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RESEARCH ARTICLE

Qunlong Liu et al.: SEER-based prognostic nomogram for cervical cancer patients

Development and validation of a SEER-based prognostic nomogram for cervical cancer patients below the age of 45 years

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ABSTRACT

This study aimed to establish a nomogram for the prognostic prediction of patients with early-onset cervical cancer (EOCC) in both overall survival (OS) and cancer-specific survival (CSS). The 10,079 patients diagnosed with EOCC between 2004 and 2015 were captured within the Surveillance, Epidemiology, and End Results (SEER) database and further were divided into training and validation sets randomly. The independent prognostic factors were identified in a retrospective study of 7,055 patients training sets randomly. Besides, the prognostic nomogram was developed using R software according to multivariable Cox regression analysis. Furthermore, the model was externally validated using the data of 3,024 patients diagnosed at different times enrolled in the SEER database. In training set, the C-indexes for OS and CSS prediction were 0.831 (95% confidence interval [CI]: 0.815-0.847) and 0.855 (95%CI:0.839-0.871). The results of ROC indicated that nomograms possessed better predict performance compared with TNM-stage and SEER-stage. And the areas under the curve (AUC) of the nomogram for OS and CSS prediction in ROC analysis were 0.855 (95%CI:0.847-0.864) and 0.782 (95%CI:0.760-0.804), respectively. In addition, calibration curves presented perfect agreements between the nomogram-predicted and actual 1-, 3-, and 5-year in the validation cohort, in OS rate and CSS rate. This study established and validated a prognostic nomogram that provided an accurate prediction of 3-, 5-, and 10-year OS and CSS of EOCC patients, which contributed to clinicians to be useful for patients’ counseling and clinical trial designing.

KEYWORDS: Early-onset cervical cancer; prognostic nomogram; overall survival; cancer-specific survival; SEER
INTRODUCTION

Cervical cancer is still the fourth most common female malignant tumor in the world [1,2]. Cervical cancer is the second leading cause of cancer related death in young women aged from 20 to 39 years in 2020 [1]. The incidence rate of cervical cancer is about 500 000 cases in the world every year [3], and the number of new cases and deaths in China accounts for more than 1/4 of the world [4]. At present, surgery, radiotherapy, chemotherapy and immunotherapy are the main methods to treat this kind of cancer [5]. Clinically, patients younger than 45 years old are defined as early-onset cervical cancer. Although surgery, radiotherapy and chemotherapy have made great progress in the treatment of Cervical cancer, there are still significant differences in clinical prognosis compared with elderly patients, which requires accurate prognosis judgment and individualized treatment.

At present, the tumor lymph node metastasis (TNM) staging system proposed by the American Joint Commission on Cancer (AJCC) has been widely used to predict the prognosis of various cancers, including tumor invasion (T), regional lymph node (N) and distant metastasis (M) as predictors [4]. However, the prognosis evaluation based on TNM staging system is still limited and cannot accurately predict the prognosis. For the establishment of an individualized treatment plan, it is necessary to consider all the risk factors related to cancer, especially the treatment of EOCC patients.

In recent years, the nomogram based on the regression coefficient of each variable always integrates many prognostic factors and can better predict the survival rate[5]. It has been used to predict the prognosis of various cancers, such as gastric cancer [6], breast cancer [7] and so on. As a prognostic tool, nomogram can accurately predict the overall survival rate (OS) and cancer specific survival rate (CSS) of patients, which is attributed to the multiple
clinical variables included in the calculation. Therefore, our study established nomograms to predict the 3-, 5-, and 10-year OS and CSS of EOCC patients, which is helpful for individualized treatment preparation and life extension.

MATERIALS AND METHODS

Data source and patients

From 2004 to 2015, we adopted SEER * stat software (version 8.3.5; SEER 18 Regs Custom Data (including additional treatment fields), November 2018 sub (1975-2016 varying) database) identified 10,079 eligible patient who were diagnosed as EOCC through SEER database of the National Cancer Institute, including clinicopathological data and individualized prognosis results. The exclusion standards were as follows: (I) patients over 45 years old; (II) patients with multiple primaries tumors; (III) unknown survival time; (IV) non histological studies (V) unknown AJCC stage; (VI) unknown TNM stage; and (VII) patients without surgery. The subject screening scheme were shown in Figure 1. All eligible EOCC patients were randomly assigned to the training and validation set.

Study variables

Clinical variables included in this study, extracted from SEER database, contained the age of diagnosis, race, marital status, histological type origin, tumor primary site, histologic type, tumor grade, AJCC stage, TNM stage, SEER stage, Tumor size (cm), Chemotherapy, Radiotherapy. The age of eligible EOCC patients was divided into three groups (<37, 37-40 and >40; Fig. S1) according to the optimal cut-off value calculated by X-tile software version 3.6.1 (Yale University School of Medicine, US). The clinical characteristics included race (white, black, and others) and marital status (married, unmarried, unknown). The tumor variables included the histological type (Squamous cell carcinoma, Adenocarcinoma and others), SEER stage (localized, regional and distant), Tumor size (cm) (≤4cm, >4cm and unknown), radiotherapy (no or yes) and
chemotherapy (no or yes). Tumor grades I-IV represented well differentiated, moderately differentiated, poorly differentiated and undifferentiated tumors, respectively. OS time refered to the survival time of the patient from diagnosis to any cause of death or the date on which data were deleted. The CSS time analyzed in this study refered to the cancer-related survival time from diagnosis to death, excluding other factors. The study end point survival OS and CSS.

**Ethical statement**

Since the clinical data in this study were collected in a publicly available manner from the SEER database, there were no local ethical recognition or state government officials. Because this retrospective study was based on public data from the SEER database, informed consent was not required.

**Statistical analysis**

Kaplan Meier curve and log rank test were used to investigate the OS and CSS of EOCC patients. Objective to explore the clinical factors of OS and CSS in patients with EOCC by univariate and multivariate regression analysis. The cox proportional hazards results are used as the basis of nomogram construction and validation. R software version 3.5.1 (http://www.R-project.org) was performed for creating nomographs. Consistency index (C index) and calibration curve were used to evaluate the performance and accuracy of nomogram. The value of C index ranged from 0.50 to 1.00, which was positively correlated with the prediction performance of the model. It shows that the models accompanied with perfect discrimination ability when the value is 1.00. When the calibration curve is applied to a fully calibrated model, the prediction will fall on the diagonal 45 ° of the figure.

In addition, receiver operating characteristic (ROC) and curves were used to evaluate the predictive performance of nanograms, TNM stage and SEER stage. Statistical analyses
were conducted using Statistical Package for the Social Sciences software (version 20.0; SPSS Inc, Chicago, IL, USA). When p < 0.05, the results were statistically significant.

RESULTS

Patient baseline characteristics

A total number of 10,079 eligible patient were enrolled who were diagnosed as EOCC from 2004 to 2015 through SEER database and divided into the training set (n=7,055) and the validation set (n=3,024) randomly. For all patients, there were 5,123 (50.8%) patients aged <37, and 2,487 (24.7%) patients aged >40. In the race group, 8,138 (75.8%) patients were belonged to white and 939 (9.3%) patients were belonged to black. There were 5,067 (50.3%) married, 4,475 (44.2%) unmarried. Additionally, the majority of N stage is N0 (8806; 87.4%) while 97.7% (9847) were in M0 stage and 89.1% (8983) were in T1 stage according to laboratory examinations and postoperative pathological results. Squamous cell carcinoma was the most prevalent type of pathology in the EOCC patients, which accounting for 60.6% (6106). In the SEER stage group, 8029 (79.7%) patients were belonged to localized. There were 6191 (61.4%) patients Tumor size (cm) ≤ 4. The treatment protocol of patients includes chemotherapy (2304; 22.9%) and radiotherapy (2724; 27.0%). Baseline demographic and clinical characteristics of EOCC patients are shown in Table 1.

Identification of independent prognostic factors of OS and CSS in training set

Univariate and multivariate cox regression analysis were performed to assess the independent prognostic factors for OS and CSS. In the univariate analysis, there were age, race, marital status, histological type, grade, AJCC stage, T stage, M stage, N stage, SEER stage, tumor size (cm), chemotherapy and radiotherapy as the prognostic factors of OS and CSS. The multivariate cox analysis was further applied in our study and it was found that the four variables age, marital status, N stage and M stage were excluded from independent
prognostic factors for OS (Table 2). And the results of multivariate analysis also indicated
that race, histological type, grade, AJCC stage, T stage, SEER stage, tumor size (cm),
chemotherapy and radiotherapy were independent prognostic factors impacting the CSS of
EOCC patients (Table 3).

**Development of a prognostic nomogram for OS and CSS**

The prognostic nomograms were based on the multivariate cox regression results. The
prognostic nomogram for 3-, 5- and 10-year OS and CSS (Fig. 2A and Fig. 2B) was
comprised of the following independent prognostic factors: race, histological type, grade,
AJCC stage, T stage, SEER stage, tumor size (cm), chemotherapy and radiotherapy. The
length of the line corresponding to each variable in the nomogram represents the
contribution of predictors to survival outcomes.

Each subtype of the variables that made up the nomogram corresponds to a point on the
"Points" scale. We can calculate the total score of a specific EOCC patient by adding the
scores of each subtype corresponding to each variable. Then, a straight line can be drawn
from the position of these total scores on the "Total points" scale, providing each patient
with 3-year, 5-year, and 10-year OS and CSS probabilities.

**Validation and calibration of the nomogram for OS and CSS**

The time-dependent ROC curves of OS and CSS are used to evaluate the prediction
performance of nomogram in different sets. AUC value of 0.5 indicates that nomogram has
no predictive effect, and AUC value of 1 indicates that nomogram can completely
distinguish patients with different survival rates. The higher the value between 0.5 and 1,
the stronger the resolution of nomogram. The area under the curve (AUC) of the nomogram
for OS (Figure 3a) and CSS (Figure 3B) were 0.830 (95% CI: 0.821-0.838) and 0.855 (95%
CI: 0.847-0.864) respectively (Table 4) in the training set, which were significantly larger
than TNM stage and seer stage. The results show the same conclusion in validation set.
AUC of nomogram were 0.828 (95% CI: 0.814-0.842) for OS (Fig. S2A) and 0.861 (95% CI: 0.848-0.873) for CSS (Fig. S2B). At the same time, the clinical practicability of nomogram was verified by DCA. The results showed that nomogram had a good clinical applicability in predicting OS and CSS, which was similar to TNM stage and SEER stage in training set (Fig. 3C, D) and verification set (Fig. S2C, D).

In addition, the C-index was used to verify the nomogram. There were significant differences in OS and CSS among nomogram, TNM stage and SEER stage (Table 4). In the training set, the C-index of OS predicted by nomogram was 0.831 (95% CI: 0.815-0.847) and that of CSS was 0.855 (95% CI: 0.839-0.871), which was higher than that of TNM stage and SEER stage (P < 0.05). The results of the validation dataset showed the same conclusion. The C-index of OS predicted by nomogram was 0.832 (95% CI: 0.807-0.857) and that of CSS was 0.863 (95% CI: 0.839-0.887) (Table 4). At the same time, we made calibration curve to compare nomogram with perfect curve. The results showed that the 3-year, 5-year and 10-year OS (Fig. 5 A, B, C) and CSS (Fig. 5 D, E, F) nomograms of the training set had good consistency with the actual observation and the consistency also exists in the verification set (Fig. S3). The calibration curves are very close to the perfect curve. The above results showed that the predicted values of nomogram were in good agreement with the observed values in the training set and verification set.

**DISCUSSION**

Cervical cancer is still the fourth most common female malignant tumor in the world [1,2]. At the same time, the onset age of cervical cancer tends to be younger [10]. In addition, the mortality rate of cervical cancer ranks the first among female malignant tumors, and is one of the major diseases that seriously threaten women's lives [11]. In practice, there are conducive to improving the survival rate, which are accurately predicting the prognosis of patients with EOCC and formulating individualized treatment plan. At present, it is an
urgent need for a valuable system to comprehensively consider multiple prognostic factors to accurately predict the survival time of EOCC patients.

A nomogram is a graphical representation of a multivariable prognostic model, which integrates many prognostic factors and can be used to evaluate individual probabilities of survival at a certain time accurately. The present study focused on the prognosis prediction for EOCC patients based on the construction of nomogram. Firstly, univariate and multivariate Cox regression analysis were performed to assess the independent prognostic factors for OS and CSS. The results of multivariate analysis also indicated that race, histological type, grade, AJCC stage, T stage, SEER stage, tumor size (cm), chemotherapy and radiotherapy were independent prognostic factors impacting the CSS of EOCC patients. Then, we built up prognostic nomograms for 3-, 5- and 10-years OS and CSS of EOCC patients.

In addition, ROC curve, DCA curve and C index were used to verify the clinical practicability and predictive performance of nomogram, which showed that its significant efficacy was better than TNM stage and SEER stage. At the same time, the prediction accuracy of OS and CSS in 3-, 5- and 10- years was evaluated by the calibration curve, which was in good agreement with the actual observation results. In practical, the area under the curve (AUC) of the nomogram for OS (Figure 3a,S2A) and CSS (Figure 3B,S2B) were 0.830(95% CI: 0.821-0.838) and 0.855(95% CI: 0.847-0.864) in the training set and 0.828(95%CI:0.814-0.842) and 0.861(95%CI:0.848-0.873) in validation set respectively (Table 4). What's more, the C-index of OS and CSS predicted by nomogram was 0.831 (95% CI: 0.815-0.847) and 0.855 (95% CI: 0.839-0.871) in the training set and was 0.832 (95% CI: 0.807-0.857) and 0.863 (95% CI: 0.839-0.887) in validation set respectively (Table 4). It confirms the good prediction ability of nomogram. The results of DCA curve also proved the good clinical value of nomogram.
As a prognostic tool graphically displayed the possibility of clinical results, nomogram can accurately predict the overall survival rate (OS) and cancer specific survival rate (CSS) of patients, which is attributed to the multiple clinical variables included in the calculation. Recently, number of nomograms consisted of various clinical variables have been used to predict the prognosis of different CC patients [12-15]. Wang and Yang et al[14] analyzed the cervical cancer patients’ data recorded in SEER database and established the nomogram for the postoperative survival prediction. It provided patients with resected CC with accurate individualized prediction of OS, assisting the clinicians in decision making. Similarly, Xie et al[15] developed the nomogram for predicting cervical cancer with aged 65 years or over patients’ prognosis and comprehensive analyzed the independent prognostic factors which containing race, marriage, histological types, grade, FIGO, regional lymph node, surgery, radiotherapy, chemotherapy.

In this study, the following clinical variables including race, histological type, grade, AJCC stage, T stage, SEER stage, tumor size (cm), chemotherapy and radiotherapy, were the independent risk factors affecting the prognosis of EOCC patients. There were many studies reported that age and race as the risk factor for prognosis of various cancers[12,13,14]. Genetic differences among different races were also a significantly risk factor for tumor prognosis that had been widespread recognized [14,15]. The grade, tumor size and histological type of the tumor also significantly affected the prognosis of the patients[16,17]. In this study, the same results were supported by the statistical analysis. At present, TNM stage is the most common tumor stage system in the world, which determined by laboratory and postoperative pathological examination. However, TNM stage still had limitations and couldn't provide individualized prognosis prediction for clinicians. In addition to TNM stage, the prognosis of patients is closely related to a variety of clinical variables. Accurate prediction depends on the comprehensive
consideration of all independent risk factors. We successfully established an effective nomogram based on the following factors: race, histological type, grade, AJCC stage, T stage, SEER stage, tumor size (cm), chemotherapy and radiotherapy, which had been proved containing a better predictive performance than TNM stage and SEER stage. The establishment of nomogram will be helpful for individualized treatment of EOCC patients.

Our study still had some limitations. First of all, the SEER database did not have details information about the chemotherapy, such as the use of targeted drug, which are crucial for the prognosis of CC. Due to the lack of information on living environment, lifestyle, adjuvant therapy and commodities, it is not possible to consider all prognostic factors comprehensively, which was an intrinsic limitation of SEER research. Secondly, we did not conduct external validation to further assess this nomogram.

CONCLUSION

Our study firstly constructed the precise nomogram for predicting the 3-, 5- and 10-year OS and CSS of EOCC patients, which containing a better predictive performance than TNM stage and SEER stage. The models could assist clinicians to prepare personalized treatment for EOCC patients.

ACKNOWLEDGMENTS

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REFERENCES


### Table 1. Baseline demographic and clinical characteristics with EOCC patients in our study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total No. (%)</th>
<th>The training cohort No. (%)</th>
<th>The validation cohort No. (%)</th>
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<td>Total</td>
<td>10079</td>
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<td>&lt;37</td>
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<td>3539 (50.2)</td>
<td>1584 (52.4)</td>
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<td>37-40</td>
<td>2469 (24.5)</td>
<td>1760 (24.9)</td>
<td>709 (23.4)</td>
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<tr>
<td>&gt;40</td>
<td>2487 (24.7)</td>
<td>1756 (24.9)</td>
<td>731 (24.2)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
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<td>White</td>
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<td>Black</td>
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<td>287 (9.5)</td>
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<td>5627</td>
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### Table 2. Univariate and multivariate analysis of overall survival (OS) rates in training cohort.

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<th>Multivariate analysis^a</th>
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<td></td>
<td>(95% CI)</td>
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<td>(95% CI)</td>
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<td>Regional</td>
<td>1798</td>
<td>1250 (17.7)</td>
<td>548 (18.1)</td>
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<td>(17.8)</td>
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Abbreviations:

AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results. EOCC, early-onset cervical cancer;
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**AJCC stage**

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Abbreviations:

OS, Overall survival; AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.

<sup>a</sup>Model was adjusted by age, race, marital status, histological type, grade, AJCC stage, TNM stage, SEER stage, tumor size, chemotherapy and radiotherapy.

Table 3. Univariate and multivariate analysis of cancer-specific survival (CSS) rates in training cohort.
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</tr>
<tr>
<td>M0</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>11.80 (9.25-15.06)</td>
<td>&lt;0.00</td>
<td>-</td>
<td>0.612</td>
</tr>
<tr>
<td><strong>SEER stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional</td>
<td>8.92 (7.31-10.89)</td>
<td>&lt;0.00</td>
<td>2.82 (1.61-4.93)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Distant</td>
<td>28.68 (21.95-37.49)</td>
<td>&lt;0.00</td>
<td>4.29 (3.14-5.86)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td><strong>Tumor size (cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>6.49 (5.33-7.91)</td>
<td>&lt;0.00</td>
<td>1.66 (1.34-2.07)</td>
<td>&lt;0.00</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.30 (1.02-1.65)</td>
<td>0.031</td>
<td>1.46 (1.13-1.87)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
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</tr>
<tr>
<td>No/Unknown</td>
<td>0.10 (0.08-0.12)</td>
<td>&lt;0.00</td>
<td>0.45 (0.34-0.61)</td>
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</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/Unknown</td>
<td>0.12 (0.09-0.14)</td>
<td>&lt;0.00</td>
<td>0.61 (0.46-0.82)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Abbreviations:**

CSS, Cancer-specific survival; AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results.
Model was adjusted by age, race, marital status, histological type, grade, AJCC stage, TNM stage, SEER stage, tumor size, chemotherapy and radiotherapy.

Table 4. Comparison of C-indexes and AUC between the nomogram, SEER stage and TNM stage in EOCC patients.

<table>
<thead>
<tr>
<th>Survival types</th>
<th>Tumor stage types</th>
<th>Training cohort</th>
<th>Validation cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Hazard Ratio (95% CI)</td>
<td>P value</td>
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<td>C-indexes</td>
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<tr>
<td>OS</td>
<td>Nomogram</td>
<td>0.831 (0.815-0.847)</td>
<td>0.008</td>
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<td>SEER stage</td>
<td>0.757 (0.738-0.776)</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>TNM stage</td>
<td>0.758 (0.738-0.778)</td>
<td>0.010</td>
</tr>
<tr>
<td>CSS</td>
<td>Nomogram</td>
<td>0.855 (0.839-0.871)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>SEER stage</td>
<td>0.778 (0.757-0.799)</td>
<td>0.011</td>
</tr>
<tr>
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<td>TNM stage</td>
<td>0.779 (0.757-0.801)</td>
<td>0.011</td>
</tr>
<tr>
<td>AUC</td>
<td></td>
<td></td>
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<tr>
<td>OS</td>
<td>Nomogram</td>
<td>0.830 (0.821-0.838)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>SEER stage</td>
<td>0.751 (0.741-0.761)</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>TNM stage</td>
<td>0.749 (0.739-0.759)</td>
<td>0.010</td>
</tr>
<tr>
<td>CSS</td>
<td>Nomogram</td>
<td>0.855 (0.847-0.864)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>SEER stage</td>
<td>0.775 (0.765-0.784)</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>TNM stage</td>
<td>0.773 (0.763-0.783)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Abbreviations:

C-index, concordance index; ROC, receiver operating characteristic; SEER, surveillance, epidemiology and end results; TNM, tumor-node-metastasis; EOCC, early-
onset cervical cancer; CI, confidence intervals; OS, overall survival; CSS, cancer-specific survival.

Figure 1. Schematic of patient screening process.
**Figure 2.** The nomogram containing independent prognostic factors for the 3-, 5-, and 10-year overall survival (OS) and cancer-specific survival (CSS) prediction of EOCC patients. A, Nomogram for OS; B, Nomogram for CSS.

**Figure 3.** Receiver operating characteristic (ROC) and decision curve analysis (DCA) verified the predictive value of nomogram, TNM stage and SEER stage in training set. A,
D. DCA for CSS in training set.

Figure 4. Calibration plot of the 3-, 5-, and 10-year OS and CSS nomogram in training set.
A, 3-year OS in training set; B, 5-year OS in training set; C, 10-year OS in training set; D, 3-year CSS in training set; E, 5-year CSS in training set; F, 10-year CSS in training set.
SUPPLEMENTAL DATA

Figure S1. Estimation of the cut-off value for the age determined by X-tile software.
Figure S2. Receiver operating characteristic (ROC) and decision curve analysis (DCA) verified the predictive value of nomogram, TNM stage and SEER stage in validation set. A, ROC for OS in validation set; B. ROC for CSS in validation set; C, DCA for OS in validation set; D. DCA for CSS in validation set.
**Figure S3.** Calibration plot of the 3-, 5-, and 10-year OS and CSS nomogram in validation set. A, 3-year OS in validation set; B, 5-year OS in validation set; C, 10-year OS in validation set; D, 3-year CSS in validation set; E, 5-year CSS in validation set; F, 10-year CSS in validation set.