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A nomogram for predicting overall survival in patients with type II endometrial carcinoma: a retrospective analysis and multicenter validation study

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Abstract. – OBJECTIVE: Type II endometrial cancer (EC) is associated with high risk of metastasis and poor prognosis. We aimed to develop a nomogram for predicting survival probability in patients with type II EC.

PATIENTS AND METHODS: Data from a total of 4,117 patients with confirmed type II EC were pulled from the Surveillance, Epidemiology, and End Results (SEER) database, and were randomly divided into a training set and an internal verification set. A nomogram was constructed based on the training set. The concordance index (C-index), area under the ROC curve, and calibration plots were used to evaluate the identification and calibration of the nomogram. The SEER internal validation set and the Chinese multicenter data set (74 patients) were used to verify discriminations and corrections of the model.

RESULTS: Multivariate analysis indicated that age, marital status, tumor size, T stage, N stage, M stage, surgery, radiotherapy, and chemotherapy were independent factors affecting the prognosis of type II EC patients ($p<0.001$). The corresponding nomogram has showed excellent calibration and discrimination (C-index [95% CI], 0.752 [0.738-0.766]). The model was verified in the internal verification set (0.760 [0.739-0.781]) and the Chinese multicenter set (0.784 [0.607-0.961]). In addition, the AUC further confirmed the accuracy of the nomogram in predicting survival. The calibration curve of OS within 5 years confirmed good calibration of the nomogram.

CONCLUSIONS: This model and the corresponding risk classification system may provide useful tools for clinicians to evaluate the long-term prognosis of patients and carry out personalized clinical evaluation.

Key Words:
Endometrial Neoplasms, SEER program, Nomogram, Overall survival, Validation, Multicenter.

Introduction

One of the most common gynecological tumors in developed countries is endometrial cancer (EC), which originates from the endometrium; its incidence is continuously increasing. In 2013, there were approximately 49,560 cases of and 8,190 deaths from uterine cancer in the US[1]. In addition, it is estimated that in 2021, there will be as many as 63,570 new cases and 12,940 deaths in US. Uterine cancer is the fourth most common cancer and the sixth most common cause of cancer-related deaths among American women[2]. Although the incidence of endometrial cancer is increasing, the overall natural course of its progression is slow. Seventy percent of tumors are diagnosed at stage I, when they are confined to the uterine corpus[3]. Historically, EC

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standard treatment includes hysterectomy, bilateral salpingectomy, retroperitoneal lymph node dissection[4,5]. Although the adjuvant treatment recommendations for this cancer remain complicated and controversial, the majority of patients diagnosed with early-stage EC have good prognosis after surgery. Consequently, the overall 5-year disease-specific survival rate is as high as 80%[6,7]. However, some women with aggressive tumors are still at high risk of disease recurrence and death[8].

In the past 30 years, EC has generally been divided into two subtypes based on the histological characteristics: hormone receptor expression and grade[9]. EC with a low degree of malignancy, diploid tumors, and hormone receptor-positivity, is the most common subtype – which accounts for the vast majority of endometrial carcinomas – and has a good prognosis[9]. Type II EC is a non-endometrioid carcinoma characterized by a high grade, aneuploidy, TP53 mutation, and hormone receptor-negativity; it is usually associated with higher risk of metastasis and poor prognosis. The most common type II tumor subtypes are serous, clear cells, and carcinosarcomas[9]. Type II EC accounts for 10%-15% of EC but causes 40% of deaths due to the high incidence of associated extrauterine diseases, especially lymph node metastasis[3,10,11]. Approximately 60-70% of patients with serous carcinoma of uterus are also presented with extrauterine diseases at cancer onset, and the 5-year OS rate of these patients is only 20-25%[11-14]. Currently, little is known about type II tumors, mainly because most epidemiologic studies[15-17] lack sufficient cases to study these fewer common tumors separately; therefore, understanding this rare and more malignant tumor subtype is key for prevention, treatment, and prognosis of endometrial carcinoma.

In this study, we used data sets from the Surveillance, Epidemiology, and End Results (SEER) database[18] to evaluate type II EC patients that were registered from 2010 to 2015, with the aim of developing an effective prognostic nomogram for type II EC patients. In addition, we collected clinical data of type II EC patients diagnosed by a multicenter in China from January 2011 to October 2020, to verify the effectiveness of the developed nomogram. This nomogram can provide a more personalized and accurate estimate of overall survival rate of type II EC patients and can thus help clinicians make suitable clinical decisions.

Patients and Methods

Patient Selection

In this retrospective study, we included patients with type II endometrial cancer diagnosed in the SEER database between 2010 and 2015. All patient data were obtained using the SEER Stat software (version 8.3.8). The inclusion criteria for data extraction were as follows: (1) EC as the only or first primary tumor, as confirmed by histology; (2) the primary site of the ICD-O-3 code included corpus uteri/uterus not specified (C54.0-C55.9); (3) ICD-O-3 morphology of the International Classification of Diseases included 8310/3, 8313/3, 8441/3, 8460/3, 8461/3, 8950/3, 8951/3, 8980/3, or 8981/3[13]. The exclusion criteria were as follows: (1) patients with incomplete information (e.g., unknown marital status; unknown clinical information, including tumor size, grade, T and N stage; and unknown survival time); (2) patients who died within one month after the first visit or were followed up for less than one month. Finally, 4,117 eligible type II EC patients registered in the SEER database, between 2010 and 2015, were included in the analysis.

In addition, another 74 type II EC patients from three tertiary and first-class hospitals in Shandong Province, China, were enrolled in this study as an external verification set (diagnosed by the Weifang Hospital of Traditional Chinese Medicine, affiliated Hospital of Weifang Medical College, and Zibo Maternal and Child Health Hospital, from January 2011 to October 2020). Exclusion criteria for the training set mentioned above were also applied to the validation set. The deadline for follow-up was October 31, 2020. Patient data included in the analysis were approved by the institutional review committee of each participating agency. This is a retrospective study, and therefore informed consent from patients was not required. All patient data were analyzed anonymously.

Cohort Definition and Variable Recode

Eligible patients were included in the analysis and were randomly divided into a training set and an internal verification set, with a ratio of 7:3. Based on the training set, the variables were screened and a model was constructed. The validation set was then used to validate the results obtained using the training set. The variables in the SEER database included age (at diagnosis), year of diagnosis, marital status (at diagnosis), tumor size, grade, T stage, N stage, M stage, surgery, radiotherapy, and chemotherapy. The cutoff point between diagnostic age and tumor size was select-

ed using the X-TILE software. TNM stages were classified according to the 7th edition of AJCC TNM. According to the FIGO staging criteria in 2009, tumor stages were reclassified as follows: localized stage corresponded to FIGO stage I, regional stage corresponded to FIGO stages II and III, and distant stage corresponded to FIGO stage IV[19, 20]. The primary clinical endpoint selected in this study was overall survival (OS), which was defined as the time from the date of diagnosis to the last follow-up or death from any cause.

Performance Assessment and Validation of the Nomogram

Independent risk factors associated with prognosis of type II EC were screened out using Cox regression analysis in the training set. A nomogram was constructed based on relevant risk factors, which were used to estimate the probability of 1-, 3-, and 5-year OS in patients with type II EC. The C index (C-index) and the area under the ROC curve (time-dependent AUC) were used to evaluate the discriminant ability of the nomogram; a calibration curve was drawn to evaluate the calibration of the nomogram; Kaplan-Meier analysis was used for survival analysis. The clinical benefits and practicability of the nomogram were compared with those of FIGO staging. The accuracy and reliability of the nomograph were verified using a SEER internal validation dataset and an external Chinese multicenter validation dataset.

Survival Analysis

In each data set, risk stratification was performed according to the constructed nomogram, and then survival analysis was performed for patients in the high and low risk groups. To test whether nomogram stratified the prediction of patients at each FIGO stage, we divided patients in the SEER dataset into 4 stages according to FIGO staging criteria and performed risk stratification and corresponding survival analysis for each stage. In the end, to understand the benefits of postoperative adjuvant therapy, patients who did not receive surgical treatment were re-excluded from the analysis, and the Kaplan-Meier method was used to analyze the survival of all postoperative patients and postoperative patients over 75 years of age.

Statistical Analysis

Data included in the study were obtained using the SEER Stat 8.3.8 software. X-Tiles software (version 3.6.1) was used to determine the best cut-off value. All other analyses were carried out with R 4.0.2 ("rms", "foreign", "survival", "create Data Partition"). In two-tailed tests, a *p*-value less than 0.05 was considered to be statistically significant.

Results

Patient Characteristics

A total of 4,117 eligible patients with type II EC were identified from the SEER database and were randomly divided into either the training set (n = 2884) or the internal validation set (n = 1233), with a ratio of 7:3. The external validation set consisted of 74 patients from the Shandong region of China (Figure 1). Table I summarizes the demographic and clinical characteristics of

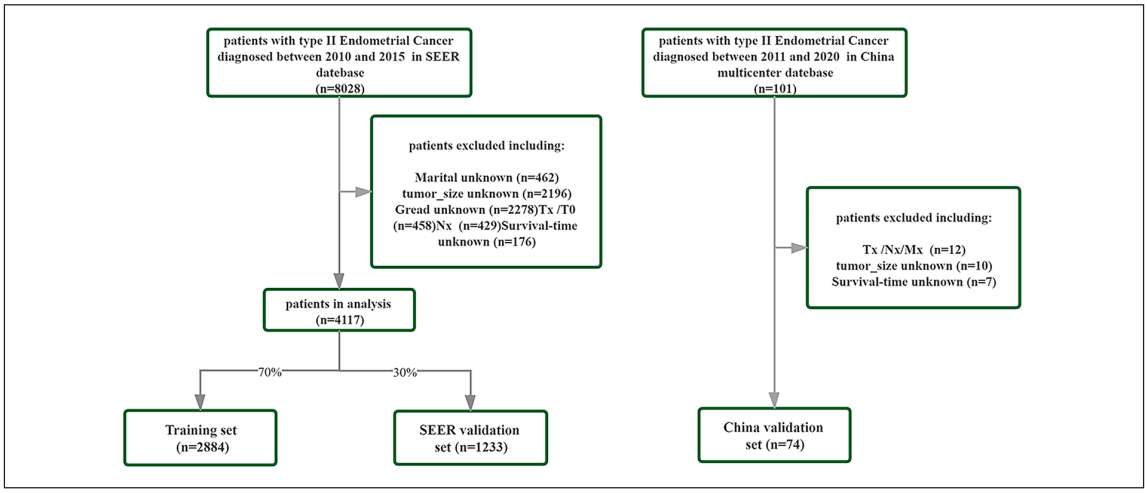

Figure 1. Flowchart illustrating patient selection for this study. Abbreviation – SEER: the Surveillance Epidemiology, and End Results database.

Table I. Baseline characteristics of patients in different cohorts.

Characteristics	Training set [cases (%)]	SEER validation set [cases (%)]	Chinese validation set [cases (%)]
Total	2,884	1,233	74
Age			
≤ 75	2,329 (80.8%)	1,002 (81.3%)	71 (95.9%)
> 75	555 (19.2%)	231 (18.7%)	3 (4.1%)
Year			
2010	339 (11.8%)	152 (12.3%)	–
2011	397 (13.8%)	166 (13.5%)	–
2012	475 (16.5%)	193 (15.7%)	–
2013	519 (18.0%)	218 (17.7%)	–
2014	546 (18.9%)	240 (19.5%)	–
2015	608 (21.1%)	264 (21.4%)	–
Marital			
Married	1,379 (47.8%)	605 (49.1%)	66 (89.2%)
Unmarried	1,505 (52.2%)	628 (50.9%)	8 (10.9%)
Grade			
Low(I/II)	132 (4.6%)	56 (4.5%)	–
High (III/IV)	2,752 (95.4%)	1,177 (95.5%)	–
Tumor size			
≤ 6.6 cm	2,044 (70.9%)	879 (71.3%)	65 (87.8%)
> 6.6 cm	840 (29.1%)	354 (28.7%)	9 (12.2%)
T stage			
T1	1,547 (53.6%)	659 (53.4%)	52 (70.3%)
T2	343 (11.9%)	143 (11.6%)	10 (13.5%)
T3	863 (29.9%)	354 (28.7%)	9 (12.2%)
T4	131 (4.5%)	77 (6.2%)	3 (4.1%)
N stage			
N0	2,053 (71.2%)	884 (71.7%)	55 (74.3%)
N1	425 (14.7%)	181 (14.7%)	6 (8.1%)
N2	406 (14.1%)	168 (13.6%)	13 (17.6%)
M stage			
M0	2,381 (82.6%)	1,007 (81.7%)	68 (91.9%)
M1	503 (17.4%)	226 (18.3%)	6 (8.1%)
FIGO stage			
I	1,255 (43.5%)	543 (44.0%)	44 (59.4%)
II	211 (7.3%)	91 (7.4%)	6 (8.1%)
III	874 (30.3%)	346 (28.1%)	17 (23.0%)
IV	544 (18.9%)	253 (20.5%)	7 (9.5%)
Surgery			
Yes	2,825 (98%)	1,201 (97.4%)	71 (95.9%)
No/unknown	59 (2%)	32 (2.6%)	3 (4.1%)
Radiation Therapy			
Yes	1,238 (42.9%)	535 (43.4%)	26 (35.1%)
No/unknown	1,646 (57.1%)	698 (56.6%)	48 (64.9%)
Chemotherapy			
Yes	1,932 (67%)	819 (66.4%)	48 (64.9%)
No/unknown	952 (33%)	414 (33.6%)	26 (35.1%)

SEER: the Surveillance Epidemiology, and End Results database.

the patients. The median follow-up period of the whole population was 34 months [quartile (IQR): 20.5-52.5], training set 35 months (IQR: 21-53), and SEER validation set 33 months (IQR: 20-52). The results of X-TILE software analysis showed that the best cutoff value for age was 75 years, and the best cutoff value of tumor size was 66 mm (Figure 2). Patients under 75 years of age (80.9%) comprised the majority of entire type II EC population. In histological grading, patients with well-differentiation accounted for 95.4% of patients with type II EC. Moreover, in terms of treatment, surgery (97.8%) was the main treatment for patients with type II EC.

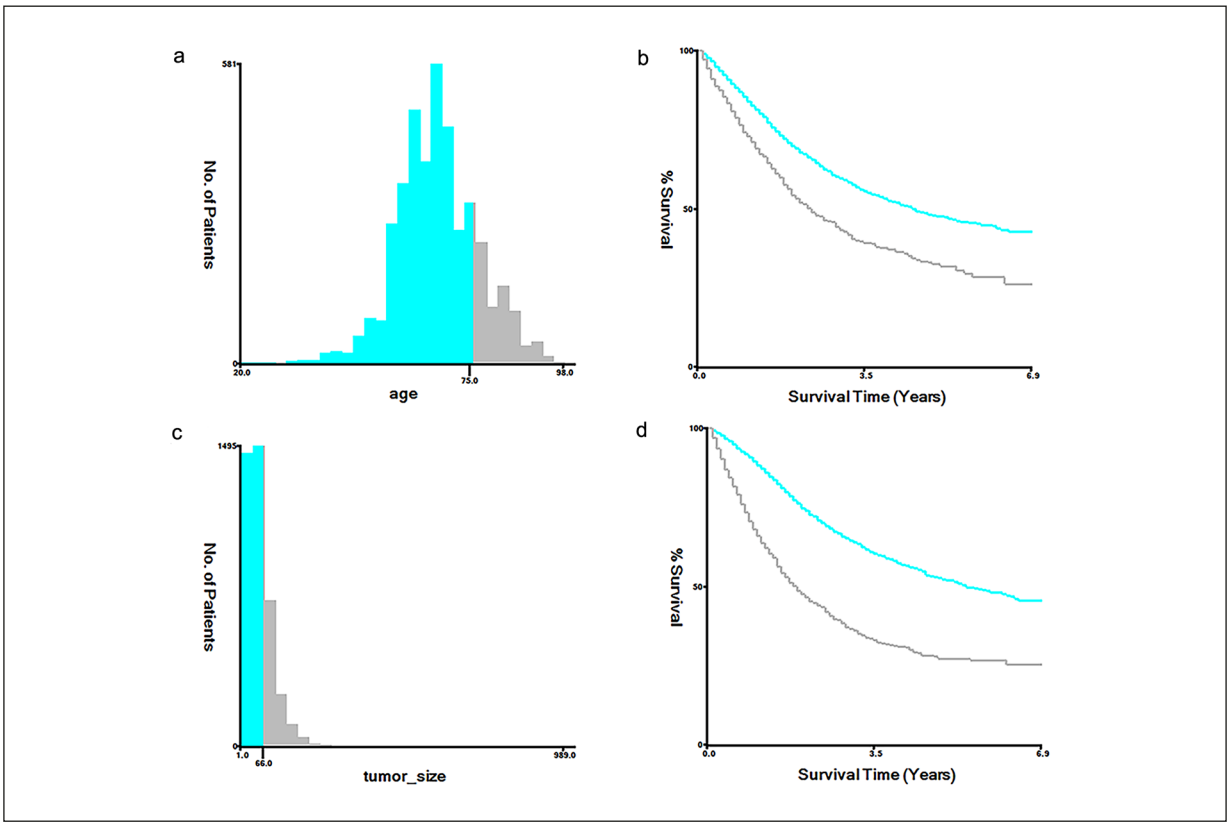

Figure 2. Identification of optimal cut-off values for age (**a, b**) and tumor size (**c, d**) *via* the X-tile software analysis.

Nomogram Variable Screening

Table II summarizes the results from the univariate and multivariate Cox regression analyses of the training cohort. In univariate regression analysis, the year of diagnosis and the grade were meaningful factors, but their effect on the model was not significant. To simplify the model for clinical applications, we eliminated these two variables when building the model. In the final multivariate Cox regression analysis, nine variables (age, marital status, tumor size, T stage, N stage, M stage, surgery, radiotherapy, and chemotherapy) were found to be significantly correlated with OS (p<0.001), and were independent prognostic factors for patients with type II EC.

Development of the Nomogram and Performance Assessment

Based on results of the Cox regression analysis, a total of nine variables were included in the final nomogram (Figure 3) to predict the long-term survival of type II EC patients. The C index (95% CI) of the nomogram in the training set was 0.752[0.738-0.766], which were significantly better than those of the FIGO staging system (0.683[0.669-0.698], p<0.001, Table III). In addition, the AUC further confirmed the accuracy of the nomogram in predicting survival (Figure 4a). The calibration curve of OS within 5 years also confirmed good calibration of the nomogram in the training set (Figure 5a).

Validation of the Nomogram

The excellent recognition ability of the nomogram was verified using the SEER internal validation dataset and the Chinese multicenter dataset. In the two verification cohorts, the C index (SEER internal verification set: 0.760 [0.739-0.781]; Chinese multicenter external verification set: 0.784[0.607-0.961]) were both >0.7, and the time-dependent AUC value (Figure 4b, 4c) for predicting OS within 5 years also performed well. Furthermore, the nomogram calibration curve in the verification set exhibited high consistency between the predicted 1-, 3-, and 5-year survival probabilities and the observed survival probability (Figure 5b, Figure 5c).

Table II. Univariate and multivariate Cox regression analyses of clinicopathologic factors with overall survival in the SEER training set.

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Year			0.040	–	–	–
2010	Reference			–	–	–
2011	0.872	0.721-1.053	0.155	–	–	–
2012	0.816	0.677-0.984	0.033	–	–	–
2013	0.825	0.682-0.997	0.047	–	–	–
2014	0.710	0.579-0.871	0.001	–	–	–
2015	0.794	0.637-0.988	0.039	–	–	–
Age						
≤ 75	Reference			Reference		
> 75	1.676	1.474-1.907	< 0.001	1.539	1.346-1.760	< 0.001
Marital						
Married	Reference			Reference		
Unmarried	1.515	1.352-1.698	< 0.001	1.354	1.204-1.521	< 0.001
Grade				–	–	–
Low (I/II)	Reference			–	–	–
High (III/IV)	1.738	1.264-2.391	0.001	–	–	–
Tumor size						< 0.001
≤ 6.6 cm	Reference			Reference		
> 6.6 cm	2.359	2.105-2.643	< 0.001	1.745	1.547-1.967	
T stage			< 0.001			< 0.001
T1	Reference			Reference		
T2	1.847	1.536-2.222	0.000	1.748	1.447-2.110	
T3	3.169	2.790-3.598	0.000	2.286	1.971-2.652	
T4	6.016	4.869-7.435	0.000	3.000	2.336-3.852	
N stage			< 0.001			< 0.001
N0	Reference			Reference		
N1	1.864	1.614-2.154	0.000	1.232	1.056-1.437	
N2	2.080	1.802-2.402	0.000	1.377	1.181-1.606	
M stage						
M0	Reference			Reference		
M1	3.209	2.838-3.629	< 0.001	1.969	1.691-2.292	< 0.001
Surgery						
Yes	Reference			Reference		
No/unknown	7.251	5.510-9.542	< 0.001	3.346	2.509-4.463	< 0.001
Radiation Therapy						
Yes	Reference			Reference		
No/unknown	1.754	1.558-1.974	< 0.001	1.345	1.186-1.524	< 0.001
Chemotherapy						
Yes	Reference			Reference		
No/unknown	1.248	1.110-1.402	< 0.001	1.675	1.471-1.907	< 0.001

CI: confidence interval; HR: Hazard Ratio.

Survival Risk Classification Based on the Nomogram

We stratified the risk of type II EC patients according to risk scores calculated using the nomogram and divided them into high-risk and low-risk groups. There were significant differences in the survival probability of patients with different risk subgroups in the training set (Figure 6a, $p<0.001$); this was further verified in the two validation sets (Figure 6b, Figure 6c, $p<0.001$). Furthermore, among the 4,191 patients included in the analysis, the nomogram presented tremendous potential in distinguishing high-risk patients with all-cause death (Figure 6d, $p<0.001$). Finally, we stratified the risk of patients in different FIGO stages according to this model, and the results of survival analysis are shown in Figure 7. There were significant differences in the survival probability of patients in the high and low risk groups in each stage ($p\leq0.05$).

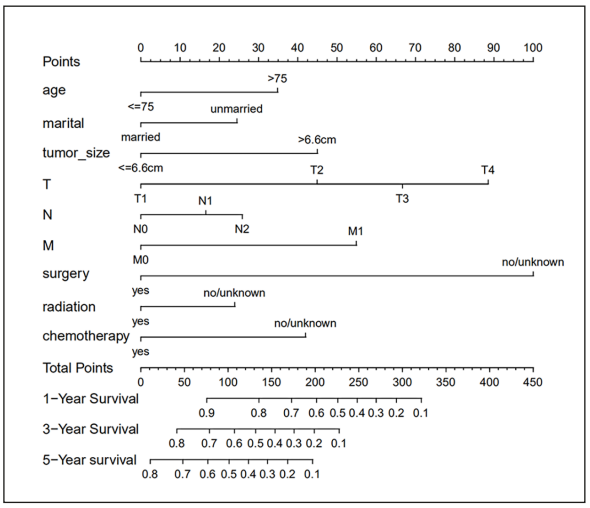

Figure 3. Nomograms to predict the 1-, 3-, and 5-year overall survival of patients with type II EC. EC: endometrial cancer; T: T stage; N: N stage; M: M stage.

Survival Analysis of Benefit from Adjuvant Therapy

In this study, data from 4.026 type II EC patients who underwent surgery, were obtained from the SEER database, and were retrospectively analyzed with the purpose of understanding the benefits of postoperative adjuvant therapy. The results of survival analysis showed that the combination of radiotherapy and chemotherapy could significantly improve disease prognosis in type II EC patients (Figure 8a, $p<0.001$). Radiotherapy was found to be superior to chemotherapy (Figure 8b, $p<0.001$) between patients receiving radiotherapy or chemotherapy alone. For this purpose, we conducted a statistical analysis of the patients who received only one treatment, and the results showed that (Figure 9): among the patients who received only radiotherapy, 77% were stage I and II patients. In contrast, patients who received chemotherapy alone were sicker, with 65% in stage III/IV. In addition, in people over 75 years of age, significant improvement in survival rate was also observed in patients who received combined radiotherapy and chemotherapy (Figure 8c, $p<0.001$). However, there was no significant difference in the effect of radiotherapy or chemotherapy alone on the overall survival in elderly patients (Figure 8d, $p=0.399$).

Table III. Performance of models in the per different cohorts.

Models	SEER Training set C-index (95% CI)	*p*-value	SEER validation set C-index (95% CI)	*p*-value
The nomogram	0.752 (0.738- 0.766)	< 0.001	0.760 (0.739-0.781)	< 0.001
The FIGO criteria-based tumor staging	0.683 (0.669-0.698)		0.699 (0.677-0.721)	

p-values were obtained by comparing nomogram with FIGO stage, respectively.

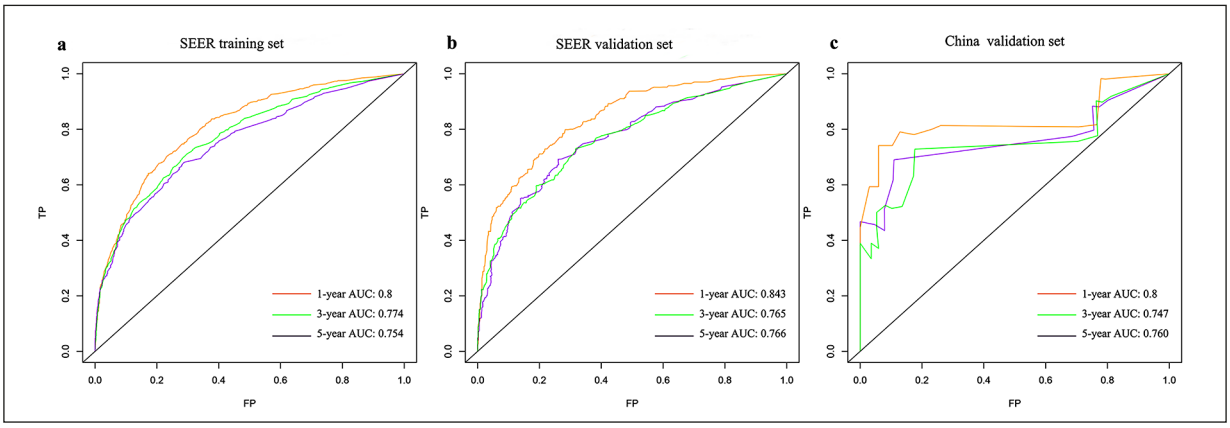

Figure 4. The AUCs of the nomograms that predicted 1-, 3- and 5-year overall survival of type II EC in the training set (**a**). Similar superiority in nomogram prediction accuracy was also observed in the SEER internal validation set (**b**) and the China multicenter validation set (**c**). Abbreviations – AUC: area under the curve; EC: endometrial cancer; OS: overall survival; SEER: the Surveillance Epidemiology, and End Results database.

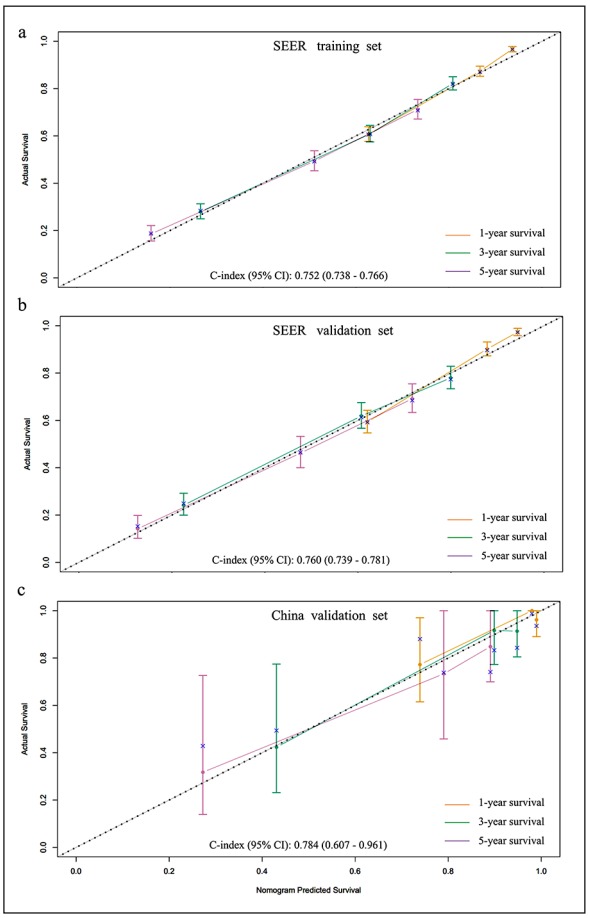

Figure 5. Calibration plots comparing the similarity between nomogram-predicted survival rates (represented by x-axis) and actual survival rates (represented by y-axis). Calibration plots of nomograms used in the SEER training set (**a**), the SEER internal validation set (**b**) and the China multicenter validation set (**c**). SEER: the Surveillance Epidemiology, and End Results database.

Discussion

Traditionally, tumor staging based on the FIGO criteria has been the primary choice for predicting disease prognosis in patients with EC[21]. However, we often observe different prognoses in patients at the same stage[22]. This prognostic heterogeneity can be explained by the fact that FIGO-based tumor staging does not consider age, marital status, adjuvant therapy, and other factors; therefore, we constructed a nomogram with more variables, and compared it with traditional tumor staging. As expected, the C-index results showed that the nomogram established in this study has better predictive ability than the traditional FIGO tumor staging. Taken together, results indicated that the nomogram we constructed can provide an easy-to-use and personalized tool to help doctors accurately predict the OS of patients with type II EC in order to make more informed and individualized decisions.

As shown in Table I, we observed that high-grade patients accounted for 95.4% of the total population, which is consistent with the results of the study by Bokhman[9]. Furthermore, regression analysis showed that although the grade can impact prognosis in patients with type II EC, it has little effect when compared with other variables. Previous studies have shown that the depth of myometrial invasion and the potential of lymphatic diffusion depend on the degree of tumor differentiation, which is an indicator of EC disease progression[3,5,9]. EC represents a range of tumors, from well to poorly differentiated (low-grade to high-grade). Poorly differentiated tumors (serous and clear cell carcinoma) are common in type II ECs[23]. Hence, to simplify the model for clinical applications, we eliminated the grade variable when building the model. It is worth noting that increasing evidence has begun to question Bokhman's dualistic model in recent years[9]. Many studies have pointed out that the correlation between the EC subtype (Bokhman's dualistic mode[9]), defined by traditional taxonomy, is imperfect. It has been suggested that the risk factor patterns of high-grade endometrioid carcinoma and type II tumors are similar[13,23], and support the hypothesis that the high-grade endometrioid carcinoma is closer to type II tumors than the non-endometrioid carcinoma[24,25]. Thus far, the theory remains controversial, and further research is necessary.

Nomogram has emerged as a common tool to evaluate the prognosis of tumors and medicine, in recent years. It predicts an individual's survival probability by combining various prognostic and determinant variables[26], and has been shown to be superior, compared to some traditional staging systems such as the American Joint Commission on Cancer (AJCC) and the International Federation of Gynecology and Obstetrics (FIGO), in predicting the prognosis of tumors[27-29]. For the past few years, among the various predictive models[30-33] for predicting the survival of patients with EC. The study[30] have been validated in patients with postoperative randomized treatment of EC, and have shown that age, tumor grade and lymphatic vascular space involvement are highly predictive of all outcomes. A nomogram that included age, race, year of diagnosis, histological grade, clinical stage, and tumor size was

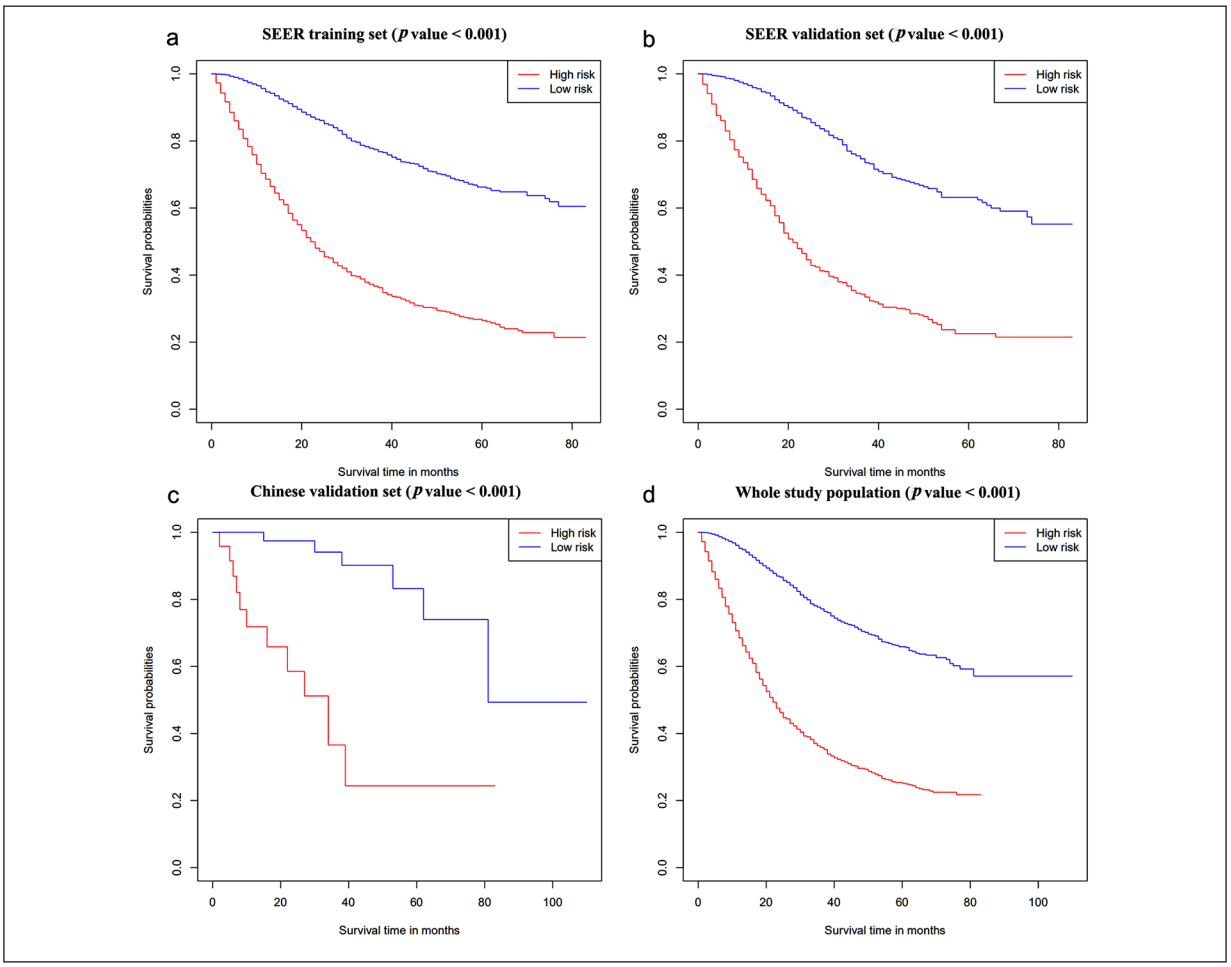

Figure 6. Kaplan-Meier survival curves of OS, categorized into low-risk and high-risk groups. (**a**) in the training set; (**b**) in the SEER internal validation set; (**c**) in the Chinese multicenter validation set; (**d**) in the whole population. OS: overall survival; SEER: the Surveillance Epidemiology, and End Results database.

constructed and verified internally[31]. A robust nomogram for predicting risk of EC recurrence was validated and evaluated using an independent multicenter external patient cohort in China[33]. These encouraging results emphasized the importance of predictive models in the diagnosis and treatment of EC. As far as we know, this is the only nomogram specifically established for patients with type II EC. Although women affected by type II EC have a poorer prognosis and high risk of metastasis and recurrence at diagnosis, most epidemiological studies only investigate EC as a whole rather than consider the different subtypes of this disease. In addition, a study[34] used the Cancer Genome Atlas (TCGA) database to determine the expression levels of pyrolysis related genes (PRGs) between normal and UCEC tissues, and established a PRGs model to predict the prognosis of UCEC. As individualized cancer treatment becomes more important, construction of a more comprehensive predictive model can provide more accurate survival prediction for patients.

Endometrial carcinoma includes a group of biological, clinical, morphological, and genetic heterogeneous tumors. During early phases of the disease, the general practice is to undergo radiotherapy and/or chemotherapy after surgery, mainly guided by standard histopathological parameters. There is currently no cure for advanced stages of the disease, and chemotherapy remains the main treatment for most patients[5]. Surgery is usually effective (results of multivariate Cox regression analysis in this study also showed that surgical treatment had a significant effect on OS in patients with type II EC)[35]; however, the use

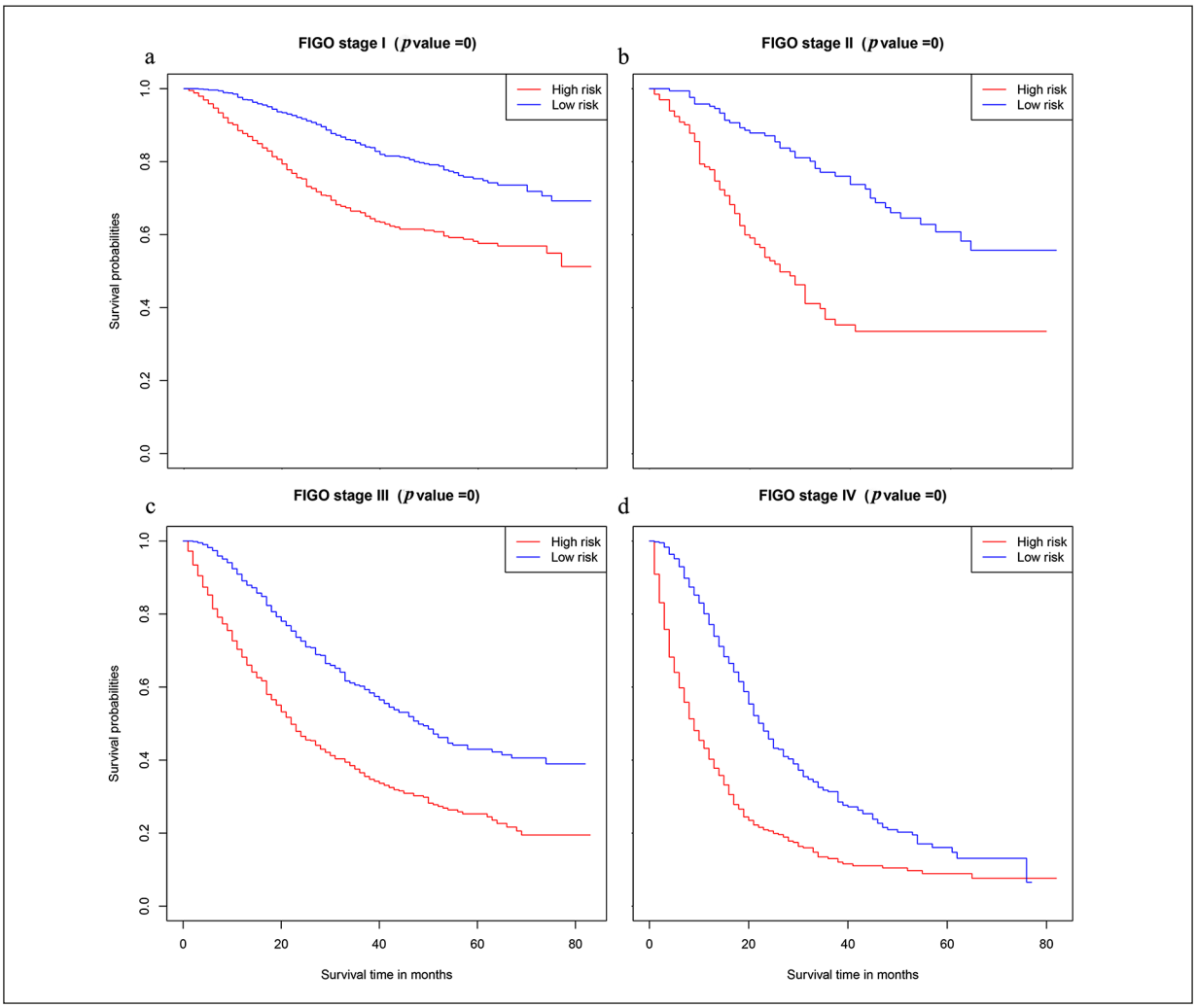

Figure 7. Kaplan-Meier survival curves of OS in SEER database, categorized into low-risk and high-risk groups. (**a**) FIGO stage I; (**b**) FIGO stage II; (**c**) FIGO stage III; (**d**) FIGO stage IV. OS: overall survival; SEER: the Surveillance Epidemiology, and End Results database. FIGO: International Federation of Gynecology and Obstetrics.

of adjuvant treatment for this cancer remains complex and controversial. In the United States, radiotherapy is usually used to treat high-risk EC tumors. Adjuvant chemotherapy is usually used in women with stage III cancer, and despite the lack of evidence, it is often used in any serous cancer stages[36,37]. A randomized trial[38] was previously conducted to compare chemotherapy with radiotherapy. Results showed that radiotherapy could delay pelvic recurrence, and chemotherapy could delay distant metastasis; however, they had no effect on the survival rate. Since chemotherapy alone increases the incidence of pelvic recurrence, a combination of extracorporeal radiotherapy and chemotherapy has been explored. The largest retrospective study on EC[39] suggested that the combination of chemotherapy and radiotherapy is beneficial for the survival of uterine serous carcinoma patients. However, no similar results were observed in the subgroup analysis of Hogberg[40], and since this was an unplanned small subgroup analysis, the efficacy of adjuvant chemoradiotherapy for serous or clear cell carcinoma could not definitively be stated.

In the present study, we retrospectively analyzed data from postoperative type II EC patients in the SEER database from 2010 to 2015. The results of the survival analysis were consistent with those of Viswanathan[39]. The combination of radiotherapy and chemotherapy was found to significantly improve disease prognosis in patients with type II EC, as compared to other treatments. In contrast to a previous clinical study[32, 38], we found that radiotherapy alone was associated

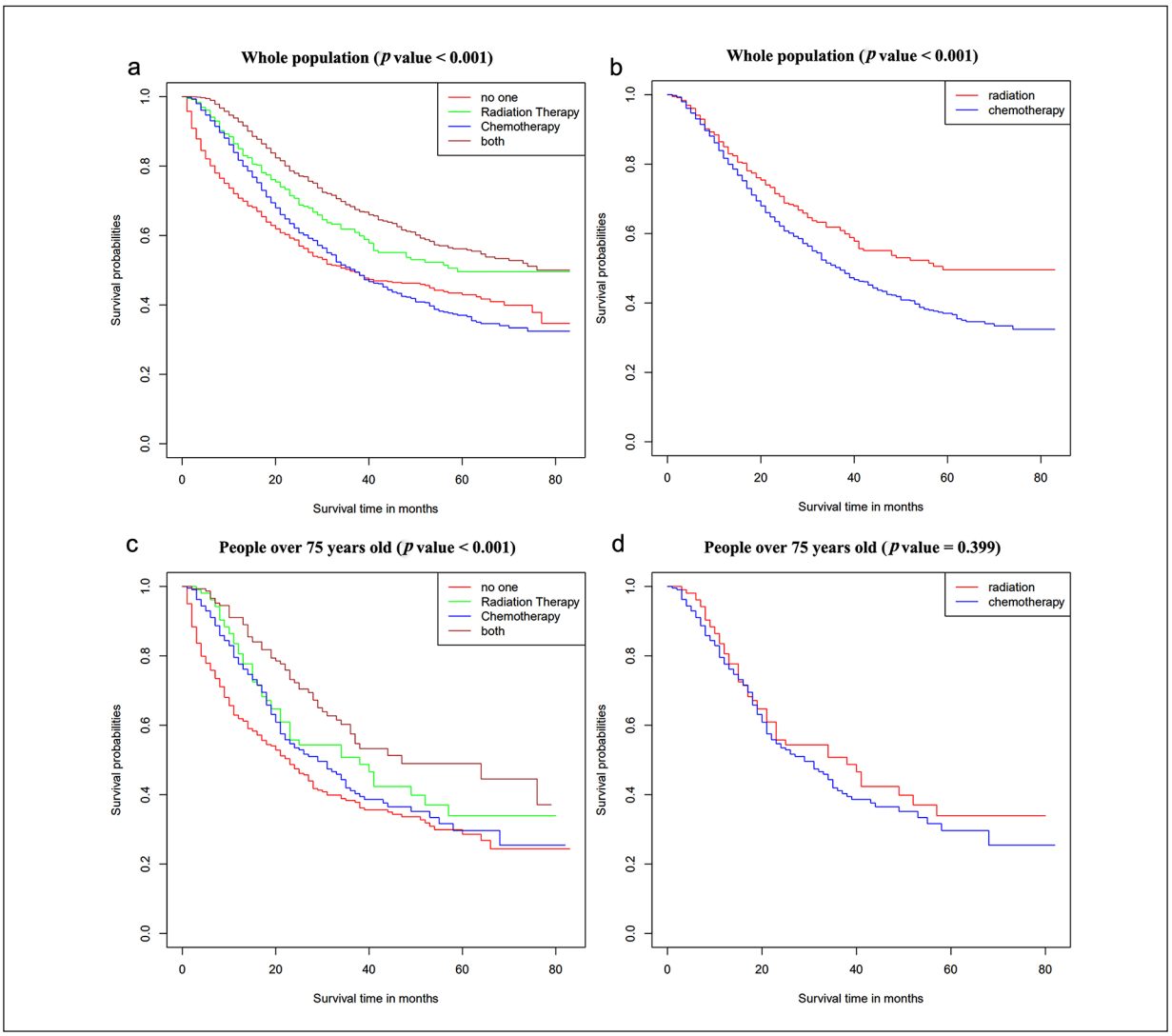

Figure 8. The Kaplan-Meier survival curves of postoperative adjuvant therapy in patients with type II EC. (**a**) postoperative patients, (**b**) postoperative patients with radiotherapy or chemotherapy alone, (**c**) postoperative patients over 75 years of age, (**d**) postoperative patients over 75 years of age with radiotherapy or chemotherapy alone. EC: endometrial cancer.

with a better prognosis (p<0.001). However, the cohort in this study includes stage IV cases who underwent non-curative surgery with distant metastasis (M1 17.4%). These patients are prone to undergo palliative chemotherapy compared to patients with regional diseases[9]. Therefore, we performed a statistical analysis of patients receiving only one treatment, and the results showed that patients receiving radiotherapy alone had a better baseline than those receiving chemotherapy, with 77% of patients in stage I/II. Nevertheless, there is little data on real benefit from chemotherapy, and which regimen/course is more desirable. Therefore, more clinical trials on these rare EC subtypes are still needed in the future.

Clinical studies[41] on the benefits of adjuvant radiotherapy and chemotherapy for women with high-risk endometrial cancer have shown that adjuvant chemotherapy based on radiotherapy can improve the progression-free survival rate in patients with high-risk endometrial cancer. However, multivariate analysis showed that only patients older than 70 years of age were associated with treatment effectiveness. Therefore, we analyzed the survival of 761 patients with postoperative type II EC, who were over 75 years of age in the SEER database. Results showed that the total survival rate of patients who received combined radiotherapy and chemotherapy was significantly improved. Hence, elderly patients

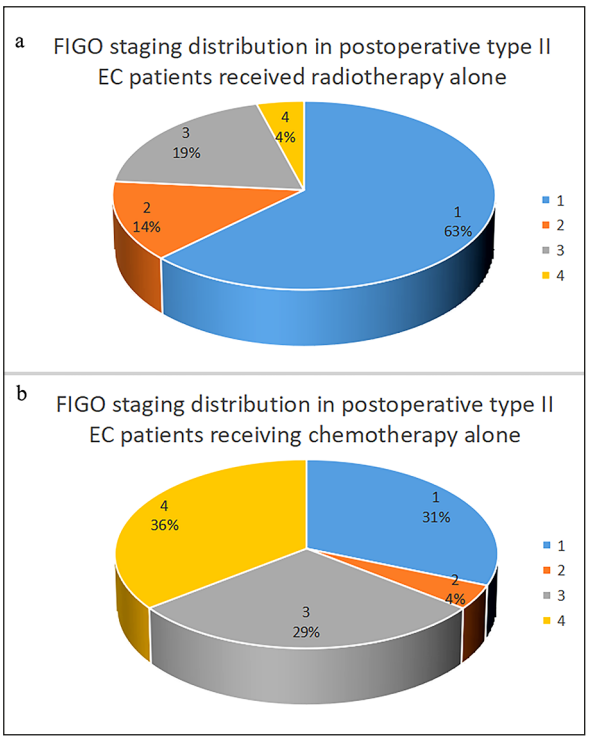

Figure 9. FIGO staging distribution in postoperative type II EC patients in SEER database. (**a**) patients receiving radiotherapy alone; (**b**) patients received chemotherapy alone. FIGO: International Federation of Gynecology and Obstetrics; EC: endometrial cancer.

should be made aware of the potential benefits of radiotherapy and chemotherapy. This is an important consideration, as in the United States, patients >70 years of age are 50% less likely to receive adjuvant therapy after surgery, as compared to younger patients[42].

One advantage of this study is that we independently analyzed type II EC prognosis and constructed a prediction model with practical application value. Secondly, more patients were included, and the overall follow-up period was longer than that in the previous studies. Moreover, our model was externally validated in a Chinese multicenter data set. The nomograph in the verification set showed excellent recognition and calibration capabilities, indicating that the nomograph based on the SEER database is also applicable to Chinese patients. However, there were several limitations to our study. In this retrospective study, since inclusion of missing data may affect reliability of the results, we excluded patients who lacked data during the data collection process. This may have led to selection bias, as nearly half of the patients were not included in our study. Then, there was no detailed information about obesity, diabetes, menarche, fertility status, endocrine therapy, and chemotherapy sequence in the SEER database. All these factors were suggested to affect the survival of patients with type II EC. A more comprehensive model that considers all the potential risk factors may yield greater predictive ability. Finally, it is worth noting that the survival benefit analysis of postoperative adjuvant therapy for type II EC patients in the SEER database was retrospective, and was an unplanned additional result; therefore, the possibility of unknown or residual variables cannot be ruled out. Our current analysis is not sufficient to clearly assess the survival benefits of postoperative adjuvant therapy for patients with type II EC, and it is necessary to encourage clinical trials for these rare subtypes.

Conclusions

In summary, based on the SEER database, we successfully developed a nomogram to predict the OS of type II EC patients. This model may serve as a strong prediction tool for clinical practice, effectively distinguish high and low risk groups, help clinicians to make personalized clinical evaluations, and provide more individualized services. This model and the corresponding risk classification system can provide a powerful predictive tool for clinical practice, effectively distinguish high and low risk groups, and help clinicians to carry out personalized clinical evaluation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Availability of Data and Material

The data are represented in the manuscript, additional data is available upon request.

Ethics Approval

Our study was reviewed and approved by the Medical Ethics Committee of Weifang Hospital of Traditional Chinese Medicine.

Informed Consent
This is a retrospective study, and therefore informed consent from patients was not required. All patient data were analyzed anonymously.

Data Availability Statement
The data presented in this study are available on request from the corresponding author.

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