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ORIGINAL RESEARCH

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Development of a novel web-based calculator for predicting overall survival in early-onset cervical cancer patients with positive lymph node metastasis

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Abstract

Background: Cervical cancer (CC) is a malignant tumor affecting the female genital system and ranks as second most common cancer among younger women. This study aimed to identify key clinicopathological and lymph nodal characteristics associated with the overall survival (OS) of CC patients aged <45 years and develop an interactive web-based calculator to assess patient prognosis. **Methods**: The Surveillance, Epidemiology and End Results (SEER) database was searched for cases diagnosed with CC from 2004 to 2015, which were then randomly divided into a training (n = 3720, 70%) and a validation (n = 1661, 30%) set. Least absolute shrinkage and selection operator (LASSO) regression was used to identify relevant predictors and construct a nomogram incorporating the most significant variables. In addition, its performance was assessed using C-index values, area under curve (AUC) values, calibration plots and Kaplan-Meier curves, and an online prediction tool was constructed. **Results**: In the training cohort, the C-index for the proposed nomogram was 0.809 (95% Confidence Interval (CI): 0.802–0.816), and in the validation set, it was 0.811 (95% CI: 0.801–0.821). The AUC values for 1-, 3- and 5-year OS were 0.880, 0.856 and 0.842 in the training set and 0.911, 0.843 and 0.829 in the validation set, respectively. The calibration curves demonstrated the reliable predictive performance of the nomogram, with the nomogram demonstrating good calibration and discrimination abilities in the validation set. **Conclusions**: The developed nomogram and online tool for CC patients aged <45 years demonstrated promising utility in potentially assisting clinicians to predict patient prognosis and develop more informed treatment strategies for these patients.

Keywords

Nomogram; Early-onset patients; Cervical cancer; SEER database; Web-based calculator

1. Introduction

Cervical cancer (CC) is a significant and prevalent cancer affecting women, particularly threatening their reproductive health. It ranks as the fourth leading cause of cancer among women worldwide and the second most common cancer among women aged 15–44 [1–3]. Approximately 500,000 new cases are diagnosed annually in developing countries, and the incidence has been shown to continuously increase every year [4]. Notably, China alone accounts for over a quarter of all new cases globally [5].

Despite notable advancements in surgical, radiotherapeutic and chemotherapeutic approaches for CC, accurately predicting the overall survival (OS) remains challenging due to individual variations in tumor behavior and heterogeneity. Early-onset CC (EOCC) refers to the occurrence of CC in patients <45 years old. However, studies focusing on the prognostic assessment, survival outcomes and treatment decisions for EOCC patients are limited. Therefore, it is of great significance to conduct prognostic prediction-related studies and develop individualized treatment approaches for CC to reduce mortality rates in this specific patient population.

Currently, the most widely used system for assessing the prognosis of CC patients is the International Federation of Gynecology and Obstetrics (FIGO) staging system, which primarily incorporates tumor features such as size and metastasis status. However, the prognostic factors for CC extend beyond these tumor characteristics. For instance, previous research has identified age, tumor size, stage, differentiation grade and pathological type as important prognostic factors for CC [6–8]. However, relying solely on these factors for treatment decisions might not be sufficient for personalized treatment. Thus, it might be both reasonable and necessary to consider all cancer-related risk factors when establishing an individualized treatment strategy for EOCC patients, urging the need for a

reliable, dynamic and flexible predictive model incorporating lymph node features to more accurately estimate the OS of EOCC patients.

In recent years, nomograms have gained significant popularity in predicting OS in cancer research [9–12]. They serve as novel and convenient predictive tools by combining various independent risk factors into a graphical scoring model. Liu *et al.* [13] identified race, American Joint Committee on Cancer (AJCC) stage, grade and other clinicopathological factors as important variables influencing OS and cancer-specific survival (CSS), based on which they constructed a nomogram for CC patients under 45 years old. However, they did not incorporate important lymph node factors into their model. Jiang *et al.* [9] developed a nomogram model for predicting OS and CSS, considering factors such as examined lymph nodes (ELNs), lymph vascular space invasion (LVSI) and regional lymph node surgery (RLNS) as independent prognostic factors. Another study suggested that the staging of positive lymph nodes (PLNs) is more reliable than lymph node ratio (LNR) and log odds of PLNs (LODDS) for predicting CSS in pancreatic neuroendocrine neoplasms [14]. LNR is the ratio between the number of PLNs and the total number of ELNs. LODDS is defined as log ([number of PLNs + 0.05]/[number of negative nodes + 0.05]). The addition of 0.05 to the numerator and denominator avoids division by zero. Yan *et al.* [15] developed a nomogram using ELNs as an independent factor for CC patients aged over 50 years. Exploring lymph node factors in CC patients could be valuable, as they have been overlooked in previously reported models. Additionally, recent research has shown that dynamic web-based survival rate calculators can serve as prognostic assessment tools. However, previous studies did not develop a convenient online tool specifically for CC patients, and currently, there are no studies on nomograms and web-based calculators for EOCC patients based on clinicopathological and lymph node factors, including PLNs, LNR and LODDS.

To fill this literature gap, we designed this present study to investigate the clinicopathological and lymph node characteristics of EOCC patients. By considering these factors, we aimed to develop an updated nomogram that could provide a more accurate prediction of OS and also designed an online calculator specifically for predicting the OS of EOCC patients, which might assist in creating personalized follow-up plans feasible and tailored to EOCC patient needs.

2. Material and methods

2.1 Patients and variables criteria

For this study, we utilized the Surveillance, Epidemiology and End Results (SEER) National Cancer Institute database (https://seer.cancer.gov/), which is a freely accessible US cancer registry. We obtained permission to access the incidence SEER Research Plus Data 18 Registries, released in April 2021 and based on the November 2020 submission. Using the SEER*Stat software (version 8.4.0.1, Surveillance Research Program, National Cancer Institute, Bethesda, MD, USA), we downloaded the data specifically for EOCC from 2004 to 2015. The dataset included demographics, marital status, year of diagnosis, primary tumor location, tumor stage, surgical treatment, survival state, survival time and other relevant information. The study inclusion criteria were: (1) the ICD-O-3/WHO classification was “Cervix Uteri”; (2) diagnosis confirmed by pathological assessment; (3) survived more than 0 days; and (4) was diagnosed between 2004–2015. The exclusion criteria were: (1) diagnosis was based on autopsy or death certificate, and (2) the cause of death or survival time was unknown. The study flow chart and other criteria for patient selection are shown in Fig. 1. Ultimately, 5381 cases of EOCC were eligible for this study.

2.2 Missing data processing

Due to missing data in examining PLNs, 2127 cases were identified as lacking the necessary data for calculating LNR and LODDS (as shown in Table 1). To address this issue, we employed the multiple imputation technique to estimate the missing data, as previously reported [16, 17]. Specifically, we performed five iterations of imputation. Among the imputed datasets, the model with the largest Cronbach’s alpha value (0.771) was selected to calculate and fill in the missing LNR and LODDS data, which ensures sufficient sample size.

2.3 Statistical analysis

A total of 5381 patients aged under 45 years were randomly divided into training and validation sets at a ratio of 7:3. The chi-square test was used to compare the variables between the two sets.

In the training set, consisting of 3720 patients, we employed the LASSO regression method for predictor selection and regularization. Variables with non-zero coefficients from the LASSO regression were used to construct the nomogram prediction model. This process involved three steps: predictor selection, nomogram model construction, and prediction of 1-, 3- and 5-year OS for EOCC patients using the created nomogram. Additionally, we developed a web-based calculator for individualized predictions. The discrimination ability of the model was assessed using the concordance index (C-index) and receiver operating characteristic (ROC) curves. Calibration curves were used to evaluate the agreement between predicted and actual OS probabilities. The discriminatory power of the model was also evaluated using Kaplan-Meier curves.

The nomogram and its indicators were assessed using the R software (version 4.2.0, R Development Core Team, The University of Auckland), while other analyses were conducted using the SPSS software (version 22, Inc., Chicago, IL, USA). Statistical significance was defined as $p < 0.05$.

3. Results

3.1 Patients' baseline characteristics

The training set consisted of 3720 EOCC patients, while the validation set comprised 1661 patients. The detailed patient characteristics are shown in Table 1. Notably, no statistically significant differences ($p > 0.05$) were observed in any of the indicators between the training and validation sets, indicating that the two sets were comparable.

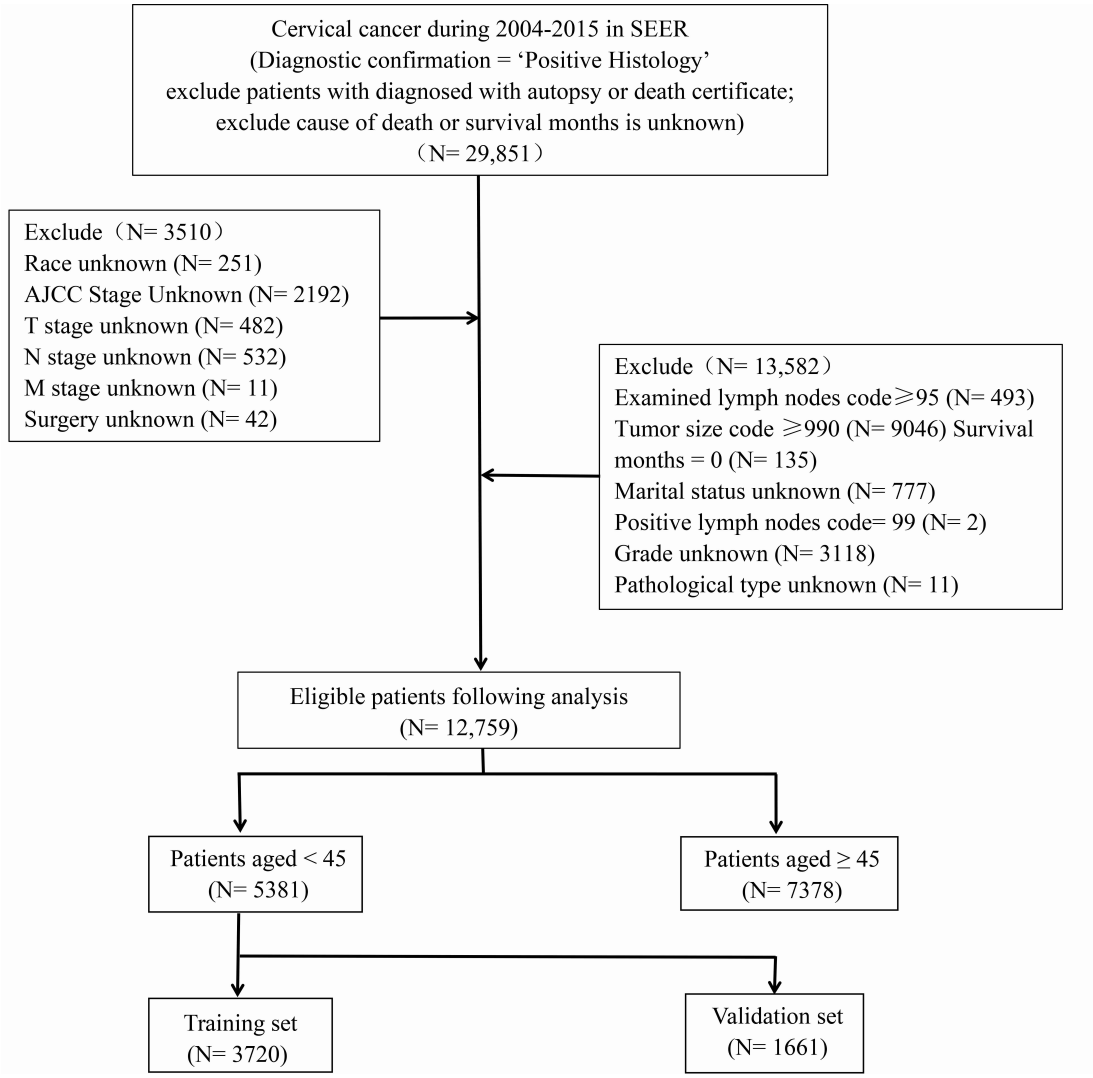

FIGURE 1. Flowchart showing the patient selection of this study. SEER: Surveillance, Epidemiology and End Results; AJCC: American Joint Committee on Cancer.

3.2 LASSO regression analysis

The potential factors of EOCC patients were identified using LASSO regression analysis [16]. After performing predictor selection and regularization, the following parameters were selected and included in the nomogram prediction model: race (coefficients 0.031), marital status (coefficients 0.150), FIGO Stage (coefficients 0.385), T stage (coefficients 0.294), M stage (coefficients 0.270), chemotherapy (coefficients 0.122), tumor size (coefficients 0.505), grade (coefficients 0.157), histology (coefficients 0.155), PLNs (coefficients 0.072), LNR (coefficients 0.325), surgery (coefficients −0.217). The results of the LASSO regression analysis are shown in Fig. 2.

3.3 Nomogram creation

The nomogram for predicting 1-, 3- and 5-year OS is presented in Fig. 3, comprising a total of 12 factors and among which the FIGO stage, T stage and grade were assigned the highest points, indicating their significant impact on EOCC patient prognosis. In addition, LNR, histology, tumor size, PLNs, marital status, M stage, surgery, chemotherapy and race were also identified as important factors influencing the prognosis.

3.4 Nomogram validation

The nomogram model demonstrated strong predictive ability, as indicated by the C-index values of 0.809 (95% CI: 0.802–0.816) in the training set and 0.811 (95% CI: 0.801–0.821) in the validation set, confirming its accuracy in predicting OS. The calibration curves for 1-, 3- and 5-year survival rates closely matched the ideal 45° reference line, indicating a high level of agreement between the predicted and actual survival rates (Fig. 4A,B). Receiver operating characteristic analysis was used to assess sensitivity and specificity, yielding AUC values of 0.880, 0.856 and 0.842 for the model's prediction of 1-, 3- and 5-year survival in the training set (Fig. 5A). In the validation set, the corresponding AUC values were 0.911, 0.843 and 0.829, respectively (Fig. 5B). These AUC values, all exceeding 0.8, demonstrate the excellent discrimination ability of our proposed nomogram.

3.5 Survival analysis

We divided all patients into two risk groups based on their overall scores: a risk-low group (overall score, ≤220) and a risk-high group (overall score, >220). As shown in Fig. 6, the

TABLE 1. Clinical characteristics of EOCC from the SEER database.

	Overall (N = 5381)	Training set (N = 3720)	Validation set (N = 1661)	*p*-value
Age (yr)				
<35	1921 (35.70%)	1337 (35.94%)	584 (35.16%)	0.814
35–39	1621 (30.12%)	1112 (29.89%)	509 (30.64%)	
>39	1839 (34.18%)	1271 (34.17%)	568 (34.20%)	
Race				
White	4118 (76.53%)	2863 (76.96%)	1255 (75.56%)	0.180
Black	780 (14.50%)	541 (14.54%)	239 (14.39%)	
Other[a]	483 (8.97%)	316 (8.49%)	167 (10.05%)	
Marital Status				
Married	2682 (49.84%)	1848 (49.68%)	834 (50.21%)	0.775
Other[b]	642 (11.93%)	439 (11.80%)	203 (12.22%)	
Single	2057 (38.23%)	1433 (38.52%)	624 (37.57%)	
FIGO Stage				
I	3322 (61.74%)	2286 (61.45%)	1036 (62.37%)	0.315
II	553 (10.28%)	385 (10.35%)	168 (10.11%)	
III	1180 (21.93%)	835 (22.45%)	345 (20.77%)	
IV	326 (6.05%)	214 (5.75%)	112 (6.74%)	
T_Stage				
T1	3927 (72.98%)	2716 (73.01%)	1211 (72.91%)	0.967
T2	970 (18.03%)	673 (18.09%)	297 (17.88%)	
T3	418 (7.77%)	287 (7.72%)	131 (7.89%)	
T4	66.0 (1.22%)	44.0 (1.18%)	22.0 (1.32%)	
N_Stage				
N0	4136 (76.86%)	2846 (76.51%)	1290 (77.66%)	0.352
N1	1245 (23.14%)	874 (23.49%)	371 (22.34%)	
M_Stage				
M0	5091 (94.61%)	3529 (94.87%)	1562 (94.04%)	0.215
M1	290 (5.39%)	191 (5.13%)	99.0 (5.96%)	
Surgery				
No/unknown	1298 (24.12%)	919 (24.70%)	379 (22.82%)	0.135
Yes	4083 (75.88%)	2801 (75.30%)	1282 (77.18%)	
Radiation				
No/unknown	2629 (48.86%)	1805 (48.52%)	824 (49.61%)	0.461
Yes	2752 (51.14%)	1915 (51.48%)	837 (50.39%)	
Chemotherapy				
No/unknown	2992 (55.60%)	2049 (55.08%)	943 (56.77%)	0.248
Yes	2389 (44.40%)	1671 (44.92%)	718 (43.23%)	
Tumor Size (cm)				
$x \leq 4$	3509 (65.21%)	2405 (64.65%)	1104 (66.47%)	0.196
$x > 4$	1872 (34.79%)	1315 (35.35%)	557 (33.53%)	

TABLE 1. Continued.

	Overall (N = 5381)	Training set (N = 3720)	Validation set (N = 1661)	*p*-value
Grade				
I	839 (15.59%)	578 (15.54%)	261 (15.71%)	0.993
II	2432 (45.20%)	1682 (45.22%)	750 (45.15%)	
III	1981 (36.81%)	1372 (36.88%)	609 (36.66%)	
IV	129 (2.40%)	88.0 (2.37%)	41.0 (2.47%)	
Histology				
SCC	3438 (63.89%)	2386 (64.14%)	1052 (63.34%)	0.222
AC	1526 (28.36%)	1034 (27.80%)	492 (29.62%)	
Other	417 (7.75%)	300 (8.06%)	117 (7.04%)	
PLNs				
0	2552 (47.43%)	1752 (47.10%)	800 (48.16%)	0.689
1	275 (5.11%)	187 (5.03%)	88.0 (5.30%)	
2	197 (3.66%)	137 (3.68%)	60.0 (3.61%)	
3	77.0 (1.43%)	48.0 (1.29%)	29.0 (1.75%)	
≥4	153 (2.84%)	105 (2.82%)	48.0 (2.89%)	
Not examined	2127 (39.53%)	1491 (40.08%)	636 (38.29%)	

[a]*Other includes American Indian/AK Native, Asian/Pacifific Islander.* [b]*Other includes Separated divorced or widowed. AC: adenocarcinoma; SCC: Squamous cell carcinoma; FIGO: International Federation of Gynecology and Obstetrics; PLNs: positive lymph nodes.*

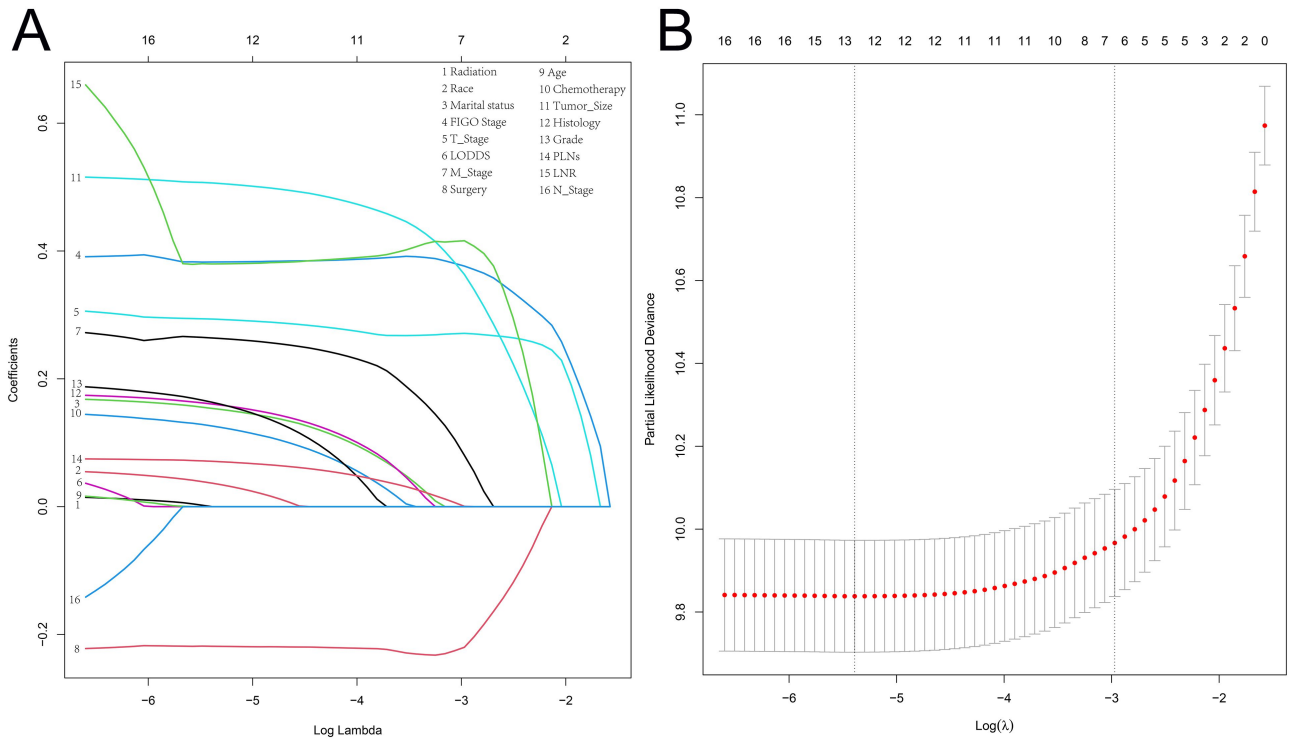

FIGURE 2. LASSO Regression Analysis for Factor Screening. (A) LASSO regression coefficient profiles of the variables were generated by plotting against the log (λ) sequence. A total of 12 non-zero coefficients were identified and used to construct the nomogram. (B) Tuning parameter selection in LASSO regression was performed using 10-fold cross-validation. The likelihood of deviance was plotted as a function of log (λ). The optimal values, determined based on the 1-standard error criteria, are indicated by the dotted vertical lines.

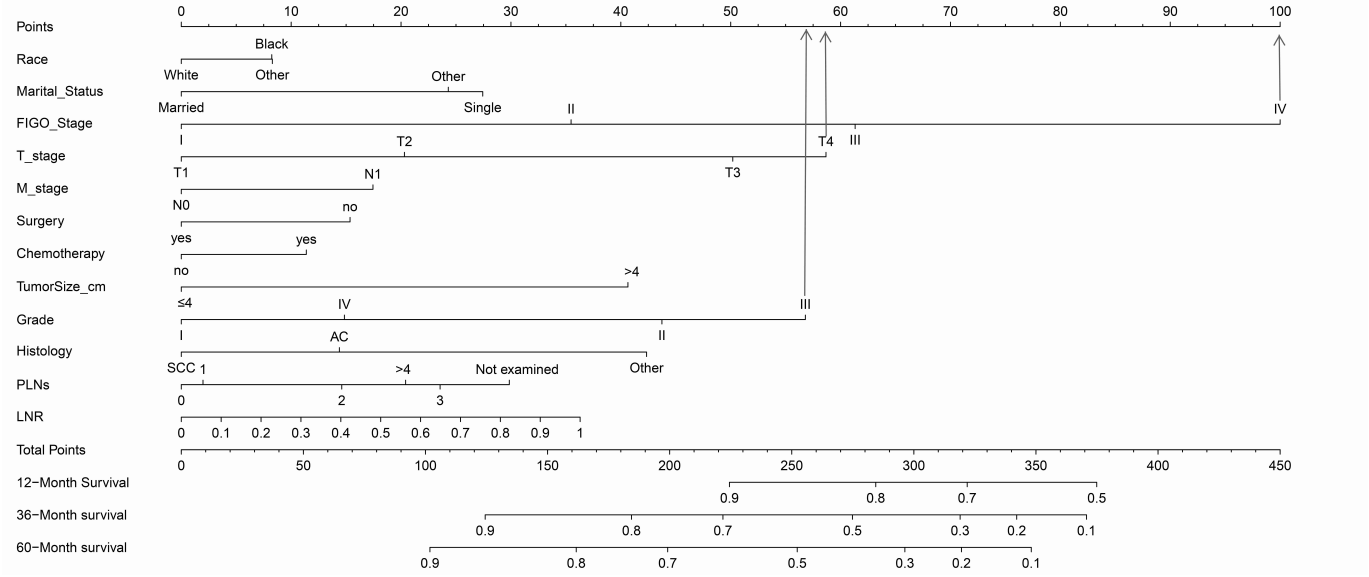

FIGURE 3. Nomogram for predicting 1-, 3- and 5-year OS of EOCC patients. The three most significant factors are highlighted using arrow. FIGO: International Federation of Gynecology and Obstetrics; PLNs: positive lymph nodes; LNR: lymph node ratio.

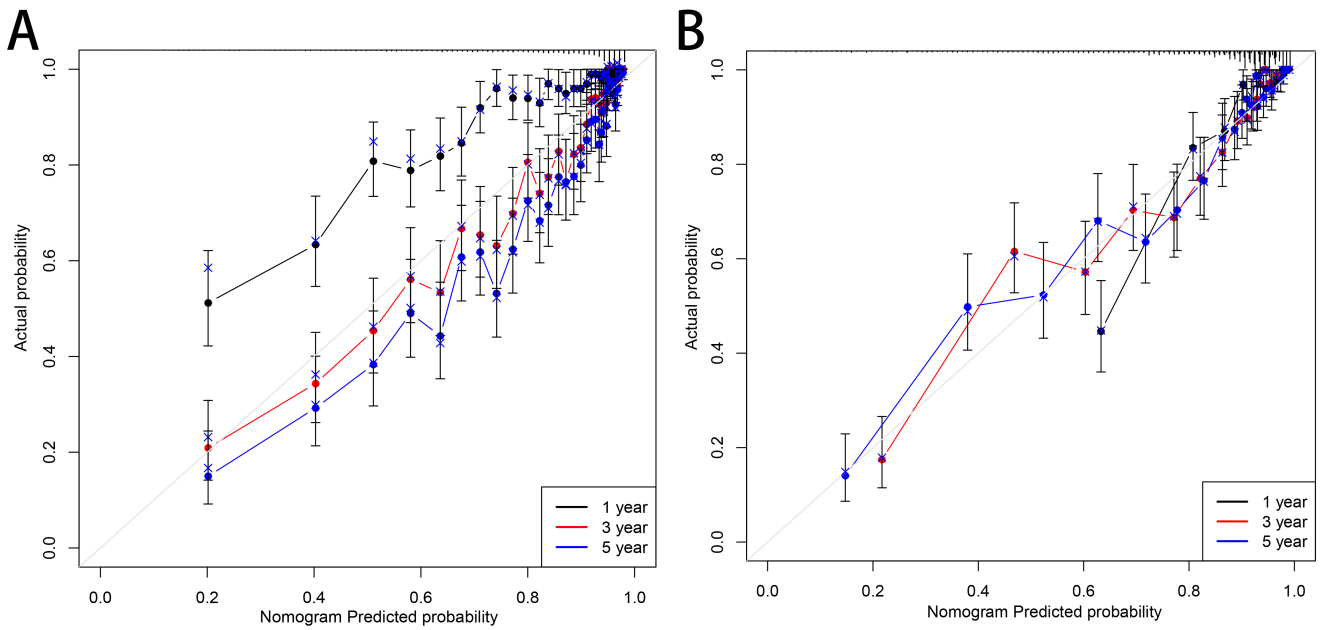

FIGURE 4. Calibration plots of the nomogram for 1-, 3- and 5-year OS prediction of EOCC patients in the (A) training set and the (B) validation set.

1-, 3- and 5-year OS rates were 78.6%, 48.6% and 41.7% for the high-risk group, while they were 98.6%, 90.9% and 86.1% for the low-risk group in the training group, respectively. For the validation group, the 1-, 3- and 5-year OS rates were 76.1%, 43.7% and 36.1% for the high-risk group and were 98.5%, 88.8% and 85.4% for the low-risk group. These findings indicate a gradual decrease in survival probability as the survival time increases, implying a lower likelihood of long-term survival. The Kaplan-Meier curves for both the validation and training sets demonstrate significant differences ($p < 0.0001$) in the survival outcomes between the two risk groups, validating the discriminative ability of our model.

3.6 Novel web-based calculator for OS prediction

To provide a more interactive and visual representation of the OS probability curves for EOCC patients based on the significant factors, a novel web-based calculator was developed based on the nomogram proposed above. The process involved several steps. First, we registered an account on "shinyapps.io" using an email address, and after obtaining authorization, we obtained the necessary keys from the web, which were then run in RStudio (version 4.2.0, R Development Core Team, The University of Auckland) using the

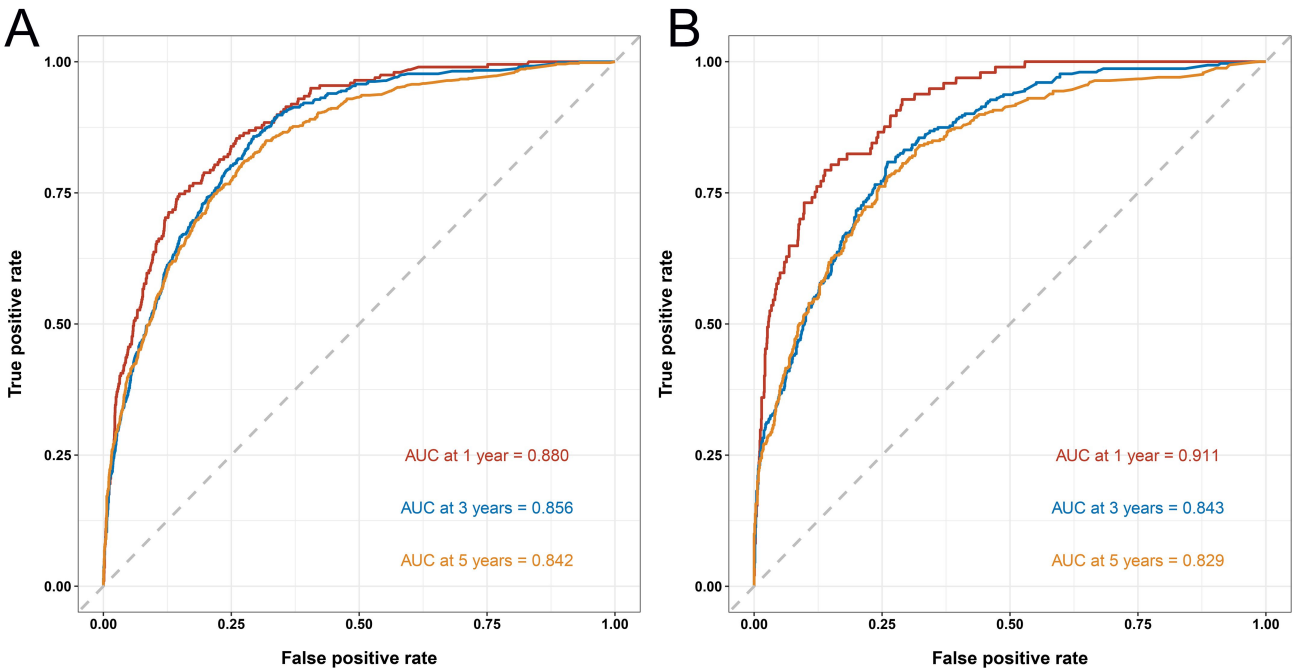

FIGURE 5. The ROC curves of the nomogram for predicting the 1-, 3- and 5-year OS of EOCC patients in the (A) training set and the (B) validation set.

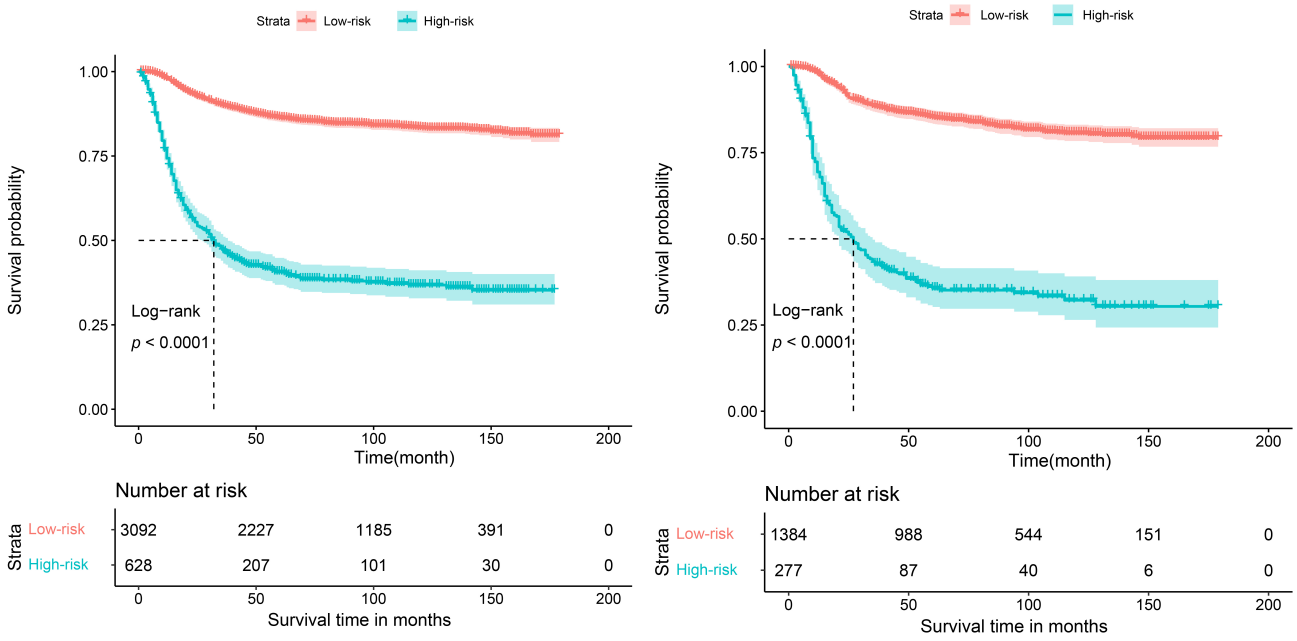

FIGURE 6. Kaplan-Meier curves for predicting the OS of EOCC patients in the (A) training set and the (B) validation set.

"shiny" and "DynNom" packages. Subsequently, a file named "ui.R" was created and published to the server along with our nomogram program. Lastly, the online calculator was successfully created and can be accessed at the following link: https://wuzhecqu.shinyapps.io/DynNomapp. Clinicians can now flexibly select different factors on the calculator to estimate the OS of their EOCC patients, which may help guide clinical decision-making.

4. Discussion

Accurate survival prediction is important for enhancing the quality of future clinical trials by minimizing potential biases in assigning treatment. However, several studies have highlighted limitations in the currently employed FIGO clinical staging system for cervical cancer, suggesting its inadequacy in providing precise prognostic information for patients [18–

20]. In response to this, our study successfully developed and validated a nomogram specifically designed to predict the OS of EOCC patients. This personalized model can serve as a valuable tool for disease monitoring and facilitating treatment decisions, addressing the need for more accurate prognostic assessment in cervical cancer.

Previous studies have highlighted the significance of PLN and LNR as important prognostic factors for survival outcomes in CC patients [21–23]. While Liu *et al.* [13] have examined a SEER-based prognostic nomogram for CC patients below the age of 45 years, the inclusion of PLNs and LNR in predicting the prognosis of patients aged <45 has not been previously reported. However, Wang *et al.* [24] developed a nomogram that incorporated LODDS, which outperformed the widely used FIGO staging system in predicting OS in CC patients after surgery. Additionally, Kwon *et al.* [25] compared the prognostic efficacy of PLN number, PLN location, LNR and LODDs in high-risk CC patients treated with radical surgery and adjuvant treatment and found that LODDs ≥−1.05 was the only significant prognostic factor for both disease-free survival (DFS) and OS. Furthermore, Olthof *et al.* [22] demonstrated that the number of positive nodes or nodal ratio could support risk stratification for survival outcomes in node-positive early-stage cervical cancer, which is consistent with our study. In this present study, we considered a total of 16 potential factors, including ELNs, PLNs, LNR and LODDS, based on previous research [20, 24, 26]. Through LASSO regression analysis, race, marital status, FIGO stage, T stage, M stage, surgery, chemotherapy, tumor size (cm), grade, histology, PLNs and LNR, were identified as influencing factors affecting the survival of EOCC patients.

To the best of our knowledge, this is the first study to simultaneously incorporate PLNs, LNR and LODDS as factors in predicting the prognosis of EOCC patients. By utilizing a large multicenter dataset, we have developed a nomogram that effectively predicts the prognosis of EOCC. Several studies have included age (mostly categorized age as ≥50 years or 65 years) in their proposed nomogram, which was shown to affect the CSS or OS of EOCC patients [15, 27]. While age is often considered an important factor in nomogram construction, it is noteworthy that our study, similar to Liu *et al*. [13]'s research, did not include age as a predictor. This decision aligns with the fact that the effect factors in the nomogram for EOCC patients may differ from those of elderly CC patients [28–30]. Furthermore, Pan *et al.* [31] developed a nomogram to predict OS rates in adolescent and young adult CC patients using variables such as FIGO stage, tumor grade and histologic type. However, their study had limitations as it did not include patients who had received chemotherapy or radiotherapy. Previous studies have demonstrated the effectiveness of radiotherapy and chemotherapy in improving the prognosis of CC patients following surgery [32]. In this study, 63.89% of EOCC patients had squamous cell carcinoma (SCC), and 28.36% had adenocarcinoma (AC), indicating a higher incidence rate of SCC compared to AC, which aligns with the findings of a previous study [13]. In addition, our proposed nomogram included chemotherapy as a variable but not radiotherapy, which may be attributed to the potential ineffectiveness of radiotherapy in patients with possible lymph node metastasis [15]. Furthermore, younger patients often prioritize preserving their reproductive function, which might lead to limitations in delivering an adequate radiation dose to target areas such as the uterus, ovaries and vagina. This observation is consistent with the results of Meng *et al.* [33], who didn't include radiotherapy as a predictor in their nomogram for predicting the CSS for cervical cancer patients below the age of 65 years. Importantly, our nomogram highlights the significant contribution of the FIGO stage to the predicted probability of 1-, 3- and 5-year OS, consistent with numerous previous studies [9, 15, 27]. Furthermore, our nomogram reveals an intriguing finding: chemotherapy was associated with poorer OS, suggesting that potential chemotherapy side effects might have had a detrimental impact on the long-term survival of EOCC patients [13, 34]. Additionally, our study indicates that CC patients with larger tumor size, not examined lymph nodes and AC histology tend to have slightly worse prognoses than those with smaller tumor size, smaller number of PLNs, and squamous cell carcinoma (SCC) histology, respectively, which were consistent with previous reports [13, 15]. Based on these existing issues in the current literature, developing an online calculator for individual prediction in EOCC patients seems essential.

Moreover, when compared to the 6th edition of the FIGO staging system, nomograms that incorporate additional clinicopathological factors and the key lymph node elements of traditional staging systems have demonstrated superior discriminant ability in predicting OS, as evident from comparisons of C-index and AUC values [35, 36]. Previous studies have recognized the lymph node status of CC as a clinically significant factor influencing treatment decisions and prognosis [25, 37]. The number of PLNs has been identified as an important characteristic affecting the 5-year OS rate of CC patients [24]. However, relying solely on the number of PLNs and regional lymph nodes may not fully capture the disease status in all cases [38], making the simultaneous consideration of PLN and LNR crucial for more accurate prediction of the survival of EOCC patients. In this study, we incorporated various lymph node factors into the nomogram to further enhance the prediction of OS. Encouragingly, our model exhibited excellent evaluation indicators, including C-index, AUC values and other metrics. In regard to related studies, the AUC values for 3- and 5-year OS in Yan *et al*. [15]'s model was 0.818, 0.802 in the training set and 0.838, 0.813 in the validation set, which are lower than those of our model. Similarly, the C-index values in Zhang *et al*. [18]'s nomogram were 0.753 and 0.751 in the training and validation cohorts, while Li *et al*. [34]'s study reported a C-index value of 0.771. Additionally, the AUC values for 3- and 5-year OS in Yang *et al*. [20]'s model was all below 0.7 in the training and validation sets. Overall, our model outperformed these previous studies in terms of predicting the OS, demonstrating its superior discrimination, calibration and promising performance.

Furthermore, the calibration curves of our nomogram demonstrated excellent agreement with the ideal 45° reference line, indicating satisfactory performance. The Kaplan-Meier curves revealed a significant difference in survival outcomes between the high-risk and low-risk groups,

underscoring the discriminative ability of our model. Also, the developed novel web-based calculator may allow clinicians to select the relevant influencing factors and generate individualized survival curves for EOCC patients (accessible at https://wuzhecqu.shinyapps.io/DynNomapp/).

5. Limitation

Firstly, as a retrospective study, it is susceptible to inherent biases that are difficult to completely eliminate. Secondly, important variables such as body mass index (BMI) index, family history of CC, obesity, smoking status and human papillomavirus (HPV) vaccine history were unavailable in the SEER database, which could have provided valuable insights into the prognostic assessment. Thirdly, the lack of external validation using a local dataset hinders the ability to further assess the generalizability of the nomogram.

6. Conclusions

In conclusion, this study highlights the prognostic factor for younger CC and introduces a novel approach by incorporating lymph node-related factors and clinicopathological findings to estimate the OS of CC patients aged <45 years. The developed web-based calculator may allow clinicians to easily and rapidly estimate their patients' survival by selecting relevant prognostic factors, which may serve as a valuable tool for making efficient and informed decisions to improve patient management and outcomes.

AVAILABILITY OF DATA AND MATERIALS

The data analyzed in this study is available at https://seer.Cancer.gov/.

AUTHOR CONTRIBUTIONS

ZW and YW—contributed to the conception and design. ZW—collected and cleaned the data; wrote the draft. QTD—analyzed the data and drew the figures and tables. YP, MJL, YXZ, SXP and ZX—contributed to manuscript writing and revision. All authors approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The data of this study is obtained from the SEER database. The patients' data is public and anonymous, so this study does not require ethical approval and informed consent. All authors have reviewed the final version of the manuscript and approved its submission.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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