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ORIGINAL RESEARCH

Development and Internal-External Validation Models for Cervical Cancer Overall Survival Prognosis: A SEER-Based Study and Chinese Data

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Objective: The study aims to develop a model to predict overall survival (OS) in cervical cancer (CC).

Methods: A total of 13,592 CC patient records were obtained from the Surveillance, Epidemiology, and End Results (SEER) database between 2000 and 2020. These patients were randomized with a 7:3 ratio into a training cohort (TC, n = 9,514) and an internal validation cohort (IVC, n = 4,078). Univariate and multivariate Cox regression were used to construct a prognostic model based on the training set and develop a nomogram to predict the 3-year, 5-year, and 10-year OS of CC patients. Additionally, medical data from 318 CC patients at Yangming Hospital Affiliated to Ningbo University, collected between 2008 and 2020, were analyzed for external validation.

Results: Univariate and multivariate Cox regression identified six predictors of prognosis in CC including age, tumor grade, tumor stage, tumor size, lymph node metastasis (LNM), and lymph vascular space invasion (LVSI) to construct the nomogram. The C-index was 0.882 (95% CI: 0.874 to 0.890), and the areas under curves (AUC) for 3-year, 5-year, and 10-year overall survival (OS) were 0.913, 0.912, and 0.906, respectively for the training cohort. The C-index was 0.885 (95% CI: 0.873 to 0.897), and the AUC for the 3-year, 5-year, and 10-year OS were 0.916, 0.910, and 0.910 for the internal validation cohort. For the external validation cohort, the C-index was 0.872 (95% CI: 0.829–0.915), with AUCs of 0.892, 0.896, and 0.903 for 3-year, 5-year, and 10-year OS, respectively.

Conclusion: The devised nomogram can be applied in clinical settings to estimate the OS probability of CC patients. This tool provides personalized predictions for the OS of CC patients, thereby assisting healthcare professionals in optimizing their clinical practices.

Keywords: cervical cancer, overall survival, nomogram, ROC, calibration chart, DCA

Introduction

Cervical cancer (CC) is one of the leading causes of cancer-related deaths among women worldwide, with over 500,000 new cases and approximately 250,000 reported deaths annually. Despite the widespread implementation of comprehensive CC screening programs in various countries, many women still succumb to this disease. Recent decades have witnessed remarkable advancements in CC management. Improved diagnostic techniques, including high-resolution imaging and molecular biomarkers, have enabled earlier detection.[1] Surgical approaches have evolved toward minimally invasive techniques with reduced morbidity, while refinements in adjuvant therapies have optimized treatment outcomes.[2] Particularly for early-stage disease, growing evidence supports the safety and efficacy of neoadjuvant chemotherapy and conservative procedures like conization.[3] Previous research has identified several prognostic factors for CC including age, level of differentiation, tumor stage, tumor size, and lymph node metastasis (LNM). However, assessing specific risks of tumor recurrence and mortality remains a significant challenge.[4]

The advent of precision medicine has led to an increasing application of clinical prediction models in disease diagnosis, treatment decision-making, patient management, and the allocation of public health resources, underscoring their growing significance.[5] These prognostic models provide quantitative assessments of cancer recurrence risk,

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mortality, and various complications, which help devise personalized prognostic treatment, support functional recovery, enhance quality of life, increase lifespan, and reduce mortality.[6]

In contrast to traditional prediction models, the recently developed nomogram serves as a personalized predictive tool to evaluate the probability of disease recurrence or patient survival in a simple graphical format[7] by comprehensively integrating and quantifying diverse prognostic risk factors with enhanced accuracy.[8]

This retrospective study aims to develop a nomogram for visually predicting the survival probability of CC. We constructed and validated a prognostic model using both internal and external data to enhance its robustness. The model demonstrated strong predictive capability through comprehensive validation processes. By establishing and validating these prognostic models, we can effectively assess patient prognosis, formulate personalized treatment plans, and design follow-up strategies to maximize benefits for cancer patients.

Materials and Methods

Patients

The Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/) is a cancer registry in the United States that provides information on cancer incidence and survival for studies related to surveillance and the development of analytical and methodological tools in the field. For this study, we extracted data where the primary tumor site (Site recode ICD-O-3/WHO 2008) was clearly identified as the cervix (C53). Inclusion criteria comprised case diagnosis between 2000 and 2020 with a behavior code in ICD-O-3 indicating malignancy. Exclusion criteria comprised: (1) non-cancer-related deaths (eg, cardiovascular events), (2) missing data (tumor type, grade, size, or treatment details), or (3) incomplete survival records.

The outcomes for CC patients included both survival and mortality. A subset of patients did not die from CC but rather from other causes, such as heart disease or cerebrovascular accidents, indicating the presence of competing risks which may affect the survival outcomes. To preclude the impact of these competing risks from impacting the survival rate, the external validation data in this study excluded cases involving death from other causes.

The prognostic model discussed in this article categorized stages of CC into four levels: IA, IB, IIA, and IIIC. The cancer staging was classified according to FIGO 2018 criteria. Patients with LNM were upgraded to stage IIIC whereas patients with LNM diagnosed before 2018 were reclassified under stage IIIC for this study.

The study used clinical data of patients newly diagnosed with CC sourced from SEER. Data spanning 2000 to 2020 were collected using SEER*Stat software version 8.4.3. Access to the SEER database was obtained for this study, and SEER database policies were strictly adhered throughout the data collection process. Publicly available data were used to construct the training cohort (TC) and internal validation cohort (IVC); thus, informed consent was not required. In contrast, informed consent was obtained for the external validation cohort (EVC). Only patients with complete clinical and pathological information, along with complete follow-up records, were considered eligible for inclusion in the study.

Predictors

For the development of the prognostic model, a total of 10 predictors were selected: age, histologic subtype, FIGO 2018 stage, tumor size, tumor grade (well-, moderate-, or poorly differentiated), LNM (yes or no), lymph-vascular space invasion (LVSI) (yes or no), invasion, radiation therapy (yes or no), and chemotherapy (yes or no).

Predictor Selection

The primary endpoint of the study was the overall survival (OS) for CC. Initially, univariate Cox regression analysis was conducted to evaluate the significance of then ten predictors. Statistically significant factors were then further analyzed using multivariate Cox regression model to identify independent factors that were predictive of OS, and the final prediction model was determined by the highest concordance index (C-index).

Model Development and internal-External Validation

Nomograms were developed to predict 3-, 5- and 10-year OS and visualize the prognostic models. To assess the performance of the models, evaluation metrics including the C-index, time-dependent receiver operating characteristic

(ROC) curves, calibration charts, and decision curve analysis (DCA) were used. External validation of the prognostic model was conducted using data collected from Yangming Hospital Affiliated to Ningbo University.

Statistical Analysis

Baseline characteristics of the study population were summarized using descriptive statistics. Patients diagnosed with CC between 2000 and 2020 were randomly divided into TC and IVC in a 7:3 ratio using random number tables. Univariate and multivariate Cox proportional hazard regression models were employed to identify significant predictive factors within TC with a significant threshold set at P less than 0.05. A nomogram was constructed based on the significant factors identified in the multivariate Cox regression analysis to predict 3-year, 5-year, and 10-year OS. The model's predictive accuracy and discriminatory ability were assessed through the C-index, ROC curves, calibration charts with bootstrap resampling (B = 1000), and DCA. Further validation was conducted using IVC and EVC data. The Kaplan–Meier method was used to examine the OS differences among significant predictors. Statistical analyses were perform ed using R software (version 4.3.2) with a significance level set at $P < 0.05$.

Results

Patients' Characteristics

Table 1 presents the characteristics of 13,592 patients included in the study. The median age of patients was 44 years (range: 20–85 years), and the median follow-up time was 9 years (range: 5–12 years). A total of 2,697 deaths (19.8%) were recorded during the study. The TC included 9,514 patients, while the IVC included 4,078 patients. A total of 1,887 patients (19.8% of the cohort) died in the TC, while 810 patients (19.9% of the cohort) died in the IVC. No significant differences in clinical variables were observed between the TC and IVC. Additionally, an EVC of 318 CC patients treated between 2008 and 2020 at Yangming Hospital Affiliated to Ningbo University, was included in the analysis.

Table 1 Characteristics of Patients with Cervical Cancer in the Training Cohort and Validation Cohort

Clinical features	Training Cohort (N=9514)	Internal Validation Cohort (N=4078)	*P* value	External Validation Cohort (N=318)
Age			0.509	
<50	6250(65.7%)	2655(65.5%)		230(72.3%)
≥50	3254(34.3%)	1423(34.5%)		88(27.7%)
Histologic subtype			0.692	
Squamous cell carcinoma	6219(65.4%)	2643(64.8%)		273(85.8%)
Adenocarcinoma	2430(25.5%)	1070(26.2%)		34(10.7%)
Other subtype	865 (9.1%)	365(9.0%)		11(3.5%)
Grade			0.839	
Well	2960(31.1%)	1287(31.6%)		66(20.8%)
Moderate	4178(43.9%)	1788(43.8%)		128(40.3%)
Poor	2376(25.0%)	1003(24.6%)		124(38.9%)
Stage			0.181	
IA	2336(24.6%)	955 (23.4%)		36(11.3%)
IB	4519(47.5%)	2015(49.4%)		129(40.6%)
IIA	481 (5.1%)	212 (5.2%)		70(22.0%)
IIIC	2178(22.8%)	896 (22.0%)		83(26.1%)
Lymph			0.261	
YES	2219(23.3%)	915 (22.4%)		85(26.7%)
NO	7295(76.7%)	3163(77.6%)		233(73.3%)

(*Continued*)

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Table 1 (Continued).

Clinical features	Training Cohort (N=9514)	Internal Validation Cohort (N=4078)	*P* value	External Validation Cohort (N=318)
LVSI			0.612	
YES	3342(35.1%)	1414 (34.7%)		94(29.6%)
NO	6172(64.9%)	2664 (65.3%)		224(80.4%)
Size			0.834	
<4cm	7359(77.3%)	3161(77.5%)		237(74.5%)
≥4cm	2155(22.7%)	917 (22.5%)		81(25.5%)
Invasion			0.619	
<1/2	6208(65.3%)	2679(65.7%)		205(64.5%)
≥1/2	3306(34.7%)	1399(34.3%)		113(35.5%)
Radiation			0.254	
YES	4485(47.1%)	1879(46.1%)		128(40.3%)
NO	5029(52.9%)	2199(53.9%)		190(59.7%)
Chemotherapy			0.849	
YES	3614(38.0%)	1542(37.8%)		145(45.6%)
NO	5900(62.0%)	2536(62.2%)		173(54.4%)
Dead			0.969	
YES	1887(19.8%)	810 (19.9%)		62 (19.5%)
NO	7627(80.2%)	3268(80.1%)		256(80.5%)

Kaplan-Meier Survival Analysis

Figure 1 illustrates the Kaplan-Meier analysis for significant predictors of OS in CC patients within the TC. The analysis highlighted several significant predictors, including age, tumor grade, tumor stage, LNM, tumor size, and LVSI. All of which had a p-value less than 0.05. The analysis underscores the impact of these factors on the survival outcomes of patients diagnosed with CC.

Univariate and Multivariate Analyses

The results of the univariate and multivariate Cox regression analyses are summarized in Table 2. A total of 10 variables were included in the univariate analysis: age, histological subtype, tumor grade, FIGO stage, LNM, LVSI, cervical stromal invasion, tumor size, radiotherapy, and chemotherapy. Among these variables, histological subtype, radiotherapy, and chemotherapy were found to be insignificant for OS in the univariate analysis. Among seven variables showing statistical significance in the univariate analysis, six variables including age, grade, FIGO stage, LNM, LVSI, and tumor size were identified as statistically significant risk factors for OS in the multivariate analysis. While stage IB showed significant association in univariate analysis (HR=1.843, P<0.001), it was not retained in the final multivariate model as its prognostic value was largely explained by tumor size and lymph node status, which showed stronger independent associations with survival outcomes. Although cervical stromal invasion showed significance in univariate analysis (P=0.032), it did not retain independent prognostic value in multivariate analysis (P=0.171), likely due to its correlation with other stronger predictors like tumor size and lymph node status in the final model.

Development and Internal-External Validation

Based on the multivariate Cox regression analysis, a nomogram was constructed as shown in Figure 2. The nomogram demonstrated good predictive performance across the cohorts. In the TC, C-index was 0.882 ± 0.004, with AUCs for 3-year, 5-year, and 10-year OS being 0.913, 0.912, and 0.906, respectively. In the IVC, the C-index was 0.885 ± 0.006, and the AUCs for 3-year, 5-year, and 10-year OS were 0.916, 0.910, and 0.910, respectively. In the EVC, the C-index was 0.872 ± 0.022, and the AUCs for 3-year, 5-year, and 10-year OS were 0.892, 0.896, and 0.903, respectively

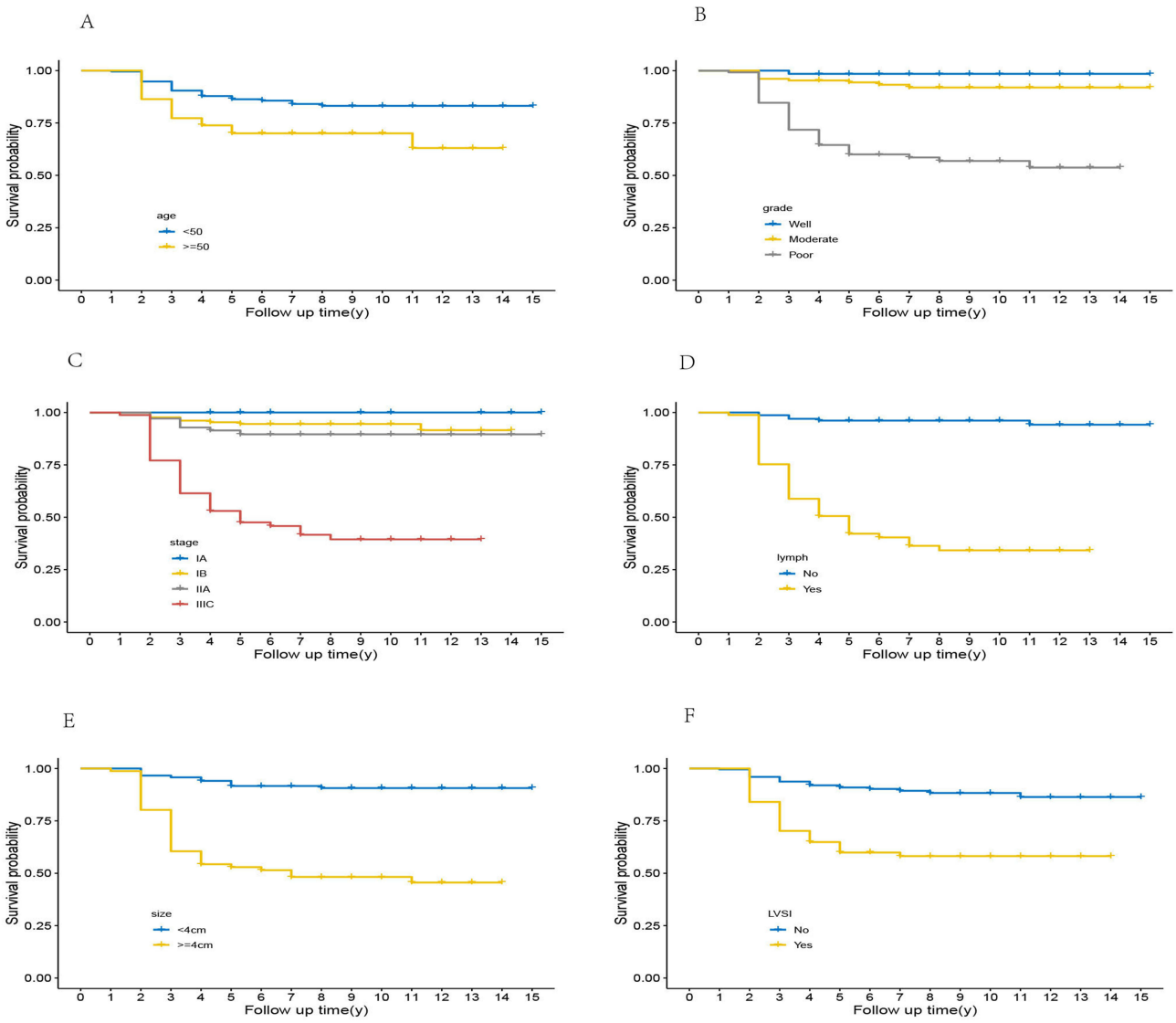

Figure 1 Kaplan-Meier curves for OS by: (**A**) age, (**B**) tumor grade, (**C**) tumor stage, (**D**) lymph node, (**E**) tumor size, and (**F**) LVSI.

(Figure 3). Calibration curves for 3-year, 5-year, and 10-year OS closely matched the reference line, indicating strong agreement between predicted and observed survival outcomes in all cohorts (Figure 4).

Clinical Applicability

DCA curves illustrated the clinical applicability of the nomogram models for predicting OS. The net benefit of the nomogram consistently exceeded the net benefit of assuming that all patients died or that none would die. This indicates superior predictive performance of the nomogram compared to traditional tumor prognostic models (Figure 5). In the TC, IVC and EVC threshold probabilities ranged from 20 to 80% for 3- and 5-year OS predictions, 20 to 90% for 10-year OS predictions in TC and IVC, and 20 to 80% for 10-year OS predictions in EVC. This threshold range (20–80%) corresponds to clinical scenarios where the nomogram can guide decisions such as selecting patients for aggressive adjuvant therapies or tailoring follow-up intervals based on predicted survival risk, offering a net benefit over assuming uniform treatment or no intervention.

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Table 2 Univariate and Multivariate Analyses of OS in the Training Cohort

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P value*
Age				
<50	Reference		Reference	
≥50	1.546(1.434–1.667)	<0.001	1.544(1.432–1.665)	<0.001
Histologic subtype				
Squamous cell carcinoma	Reference			
Adenocarcinoma	1.038(0.972–1.109)	0.261		
Other subtype	1.480(1.291–1.698)	0.063		
Grade				
Well	Reference		Reference	
Moderate	1.064(1.011–1.120)	0.018	1.114(1.057–1.175)	0.032
Poor	1.295(1.169–1.434)	<0.001	1.152(1.047–1.268)	0.004
Stage				
IA	Reference		Reference	
IB	1.843(1.602–2.120)	<0.001		
IIA	2.733(2.040–3.662)	<0.001	2.975(2.282–3.878)	<0.001
IIIC	4.817(2.782–8.340)	<0.001	5.105(2.961–8.800)	<0.001
Lymph				
NO	Reference		Reference	
YES	2.493(1.919–3.238)	<0.001	2.044(1.227–3.404)	0.006
LVSI				
NO	Reference		Reference	
YES	1.520(1.337–1.729)	<0.001	1.450(1.289–1.630)	<0.001
Size				
<4cm	Reference		Reference	
≥4cm	3.232(2.931–3.563)	<0.001	3.334(3.309–3.659)	<0.001
Invasion				
<1/2	Reference			
≥1/2	1.451(1.238–1.702)	0.032		
Radiation				
NO	Reference			
YES	1.198(0.992–1.368)	0.061		
Chemotherapy				
NO	Reference			
YES	1.058(0.926–1.209)	0.408		

Notes: Invasion (≥1/2) was significant in univariate analysis (P=0.032) but excluded from the final multivariate model due to collinearity with tumor size and lymph node status (P=0.171).

Discussion

Precision medicine has gained significant attention within the global medical community, particularly with the rise of big data, which offers promising opportunities for personalized care and improved outcomes.[9] As personalized medicine evolves, more effective tools are required to provide clinicians with accurate risk calculation on specific events and individual clinical outcomes.[10] Accurately predicting personalized event probabilities using collected patient-specific information is essential for tailoring treatment plans. Predictive assessments are clinically important for both patients and physicians, as the construction of prognostic models enables treatment customization based on the unique characteristics of each patient.[11] CC has the highest incidence among gynecological cancers. Although widespread screening has reduced both incidence and mortality rates, there remains a significant lack of tools to individualize postoperative survival predictions for these patients. Thus, identifying prognostic factors and developing predictive models is of paramount importance. Such model can optimize treatment plans and guide the care of CC patients.[12]

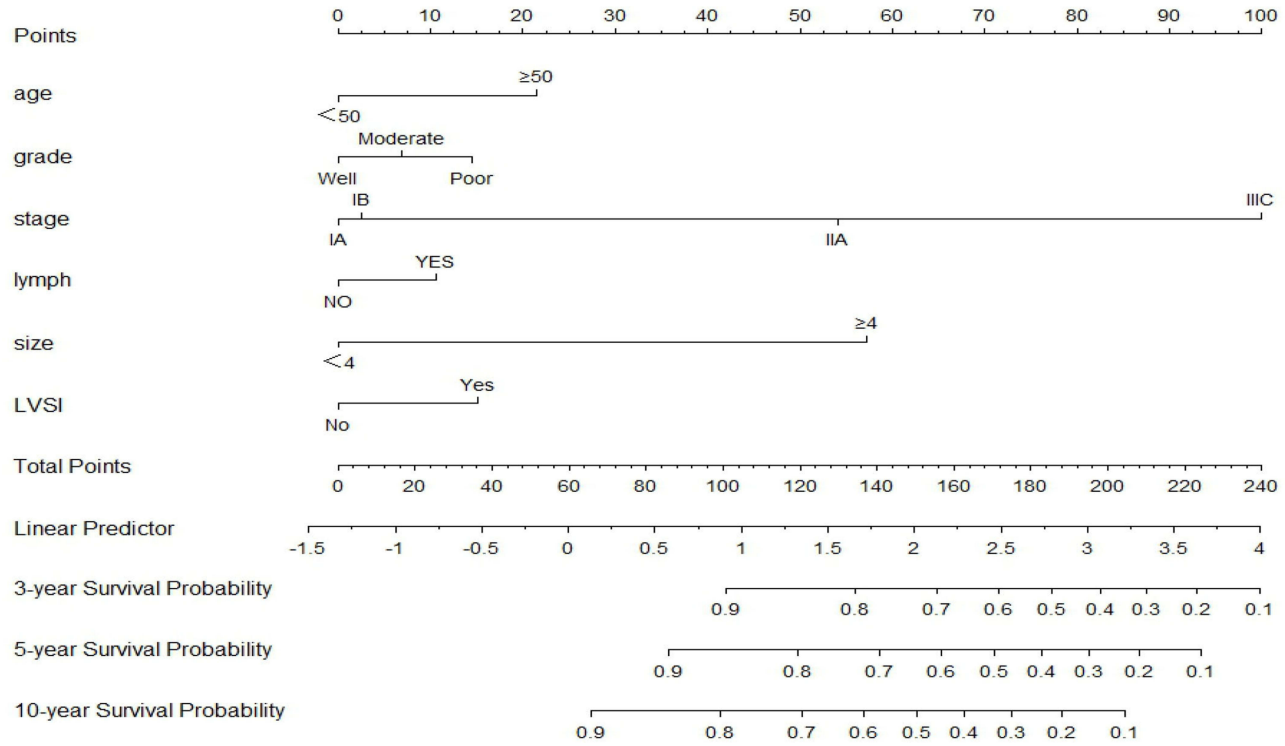

Figure 2 Nomogram for predicting survival rate of cervical cancer. Age; grade; stage; lymph; size; LVSI; overall survival.

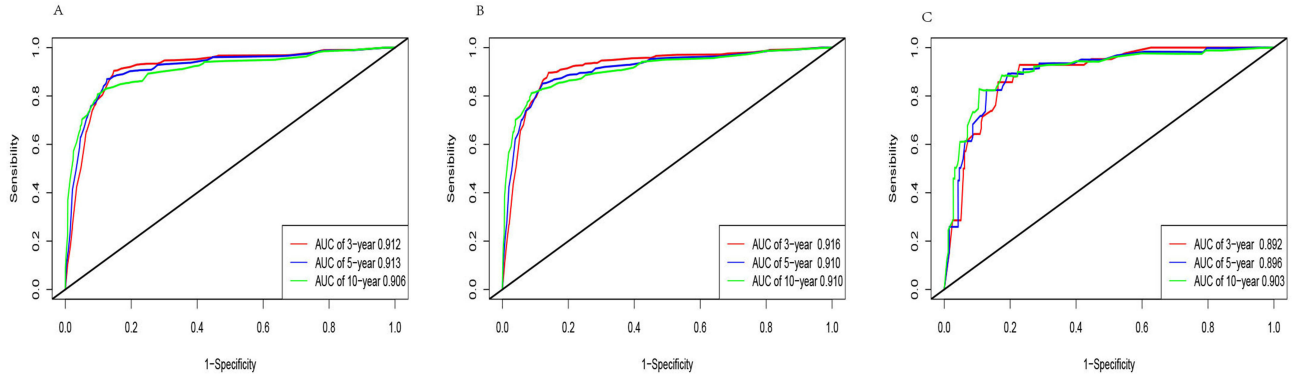

Figure 3 ROC for 3-, 5-and 10-year OS in the training cohort (**A**), internal validation cohort (**B**) and external verification cohort (**C**).

This study analyzed a total of 13,592 patients diagnosed with CC were sourced from the SEER Program, which was divided into two cohorts (TC and IVC). Cox regression analysis was used to develop a prognostic model that incorporates six independent prognostic factors, namely age, tumor grade, FIGO stage, LNM, LVSI, and tumor size. The construction of a nomogram based on these factors provides a valuable tool for clinicians to predict the survival rates of CC and devise individualized treatment plan.

Compared to ovarian cancer, CC patients generally experience a more favorable prognosis and longer survival.[13] While previous studies typically focus on predicting 5-year OS, this study extends the prediction to 10 years. The nomogram developed in this study assesses the prognostic value for disease progression and calculates the OS probabilities of CC patients.[14] The nomogram, incorporating six clinical-pathological predictors, showed excellent calibration.[15] In IVC, the model showed strong performance, achieving a C-index of 0.885 and the ROC analysis demonstrated satisfactory predictive performance at 3, 5, and 10 years, with AUC values of 0.916, 0.910, and 0.910, respectively. Similarly, the EVC yielded promising results, with the model achieving a C-index of 0.872. The ROC

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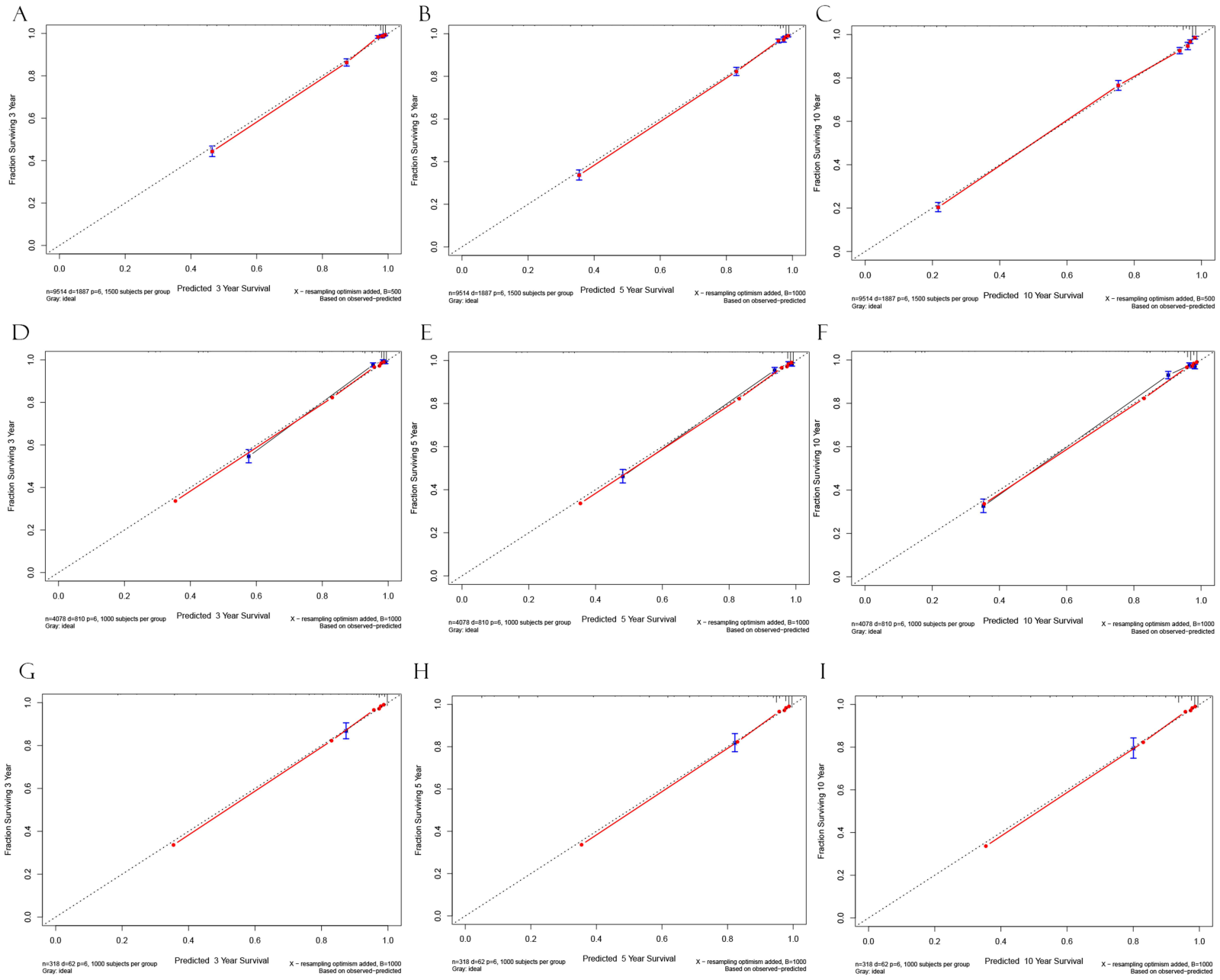

Figure 4 Calibration curves for predicting 3-year survival of patients with cervical cancer, 5-and 10-year survival of patients with cervical cancer (**A–C**) for training cohort, internal validation (**D–F**) and external verification (**G–I**).

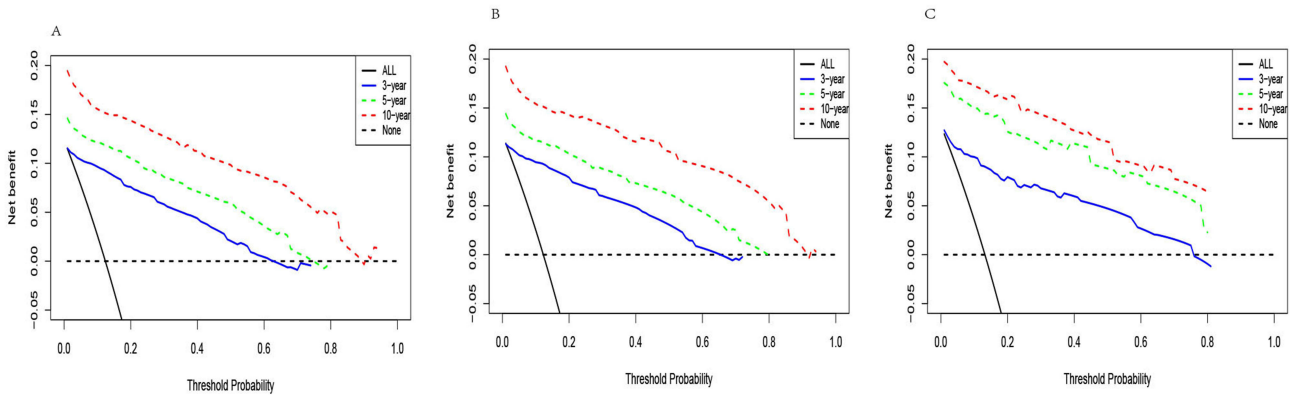

Figure 5 DCA for 3-, 5-and 10-year OS in the training cohort (**A**), internal validation cohort (**B**) and external verification cohort (**C**).

analysis confirmed satisfactory performance at 3, 5, and 10 years, with AUC values of 0.892, 0.896, and 0.903, respectively. The slightly lower AUC values in the EVC (eg, 3-year OS AUC=0.892 vs 0.916 in IVC) may be attributed to population heterogeneity, including differences in racial and ethnic backgrounds between the SEER-based cohorts and the Chinese EVC, as well as potential variations in treatment practices across regions and healthcare settings. Based on these findings, the model is considered strong in prognostic prediction.[16,17]

There are several prediction models for CC, each with its advantages and disadvantages. Many of these models are based on data from the SEER program, primarily conducted in the United States.[18] However, it remains uncertain whether these models can be generalized to other racial and ethnic groups, particularly Asian populations and East Asian individuals. Furthermore, while many prediction models undergo internal validation, they often lack external validation.[19] Even when external validation is conducted, it usually includes data from the same region, country, and ethnic group as the original study, limiting the generalizability of the findings.[20] The lack of external validation across different regions, countries, and ethnic groups represents a notable gap in current research. To address these limitations, this study established a prognostic model and conducted internal validation using SEER data. Additionally, the model was externally validated with data from the Chinese population, thereby enhancing its reliability. This dual-validation approach not only improves the model's applicability to diverse populations but also contributes to a broader understanding of CC prognosis across different demographic groups.

While this dual-validation approach suggests potential applicability to diverse populations, the smaller sample size of the Chinese cohort (n=318) compared to the SEER-based cohorts, which primarily represent the US population, warrants caution in generalizing findings across different ethnic groups. Multi-center, large-sample validation studies are needed to further confirm the model's generalizability.[19,20] The clinical practicality of the model is crucial for its promotion in clinical use.[21] The data collected from Yangming Hospital for the IVC were consistent with those in the SEER database. Notably, LNM and tumors larger than 4 cm significantly impact postoperative recurrence rates and OS, underscoring their clinical relevance.[22] In comparison to traditional ROC curves, DCA emphasizes clinical practicality, serving as a critical indicator for the efficacy of predictive models in clinical settings and their potential impact on patient outcomes.[23,24] In this study, the C-index of the nomogram reached 0.882, indicating favorable discrimination potential. Furthermore, the net benefit of the predictive model was equally favorable, supporting its clinical usefulness and validation by external data. Consequently, the prediction model holds promise for clinical promotion, enabling the better planning of personalized treatment that can significantly benefit patients.[25]

Compared to previous studies, this study boasts a larger sample size, thereby enhancing the reliability and potential applicability of the findings to diverse racial and population groups.[26] As artificial intelligence continues to evolve, prognostic models are expected to become increasingly accurate. The prognostic model developed based on data from the US national database has also demonstrated its relevance to the Chinese population. Moreover, further development of an easily accessible online prediction tool in the future, could facilitate clinicians in making informed treatment decisions.[27]

Prognostic models can be effectively utilized in clinical practice to evaluate the probability of postoperative recurrence and mortality in CC patients based on clinical and pathological data as well as surgery-related conditions. These pieces of information are helpful to formulate an individualized follow-up plan, and guide disease monitoring and treatment.[28] With the help of a well-established prognostic model, the 3-year, 5-year, and 10-year survival rates of patients with lymph node metastasis and tumors larger than 4 cm can be easily predicted which enables physicians to make informed decisions and develop individualized disease management plans, ultimately leading to improve survival for patients.[29] The exclusion of cervical stromal invasion from the final model, despite its univariate significance, reflects its shared variance with other incorporated factors such as tumor size and lymph node metastasis. This suggests these variables may capture overlapping biological aggressiveness information, with tumor size and nodal status providing stronger independent predictive value.

The ETERNITY project[30] showed that sentinel lymph node (SLN) mapping in early-stage cervical cancer has comparable oncologic outcomes to systematic lymphadenectomy, with similar disease-free (p=0.332) and overall survival (p=0.769) rates. SLN ultrastaging detected micrometastases in 2.4% of cases, potentially missed by conventional methods. SLN mapping may reduce surgical morbidity, especially in fertility-sparing approaches, and could enhance future prognostic models for risk stratification.

However, this study has some limitations. Although the EVC included data from patients of different races and countries, this diversity may have introduced potential biases. Additionally, the study relies solely on clinical and pathological data, excluding molecular or genetic markers, which may limit the model's ability to capture tumor-specific biological behaviors that could enhance prognostic accuracy. Incorporating such markers, as demonstrated in studies on clinicopathological characteristics and survival outcomes,[28,29] could improve individualized risk predictions in future models. With the advancement of genomics and proteomics, new molecular or genetic markers should be incorporated into future prediction models to enhance the accuracy of individual risk estimations[31,32] for more comprehensive prediction of survival outcomes among CC patients. While our model demonstrated good performance in the external validation cohort (n=318), the relatively small sample size may limit generalizability to more heterogeneous populations. Future studies with larger, multi-center validation cohorts are needed to further verify the model's robustness across diverse clinical settings.

The present study showcased that prognostic data garnered from SEER database could help identify prognostic factors influencing prognosis for the development of a prognostic model and construction of nomograms to predict the 3-year, 5-year, and 10-year OS rates of CC. Both IVC and EVC confirmed the predictive performance of the model and the EVC derived from the Chinese population further supports the reliability of the model to a wider population. Its clinical application could be further promoted and implemented in various settings and different countries, ultimately benefiting a diverse patient population.

Ethics Approval and Consent to Participate

Our research utilizes de-identified data from the SEER database, which is exempt from IRB review under 45 CFR 46.101(b)(4), and clinical data from Yangming Hospital Affiliated to Ningbo University, approved by Yiyao People's Hospital Medical Ethics Committee (Approval No. 2023-04-001) with informed consent for clinical data use only.

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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 the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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