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ORIGINAL RESEARCH

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Nomograms for predicting the survival rate of stage T1–T2 uterine cervical adenocarcinoma patients after hysterectomy

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Abstract

To explore factors associated with the overall survival (OS) and cancer-specific survival (CSS) of patients with stage T1–T2 uterine cervical adenocarcinoma (UAC) after hysterectomy and develop nomogram models to predict their prognosis. The data of stage T1–T2 UAC patients after hysterectomy, diagnosed from 2004 to 2015 in the Surveillance, Epidemiology, and End Results (SEER) database, were retrieved and divided into a training cohort (n = 2103) and internal validation cohort (n = 1052). Another dataset of eligible patients (n = 107) diagnosed from 2013 to 2019 at the Fujian Maternal and Child Health Hospital was retrieved as the external validation set. Nomograms were developed by the results of univariate and multivariate Cox regression models of OS and CSS. C-index, calibration curve, receiver operating characteristic (ROC) curve and area under the curve (AUC) value were used to assess the prediction model. Age, race, marital status, tumor grade, T stage, tumor size and number of positive lymph nodes were identified as independent prognostic factors for OS and CSS. The number of primary tumors was a specific influencing factor for OS, and postoperative radiotherapy was a beneficial factor for CSS. The C-indexes of OS and CSS nomograms constructed in this study in the training cohort were 0.825 (0800–0.850) and 0.820 (0.789–0.851), higher than the 0.701 (0.671–0.731) and 0.735 (0.702–0.768) of the International Federation of Gynecology and Obstetrics (FIGO) stage, $p < 0.001$. The prediction ability of the nomogram models was successfully validated in both the internal and external validation cohorts. The established nomogram models had high prediction accuracy for predicting the OS and CSS of stage T1–T2 UAC patients after hysterectomy and were superior to the FIGO stage. They could help clinicians accurately predict patients' prognoses and select the best treatment plan.

Keywords

Uterine cervical adenocarcinoma; Overall survival; Cancer-special survival; Nomogram; FIGO

1. Introduction

Cervical cancer is the most common malignant tumor of the female reproductive system [1]. Uterine cervical adenocarcinoma (UAC) is the second commonly seen histological type of cervical cancer, whose absolute incidence has been going up over the recent years [2], especially in young women of childbearing age [3, 4]. Currently, UAC accounts for about 20% of all cervical cancers [5].

Some studies have shown that the epidemiology, transmission and recurrence patterns, as well as the prognosis factors of UAC, are differ from those of squamous cell carcinoma (SCC) [6, 7]. However, the National Comprehensive Cancer Network (NCCN) guidelines recommend similar treatment strategies for UAC and SCC. Presently, radical surgery or concurrent chemoradiotherapy (CCRT) is the main therapy method for early UAC [8]. Data analysis of the Surveillance, Epidemiology and End Results (SEER) from 2004 to 2016 showed that >60% of patients with UAC underwent surgery, while only 12.7% underwent CCRT [9]. However, there are no specific prognostic and clinical decision tools for early UAC patients undergoing hysterectomy. These patients still use the International Federation of Gynecology and Obstetrics (FIGO) stage to predict prognosis and guide therapy. However, FIGO stage only included the anatomical characteristics of cancer, neglecting other prognostic factors, such as age, race, tumor grade and so on [10]. Even though the retroperitoneal lymphatic status was included in the FIGO system in 2018, there are still significant survival differences among patients of the same FIGO stage [11], especially for those with larger tumors. Therefore, it is very important to construct a specific prognostic tool to help clinicians accurately predict the prognoses of

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early UAC patients undergoing hysterectomy and propose the optimal treatment plan to improve treatment outcomes.

Nomogram is a visual prediction model used to generate the probability of clinical events for individual patients [12, 13]. It is widely applied to the prognosis assessment of many kinds of cancers, including cervical squamous cell carcinoma, lung carcinoma and prostatic carcinoma [14, 15]. In this study, we developed the nomogram models for patients with stage T1–T2 UAC undergoing hysterectomy to predict their survival based on the Surveillance, Epidemiology and End Results (SEER) database.

2. Materials and methods

2.1 Data source

The SEER program covers about 32% patients with malignant tumor in the United States [16]. For this study, we screened the data of patients with UAC between 2004 and 2015 from the SEER-18 database by the SEER*stat software (version 8.3.6; National Cancer Institute, Rockville, MD, USA). The primary tumor site codes were: C53.0–53.1 and C53.8–53.9. The histology codes were: 8140–8490 [17]. Another dataset of UAC patients meeting the same standards at the Department of Obstetrics and Gynecology of Fujian Maternity and Child Health Hospital from 2013 to 2019 were used as the external validation. All patients were followed up regularly, every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. This was a retrospective study and did not include any personal identifying data or patients' information. All Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were followed and this study was according to the Declaration of Helsinki. Patients from the SEER database were randomized to a training cohort or an internal validation cohort in a 2:1 ratio. Patients from the Fujian Maternity and Child Health Hospital were used as an independent external validation cohort.

2.2 Inclusion and exclusion criteria

The study inclusion criteria were: (1) patients from the SEER database diagnosed from 2004 to 2015; patients from the Fujian Maternity and Child Health Hospital diagnosed from 2013 to 2019; (2) cervical adenocarcinoma was the first primary tumor; (3) classified as the American Joint Committee for Cancer (AJCC) tumor stage T1–T2. The exclusion criteria were: (1) pathological types of non-adenocarcinoma; (2) presence of distant metastasis or M1 disease; (3) tumors classified as AJCC tumor stages T3 and T4; (4) died of surgical complications (postoperative survival time <1 month); (5) received preoperative, intraoperative radiotherapy or CCRT. All patients underwent total or radical hysterectomy together with lymph biopsy or resection. Collect all their clinical information, including demographic, clinical, therapeutic and survival data. The flowchart is shown in Fig. 1.

2.3 Variables

The patients' detailed collected information included age, race, marital status, histology, tumor grade, AJCC T stage, AJCC N stage, hysterectomy type, radiation, chemotherapy, tumor size, number of positive lymph nodes (LNs), number of LNs examined, multi-primary tumors, survival state, survival time. Age was classified as $\leq$39, 40–59 and $\geq$60 years old. Race was divided into white, black and others. Marital status was divided into married, single and others. The other definitions were widowhood, divorce and separation. Tumor histology was divided into adenocarcinoma, endometrioid carcinoma, clear cell adenocarcinoma, mucinous adenocarcinoma, serous/papillary adenocarcinoma, and rare type adenocarcinoma. Concerning tumor grading, owing to the limited number of grade IV cases, grade III and IV cases were combined into a group. Thus, tumor grade was divided into grades I, grades II and grades III–IV. The AJCC T stage was subdivided into T1A, T1B and T2, and the AJCC N stage into N0 and N1. Hysterectomy types were divided into total (pan/simple), radical and NOS (Not Other Specific). The status of chemotherapy and radiotherapy was recorded as Yes or No. Tumor size was defined as the maximum diameter of tumor, which was divided into three groups: $\leq$2.0 cm, 2.1–4.0 cm and $>$4.0 cm [18]. According to previous studies, patients with different number of positive LNs have different prognoses, so the number of positive lymph nodes was divided into 0, 1–3 and $>$3 [19]. The number

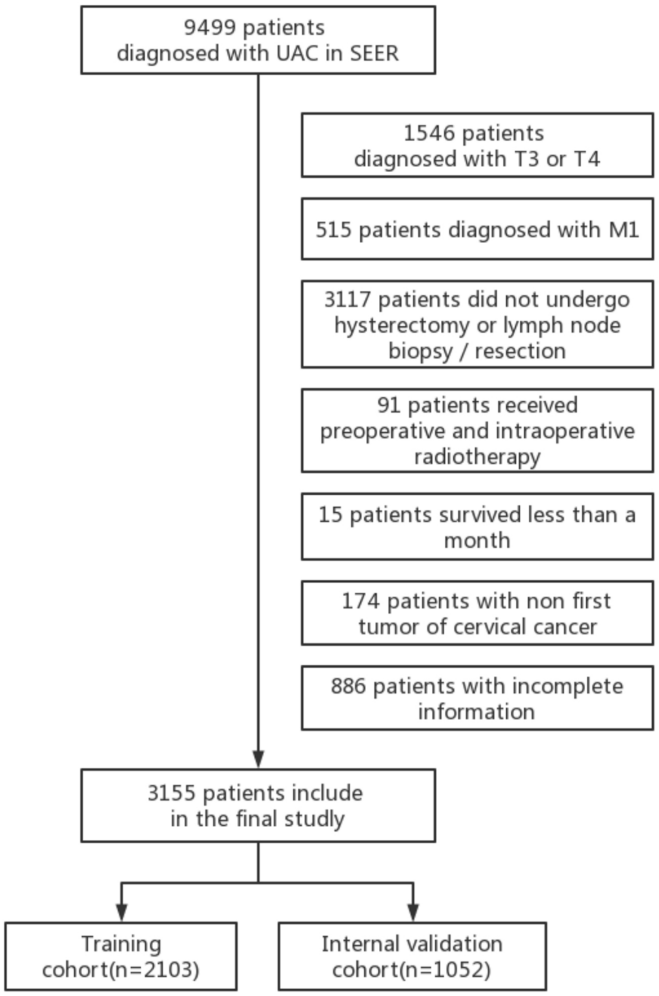

FIGURE 1. Flowchart of the data process. UAC: uterine cervical adenocarcinoma; SEER: Surveillance, Epidemiology and End Results.

TABLE 1. Demographic and clinical characteristics of the training cohort and the internal validation cohort.

Variables	Training Cohort (n = 2103) n (%)	Internal Validation Cohort (n = 1052) n (%)	*p*-Value
Age (yr)			
≤39	723 (34.4)	346 (32.9)	0.159
40–49	726 (34.5)	397 (37.7)	
50–59	366 (17.4)	188 (17.9)	
≥60	288 (13.7)	121 (11.5)	
Race			
white	1783 (84.8)	890 (84.6)	0.966
black	98 (4.7)	48 (4.6)	
others	222 (10.6)	114 (10.8)	
Marital Status			
married	1316 (62.6)	672 (63.9)	0.772
single	462 (22.0)	222 (21.1)	
others	325 (15.5)	158 (15.0)	
Histology			
adenocarcinoma	1473 (70.0)	740 (70.3)	0.993
endometrioid carcinoma	195 (9.3)	97 (9.2)	
clear cell adenocarcinoma	59 (2.8)	32 (3.0)	
mucinous adenocarcinoma	189 (9.0)	88 (8.4)	
serous/papillary adenocarcinoma	58 (2.8)	30 (2.9)	
rare type adenocarcinoma	129 (6.1)	65 (6.2)	
Grade			
Grade I	780 (37.1)	393 (37.4)	0.848
Grade II	910 (43.3)	444 (42.2)	
Grade III and IV	413 (19.6)	215 (20.4)	
Stage T			
T1A	404 (19.2)	216 (19.9)	0.506
T1B	1520 (72.3)	756 (69.6)	
T2	179 (8.5)	114 (10.5)	
Stage N			
N0	1865 (88.7)	938 (89.2)	0.686
N1	238 (11.3)	114 (10.8)	
Hysterectomy Type			
total (simple/pan)	717 (34.1)	352 (33.5)	0.706
radical	1220 (58.0)	624 (59.3)	
NOS	166 (7.9)	76 (7.2)	
Radiation			
No	1513 (71.9)	791 (75.2)	0.053
Yes	590 (28.1)	261 (24.8)	
Chemotherapy			
No	1702 (80.9)	863 (82.0)	0.454
Yes	401 (19.1)	189 (18.0)	
Tumor Size (cm)			
≤2.0	1132 (53.8)	570 (54.2)	0.178
2.1–4.0	709 (33.7)	384 (36.5)	
>4.0	262 (12.5)	98 (9.3)	

TABLE 1. Continued.

Variables	Training Cohort (n = 2103) n (%)	Internal Validation Cohort (n = 1052) n (%)	*p*-Value
Number of Positive LNs			
0	1867 (88.8)	939 (89.3)	
1–3	202 (9.6)	95 (9.0)	0.787
>3	34 (1.6)	18 (1.7)	
Number of LNs Examined			
1–15	871 (41.4)	425 (40.4)	
16–30	860 (40.9)	461 (43.8)	0.744
>30	372 (17.7)	166 (15.8)	
Multi-Primary Tumors			
one primary only	1918 (91.2)	976 (92.8)	0.131
1st of 2 or more primary tumors	185 (8.8)	76 (7.2)	
Survival State			
survive	1842 (87.6)	942 (89.5)	
dead of other cause	69 (3.3)	32 (3.0)	0.242
dead of cervical cancer	192 (9.1)	78 (7.4)	

NOS: Not Other Specific; LNs: lymph nodes.

of lymph nodes examined was divided into 1–15, 16–30 and >30. A primary tumor was referred to a malignant tumor that originated in an organ or tissue. The number of primary tumors was divided into 1 and ≥2. Overall survival (OS) and cancer-specific survival (CSS) were calculated as the time from diagnosis to death from any cause or cervical adenocarcinoma.

2.4 Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) and compared by the T-test. Categorical variables were described as counts or percentages and were compared by the Pearson chi-square and linear correlation chi-square. The Kaplan-Meier (KM) method and logarithmic rank test were used to compare survival curves for different groups. Univariate and multivariate Cox regression models were used to estimate hazard ratios (HR) and accurate 95% confidence intervals (CI) for prognostic factors in stage T1–T2 patients with UAC undergoing hysterectomy. The independent prognostic factors in the Cox regression model were applied to construct nomograms for predicting the probabilities of OS and CSS. The predictive ability of the nomogram was evaluated using the conformance index (C-Index) and calibration curves. A conformance index >0.7 indicated a strong prediction ability. A calibration curve was applied to show consistency between observations and predictions. In addition, the predictive power between the new nomogram models and FIGO stage was compared by receiver operating characteristic (ROC) curves and area under ROC curves (AUC) values. A risk score for the patient's survival could be calculated using the nomogram in the training cohort. The X-Tile software (version 3.6.1, Yale University, New Haven, CT, USA) was used to calculate the best cut-off value for OS and CSS, based on which the patients were divided into a low- or high-risk group [20]. All statistical analyses were performed using R version 4.1.3 and X-Tile software. p value < 0.05 was considered statistically significant.

3. Results

3.1 Patients characteristics

3155 eligible UAC patients from the SEER database were randomly divided into the training (n = 2013) cohort and the internal validation (n = 1052) cohort (Table 1). Our initial analysis showed no statistically significant differences in demographics and clinical characteristics between two cohorts.

3.2 Prognostic factors of OS and CSS

Univariate and multivariate Cox regression analyses were applied to calculate the factors associated with patients' OS (Table 2) and CSS (Table 3). The independent prognostic factors of OS were age, race, marital status, tumor grade, T stage, tumor size, number of positive LNs and number of primary tumors, while those for CSS were age, race, marital status, tumor grade, T stage, tumor size, number of positive LNs and radiation therapy.

3.3 Construction of nomogram

The nomogram was constructed according to univariate and multivariate Cox regression models. The significant factors in univariate analysis were included in the model. Backward stepwise selection in the multivariate model was used to screen factors with p value < 0.05. The final factors were used to

TABLE 2. Univariate and mutivariate Cox regression analysis of OS.

Variables	Univariate analysis HR (95% CI)	*p*	Multivariate Analysis HR (95% CI)	*p*
Age (yr)				
≤39	Reference		Reference	
40–49	1.188 (0.817–1.729)	0.367	0.868 (0.593–1.271)	0.467
50–59	2.367 (1.619–3.460)	<0.001	1.687 (1.138–2.500)	0.009
≥60	5.642 (4.013–7.933)	<0.001	2.660 (1.837–3.852)	<0.001
Race				
white	Reference		Reference	
black	2.798 (1.886–4.153)	<0.001	2.223 (1.479–3.343)	<0.001
others	1.067 (0.710–1.605)	0.755	1.102 (0.728–1.670)	0.645
Marital Status				
married	Reference		Reference	
single	1.423 (1.042–1.943)	0.026	1.146 (0.831–1.580)	0.407
others	2.716 (2.047–3.604)	<0.001	1.834 (1.358–2.476)	<0.001
Histology				
adenocarcinoma	Reference			
endometrioid carcinoma	1.282 (0.853–1.928)	0.232		
clear cell adenocarcinoma	2.424 (1.404–4.186)	0.001		
mucinous adenocarcinoma	1.597 (1.081–2.360)	0.019		
serous/papillary adenocarcinoma	1.814 (0.985–3.341)	0.056		
rare type	1.312 (0.806–2.135)	0.275		
Grade				
Grade I	Reference		Reference	
Grade II	2.072 (1.468–2.925)	<0.001	1.584 (1.116–2.250)	0.010
Grade III and IV	4.846 (3.428–6.850)	<0.001	2.233 (1.545–3.227)	<0.001
Stage T				
T1A	Reference		Reference	
T1B	3.201 (1.888–5.425)	<0.001	1.750 (1.008–3.039)	0.047
T2	14.792 (8.487–25.783)	<0.001	3.697 (1.979–6.906)	<0.001
Stage N				
N0	Reference			
N1	4.755 (3.677–6.149)	<0.001		
Hysterectomy Type				
total (simple/pan)	Reference			
radical	0.897 (0.689–1.167)	0.417		
NOS	1.221 (0.789–1.889)	0.370		
Radiation				
No	Reference		-	-
Yes	3.031 (2.377–3.865)	<0.001	-	-
Chemotherapy				
No	Reference		-	-
Yes	3.178 (2.476–4.079)	<0.001	-	-
Tumor Size (cm)				
≤2.0	Reference		Reference	
2.1–4.0	2.202 (1.671–2.093)	<0.001	1.566 (1.140–2.152)	0.006
>4.0	7.494 (5.345–10.506)	<0.001	1.801 (1.231–2.634)	0.002

TABLE 2. Continued.

Variables	Univariate analysis HR (95% CI)	*p*	Multivariate Analysis HR (95% CI)	*p*
Number of Positive LNs				
0	Reference		Reference	
1–3	4.520 (3.432–5.952)	<0.001	2.354 (1.743–3.181)	<0.001
>3	7.020 (4.203–11.723)	<0.001	2.950 (1.705–5.102)	<0.001
Number of LNs Examined				
1–15	Reference			
16–30	0.777 (0.593–1.018)	0.067		
>30	0.864 (0.616–1.210)	0.395		
Multi-Primary Tumors				
one primary only	Reference		Reference	
1st of 2 or more primary tumors	3.048 (2.284–4.076)	<0.001	2.178 (1.615–2.939)	<0.001

HR: hazard ratios; CI: confidence intervals; NOS: Not Other Specific; LNs: lymph nodes.

construct the nomogram (Fig. 2). T staging contributed the most to OS and CSS, followed by the number of positive LNs. By measuring the specific score points of each variable, the total score of CSS or OS and the individual survival probability could be easily calculated. The calibration curves showed significant coherence between predicted and observed survival data in each groups (Figs. 3, 4).

3.4 Verification of nomogram

The characteristics of 107 UAC patients from Fujian Maternity and Child Health Hospital are shown in Table 4. We compared the C-index of the nomogram with that of the FIGO stage. The results showed that the C-index of the nomogram predicting OS in the training cohort was 0.825 (0.800–0.850), higher than that of the FIGO stage (0.701 (0.671–0.731), $p < 0.001$). The C-index of the nomogram for predicting CSS in the training cohort was 0.820 (0.789–0.851), which was also higher than that of the FIGO stage (0.735 (0.702–0.768), $p < 0.001$). The internal and external validation cohort showed similar results, confirming that the nomogram had better OS and CSS prediction ability than the FIGO stage (Table 5).

In addition, the nomogram was used to calculate the 3- and 5-year prediction scores of the three datasets and corresponding ROC curves were plotted (Fig. 5). AUC was applied to assess the prediction ability. Our results showed that the AUC values of the 3- and 5-year OS of the training cohort were 0.862 and 0.843, while those of the FIGO stage were 0.718 and 0.717. Similarly, the AUC of the 3- and 5-year CSS nomogram was higher than those of the FIGO stage. Similar results were obtained for the internal and external validation cohorts (Table 6).

3.5 Threshold selection of nomogram

To assess the practicability and effectiveness of the nomogram models, the X-tile software was applied to determine the optimal threshold of risk score. The OS and CSS nomograms were both divided into a low-risk group (OS, total score <235; CSS, total score <211) and a high-risk group (OS, total score ≥235; CSS, total score ≥211). Patients from the internal and external validation cohorts were scored individually, and the corresponding KM survival curves were drawn. The results showed that the survival of the high and low-risk groups was significantly different ($p < 0.0001$) (Fig. 6). KM curves showed that the OS and CSS of high-risk patients were significantly worse than those of low-risk patients.

4. Discussion

UAC is the second commonly seen type of cervical cancer. Although the incidence rate of cervical cancer has shown an overall decrease [21], the incidence rate of UAC has increased [22]. At present, the main treatment of UAC remains radical surgery or CCRT, but the sensitivity of UAC to radiotherapy is lower than that of SCC [23], and the survival outcomes of UAC patients are worse than SCC patients [24, 25]. Therefore, more patients with UAC undergo surgery. According to the statistics of the National Cancer Institute, more than 60% of UAC patients underwent surgical treatment [9]. Previous studies showed that the recurrence mode, prognostic factors and response to treatment of UAC patients were different from those of SCC patients [6, 7], however, UAC is still classified using the same FIGO staging system like SCC, causing inaccuracies in prognostic evaluation of patients. Using the SEER database, this study first determined the independent prognostic factors of T1–T2 stage UAC patients undergoing hysterectomy, based on which a practical nomogram was developed to predict OS

TABLE 3. Univariate and mutivariate Cox regression analysis of CSS.

Variables	Univariate Analysis HR (95% CI)	*p*	Multivariate Analysis HR (95% CI)	*p*
Age (yr)				
≤39	Reference		Reference	
40–49	1.105 (0.740–1.649)	0.625	0.821 (0.545–1.236)	0.345
50–59	1.651 (1.068–2.555)	0.024	1.313 (0.836–2.062)	0.238
≥60	3.866 (2.632–5.600)	<0.001	1.997 (1.307–3.050)	0.001
Race				
white	Reference		Reference	
black	2.849 (1.804–4.498)	<0.001	2.274 (1.420–3.642)	0.001
others	1.114 (0.699–1.776)	0.651	1.108 (0.690–1.779)	0.670
Marital Status				
married	Reference		Reference	
single	1.498 (1.060–2.117)	0.022	1.146 (0.803–1.635)	0.452
others	2.093 (1.477–2.965)	<0.001	1.536 (1.059–2.227)	0.024
Histology				
adenocarcinoma	Reference			
endometrioid carcinoma	1.100 (0.662–1.828)	0.714		
clear cell adenocarcinoma	1.615 (0.753–3.461)	0.218		
mucinous adenocarcinoma	1.842 (1.204–2.816)	0.005		
serous/papillary adenocarcinoma	1.989 (1.010–3.917)	0.047		
Rare Type	1.379 (0.792–2.399)	0.256		
Grade				
Grade I	Reference		Reference	
Grade II	2.662 (1.723–4.112)	<0.001	1.841 (1.183–2.865)	0.007
Grade III and IV	6.435 (4.168–9.935)	<0.001	2.959 (1.868–4.686)	<0.001
Stage T				
T1A	Reference		Reference	
T1B	4.226 (2.067–8.642)	<0.001	2.210 (1.050–4.653)	0.037
T2	22.563 (10.798–47.143)	<0.001	5.383 (2.371–12.224)	<0.001
Stage N				
N0	Reference			
N1	6.346 (4.756–8.469)	<0.001		
Hysterectomy Type				
total (simple/pan)	Reference			
radical	0.899 (0.662–1.220)	0.495		
NOS	1.152 (0.685–1.983)	0.594		
Radiation				
No	Reference		Reference	
Yes	3.141 (2.365–4.170)	<0.001	0.691 (0.483–0.988)	0.043
Chemotherapy				
No	Reference		-	-
Yes	3.832 (2.880–5.099)	<0.001	-	-
Tumor Size (cm)				
≤2.0	Reference		Reference	
2.1–4.0	2.889 (2.061–4.050)	<0.001	1.863 (1.255–2.765)	0.002
>4.0	10.140 (6.819–15.077)	<0.001	2.461 (1.565–3.870)	<0.001

TABLE 3. Continued.

Variables	Univariate Analysis HR (95% CI)	*p*	Multivariate Analysis HR (95% CI)	*p*
Number of Positive LNs				
0	Reference		Reference	
1–3	6.060 (4.460–8.234)	<0.001	3.148 (2.179–4.548)	<0.001
>3	9.084 (5.211–15.837)	<0.001	3.474 (1.880–6.418)	<0.001
Number of LNs Examined				
1–15	Reference			
16–30	0.851 (0.620–1.168)	0.317		
>30	1.016 (0.692–1.492)	0.934		
Multi-Primary Tumors				
one primary only	Reference		-	-
1st of 2 or more primary tumors	1.891 (1.281–2.792)	0.001	-	-

HR: hazard ratios; CI: confidence intervals; NOS: Not Other Specific; LNs: lymph nodes.

TABLE 4. Demographic and clinical characteristics of the external validation cohort.

Variables	External Validation Cohort (n = 107) n (%)	Variables	External Validation Cohort (n = 107) n (%)
Age (yr)		Stage T	
≤39	19 (17.8)	T1A	3 (2.8)
40–49	64 (59.8)	T1B	79 (73.8)
50–59	19 (17.8)	T2	25 (23.4)
≥60	5 (4.6)	Tumor size (cm)	
Race		≤2.0	60 (56.1)
white	0 (0)	2.1–4.0	26 (24.3)
black	0 (0)	>4.0	21 (19.6)
others	107 (100)	Radiation	
Marital Status		No	85 (79.4)
married	106 (99.1)	Yes	22 (20.6)
single	1 (0.9)	Number of positive LNs	
others	0 (0)	0	94 (87.9)
FIGO stage		1–3	8 (7.5)
IA	3 (2.8)	>3	5 (4.6)
IB	74 (69.2)	Multi-primary tumors	
II	17 (15.9)	One primary only	107 (100)
III	13 (12.1)	1st of 2 or more primary tumors	0 (0)
Grade		Survival state	
Grade I	31 (29.0)	Survive	99 (92.5)
Grade II	47 (43.9)	Dead of other cause	1 (0.9)
Grade III and IV	29 (27.1)	Dead of cervical cancer	7 (6.6)

LNs: lymph nodes; FIGO: International Federation of Gynecology and Obstetrics.

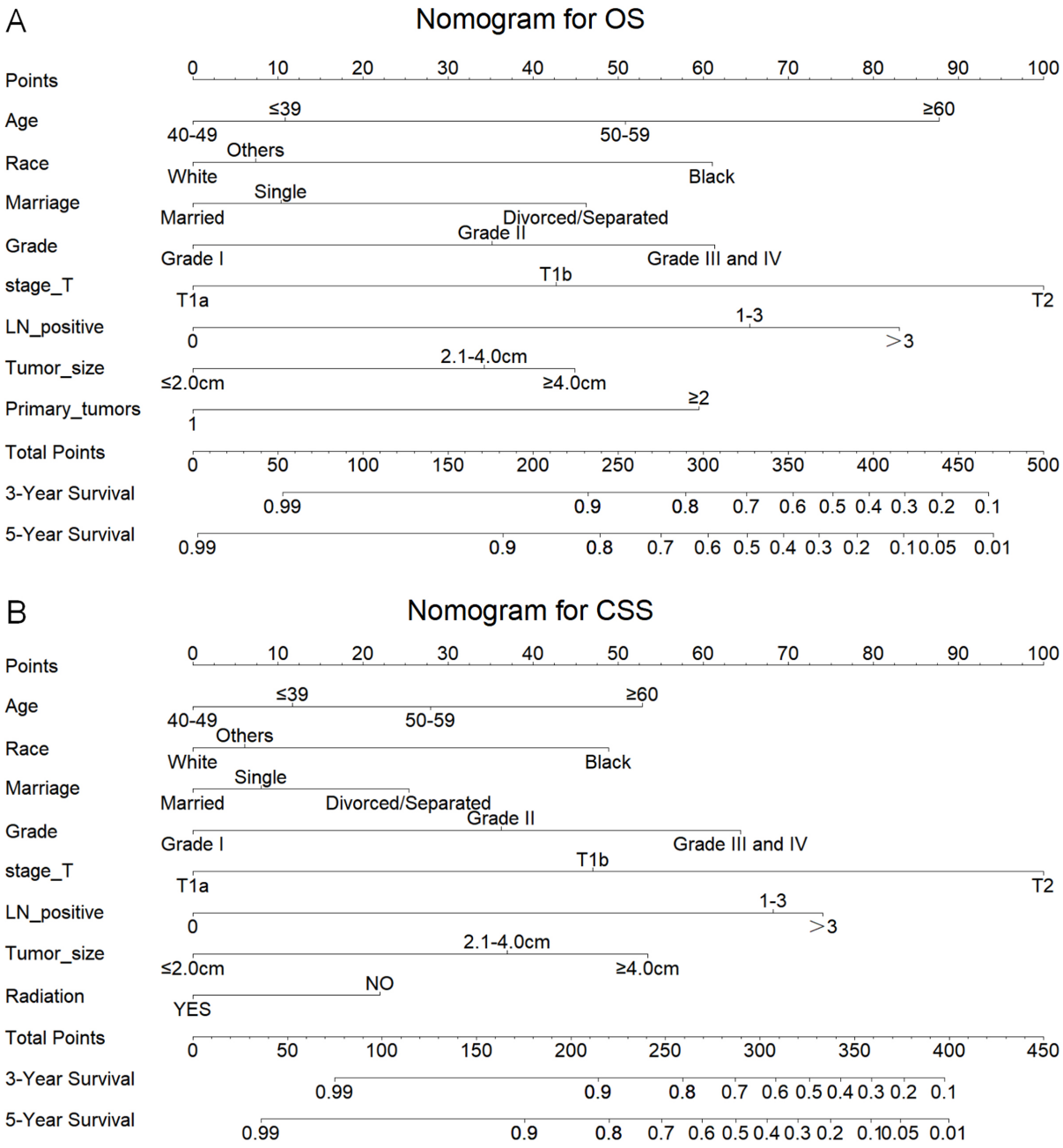

FIGURE 2. Nomogram predicting the 3- and 5-year OS (A) and CSS (B). OS: overall survival; CSS: cancer-specific survival.

TABLE 5. C-indexes for the Nomogram and FIGO stage systems in patients.

Patients	Model	OS (95% CI)	*p*	CSS (95% CI)	*p*
Training Cohort	Nomogram	0.825 (0.800–0.850)	$p < 0.001$	0.820 (0.789–0.851)	$p < 0.001$
	FIGO stage	0.701 (0.671–0.731)		0.735 (0.702–0.768)	
Internal Validation Cohort	Nomogram	0.790 (0.748–0.832)	$p < 0.001$	0.800 (0.753–0.847)	$p < 0.001$
	FIGO stage	0.696 (0.646–0.746)		0.747 (0.692–0.802)	
External Validation Cohort	Nomogram	0.911 (0.847–0.975)	$p < 0.001$	0.892 (0.821–0.963)	$p < 0.001$
	FIGO stage	0.779 (0.704–0.854)		0.754 (0.669–0.839)	

OS: overall survival; CSS: cancer-specific survival; FIGO: International Federation of Gynecology and Obstetrics.

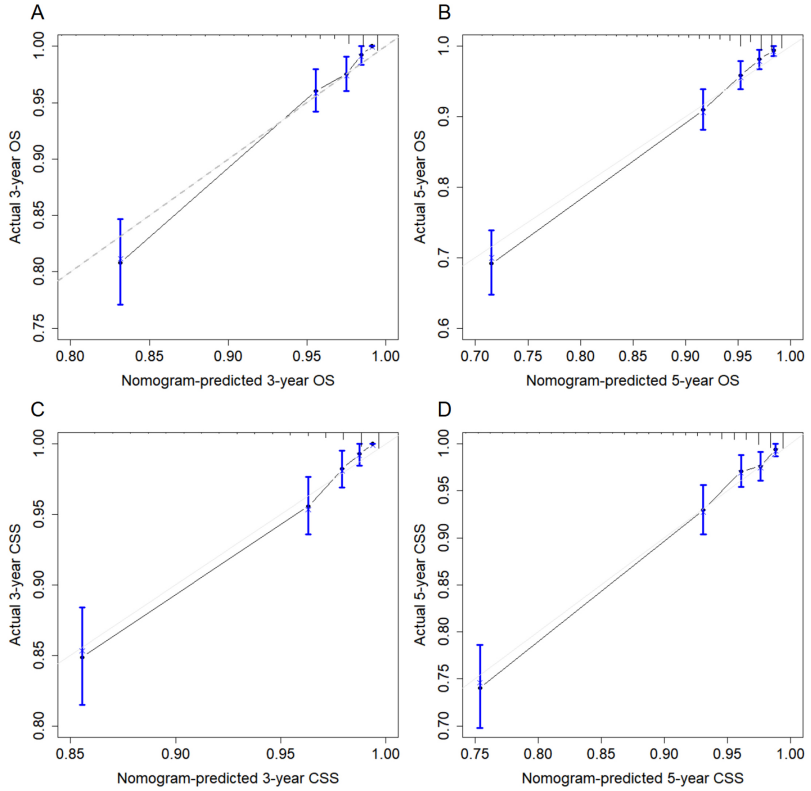

FIGURE 3. Calibration curves of training cohort. The calibration curves of training cohort show the nomograms-predicted rates (X-axis) are correspondent with actual survival rates (Y-axis), including 3-year OS (A) and 5-year OS (B), 3-year CSS (C) and 5-year CSS (D). OS: overall survival; CSS: cancer-specific survival.

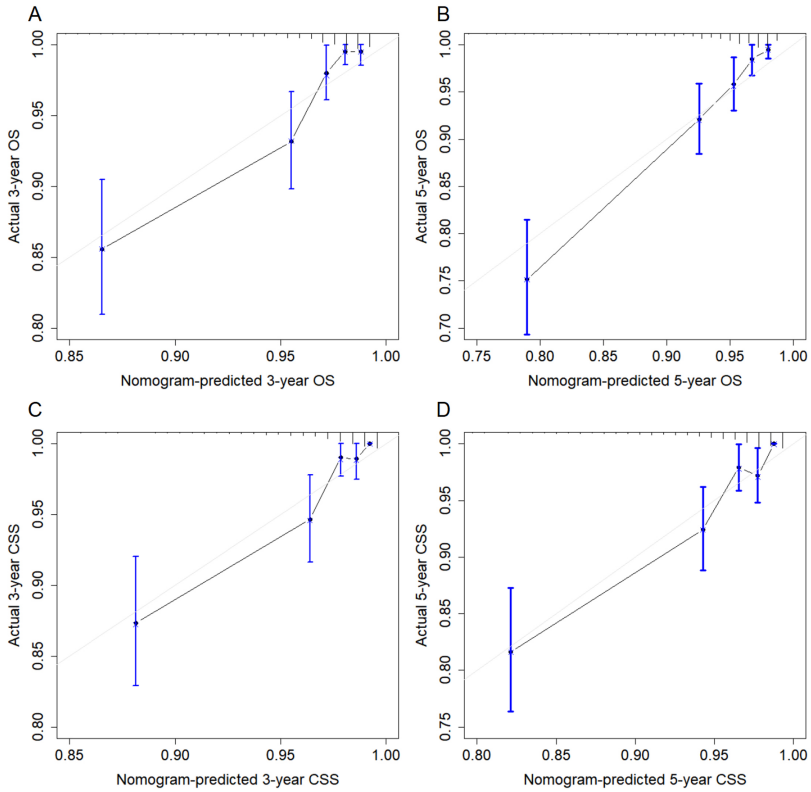

FIGURE 4. Calibration curves of internal validation cohort. The calibration curves of internal validation cohort show the nomograms-predicted rates (X-axis) are correspondent with actual survival rates (Y-axis), including 3-year OS (A) and 5-year OS (B), 3-year CSS (C) and 5-year CSS (D). OS: overall survival; CSS: cancer-specific survival.

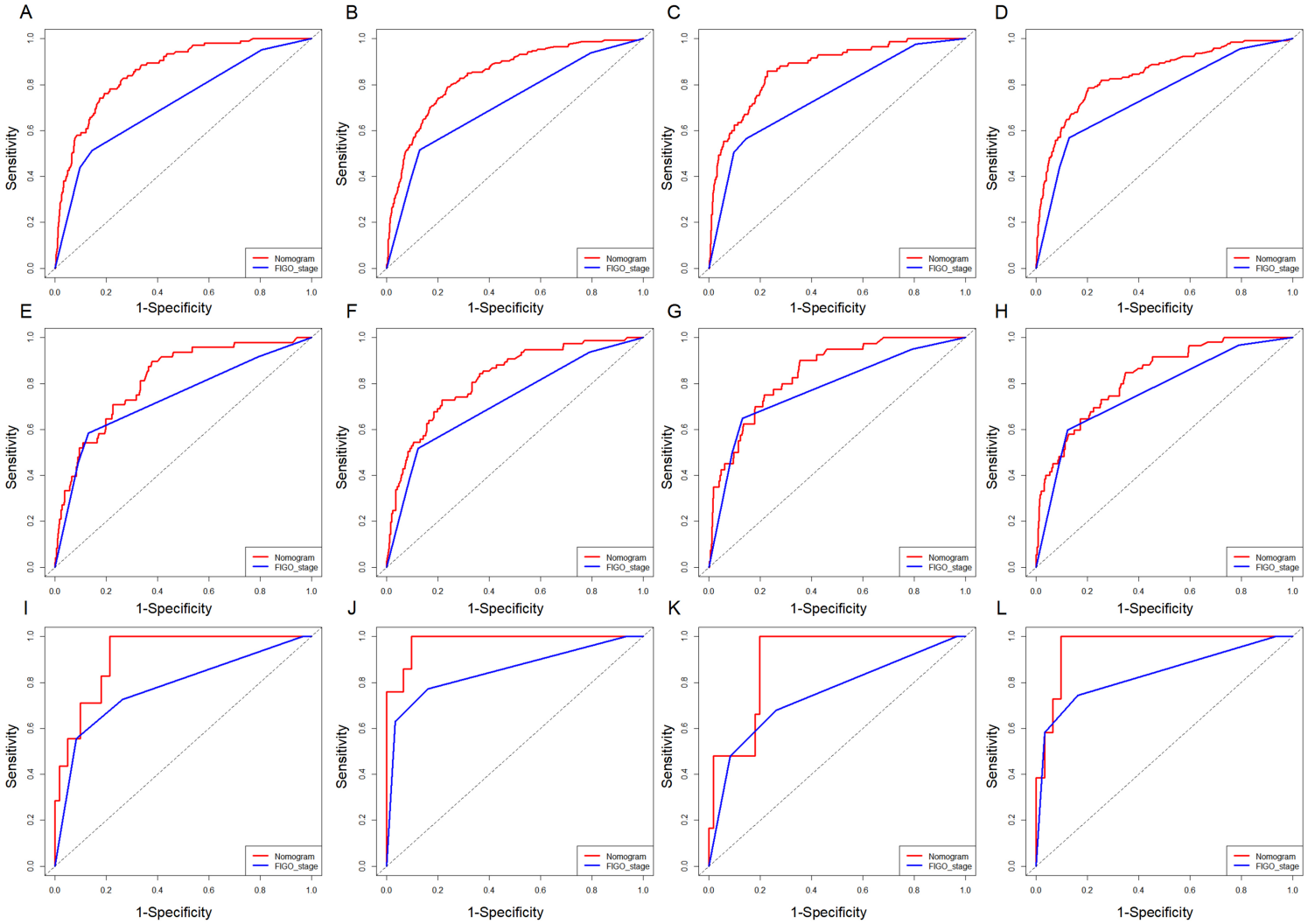

FIGURE 5. ROC curves. (A) The 3-year OS nomogram of the training cohort; (B) the 5-year OS nomogram of the training cohort; (C) the 3-year CSS nomogram of the training cohort; (D) the 5-year CSS nomogram of the training cohort; (E) the 3-year OS nomogram of the internal validation cohort; (F) the 5-year OS nomogram of the internal validation cohort; (G) the 3-year CSS nomogram of the internal validation cohort; (H) the 5-year CSS nomogram of the internal validation cohort; (I) the 3-year OS nomogram of the external validation cohort; (J) the 5-year OS nomogram of the external validation cohort; (K) the 3-year CSS nomogram of the external validation cohort; (L) the 5-year CSS nomogram of the external validation cohort. FIGO: International Federation of Gynecology and Obstetrics.

TABLE 6. Comparison of AUC values between Nomogram and FIGO stage.

Patients	Model	OS		CSS	
		3-year	5-year	3-year	5-year
Training Cohort	Nomogram	0.862	0.843	0.871	0.843
	FIGO stage	0.718	0.717	0.751	0.748
Internal Validation Cohort	Nomogram	0.818	0.822	0.846	0.827
	FIGO stage	0.737	0.210	0.778	0.767
External Validation Cohort	Nomogram	0.918	0.980	0.895	0.958
	FIGO stage	0.779	0.852	0.749	0.834

OS: overall survival; CSS: cancer-specific survival; FIGO: International Federation of Gynecology and Obstetrics.

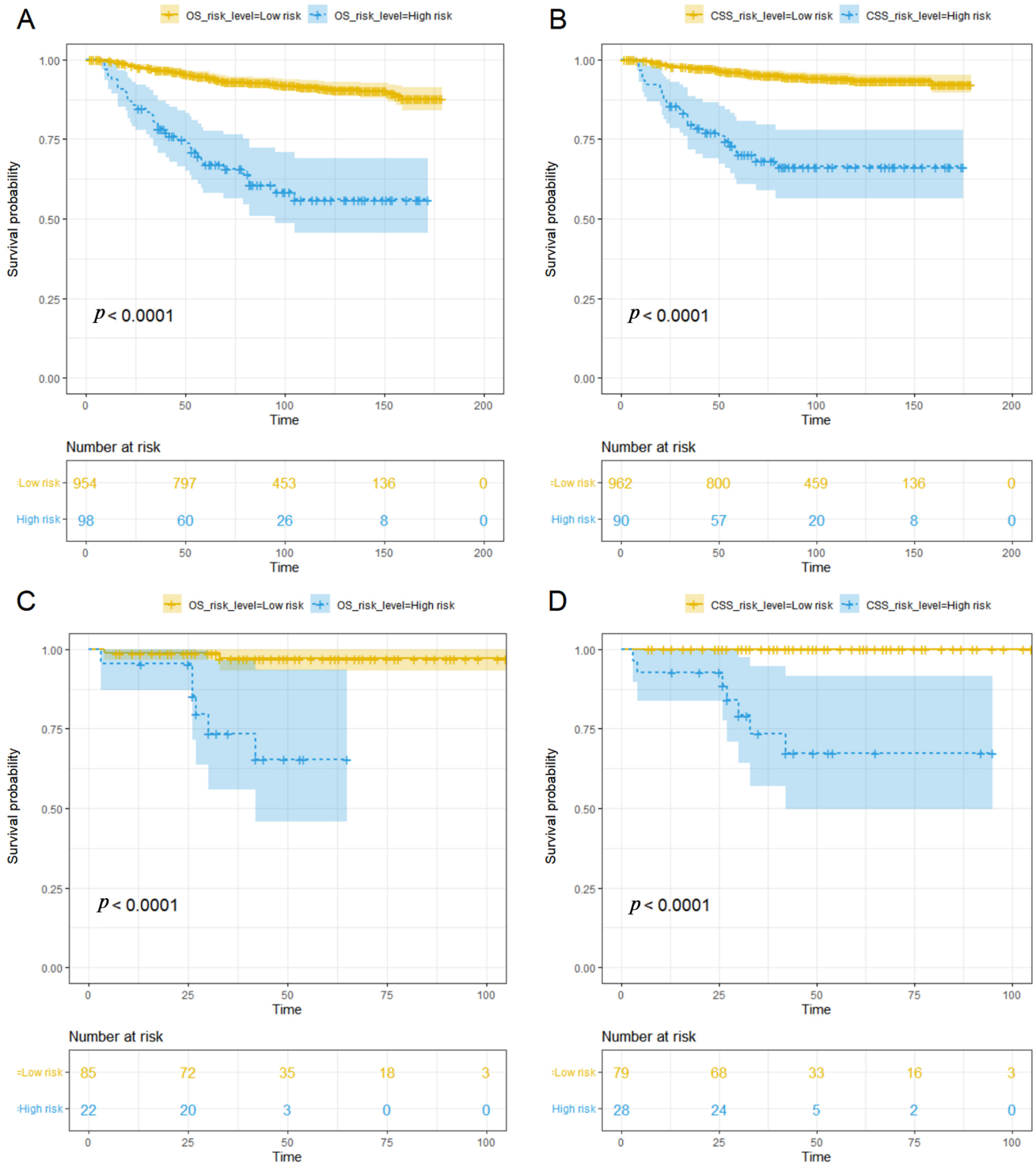

FIGURE 6. Kaplan-Meier Survival Curve. KM curve for the high and low-risk groups according to the OS nomogram of the internal validation cohort (A); the CSS nomogram of the internal validation cohort (B); the OS nomogram of the external validation cohort (C); the CSS nomogram of the external validation cohort (D). OS: overall survival; CSS: cancer-specific survival.

and CSS. The results of the internal and external validation cohorts showed that the prediction ability of the nomogram was superior to the FIGO staging system.

This study showed that age, race, marital status, tumor grade, T stage, tumor size and number of positive lymph nodes were the independent prognostic factors for OS and CSS. The number of primary tumors was a specific influencing factor for OS, and postoperative radiotherapy was a good influencing factor for CSS. Presently, the FIGO classification, the most commonly used staging stage for cervical cancer, is not the only factor affecting the prognosis of these patients. It is reported that sociodemographics and clinicopathological characteristics are also very important. Age [26], T stage [25], lymph node positivity [27] and tumor size [28] have all been shown to be associated with prognosis, which was concordant with our study findings.

In this study, after subdividing the patients' age into four groups (≤39, 40–49, 50–59 and ≥60), we found that patients ≥50 years old had poor OS, and those ≥60 years old had poor CSS. Further, the number of positive LNs was divided into three groups, and the results showed that patients with 3 positive LNs had worse survival outcomes than those with 1–3 or no positive LNs. Currently, the NCCN guidelines have not included tumor grade as a high-risk or medium-risk factor of cervical cancer [8]. However, our results and other studies found that worse differentiation was related to worse survival [29]. In addition, we also found that marital status and postoperative radiotherapy were associated with survival outcomes. The prognosis of married cervical cancer patients was better. It might owe to the early diagnosis and comprehensive adjuvant treatment of married patients [30, 31]. For adjuvant treatment, some studies showed that chemotherapy was beneficial to prognosis [32], while others reported that postoperative radiotherapy could improve the survival rate of patients with early cervical cancer [33]. Our study found that patients receiving postoperative radiotherapy have better CSS, which needs more confirmation studies.

The proposed nomograms could be considered highly innovative and practical. Due to the low incidence rate of UAC, few studies have specifically targeted UAC patients. Feng *et al.* [34] included 1683 stage IIIC cervical cancer patients and developed a nomogram for predicting OS and CSS, involving 337 (20%) UAC patients. The C-indexes of their OS and CSS nomogram were 0.701 and 0.735. Zhou *et al.* [15] analyzed 1563 stage IA–IIB patients undergoing surgery for cervical cancer, of whom 168 patients (10.7%) had UAC, and developed a nomogram for OS, which showed a C-index of 0.71. However, past literature were limited due to the small number of UAC patients investigated and the inability to form a patient-specific prediction model for UAC. Our study only evaluated UAC patients after hysterectomy, had a sufficient sample size (n = 3155), and constructed a stable prediction model specifically for UAC patients after hysterectomy. Second, compared with the FIGO stage, our proposed nomograms contain more independent prognostic factors, including demographic characteristics (age, race, marital status and number of primary tumors) and tumor characteristics (tumor size, tumor grade, T stage and number of positive LNs). These variables are easy to obtain clinically, making the proposed nomograms practical and easy for comprehensive and accurate prognosis prediction. Third, our nomograms' predictive ability was verified via internal and external validation. The C-indexes of the OS and CSS predictive nomogram of the training cohort were 0.825 (0.800–0.850) and 0.820 (0.789–0.851), which were higher than the FIGO stage, $p < 0.001$. The C-index of internal and external validation cohorts showed similar results, indicating that the nomogram had higher survival prediction accuracy than the traditional FIGO staging system. After internal and external verification, the applicability of the nomogram was confirmed in different populations [35]. Finally, we calculated the prediction threshold of the nomogram, which could be used to divide the population into low-risk and high-risk groups and its practical value was verified by KM survival curves.

There were several limitations in our study. First, the SEER database did not include some prognostic information, such as depth of infiltration, lymphatic vascular infiltration, biomarker and adjuvant therapy information, which might limit further analysis. Second, selection bias might have been unavoidable since this was a retrospective study. Third, the nomogram was based on 84.8% white and only 4.7% black populations, indicating that the accuracy for black people might be lower but needs further verification in future studies. Lastly, although external validation was performed, the cohort was from a single center, and the sample size was quite small. Thus, the results of this study should be further verified in future better designed larger sample size prospective studies.

5. Conclusion

In conclusion, age, race, marital status, tumor grade, T stage, tumor size and number of positive lymph nodes were identified as independent prognostic factors for OS and CSS. Number of primary tumors was a specific influencing factor for OS and postoperative radiotherapy was a good influencing factor for CSS. Moreover, using multivariate Cox proportional hazards regression analysis, this study established nomograms for predicting the 3-year and 5-year OS and CSS of UAC patients at T1–T2 stage after hysterectomy. Internal and external validations showed that the proposed nomograms had good prediction and clinical application values. In the future, prospective multicenter research is needed to confirm the clinical reliability of the proposed prediction models.

AUTHOR CONTRIBUTIONS

HZ—Data curation, Formal analysis, Writing-Original Draft/Review & Editing; SYZ—Data curation, Writing-Original Draft; HY—Conceptualization, Methodology, Supervision, Writing-Review & Editing; XQZ—Conceptualization, Methodology, Supervision, Writing-Review & Editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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