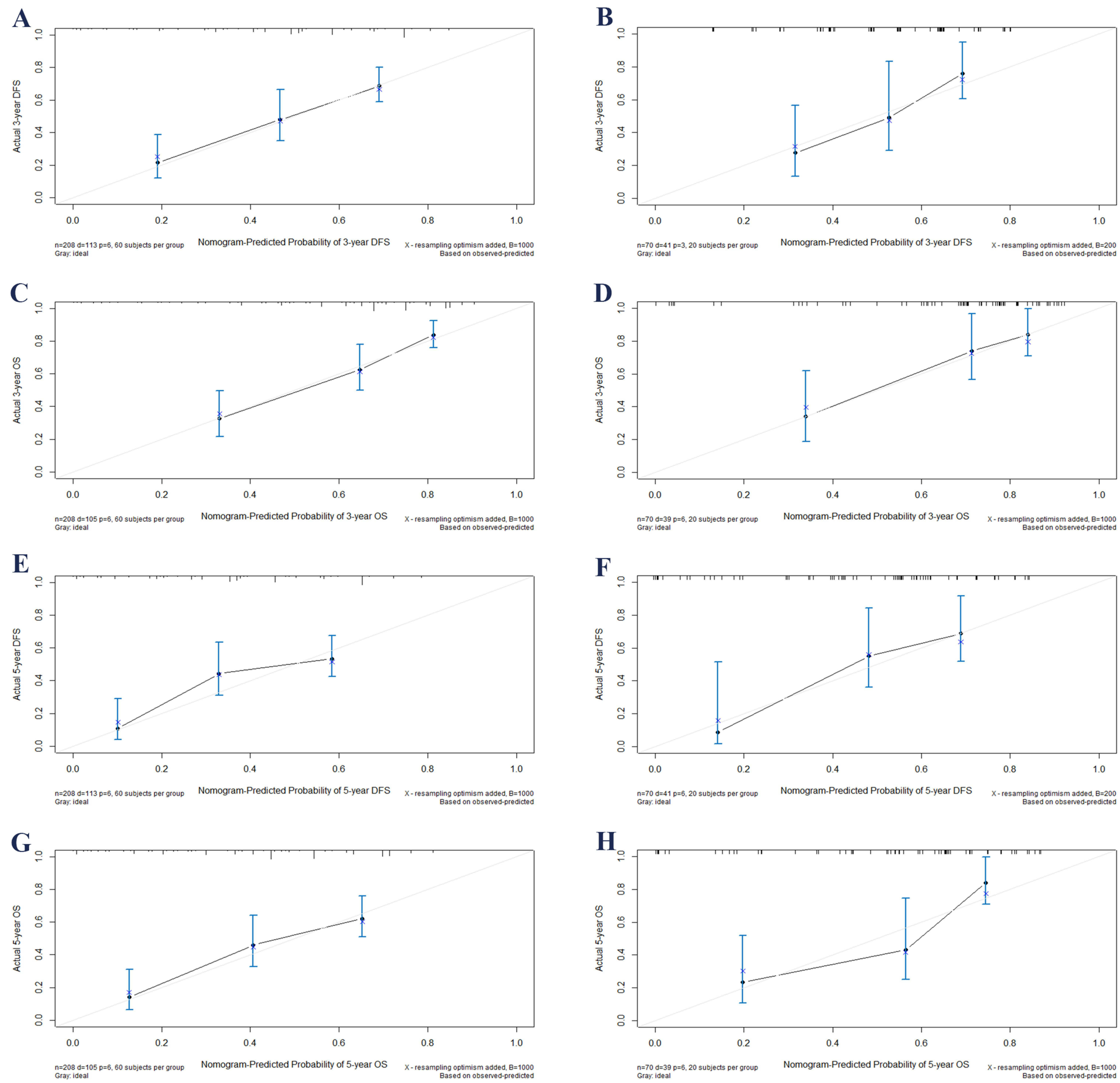

Figure 4 Calibration plots for 3- and 5-year DFS and OS in postoperative HSCC patients. Calibration plots of 3-, and 5-year DFS in the training cohort (**A** and **E**), as well as in the validation cohort (**B** and **F**). Calibration plots of 3-, and 5-year OS in the training cohort (**C** and **G**), as well as in the validation cohort (**D** and **H**).
Abbreviations: HSCC, hypopharyngeal squamous cell carcinoma; OS, overall survival; DFS, disease-free survival.

Discussion

With the continuous accumulation of clinical data, precise individualized prognosis assessment has emerged as an essential component of personalized medical care. In this context, diverse predictive models have been extensively utilized in tumor prognosis assessment.[24] Their predictive performance in various malignant tumors surpasses that of the traditional AJCC TNM staging system,[23,24] and thus they are regarded as a significant supplement to AJCC staging. For the specific cohort of HSCC patients who have undergone radical surgery, several nomograms and risk stratification models have been developed in relevant research, offering references for prognosis assessment and clinical decision - making.[20,35–37] Based on this, our study integrated novel clinical indicators such as the CALLY index and ACCI to develop and validate a nomogram model for predicting the DFS and OS of HSCC patients post - surgery. The results indicated that the newly established nomogram model exhibited good discriminatory ability in the prediction of DFS and

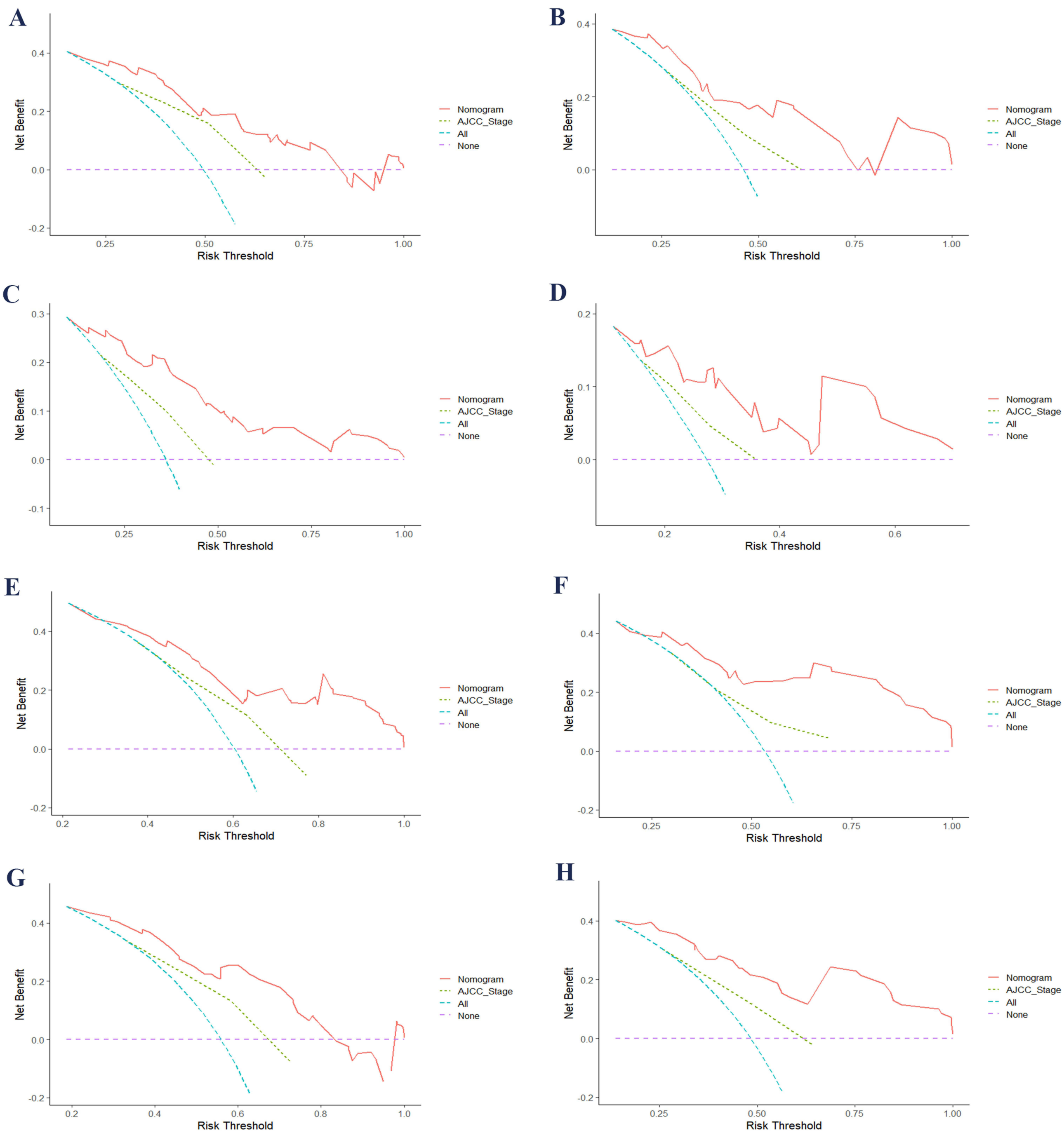

Figure 5 DCA comparing the nomograms with the AJCC staging system for DFS and OS. DCA plots for 3- and 5-year DFS in the training (**A** and **E**) and validation (**B** and **F**) cohorts, as well as 3- and 5-year OS in the training (**C** and **G**) and validation (**D** and **H**) cohorts.
Abbreviations: AJCC, American Joint Committee on Cancer; DCA, decision curve analysis; DFS, disease-free survival; OS, overall survival.

Table 4 The NRI, and IDI of the Nomograms Compare to AJCC Stage System for DFS and OS Prediction

	Training Cohort		*P*	Validation Cohort		*P*
	Value	95% CI		Value	95% CI	
IDI (vs AJCC stage)						
For 3-year DFS	0.135	0.049–0.213	**<0.001**	0.178	0.096–0.318	**<0.001**
For 5-year DFS	0.110	0.033–0.203	**<0.001**	0.182	0.096–0.321	**<0.001**
For 3-year OS	0.184	0.097–0.303	**<0.001**	0.210	0.094–0.371	**<0.001**
For 5-year OS	0.134	0.061–0.220	**<0.001**	0.203	0.067–0.408	**<0.001**
NRI (vs AJCC stage)						
For 3-year DFS	0.401	0.070–0.547	**<0.001**	0.280	0.062–0.626	**<0.001**
For 5-year DFS	0.366	0.150–0.488	**<0.001**	0.402	0.166–0.638	**<0.001**
For 3-year OS	0.412	0.219–0.574	**<0.001**	0.388	0.147–0.670	**<0.001**
For 5-year OS	0.414	0.198–0.522	**<0.001**	0.392	0.101–0.708	**<0.001**

Note: Bold values indicate statistical significance at p<0.05.
Abbreviations: AJCC, American joint committee on cancer; CI, confidence interval; DFS, disease-free survival; IDI, integrated discrimination improvement; NRI, net reclassification index; OS, overall survival.

OS (C - indexes were 0.736 and 0.720, respectively), suggesting that it can offer a more precise instrument for risk stratification and clinical decision - making for postoperative HSCC patients.

A range of indicators reflecting the body's nutritional status and inflammatory levels has gradually garnered attention and is increasingly recognized as potential prognostic biomarkers for tumors.[38–45] These markers are not only valuable in assessing the risk of postoperative complications but also play a significant role in predicting the prognosis of various malignant tumors.

Among a multitude of inflammation - nutrition - related indicators, CRP levels are frequently employed to evaluate the body's inflammatory state.[46] Serum albumin levels serve as assessment indicators for patients' nutritional status,[47–49] and it is well - established that lymphocyte counts are used as indicators reflecting immune function. The molecular and immunologic underpinnings of multiple head and neck cancers provide a mechanistic rationale for the observed prognostic impact of inflammation–nutrition indices. Litsou et al highlighted that specific molecular pathways and immune interactions significantly influence tumor behavior and patient outcomes,[50] supporting the inclusion of systemic markers such as the CALLY index in risk stratification. The CALLY index comprehensively reflects nutritional status, immune function, and inflammatory level. It was initially proposed by Iida H et al[28] This study was conducted on 384 patients with hepatocellular carcinoma who underwent hepatectomy in four university hospitals in Japan, and it was found that the CALLY index was an independent factor influencing prognosis. This discovery offers clinicians a straightforward and efficient tool for the early assessment of patients overall health status, thereby providing a robust foundation for individualized treatment strategies. With the introduction of this index, the utilization of the CALLY index has progressively extended to multiple medical domains. In the realm of internal medicine, the CALLY index is extensively employed to evaluate diseases associated with malnutrition, immunosuppression, and systemic inflammatory response, particularly in the prognostic assessment of various internal ailments such as autoimmune disorders,[51] cardiovascular diseases,[52] cerebrovascular diseases,[53] chronic obstructive pulmonary disease (COPD),[54] and sarcopenia.[55] In these areas, the CALLY index, serving as a comprehensive biomarker, not only aids in survival prediction but also effectively directs the selection of treatment strategies, especially for patients with malnutrition or abnormal immune - regulatory function.

With the deepening of research, an increasing number of studies have focused on the relationship between the CALLY index and malignant tumors, achieving remarkable clinical results. Kazuhiro Mizota et al found in a retrospective study of 1215 patients with surgically resected non-small cell lung cancer that the CALLY index was an independent prognostic factor for both recurrence-free survival (RFS) and OS.[30] This is comparable to the conclusion of another study conducted on the population suffering from non - small cell lung cancer.[56] Within the domain of digestive system tumors, the CALLY index has been extensively utilized in the prognostic evaluation of esophageal

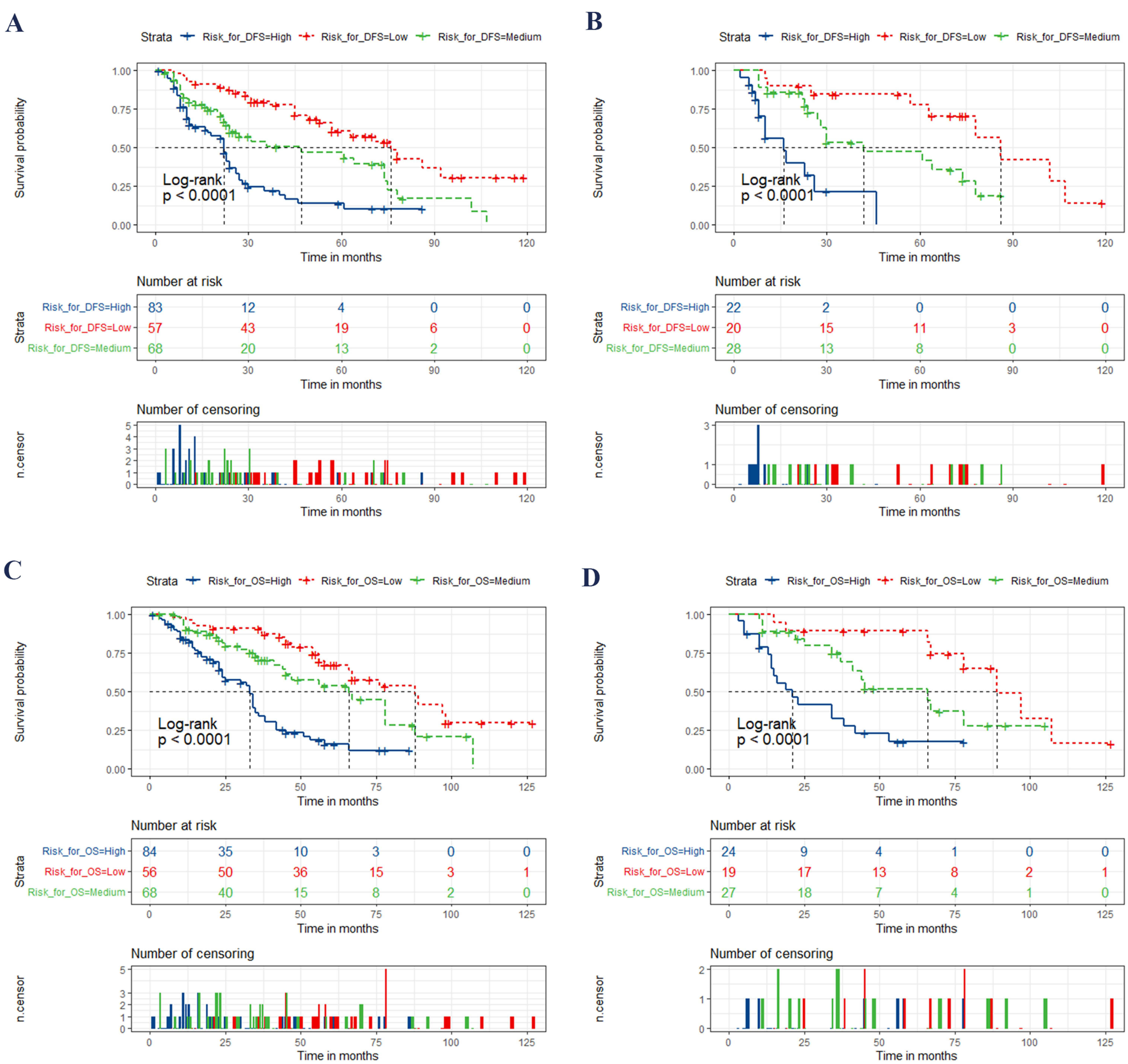

Figure 6 Kaplan-Meier curves for HSCC patients undergone radical surgery based on the new risk stratification system. Prediction of DFS (**A** and **B**) and OS (**C** and **D**) in training and validation cohorts.

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

cancer, colorectal cancer, gastric cancer, and other related malignancies. The research conducted by Ma Ruiya et al indicates that a low CALLY index serves as an independent prognostic factor in patients with esophageal cancer for both overall survival and disease - free survival, and it is also an independent predictor of postoperative surgical site infection.[57] A retrospective analysis of patients diagnosed with colorectal cancer indicated that the CALLY index serves as an independent prognostic factor for OS, and the nomogram model is capable of more precisely predicting the prognosis of patients and outperforms the TNM staging.[29] Another retrospective analysis of gastric cancer patients in the International Study of Cancer Outcomes and Clinical Care (INSCOC) database demonstrated that patients with a CALLY > 1.12 exhibited a significantly longer overall survival period compared to those with a CALLY ≤1.12, implying that the CALLY index possesses independent prognostic value for gastric cancer.[32] Furthermore, researchers have discovered that the CALLY index is independently correlated with OS and RFS in patients who have undergone radical resection for intrahepatic cholangiocarcinoma.[58] This study also established a nomogram model based on this index, which is more

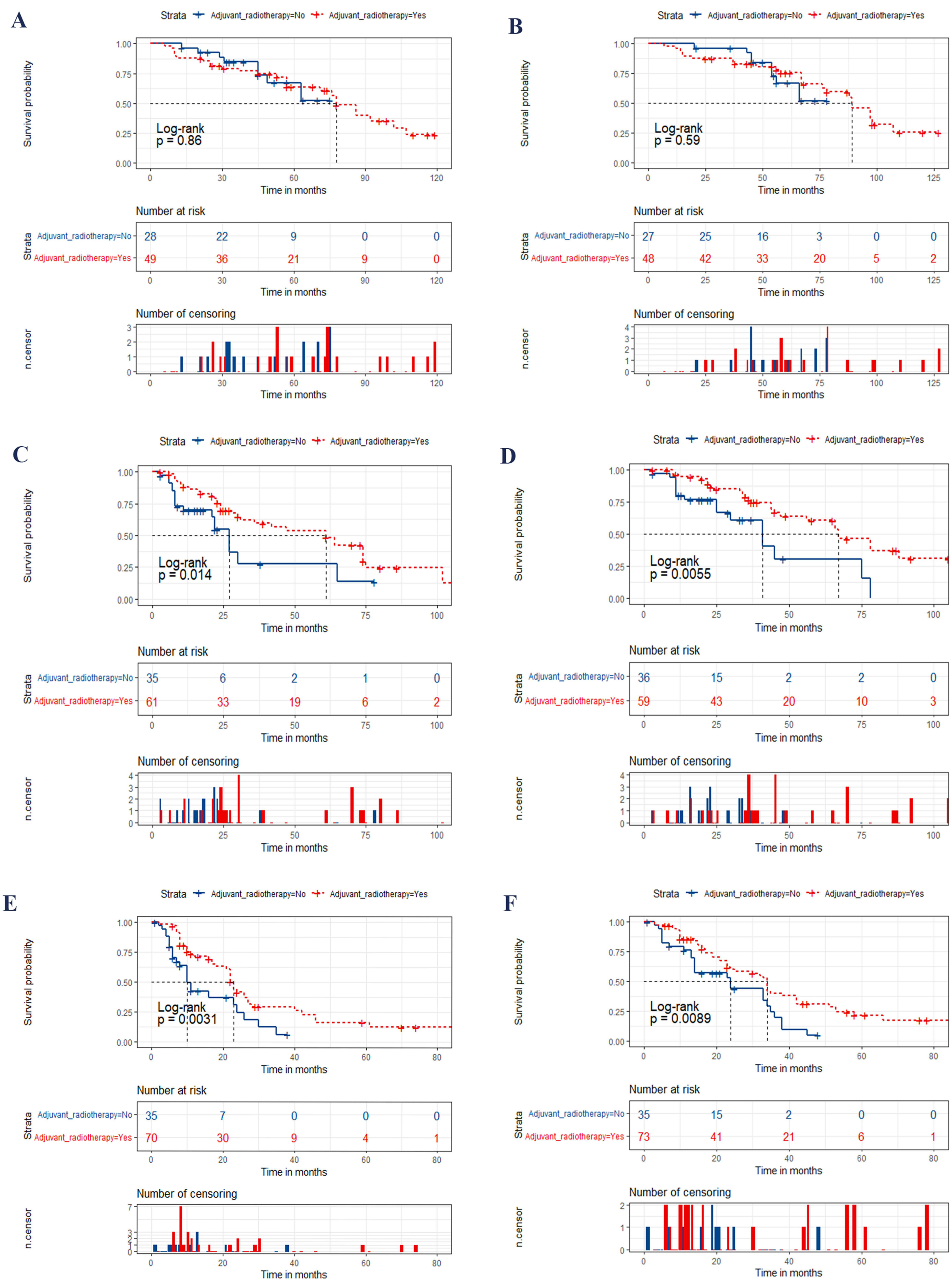

Figure 7 Kaplan–Meier curves based on the newly developed risk stratification system were used to evaluate the effect of adjuvant radiotherapy on DFS and OS across different risk groups. Curves (**A, C**, and **E**) depict the impact of adjuvant radiotherapy on DFS in the high-, medium-, and low-risk groups, respectively, while curves (**B, D**, and **F**) illustrate the corresponding effects on OS in the high-, medium-, and low-risk groups.

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

effective than TNM staging in predicting long - term survival ability. The application and exploration of the CALLY index in head - and - neck tumors are relatively limited. A retrospective study was conducted to analyze the prognostic value of the CALLY index in patients with oral squamous cell carcinoma who had undergone radical surgery. The study found that a CALLY index < 0.65 was significantly associated with poorer OS and DFS, and this index was an independent prognostic risk factor.[31] In the research on HSCC, a single - center study incorporated 71 patients diagnosed with hypopharyngeal squamous cell carcinoma who underwent radical chemoradiotherapy.[59] It was discovered that patients with a CALLY index equal to or greater than 1.47 exhibited significantly superior median Progression - Free Survival, Local Recurrence - Free Survival, and OS. Moreover, the CALLY index emerged as an independent prognostic factor in the multivariate analysis. Nevertheless, this study did not encompass HSCC patients who received surgical treatment. Consequently, this study can act as a significant addition to the prior research. These previous research results not only prove the clinical application value of the CALLY index in multiple tumor types, but also further promote the importance of this indicator in individualized treatment, especially in postoperative assessment, recurrence risk prediction and chemotherapy response monitoring, demonstrating broad potential and practical application prospects. Building upon prior research, this study investigates the prognostic utility of the CALLY index in patients with HSCC following surgical resection. The findings aim to address an existing gap in the literature and advance the development of a more precise, individualized prognostic assessment tool for this patient population.

Comorbidities exert an adverse influence on the prognosis of HSCC.[60–62] The ACCI is a commonly utilized tool for evaluating comorbidities among patients with malignant tumors. By comprehensively taking into account the influence of various comorbidities on prognosis and integrating the patient's age factor, it facilitates the assessment of the overall health status, the prediction of the patient's prognosis, and the provision of an indication of the patient's tolerance to treatment.[41,63–67] In this study, the ACCI was verified as an independent prognostic factor for HSCC patients following surgery, significantly impacting DFS and OS (all $p < 0.05$), which is in line with previous research.[7,68] Further analysis demonstrated that patients with ACCI ≥ 6, typically accompanied by multiple comorbidities or an advanced age, have a less favorable prognosis. Incorporating the ACCI into the nomogram can aid clinicians in better balancing aggressive treatment and the patient's tolerance when formulating treatment plans.

ECOG PS is a widely-adopted standard for assessing the functional status of cancer patients, with its score directly reflecting patients' capabilities in performing daily activities and their physical well-being, and demonstrating a significant correlation with prognosis across diverse malignant tumors.[69–71] In this study, patients with an ECOG PS score of 2 exhibited a comparatively poorer prognosis, which is in line with the findings reported in previous studies.[72,73] A suboptimal functional status often implies a less favorable prognosis, potentially because of patients' inferior overall health conditions, which can influence their treatment tolerance and treatment outcomes. Patients with a higher ECOG PS score typically experience more advanced disease progression and may present with multiple comorbidities, resulting in a shorter survival period and a less satisfactory treatment response.

This study discovered that certain indicators in pathological examination reports (ENE and surgical margin) were also significantly correlated with prognosis and were ultimately incorporated into the model. ENE denotes the spread of cancer beyond the lymph nodes, which serves as a crucial prognostic factor for head and neck cancers and can notably impact the survival duration of patients.[74–77] In our research, multivariate Cox regression analysis indicated that positive ENE was linked to poor DFS and OS, which was in line with existing studies.[78–80] The surgical safety margin represents an important influencing factor for the prognosis of head and neck tumors. Although diverse studies have varying definitions of "close margin", a larger safety margin is generally associated with a more favorable prognosis,[81–83] which was also validated in this study. Clinical research and clinical guidelines suggest that for patients with ENE or close margins, more aggressive postoperative adjuvant therapy, such as adjuvant concurrent chemoradiotherapy, might be required.[6,84]

Regarding postoperative adjuvant therapy, existing evidence underscores its pivotal role in enhancing local tumor control and mitigating recurrence risk in hypopharyngeal carcinoma.[72,73] This study also investigated the role of postoperative adjuvant radiotherapy in enhancing survival. Building upon the risk stratification system established by the risk score of the prognostic model, our research further determined that not all patients within the risk subgroups could attain an improvement in survival after undergoing adjuvant radiotherapy. Notably, high- and medium-risk patients demonstrated statistically significant improvements in both DFS and OS. In contrast, low-risk patients derived no discernible survival advantage - neither in DFS nor in OS - while remaining exposed to the potential toxicities associated with radiotherapy. However, it is important to note that despite the lack of a significant survival advantage observed in this subgroup of patients, approximately 64% of the low - risk patients in this study still underwent adjuvant radiotherapy (Table S5). This may reflect the consideration of traditional high - risk pathological features (eg, positive margins, ENE) in clinical practice. Therefore, for low - risk patients, decisions regarding whether to administer adjuvant radiotherapy should be made on an individualized and prudent basis, taking into account the clinical realities, rather than relying solely on risk scores. These findings suggest that risk stratification methods can offer a reference for adjuvant treatment decisions. However, whether omitting adjuvant radiotherapy is a clinically justifiable and patient - centered strategy for low - risk individuals necessitates further validation through prospective studies.

This study represents the first endeavor to investigate the relationship between the CALLY index and DFS as well as OS among patients subsequent to HSCC surgery. The findings indicate that patients with a CALLY index ≥ 2.38 exhibit a more favorable prognosis regarding DFS and OS, with statistically significant results ($p < 0.05$), thereby offering a novel reference for clinical treatment. Moreover, the incorporation of the CALLY index into the prognostic nomogram model constitutes an innovative attempt. Through a variety of rigorous validation methods, we have confirmed that the new model demonstrates excellent performance and outperforms the traditional AJCC staging system in terms of its effectiveness. Although this study offers significant clinical evidence for the prognosis assessment, it is not without limitations. First, the sample size is relatively small, which can compromise the statistical power, elevate the risk of estimation bias and random variation, and consequently undermine the robustness and reproducibility of the results. Second, as a retrospective study, it relies on historical case - based data, which may give rise to retrospective bias. Moreover, the complete case analysis method or multiple imputation method was employed to address the missing data. Despite the widespread use of these methods in handling missing data, they may still introduce selective bias, thus affecting the external validity of the conclusion. Although the nomogram model was evaluated in the internal training set and an independent validation set in this study, the generalization ability of the model requires verification through large - scale, multi - center prospective cohort studies. In particular, its applicability across different regions, treatment regimens, and disease stages necessitates further confirmation. Finally, certain potential prognostic factors were not incorporated into the study, including lifestyle, psychological state, economic status, educational level, treatment compliance, surgical techniques, pain score, etc. Future studies could incorporate more clinical variables to enhance the accuracy of risk stratification and predictive capacity.

Conclusion

This study discovered that the CALLY index serves as an independent prognostic factor for DFS and OS in HSCC patients following radical surgery. Moreover, a nomogram model was constructed based on the CALLY index and other clinicopathological factors, and its performance surpasses that of the AJCC staging system. Furthermore, adjuvant radiotherapy might provide potential survival advantages to high - risk and medium - risk subgroups, whereas low - risk patients may not derive benefits from it.

Abbreviations

ACCI, age-adjusted Charlson comorbidity index; AJCC, American Joint Committee on Cancer; AUC, area under the curve; BMI, body mass index; CALLY, CRP-albumin-lymphocyte; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRT, conformal radiotherapy; DCA, decision curve analysis; DFS, disease-free survival; ECOG PS, eastern cooperative oncology group performance status; ENE, extranodal extension; HR, hazard ratio; HSCC, hypopharyngeal squamous cell carcinoma; IDI, integrated discrimination improvement; IMRT, intensity - modulated radiotherapy; INSCOC, International Study of Cancer Outcomes and Clinical Care; IQR, interquartile range; OS, overall survival; RECORD, REporting of studies Conducted using Observational Routinely-collected health Data; RFS, recurrence-free survival; ROC, receiver operating characteristic; TC, total cholesterol; TNM, Tumor-Node-Metastasis; VI, vascular invasion; VIF, variance inflation factor; VMAT, volumetric - modulated arc therapy.

Data Sharing Statement

The corresponding author can provide the data upon a reasonable request.

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Xinxiang Medical University (Ethics approval number: EC-LW026-019). Informed consent was formally waived by the Ethics Committees due to the retrospective nature of this study.

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Author Contributions

XM; Data curation, Formal analysis, Visualization, Writing – original draft. JW; Investigation, Data curation, Writing – review & editing. WS; Investigation, Data curation, Writing – review & editing. SY; Investigation, Data curation, Writing – review & editing. KZ; Investigation, Data curation, Writing – review & editing. XL; Investigation, Data curation, Writing – review & editing. KC; Investigation, Data curation, Writing – review & editing. LT; Investigation, Data curation, Writing – review & editing. HC; Methodology, Formal analysis, Funding acquisition, Writing – original draft, Writing – review & editing. XX; Conceptualization, Methodology, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing. All authors 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

All the authors declare no conflicts of interest, financial or otherwise, related to the research.

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