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Nomograms for Predicting Overall and Cancer-Specific Survival Among Second Primary Endometrial Cancer in Primary Colorectal Carcinoma Patients

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Background: Endometrial cancer (EC) is one of the most frequent gynecologic cancers, approximately 20% of patients are regarded as high-risk with poor prognosis. However, more details of patients with second primary endometrial cancer (SPEC) after colorectal cancer (CRC) remain poorly understood. We therefore proposed to construct two nomograms to predict 3- and 5-year overall survival (OS) and cancer-specific survival (CSS) rates to facilitate clinical application.

Methods: A total of 1631 participants were identified in the SEER database from 1973 to 2020. We constructed and validated the nomograms for predicting OS and CSS. The receiver operating characteristic curves, calibration plot, decision curve analysis, C-index, net reclassification improvement, and integrated discrimination improvement were applied to evaluate the predictive performance. Finally, the Prognostic index was calculated and used for risk stratification of Kaplan-Meier survival analysis based on different treatment options.

Results: Nomograms of OS and CSS were formulated based on the independent prognostic factors utilizing the training set. The 3- and 5- years of OS nomogram demonstrated good discrimination (AUC = 0.840 and 0.829, respectively), well-calibrated power, and excellent clinical effectiveness. Our nomograms of predicting OS and CSS had a concordance index of 0.801 and 0.866 compared with 0.676 and 0.746 for the AJCC staging system, and more importantly, demonstrated a better forecast accuracy. Chemoradiotherapy displayed a significant survival benefit in the high-risk groups, but proceeding to surgery plus chemotherapy showed a favorable survival for the low groups based on all patients.

Conclusion: We developed and internally validated multivariable models that predict OS and CSS risk of SPEC in patients with a CRC to help clinicians make applicable clinical decisions for patients.

Keywords: endometrial neoplasms, colorectal carcinoma, nomogram, overall survival, cancer-specific survival

Introduction

Endometrial carcinoma (EC) is the most common gynecologic cancer in developed countries and accounts for more than 2% of deaths due to cancer in women worldwide, with the American Joint Committee on Cancer (AJCC) stage and histological type being associated with the treatment options and final prognosis.[1,2] Recent cohort studies have identified an approximately 3-fold increased risk of uterine corpus cancer in women with previous rectal cancer who underwent radiotherapy.[3,4] However, current research on the prognosis of second primary endometrial cancer (SPEC) in patients with colorectal cancer (CRC) is limited.

CRC is the third most prevalent cancer and the second leading cause of cancer-related deaths worldwide, accounting for approximately 10% of all newly diagnosed malignant tumors per year.[5] Studies have reported an imbalance of intestinal flora and disruption of barrier function in the intestines of people with CRC indicating that dysbiosis of

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intestinal microbiota may contribute to CRC.[6] In addition, gut microbiota may lead to insulin resistance,[7] abnormal estrogen metabolism,[8] or chronic inflammation via multiple pathways,[8] and hence be involved in the occurrence and progression of EC. Recently, a Mendelian randomization study validated that gut microbiota may be causally associated with both CRC and EC.[9] Therefore, the previous results indicate an underlying bidirectional link across CRC, intestinal dysbacteriosis, and EC. The incidence of CRC and EC has increased significantly with global aging, improved diagnostic accuracy using imaging techniques in EC,[10] and increased attention of clinicians toward the treatment decisions for SPEC among patients with CRC. Although several clinical prediction models have been reported for EC,[11,12] data on the concordance of these remain limited, suggesting that the prognosis of EC varies across patients with different characteristics. However, compared to that in primary EC, the use of surgery, radio- and chemotherapy, or a combination of these therapies for the treatment of CRC aggravates intestinal microbiota dysbiosis further, possibly leading to worse physical and psychological conditions. Therefore, the options for clinical treatment of SPEC in patients with CRC are still uncertain. Overall, the identification of appropriate prognostic factors is imperative to establish survival prediction models and making better clinical decisions.

We aimed to use the Surveillance, Epidemiology, and End Results (SEER) database to construct and verify two nomogram prognostic models for predicting 3- and 5-year survival rates of patients with SPEC in CRC, which could be useful for prognostic prediction, treatment strategy selection, and follow-up management of the patients.

Materials and Methods

Study Populations and Data Collection

Data were obtained from the Surveillance, Epidemiology and End Results (SEER) database (SEER*Stat software 8.4.2), which serves as an authoritative, federally funded cancer reporting system for the time ranges 1975–2020 and 2010–2020. Personal information of patients was not identifiable, and the information on SEER database is publicly available; therefore, no ethical approval or informed consent from patients was required. All primary cancer sites were coded according to the *International Classification of Diseases for Oncology, Third Edition*. The study was conducted in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. It was approved by the Ethical Review Committee of the Fuzhou First General Hospital (Ethics No. 202309013).

We first identified individuals with an initial primary cancer, diagnosed as CRC, based on the ICD-O-3 codes/WHO 2008 (colon and rectum) and sequence number (the first of two or more primary cancers). Secondly, patients with SPEC were identified depending on the "person selection" function of SEER records of the primary site labels (C54.0–C54.9, C55.9) and sequence number (second of two or more primary cancers). Subsequently, 3170 individuals were selected. All eligible participants were further screened based on the following exclusion criteria: duplicate participants (n = 1526), Leiomyosarcoma of myometrium or corpus uteri (n = 8), and patients with unknown survival time (n = 7).

Finally, 1631 patients were screened in this study and randomly allocated into training and validation groups (7:3 ratio) for the development and validation of the nomogram, respectively. The flowchart for participants selection is presented in Figure 1. The primary endpoints consisted of overall survival (OS) and cancer-specific survival (CSS) rates at 3 and 5 years respectively. OS events included deaths from any cause whereas CSS events included deaths resulting from EC.

Study Variables and Outcomes

The following 19 clinicopathological variables of patients with SPEC in CRC were downloaded from the SEER database: age, race, marital status, median household income, previous CRC-related variables (histology, location, radiation, and chemotherapy), time interval between CRC and SPEC, SEER summary stage, histologic types, grade, treatment type, lymph node-positive, distant lymph node metastasis, metastasis outside the pelvic reproductive system (including the bone, lung, liver, brain, bladder, or vulva), treatment duration, tumor size, date of last follow-up visit, and patient status at last visit. The optimal cut-off values for age were 20-, 50-, and 70-years, and time interval was 1 and 5 years. The optimal cut-off value for tumor size was 2 cm. Treatment duration was defined as the duration from diagnosis

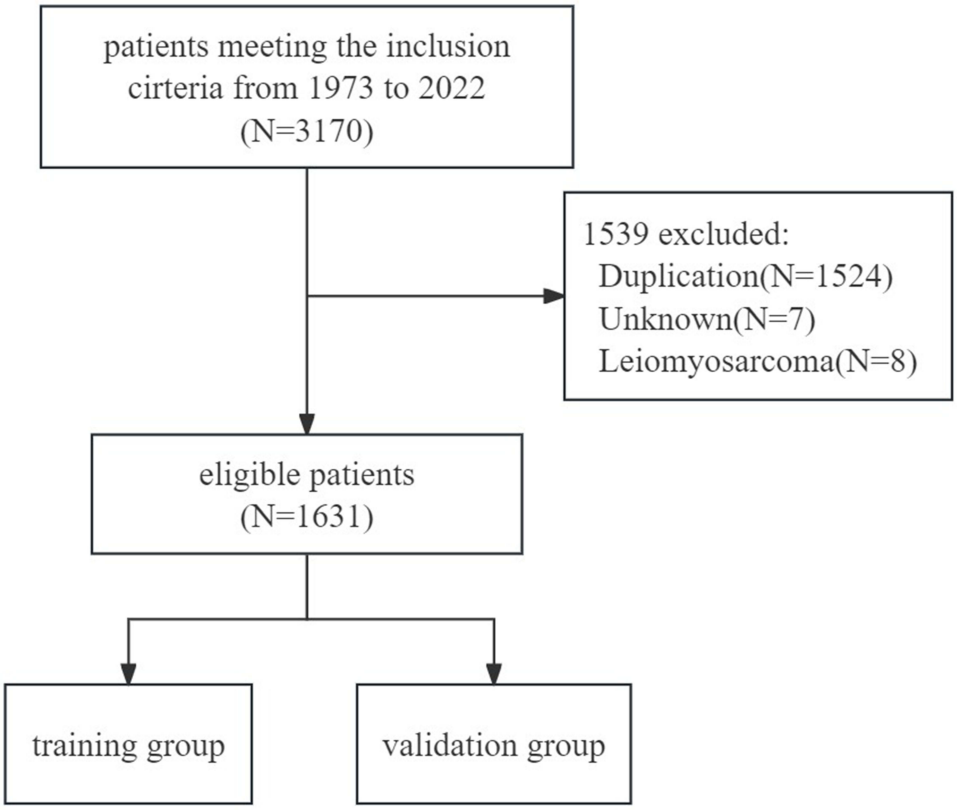

Figure 1 Flow chart of patient selection from the Surveillance, Epidemiology, and End Results (SEER) database.

to treatment (in months), with the optimal cut-off value of 1 month. Distant lymph node metastasis implied metastasis of lymph nodes beyond the pelvis and para-aortic regions, including the mediastinal and supraclavicular lymph nodes.

Metastasis outside the pelvic reproductive system referred to metastasis to the bone, lung, liver, brain, bladder, vulva, and other sites. The reclassification stage was recorded according to the 8th edition of the AJCC and categorized as stages I–IV.[13] Additionally, the histologic types were classified as endometrioid and non-endometrioid and designated as grade I, II, or III.[14,15]

Statistical Analysis

Variables based on previous reports or clinical consensus were included in the comparison between the training and validation groups. Categorical variables were expressed in percentages (95% confidence interval [CI]) and compared using chi-square tests. The least absolute shrinkage and selection operator (LASSO) regression and Cox regression analysis were used to construct OS- and CSS-associated prognostic nomograms. Model discrimination was evaluated using the area under the receiver operating characteristic curve (ROC), concordance index (C-index), net reclassification improvement (NRI), and integrated discrimination improvement (IDI) compared to the traditional AJCC stage system. Calibration curves evaluated the concordance between observed and predicted survival probabilities. Decision curve analysis (DCA) was implemented to illustrate the clinical performance of the model. We derived the prognostic index (PI) for each patient from the regression coefficients observed in the final multivariable Cox regression model. Kaplan–Meier (K–M) survival analysis was performed to evaluate the clinical effectiveness of the risk stratification system, and the significance was evaluated by a Log rank test. Statistical analyses were performed using R software (version 4.3.1) and STATA software (Stata 16.0, College Station, Texas 77845, USA). A p-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics of Participants

The median follow-up time was 78 months (73–86 months), and 711 patients died during follow-up. The median OS was 95 months (88–101 months), and the 3- and 5-year OS rates were 67% (64%–69%) and 59% (57%–62%), respectively. The median CSS was 52 months (46–56 months), and the 3- and 5-year CSS rates were 83% (81%–85%) and 80% (78%–82%), respectively.

The distribution of white race and age over 60 years was 78.6% and 73.70% respectively; 268 (16.43%) and 673 (41.26%) had received radiation therapy and chemotherapy, respectively, during previous CRC treatment; however, a minority of the tumors (22.44%) were located in the rectum. The majority of SPEC cases (66.95%) revealed endometrioid histology. Among the patients with information on AJCC stage, 69.59% were in early stage (I–II) whereas 22.5% were in late stage (III–IV). Most patients underwent surgery. The clinical and disease characteristics of patients in the training and validation samples of the model were similar and summarized in Table 1.

Table 1 Baseline Characteristics of the Included Patients

Characteristic	Total (n = 1631)	Training Group (n = 1143)	Validation Group (n = 488)	*p*-value
Age (%)				0.893
20–49	0.07(0.06–0.08)	0.07(0.05–0.08)	0.07(0.05–0.10)	
50–69	0.48(0.46–0.50)	0.48(0.45–0.51)	0.48(0.44–0.52)	
≥70	0.45(0.43–0.47)	0.45(0.42–0.48)	0.45(0.40–0.49)	
Race (%)				0.122
black	0.12(0.10–0.13)	0.12(0.10–0.14)	0.11(0.08–0.14)	
white	0.79(0.77–0.81)	0.77(0.75–0.80)	0.82(0.78–0.85)	
others	0.10(0.08–0.11)	0.11(0.09–0.13)	0.08(0.06–0.11)	
Marital status (%)				0.858
Single	0.13(0.12–0.15)	0.14(0.12–0.16)	0.13(0.1–0.16)	
Married or Domestic Partner	0.46(0.43–0.48)	0.45(0.42–0.48)	0.47(0.43–0.52)	
Widowed or Divorced or Separated	0.35(0.33–0.37)	0.35(0.32–0.38)	0.34(0.3–0.39)	
Unknown	0.06(0.05–0.07)	0.06(0.05–0.08)	0.06(0.04–0.08)	
Median household income (%)				0.528
<$70,000	0.45(0.43–0.48)	0.46(0.43–0.49)	0.44(0.4–0.49)	
≥$70,000	0.55(0.52–0.57)	0.54(0.51–0.57)	0.56(0.51–0.6)	
Interval time (%)				0.852
<1	0.17(0.15–0.19)	0.17(0.15–0.19)	0.17(0.14–0.20)	
1–5	0.44(0.42–0.47)	0.44(0.41–0.47)	0.45(0.41–0.50)	
≥5	0.39(0.37–0.41)	0.39(0.37–0.42)	0.38(0.34–0.42)	
Colorectal cancer histology (%)				0.919
Adenocarcinoma	0.83(0.81–0.85)	0.83(0.81–0.85)	0.84(0.8–0.87)	
Mucous tumor	0.09(0.08–0.11)	0.09(0.08–0.11)	0.09(0.07–0.12)	
Others	0.08(0.06–0.09)	0.08(0.06–0.09)	0.07(0.05–0.10)	
Colorectal cancer location (%)				0.399
Colon	0.78(0.75–0.8)	0.77(0.74–0.79)	0.79(0.75–0.82)	
Rectum	0.22(0.2–0.25)	0.23(0.21–0.26)	0.21(0.18–0.25)	
Colorectal cancer Radiation				0.750
Yes	0.16(0.15–0.18)	0.17(0.15–0.19)	0.16(0.13–0.20)	
No	0.84(0.82–0.85)	0.83(0.81–0.85)	0.84(0.80–0.87)	
Colorectal cancer Chemotherapy (%)				0.068
Yes	0.41(0.39–0.44)	0.40(0.37–0.43)	0.45(0.4–0.49)	
No	0.59(0.56–0.61)	0.6(0.57–0.63)	0.55(0.51–0.60)	
Grade (%)				0.070
I	0.28(0.26–0.30)	0.27(0.25–0.30)	0.28(0.24–0.32)	
II	0.20(0.18–0.22)	0.18(0.16–0.21)	0.23(0.19–0.27)	

(*Continued*)

Table 1 (Continued).

Characteristic	Total (n = 1631)	Training Group (n = 1143)	Validation Group (n = 488)	*p*-value
III	0.28(0.26–0.30)	0.28(0.26–0.31)	0.28(0.24–0.32)	
Unknown	0.25(0.22–0.27)	0.26(0.24–0.29)	0.21(0.18–0.25)	
Histology (%)				0.439
Endometrioid	0.67(0.65–0.69)	0.68(0.65–0.70)	0.66(0.61–0.70)	
Non Endometrioid	0.33(0.31–0.35)	0.32(0.3–0.35)	0.34(0.3–0.39)	
Summary stage (%)				0.698
Location	0.62(0.6–0.64)	0.61(0.59–0.64)	0.64(0.6–0.68)	
Regional	0.22(0.2–0.24)	0.22(0.2–0.25)	0.22(0.19–0.26)	
Distant	0.09(0.07–0.10)	0.09(0.08–0.11)	0.08(0.06–0.11)	
Unknown	0.07(0.06–0.08)	0.07(0.06–0.09)	0.06(0.04–0.09)	
AJCC Stage (%)				0.647
I/II	0.70(0.68–0.72)	0.69(0.66–0.72)	0.72(0.67–0.75)	
III/IV	0.23(0.21–0.25)	0.23(0.21–0.26)	0.21(0.18–0.25)	
Unknown	0.08(0.06–0.09)	0.08(0.06–0.09)	0.07(0.05–0.10)	
Treatment (%)				0.908
Surgery only	0.54(0.51–0.56)	0.53(0.5–0.56)	0.56(0.51–0.60)	
Surgery and chemotherapy	0.12(0.1–0.13)	0.11(0.1–0.13)	0.12(0.09–0.15)	
Surgery and radiation	0.12(0.1–0.14)	0.12(0.1–0.14)	0.11(0.09–0.14)	
Surgery, radiation, and chemotherapy	0.08(0.06–0.09)	0.08(0.06–0.09)	0.08(0.06–0.10)	
Chemotherapy only	0.02(0.02–0.03)	0.02(0.02–0.03)	0.02(0.01–0.03)	
Radiation only	0.02(0.01–0.03)	0.02(0.01–0.03)	0.02(0.01–0.03)	
Radiation and chemotherapy	0.01(0–0.01)	0.01(0–0.02)	0.01(0–0.02)	
Unknown	0.10(0.09–0.12)	0.11(0.09–0.13)	0.10(0.07–0.13)	
Months to treatment (%)				0.857
≤1	0.66(0.63–0.68)	0.65(0.62–0.68)	0.67(0.62–0.71)	
>1	0.25(0.23–0.27)	0.25(0.23–0.28)	0.24(0.21–0.28)	
Unknown	0.10(0.08–0.11)	0.10(0.08–0.12)	0.09(0.07–0.12)	
Regional Nodes positive (%)				0.100
Yes	0.09(0.08–0.11)	0.09(0.08–0.11)	0.09(0.07–0.12)	
No	0.75(0.73–0.77)	0.74(0.71–0.76)	0.78(0.74–0.81)	
Unknown	0.16(0.14–0.18)	0.17(0.15–0.19)	0.13(0.1–0.16)	
Distant lymph nodes (%)				0.784
Yes	0.02(0.02–0.03)	0.02(0.01–0.03)	0.02(0.01–0.04)	
No	0.38(0.36–0.41)	0.38(0.35–0.41)	0.39(0.35–0.43)	
Unknown	0.60(0.57–0.62)	0.60(0.57–0.63)	0.59(0.54–0.63)	
Metastasis outside the pelvic reproductive system (%)				0.816
Yes	0.07(0.06–0.08)	0.07(0.06–0.09)	0.06(0.05–0.09)	
No	0.83(0.81–0.85)	0.83(0.81–0.85)	0.84(0.81–0.87)	
Unknown	0.10(0.09–0.11)	0.10(0.09–0.12)	0.09(0.07–0.12)	
Tumor size (%)				0.542
<2	0.12(0.11–0.14)	0.13(0.11–0.15)	0.11(0.08–0.14)	
≥2	0.50(0.48–0.53)	0.50(0.47–0.53)	0.51(0.47–0.55)	
Unknown	0.38(0.36–0.40)	0.38(0.35–0.40)	0.38(0.34–0.43)	
OS				0.936
No	0.56(0.54–0.59)	0.56(0.53–0.59)	0.57(0.52–0.61)	
Yes	0.44(0.41–0.46)	0.44(0.41–0.47)	0.43(0.39–0.48)	
CSS				0.335
No	0.84(0.82–0.85)	0.83(0.81–0.85)	0.85(0.82–0.88)	
Yes	0.16(0.15–0.18)	0.17(0.15–0.19)	0.15(0.12–0.18)	

Notes: Values are percentages (95% confidence interval, 95% CI). Race others include American Indian/Alaska Native and Asian/Pacific Islander.
Abbreviations: OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; AJCC, American Joint Committee on Cancer.

Univariate K–M Survival Analysis

K–M analysis was used to evaluate the association between each variable in the baseline data table and OS of the patient, demonstrating that patients with SPEC who underwent surgery combined with radiotherapy and chemotherapy had better survival. Further details of this analysis are illustrated in Supplementary Figure 1.

Independent Prognostic Factors in the Training Cohort

LASSO regression analysis (Supplementary Figure 2) was performed to identify the possible predictors that were statistically significant ($p < 0.05$) under univariate Cox regression analysis within the training set (Supplementary Table 1). Finally, by multivariate Cox regression analysis, age, CRC radiation, grade, histology, summary stage, treatment, and tumor size were identified as significant predictors for OS while grade, histology, AJCC stage, treatment, and tumor size were independent predictors for CSS in patients with SPEC following CRC (Figure 2).

Prognostic Nomogram for OS and CSS

A prognostic nomogram that integrated all significant independent factors for OS and CSS in the training cohort is depicted in Figure 3. By combining each possible point, the predicted risks of OS and CSS at 3 and 5 years were calculated. In addition, ROC curves were used to assess the discrimination ability of the 3- and 5-year OS for the training (AUC = 0.840 and AUC = 0.843, respectively) and validation groups (AUC = 0.829 and AUC = 0.804, respectively); moreover, the 3- and 5-year CSS for the training (AUC = 0.817 and AUC = 0.700, respectively) and validation groups were calculated (AUC = 0.936 and AUC = 0.804, respectively) (Figure 4). Furthermore, the calibration plots of the training and validation groups for the probability of OS and CSS at 3 or 5 years demonstrated an optimal agreement between predicted and actual survival rates (Supplementary Figure 3). Overall, the nomograms exhibited considerable discriminative and calibration abilities. Furthermore, DCA revealed that our models were useful for threshold probabilities between 1% and 70%, having high predictive value and clinical utility (Supplementary Figure 4).

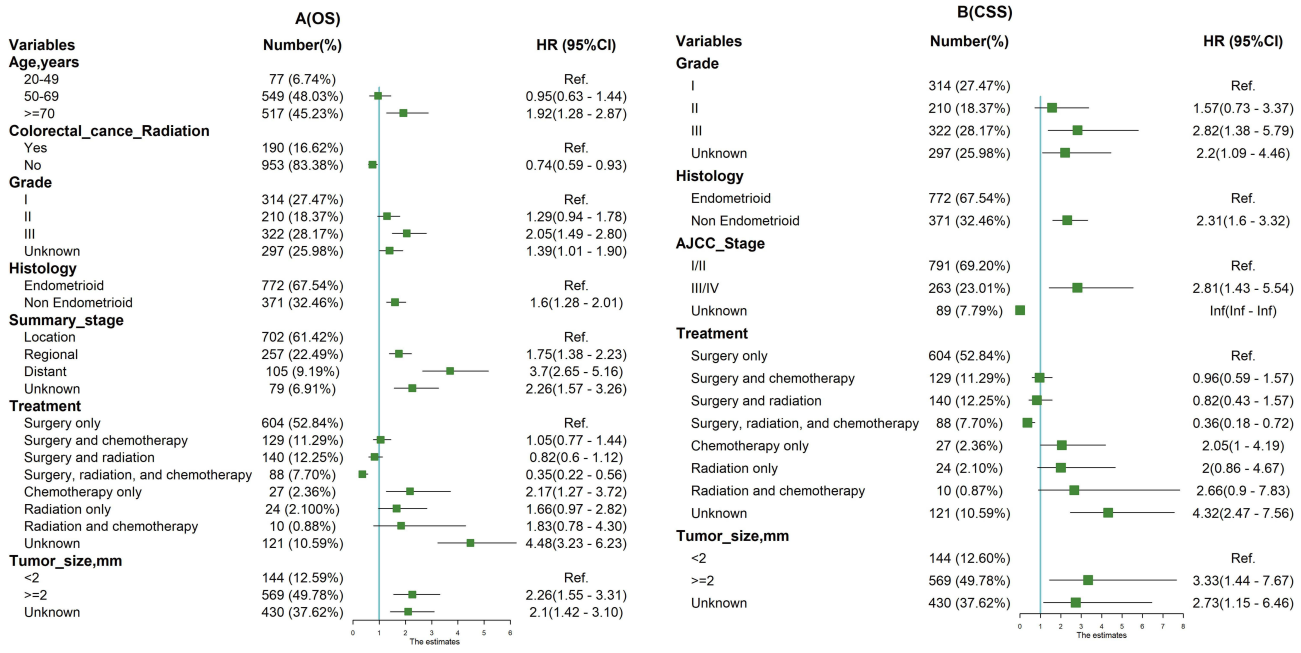

Figure 2 Forest plot of multivariable Cox regression model illustrating the significative prognostic factors on OS and CSS respectively. (**A**) Forest plot for OS; (**B**) Forest plot for CSS.

Abbreviations: HR, hazard ratio; CI, confidence interval; OS, overall survival; CSS, cancer-specific survival.

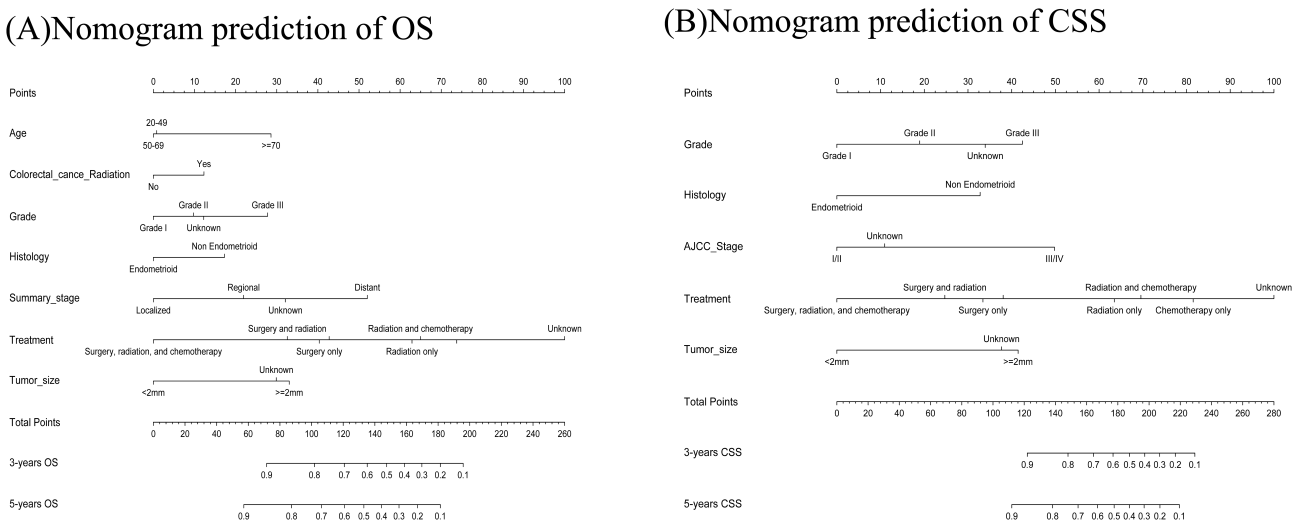

Figure 3 Nomogram for predicting the probability of OS and CSS at 3- and 5- years for elderly endometrial cancer (EC) patients following colorectal cancer (CRC). (**A**) Nomogram for OS; (**B**) Nomogram for CSS. Each clinical characteristic is translated into a risk score. The individual risk scores are summed together by the reader. The total scores can correspond to predicted 3- and 5-year OS and CSS probabilities.
Abbreviations: OS, overall survival; CSS, cancer-specific survival.

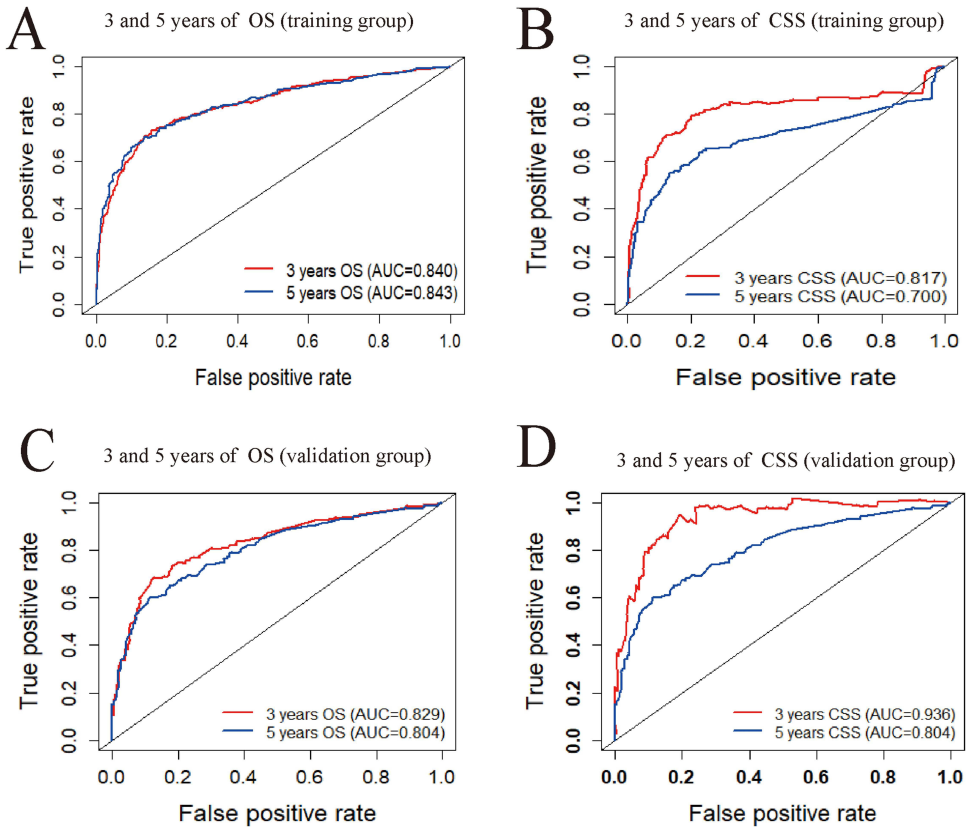

Figure 4 Time-dependent ROC curves of the nomogram for 5- and 10-year predictions. AUC for predicting OS in the training (**A**) and validation set (**C**); AUC for predicting CSS in the training (**B**) and validation cohort (**D**), respectively.
Abbreviations: AUC, an area under the curve; ROC, receiver operator characteristic; OS, overall survival; CSS, cancer-specific survival.

Comparison of Clinical Values Between Nomograms and AJCC Staging System

We estimated the c-index, IDI, and NRI by comparing the nomograms with the 8th edition of the AJCC staging system. Concordance was higher for the nomogram (c -index = 0.801 (95% CI, 0.779–0.822) and 0.866 (95% CI,

0.841–0.891) for OS and CSS, respectively) than for the AJCC staging system (c-index = 0.676 (95% CI, 0.654–0.698) and 0.746 (95% CI, 0.715–0.777), respectively) in the training set. IDI for the 3- and 5-year OS of the training group was 0.153 (95% CI, 0.114–0.196) and 0.149 (95% CI, 0.108–0.195), and NRI was 0.381 (95% CI, 0.313–0.466) and 0.403 (95% CI, 0.306–0.468), respectively (P < 0.001) (Supplementary Table 2). Results of these values for the validation group are presented in Supplementary Table 2, indicating that our nomogram was superior in predicting prognosis than the traditional AJCC staging system.

Risk Stratification in Patients with SPEC in CRC

The PI value for each patient was obtained from the independent predictor of the nomogram, and the patients were stratified into low- and high-risk groups accordingly. The risk stratification system showed that the 3- and 5-year OS of the low-risk patients were significantly higher than those of the high-risk patients in both training and validation groups. A similar performance was achieved on the ability to predict CSS (Supplementary Figure 5).

We performed K–M analysis and Log rank tests for 3-year OS to clarify the efficacy of treatment in the two-risk stratification subgroups (low-risk PI < 1.88 and high-risk PI ≥ 1.88). Our results showed that patients with CRC-associated SPEC receiving chemoradiotherapy had a better prognosis in the high-risk group whereas surgery combined with chemotherapy was incapable of improving the outcome in the low-risk group (Figure 5A and B). Similar results were observed in the CSS nomogram (low-risk PI < 2.89 and high-risk PI ≥ 2.89) (Figure 5C and D). Therefore, this method may help clinicians improve prognosis prediction and make better clinical decisions.

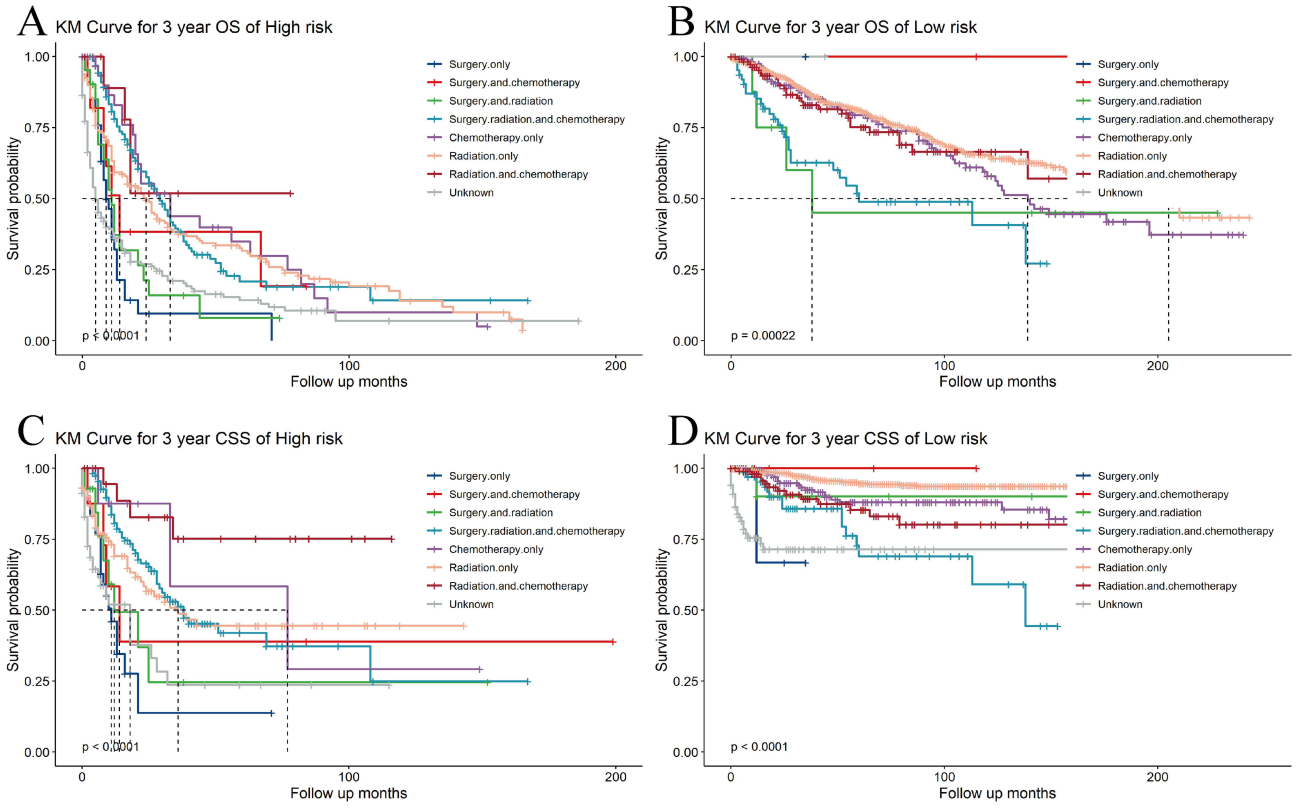

Figure 5 Survival analysis of the treatment methods of EC patients following CRC by risk stratification. (**A**) 3- year OS by high-risk patient; (**B**) 3- year OS by low-risk patient; (**C**) 3- year CSS by high-risk patient; (**D**) 3- year CSS by low-risk patient.
Abbreviations: OS, overall survival; CSS, cancer-specific survival; EC, endometrial cancer; CRC, colorectal cancer.

Discussion

In this study, the nomograms demonstrated good performance and accuracy in both training and validation cohorts, and their prediction was supported by c-index, calibration, ROC curves, and DCA. The nomograms revealed a better accuracy in survival prediction than the AJCC staging systems.

Age, CRC-targeted radiation, grade, histology, SEER stage, treatment, and tumor size were included in the OS prediction model. Compared to most other nomograms of FPEC, our findings supported that CRC-targeted radiation was negatively correlated with the OS of patients with SPEC. Especially, evaluation of the underlying risk of second primary cancer (SPC) after radiotherapy for pelvic cancers, including the prostate,[16] bladder,[17] cervix uteri,[18] and rectum,[3,4] substantiated the claims of an increased incidence of SPEC in patients undergoing pelvic radiotherapy, regardless of 1-, 5-, or 10-year incubation period.[3,19] Additionally, Guan et al indicated that 10-year survival rates in patients with radiotherapy-associated SPC were less than that in matched patients with first primary cancer.[3] Collectively, the variable of CRC-targeted radiation played a significant role in the nomogram of OS rates. Besides CRC-targeted radiation, other significant predictors of our OS nomogram, were adopted from various previous studies on different populations of EC. This phenomenon could partially be attributed to the similar clinicopathological features between FPEC and SPEC in Japanese patients, as reported by Keiichiro Nakamura et al, which implied the reliability of clinical interpretation of the OS nomogram from another aspect.[20] Unlike the large sample model emphasizing a major impact of age at diagnosis on patient survival, constructed by Sun et al,[21] our study did not adjust for age at diagnosis. To minimize the offset due to the impact of the survival rate of patients with EC over time and with medical technology advances, we reclassified the tumor stage of all cases according to the 8th edition of the AJCC staging system, added the SEER summary stage, and modified pathological grading based on previous reports, as the period of case selection spanned two SEER databases from 1973 to 2020.

A controversial finding was that age did not remain an independent predictor of CSS in this study, contrary to many studies on EC where age is a crucial prognostic factor. However, the current study participants were predominantly over 60 years of age, above the average age of 58–61 years of FPEC,[22] compared to similar age distribution-based studies. Consistent with the work by Fleming et al, which reported that age greater than 70 years in patients with EC was not a statistically significant predictor of poor outcomes after adjusting for other poor prognostic variables.[23] Previous research on patients with low CLDN6 expression further supported our finding.[24] Additionally, the fact that mortality of EC increases with age and is associated with medical comorbidities, such as obesity and diabetes, cannot be ignored. Thus, patients who died from EC were older and had more prevalent chronic diseases, such as hypertension, diabetes, and obesity, thereby masking the true underlying impact of age.

A notable similarity among both nomograms was the equal importance of treatment features supporting survival benefits, although treatment data solely relied on broad categories. Additionally, the survival outcomes of surgery combined with radiotherapy and chemotherapy appeared to be the highest by unadjusted survival analysis. Nevertheless, further risk stratification tests suggested that not all patients benefit from multimodality therapy. We observed that patients who received radiotherapy plus chemotherapy had higher survival rates than other treatments in the high-risk group, whereas surgery plus chemotherapy was the better choice for the low-risk group. This finding may at first appear incongruent with the results from traditional therapeutic methods, mainly by surgery supplemented by radiotherapy and chemotherapy. However, the strategies for the treatment of EC have been alterable owing to the heterogeneity of high-risk populations. Gynecologic Oncology Group (GOG) 122 is a pivotal study that changed our impression of EC and chemotherapy.[25] A randomized trial included women with early-stage, high-risk, and stage III EC and reported significant improvements in recurrence-free survival and OS trends with chemotherapy plus radiation than with chemotherapy alone.[26] On the contrary, Professor Daniela Matei's team revealed that chemotherapy plus radiation did not significantly improve relapse-free survival rate in terminal EC, although it controlled distant metastasis.[27] Briefly, adjuvant radiotherapy may have an impact on the patients who underwent chemotherapy as primary treatment, thereby explaining our findings of patients with high-risk EC benefitting the most from chemoradiotherapy. Radiotherapy has been the standard adjuvant treatment for EC historically; however, chemotherapy has lately emerged as a primary treatment alternative in early EC.[28] Adjuvant radiation use has been greatly reduced based on the results of postoperative radiotherapy in EC (ORTEC)-1.[29] The GOG-122 study revealed that

postoperative adjuvant chemotherapy is superior to whole adjuvant abdominal irradiation for patients with EC, consistent with multiple randomized controlled trials.[30–32] In fact, adjuvant chemotherapy could delay metastases, and the side effects could be acceptable; however, chemotherapy failed to prevent local recurrence, as reported by the trials. Notably, our results could partially be attributed to the population differences between the target patients with SPEC in CRC and that with FPEC; although randomized studies on the comparison of treatments of patients with SPEC would be worth further exploration. More individualized treatment would therefore be suggested for patients with EC after CRC.

The advantage of this study was that it was the first study with a long observation period that explored the prognostic value of patients with SPEC, made up for the lack of a second primary EC, and provided guidance for personalized medicine in clinical decision-making. Moreover, our nomograms greatly simplified the complex process of the condition of patients with SPEC, making it easier for clinicians to judge the prognosis, and thereby offered more convenience to the clinicians. There are, however, several limitations of this study. First, as our nomogram was based on the data of Western countries, it may not be generalizable to all populations. Second, the prognostic model was not externally validated, and practical advantages in prospective clinical use remain unclear. Third, the current study ignored the effect of diagnosis year, which may have an unexpected impact on patient outcomes considering the advancement in medical technology over time. Finally, the relatively small sample size might limit the statistical power; further research using large sample sizes would be necessary to verify the same.

Conclusions

In this study, two objective and accurate prediction nomograms informed the patients about their prognosis and provided oncologists some reference for clinical decision-making based on subpopulation at different risks.

Abbreviations

EC, Endometrial carcinoma; AJCC, American Joint Committee on Cancer; SPEC, Second primary endometrial cancer; CRC, Colorectal cancer; SEER, Surveillance, Epidemiology, and End Results; OS, Overall survival; CSS, Cancer-specific survival.

Data Sharing Statement

This research data will be openly available at https://seer.cancer.gov/seerstat/.

Patient Consent Statement

This study was exempted from review; hence, no written informed consent was required from the patients.

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Author Contributions

The author made a significant contribution to the work reported, be it in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all of these areas. They took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, agreed on the journal to which the article will be submitted, and are accountable for all aspects of the work.

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Disclosure

This paper has been uploaded to [Research Square] as a preprint: [https://assets-eu.researchsquare.com/files/rs-4677808/v1/b280e086-7239-4866-a595-59715ec58bd4.pdf?c=1728292185]. The author(s) report no conflict of interest in this work.

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