Technology in Cancer Research & Treatment
Volume 21: 1-10

DOI: 10.1177/15330338221110673
journals.sagepub.com/home/tct
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A Prognostic Nomogram for Predicting Overall Survival in Patients With Small-Cell Carcinoma of the Uterine Cervix: A SEER Population-Based Study

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Abstract

Background: This study aimed to develop a prognostic model based on the Surveillance, Epidemiology, and End Results (SEER) database to predict the overall survival (OS) of small cell carcinoma of the uterine cervix (SmCC). **Methods:** Between 1975 and 2016, a total of 401 patients were included, and their comprehensive sociodemographic and clinicopathological characteristics were collected. Univariate and multivariate Cox regression models were used to screen for independent prognostic factors. The identified factors were used to conduct a nomogram for predicting the OS of SmCC. The performance of the nomogram was determined using area under the receiver operating characteristic curve (AUC), concordance index (C-index), calibration curve, and decision curve analysis (DCA) metrics. **Results:** The median survival time of all patients was about 24 months (95% confidence interval [95% CI] [1.50-2.17]). Age (hazard ratio [HR] = 1.693 for 45-59 vs 21-34, 95% CI [1.140-2.513], $P = .009$; HR = 2.836 for 60-92 vs 21-34, 95% CI [1.851-4.345], $P < .001$), positive nodes (HR = 2.384, 95% CI [1.437-3.955], $P < .001$), regional nodes number ≥12 (HR = 0.500, 95% CI [0.282-0.886], $P = .018$), and treatment method (HR = 0.409 for surgery vs no, 95% CI [0.267-0.628], $P < .001$; HR = 0.649 for chemotherapy vs no, 95% CI [0.478-0.881])], $P = .006$) were independent factors of OS. Young patients who had surgical resection or chemotherapy, negative lymph nodes, and regional lymph nodes ≥12 had a longer survival time. These clinical factors were utilized to construct a nomogram for predicting OS. The AUC and C-index were higher than 0.7, indicating the good discriminating ability of the nomogram. The calibrations were all around the 45-degree line, indicating excellent consistency between the prediction of the model and actual observations. The DCA plots supported the clinical utility of the nomogram. **Conclusion:** The constructed nomogram is expected to help predict the prognosis of SmCC and guide patient treatment.

Keywords

nomogram, small cell carcinoma of the uterine cervix, overall survival, prognostic model

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Abbreviations

AIC, Akaike Information Criterion; AUC, area under the ROC curve; CCS, cause-specific survival; 95% CI, 95% confident interval; c-index, concordance index; DCA, decision curve analysis; DFS, disease-free survival; HR, hazard ratio; ICD-0-3, International Classification of Diseases for Oncology, Third edition; NETs, neuroendocrine tumors; NECC, neuroendocrine carcinoma of the cervix; OS, Overall survival; ROC, receiver operating characteristic; SCC, squamous cell carcinoma of the cervix; SmCC, small cell carcinoma of the uterine cervix; SEER, Surveillance, Epidemiology, and End Results

Received: March 7, 2022; Revised: May 30, 2022; Accepted: June 9, 2022.

Introduction

Small cell carcinoma of the uterine cervix (SmCC) are neuroendocrine tumors (NETs) with neuroendocrine functions. SmCC is histologically categorized into 3 subtypes based on morphological features: small-cell carcinoma (not otherwise specified), small-cell carcinoma (intermediate cell), and combined small-cell carcinoma. It is a rare pathologic form, accounting for only 1% to 2% of all cervical cancers.[1–3] When compared to other types of cervical cancer, such as squamous cell carcinoma of the cervix (SCC), adenocarcinoma, and adenosquamous cell carcinoma, SmCC has a higher degree of malignancy, early distant metastases, shorter disease course, and faster disease progression. SmCC patients were 1.8 times more likely to die than SCC patients.[4] According to a previous study,[5] the 5-year overall survival (OS) rate of SmCC was 35.7%, which was lower than the SCC rate of 60.5% (hazard ratio [HR] 0.55, 95% confidence interval [95% CI]:0.43-0.69) and the adenocarcinoma rate of 69.7% (HR 0.48, 95% CI:0.37-0.61). Because of its rarity, there is currently no consensus on effective treatment for SmCC, making it a significant therapeutic challenge for gynecologic oncologists.[6]

Identifying prognostic risk factors and developing prognostic-predictive models could aid in the identification of high-risk patients and guiding therapeutic decisions. Previous studies[7–10] showed that International Federation of Gynaecology and Obstetrics (FIGO) stage, lymph node status, and chemotherapy were independent prognostic factors of OS. However, because of the disease's rarity, most studies enrolled a small sample size or were single centered, indicating that their results are not highly reliable. To date, no study has investigated the impact of distinct pathological subtypes on the prognosis of SmCC. Furthermore, predictive models for estimating the prognosis of SmCC are rare. In 2020, Huang et al[11] established 2 prognostic nomograms to predict OS of FIGO stages I to IIA and IIB to IV separately, based on the Surveillance, Epidemiology, and End Results (SEER) database and Chinese Periodical Database, clustering age, lymph node involvement, cancer-directed surgery, chemotherapy, radiation for FIGO stages I to IA and age, cancer-directed surgery, chemotherapy, radiation, and tumor size for FIGO stages IIB to IV. However, both prediction models had low discrimination (with concordance index [c-index] = 0.67, 95% CI: 0.61-0.73 and 0.67, 95% CI: 0.62-0.72), and nomogram calibration for FIGO stages IIB to IV was poor. Therefore, it is urgent to build a more reliable prognostic-predictive model to guide therapeutic decisions.

The SEER database contains nearly 35% of the US population and is the largest publicly available cancer database. The database provides a unique opportunity for studying rare cancers. In this study, we used SEER data to investigate potential clinicopathologic and demographic factors associated with the OS of SmCC including pathological subtypes and the No. of regional lymph nodes dissection that have never been explored. These factors were used to establish a new prognostic nomogram model with better performance for SmCC.

Materials and Methods

Data Source and Patient Selection

This study included patients who had been enrolled in the SEER Program of the United States National Cancer Institute between 1975 and 2016. The SEER*Stat software (version 8.3.8) was used to collect demographic and clinical data from patients. Because the data is public and does not compromise patients' privacy, approval by the ethics committee review was not required. In our classification of small cell neuroendocrine carcinoma of the cervix (NECC) using the International Classification of Diseases for Oncology, Third edition (ICD-0-3), we included tumor histology codes of 8041/3, 8044/3, and 8045/3, which corresponded to small-cell carcinoma (not otherwise specified), small-cell carcinoma (intermediate cell), and combined small-cell carcinoma, respectively. Furthermore, all of the patients included in this study were first to visit and metastasis-free at their first visit, and the primary site in all the cases was the cervix. Patients having a history of malignant tumors and follow-up durations of less than 1 month were excluded. Patients lacking information on their surgical treatment, regional lymph nodes examination, or outcome indexes were also excluded.

Processing of Variables

This study examined 10 variables, including age at diagnosis, marital status, race, primary site, regional nodes, pathological type, positive nodes, surgery, radiation, and chemotherapy. Positive nodes, surgery, radiation, and chemotherapy were all binary variables (YES or NO). Patients were divided into

4 groups depending on their age at diagnosis: 21 to 34, 35 to 44, 45 to 59, and 60 to 92 years old. Patients were divided into 3 marital status groups: Married, Single, and Separated/Divorced/Widowed groups. Patients were classified as White, Black, or Others based on their race. The primary site was divided into 2 categories: the cervix uteri, and Others (Endocervix /Exocervix/Overlapping lesion of cervix uteri). Using the *R* package *survMisc* (version 0.5.5), 11 was determined as the optimum cut-off value for the continuous variable of regional nodes and was used to transform into 3 categorical variants: negative (0), 0 to 11, and 12 to 60. The pathology type was subdivided into 2 groups: SCNECC-NOS and SCNECC-Others (intermediate cell and combined small-cell carcinoma). In this study, the endpoint was OS. Pearson's chi-squared test was performed to compare clinicopathological factors between SCNECC-NOS and SCNECC-Others groups.

Statistical Analysis

Kaplan–Meier survival curves were generated using the "survival" package in R and used to estimate the OS in different groups. The log-rank test was used to compare the differences between the curves. To predict independent prognostic factors associated with OS, the HR and 95% CI were estimated using univariate and multivariate Cox regression in the R "survival" package. Additionally, different Cox models were to each subgroup during the subgroup analysis. Next, all parameters identified as independent predictors were included in the subgroups' Cox models. The predictive model was established using the stepwise variable selection method, and the best model fit was obtained using the Akaike Information Criterion (AIC). The nomogram package in R was used to construct a nomogram for predicting the OS at 24-, 36-, and 60 months. Finally, the discriminatory power of the model was compared using stepwise selection regression, and based on all clinicopathological factors. Several assessment indicators were used to evaluate the model's prediction performance. The time-dependent receiver operating characteristic (ROC) and c-index was used to assess the model's prediction performance, with an area under the ROC curve (AUC) and c-index value closer to 1 indicating excellent discriminating ability. The calibration curve was used to evaluate the degree of consistency between the model-based predicted OS and the patient's actual OS, and a slope of 45° indicated a high level of consistency. A decision curve analysis (DCA) plot was used to assess the clinical value of the prediction model by determining the net clinical benefit at disparate threshold probabilities. The Brier score was used to compare differences between the predicted and observed outcomes; with a score close to 0 indicating excellent prediction accuracy. In addition, the bias-corrected C-index and Brier score was computed using the bootstrap sampling method (B = 1000) for internal validation. A two-tailed *P*-value < .05 was considered statistically significant. R statistical software (version 4.0.5) was used to perform all statistical analyses.

Results

Patients Characteristics

A total of 401 patients met the inclusion criteria and were included in this study. There were 375 patients diagnosed with SmCC-NOS and 26 with SmCC-Others. As shown in Table 1, the difference in clinical and sociodemographic characteristics between the 2 groups was not statistically significant ($P > .05$).

Kaplan-Meier Survival Analysis and Log-Rank Test

The Kaplan–Meier plot and log-rank test were used to compare the OS of patients with regard to age, race, primary site, treatment method (surgery, radiotherapy, and chemotherapy), marital status, tumor type, regional lymph nodes numbers, and status (positive or not). As shown in Figure 1A, younger patients had a much better prognosis than older patients. Patients who underwent chemotherapy, radiotherapy, and surgery had a longer OS (Figure 1B-D). Furthermore, patients with regional lymph nodes ≥12 had a better prognosis (Figure 1E), married individuals survived longer than unmarried individuals (Figure 1F), and blacks seemed to have a worse prognosis compared with whites and other races (Figure 1G). However, there was no statistically significant difference in OS across patients with different tumor types, lymph nodes status, and primary site ($P > .05$) (Figure 1H-J).

Univariate and Multivariate Analysis of Prognostic Factors for OS in SmCC Patients

Univariate and multivariate analyses were performed to identify the independent prognostic factors of SmCC. All variables satisfied the proportional hazards assumption. Univariate analysis revealed that blacks, patients above the age of 45 years, and the No. of regional nodes were all associated with a higher risk. Furthermore, patients who underwent surgery, chemotherapy or radiotherapy had a decreased risk of death than those who did not. In multivariate analysis, age (HR = 1.693 for 45-59 vs 21-34, 95% CI [1.140-2.513], $P = .009$; HR = 2.836 for 60-92 vs 21∼34, 95% CI [1.851-4.345], $P < .001$), positive nodes (HR = 2.384, 95% CI [1.437-3.955], $P < .001$), regional nodes number≥12 (HR = 0.500, 95% CI [0.282-0.886], $P = .018$), and treatment method (HR = 0.409 for surgery vs No, 95% CI [0.267-0.628], $P < .001$; HR = 0.649 for chemotherapy vs No, 95% CI [0.478-0.881], $P = .006$) were found to be independent prognosis indicators for OS in SmCC. Table 2 shows detailed information.

Subgroup Analyses and Interaction Tests

As shown in Figure 2A, subgroup univariate analysis revealed significant interactions between tumor type and race or radiotherapy (*P* for interaction = .024, .015, respectively), but no evidence of significant interactions by age, primary site, surgery,

Table 1. Clinical and Sociodemographic Characteristics of Patients With SmCC in the SEER Database From 1975 to 2016.

Variables	Total (n = 401)	SmCC-NOS (n = 375)	SmCC-Others (n = 26)	*P*
Survival Months, Median (Q1, Q3)	18 (9, 47)	18 (9, 43.5)	15.5 (8.5, 70)	.991
Outcome, n (%)				.603
Dead	258 (64)	243 (65)	15 (58)	
Live	143 (36)	132 (35)	11 (42)	
Age, Median (Q1, Q3)	46 (36, 59)	45 (36, 58)	50.5 (40.5, 65.25)	.133
Race, n (%)				.467
Black	62 (15)	56 (15)	6 (23)	
Others	52 (13)	50 (13)	2 (8)	
White	287 (72)	269 (72)	18 (69)	
Primary site, n (%)				.779
Cervix uteri	343 (86)	321 (86)	22 (85)	
Others	58 (14)	54 (14)	4 (15)	
Surgery, n (%)				.296
NO	217 (54)	206 (55)	11 (42)	
YES	184 (46)	169 (45)	15 (58)	
Radiation, n (%)				.924
NO	282 (70)	263 (70)	19 (73)	
YES	119 (30)	112 (30)	7 (27)	
Chemotherapy, n (%)				.306
NO	84 (21)	76 (20)	8 (31)	
YES	317 (79)	299 (80)	18 (69)	
Marital, n (%)				.899
Divorced/Unknown	108 (27)	102 (27)	6 (23)	
Married	174 (43)	162 (43)	12 (46)	
Single/Unmarried	119 (30)	111 (30)	8 (31)	
Regional nodes, n (%)				.268
0	263 (66)	247 (66)	16 (62)	
0 to 11	44 (11)	43 (11)	1 (4)	
12 to 60	94 (23)	85 (23)	9 (35)	
Nodes positive, n (%)				.399
NO	339 (85)	315 (84)	24 (92)	
YES	62 (15)	60 (16)	2 (8)	

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; SmCC, small cell carcinoma of the uterine cervix.

Table 2. Results of Univariate and Multivariate Cox Regression Analyses.

	Univariate analysis HR (95% CI)	*P* value	Multivariate analysis HR (95% CI)	*P* value
Race: Others versus Black	0.666 (0.427-1.038)	.073	0.907 (0.576-1.428)	.673
Race: White versus Black	0.714 (0.516-0.988)	.042	1.053 (0.750-1.480)	.765
Primary site: Others versus cervix uteri	0.940 (0.664-1.332)	.729	1.213 (0.841-1.750)	.302
Surgery: YES versus NO	0.377 (0.291-0.488)	<.001	0.409 (0.267-0.628)	<.001
Radiation: YES versus NO	0.687 (0.523-0.903)	.007	1.354 (0.925-1.983)	.119
Chemotherapy: YES versus NO	0.664 (0.496-0.888)	.006	0.649 (0.478-0.881)	.006
Regional nodes: 0 to 11 versus 0	0.653 (0.436-0.978)	.039	0.798 (0.457-1.394)	.428
Regional nodes: 12 to 60 versus 0	0.375 (0.268-0.525)	<.001	0.500 (0.282-0.886)	.018
Nodes positive: YES versus NO	0.887 (0.637-1.234)	.476	2.384 (1.437-3.955)	<.001
Marital: Married versus Divorced/Unknown	0.577 (0.432-0.771)	<.001	0.948 (0.698-1.289)	.734
Marital: Single/Unmarried versus Divorced/Unknown	0.757 (0.553-1.036)	.082	1.201 (0.853-1.692)	.295
Age category: 35 to 44 versus 21 to 34	1.141 (0.762-1.710)	.522	1.104 (0.727-1.676)	.643
Age category: 45 to 59 versus 21 to 34	1.689 (1.168-2.444)	.005	1.693 (1.140-2.513)	0.009
Age category: 60 to 92 versus 21 to 34	3.211 (2.214-4.658)	<.001	2.836 (1.851-4.345)	<.001
Tumor type: SmCC-Others versus SmCC-NOS	0.875 (0.520-1.475)	.617	1.002 (0.587-1.710)	.994

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; SmCC, small cell carcinoma of the uterine cervix.

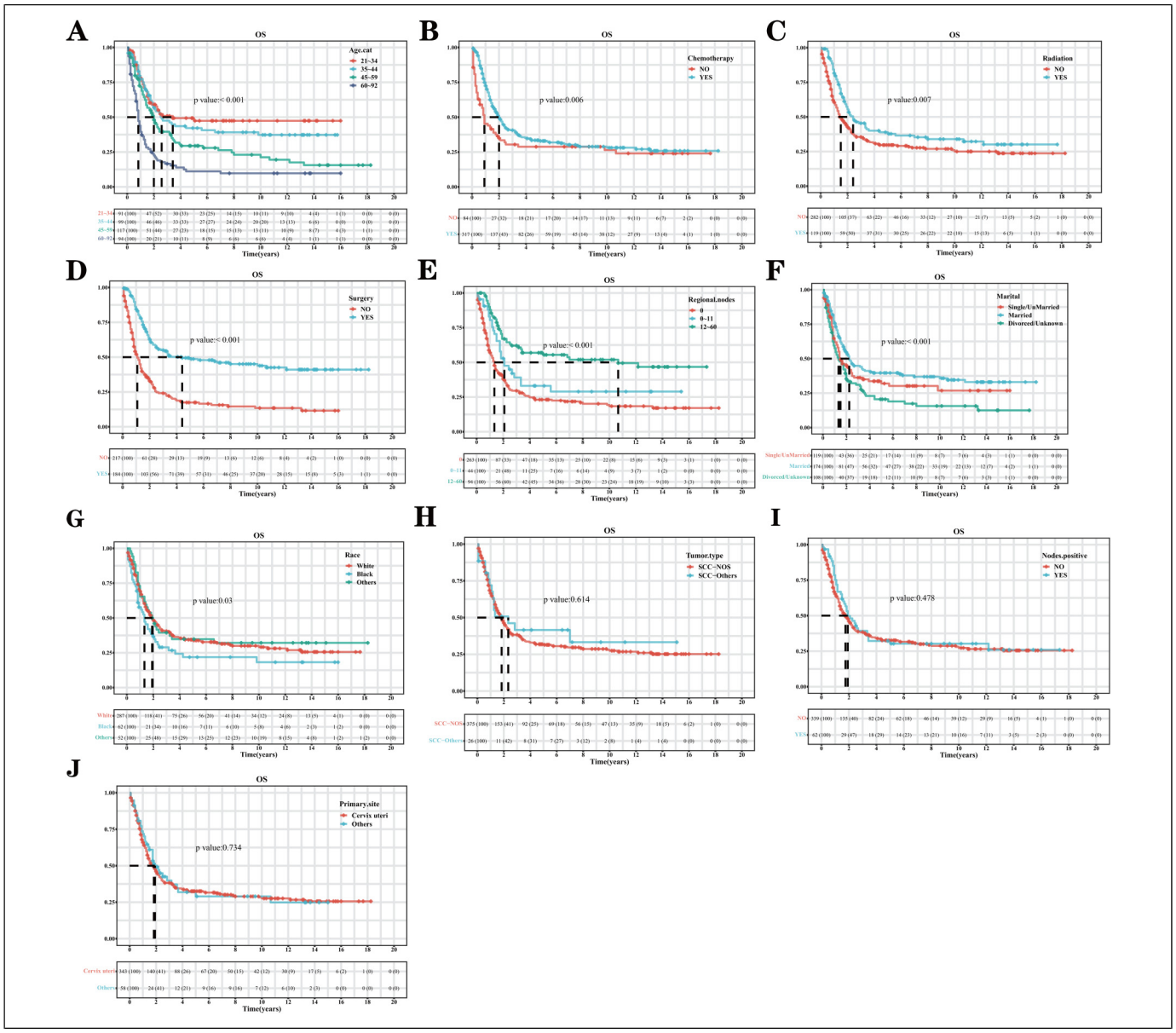

Figure 1. Estimated overall survival (OS) based on age (A), chemotherapy (B), radiotherapy (C), surgical treatment (D), regional nodes (E), marital status (F), race (G), tumor type (H), node positive (I), and primary site (J).

chemotherapy, regional nodes, lymph nodes positive, or marital status (P for interaction > .05). However, in the multivariate analysis, only race showed an interaction with tumor type (P for interaction = .018) (Figure 2B).

Development and Validation of a Prognostic Nomogram for SmCC

A prognostic nomogram that could predict the 24, 36, and 60 months OS was constructed using the multivariate Cox model (Figure 3). It included 6 variables: age, positive nodes, regional nodes number, chemotherapy, radiotherapy, and surgery. The risk line and scatterplot depicted the distribution of risk scores among all patients. As shown in Figure 4A, the AUC of ROC curve for the OS at 24, 36, and 60 months prediction in all models (the model based on all clinicopathological factors) was 0.744 (95% CI: 0.693-0.795), 0.76 (95% CI: 0.708-0.812), 0.795 (95% CI: 0.742-0.847), whereas in the stepwise model it was 0.735 (95% CI: 0.683-0.786), 0.75 (95% CI: 0.698-0.803), and 0.783 (95% CI: 0.728-0.837) (Figure 4B). The all model had a bootstrap-corrected c-index of 0.716, standard error (SE): 0.0170, while the stepwise model had a c-index of 0.707, SE: 0.0169. Brier scores for the 24-, 36-, and 60 months OS prediction model were <0.25 in both the all model and the stepwise model, and the numeric values remained <0.25 following internal validation with bootstrapping. The calibrations at 24-, 36-, and 60

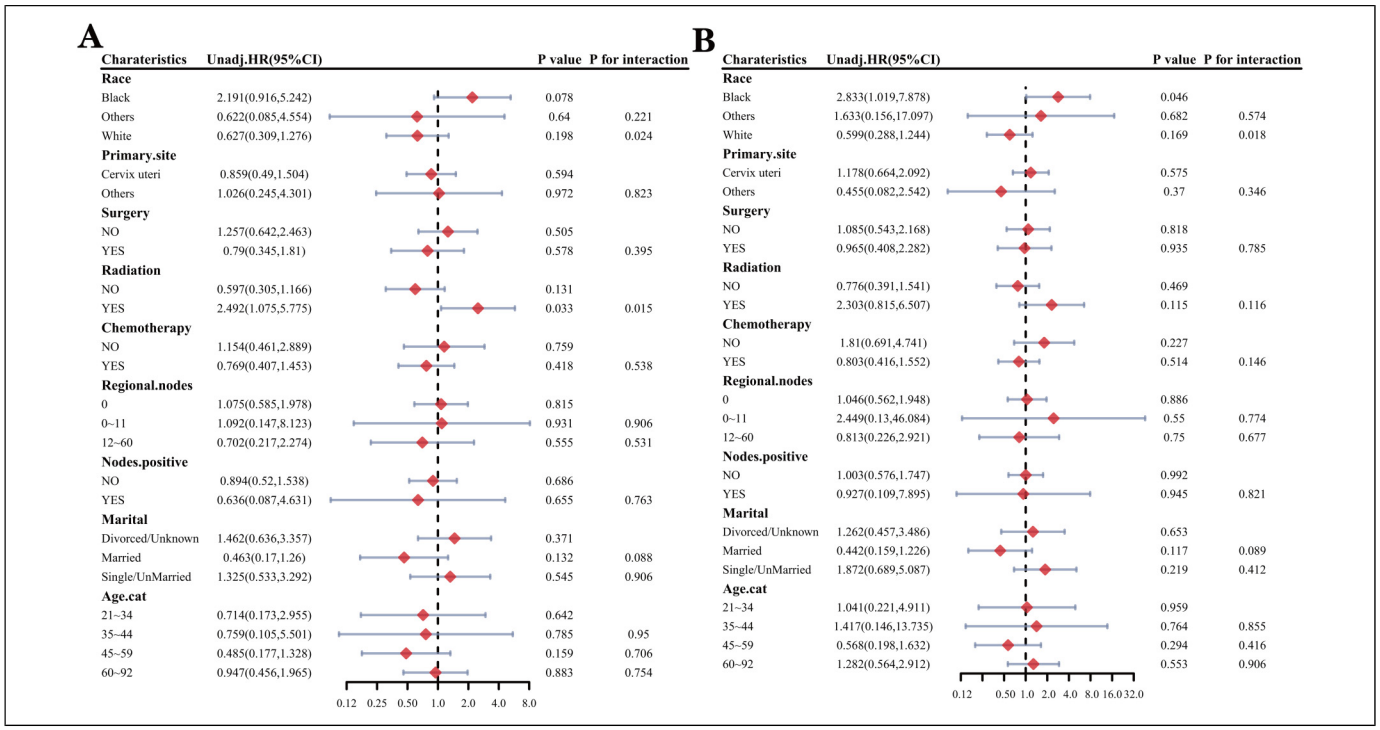

Figure 2. Forest plot used for subgroup analyses, as well as an interaction test between tumor type and other factors. (A) Univariate analysis and (B) Multivariate analysis.

months were all around the 45-degree line in both the all model and stepwise model, suggesting that the model was well calibrated (Figure 5A-5B). The DCA plots showed that both the all model and the stepwise model exhibited an excellent net benefit for 24-, 36-, and 60 months OS, supporting the clinical utility of both prediction models (Figure 6).

Discussion

Because of the low incidence but high mortality rate of SmCC, there are currently no known prognostic indicators or proven effective therapeutic approaches.

Using the SEER database, we found that surgery, chemotherapy, positive nodes, regional nodes number, and age were independent factors affecting the OS of SmCC. Young patients with negative lymph nodes and regional lymph nodes r≥12 who underwent surgical resection or chemotherapy had a high survival rate. All significant clinical indicators were used to construct a nomogram model to predict the OS of SmCC patients. The nomogram model's c-index was 0.707, which exceeded that reported in a previous study's (c-index = 0.67, 95% CI: 0.61-0.73), and our model's calibration was better, all of which indicated that our model performed better. We also used additional model assessment metrics, including AUC value and DCA to confirm that the predicted values of the nomograms were as expected.

The median survival time for all included patients in the present study was approximately 24 months, with an estimated 5-year OS rate of 31.4%, comparable to a previous SEER study,[12] but shorter than a previous systematic review reporting a median OS time of 40 months.[1] The discrepancy may be explained by the fact that the latter study included 7.6% of other NECC histological subtypes, which had a better prognosis. A retrospective study of 25 patients who underwent radical radiotherapy (with or without chemotherapy) reported a median OS of 53.8 months.[13] The study's results, however, were not reliable due to the small sample size.

The median age at the time of diagnosis in the present study was 46 years old, ranging from 36 to 59 years old, which was comparable to that reported in the previous study.[6] Age at diagnosis was considered to be an independent predictive factor in the majority of previous studies.[5,7,12,14] Although the cut-off values varied, there was a consistent pattern of increasing age with a poor prognosis.

The presence of positive lymph nodes was found to be negatively correlated with OS, while the detection of ≥12 regional lymph nodes was positively correlated with OS. This finding was also consistent with previous studies.[7,8,13] Lymph node metastases are the most predominant cervical cancer metastatic mechanisms. The greater the number of dissected regional lymph nodes, the better the understanding of lymph nodes status (eg, negative or positive), and the lower the risk of leaving metastatic lymph nodes behind.

According to the 2021 NCCN cervical cancer guidelines,[15] radical surgery should be considered first in patients with early stage SmCC, whereas primary surgical treatment is not recommended for patients with stage IB3/IIA2 SmCC. Because SmCC is sensitive to chemotherapy, thus, it should be applied in the management of SmCC patients at all stages.

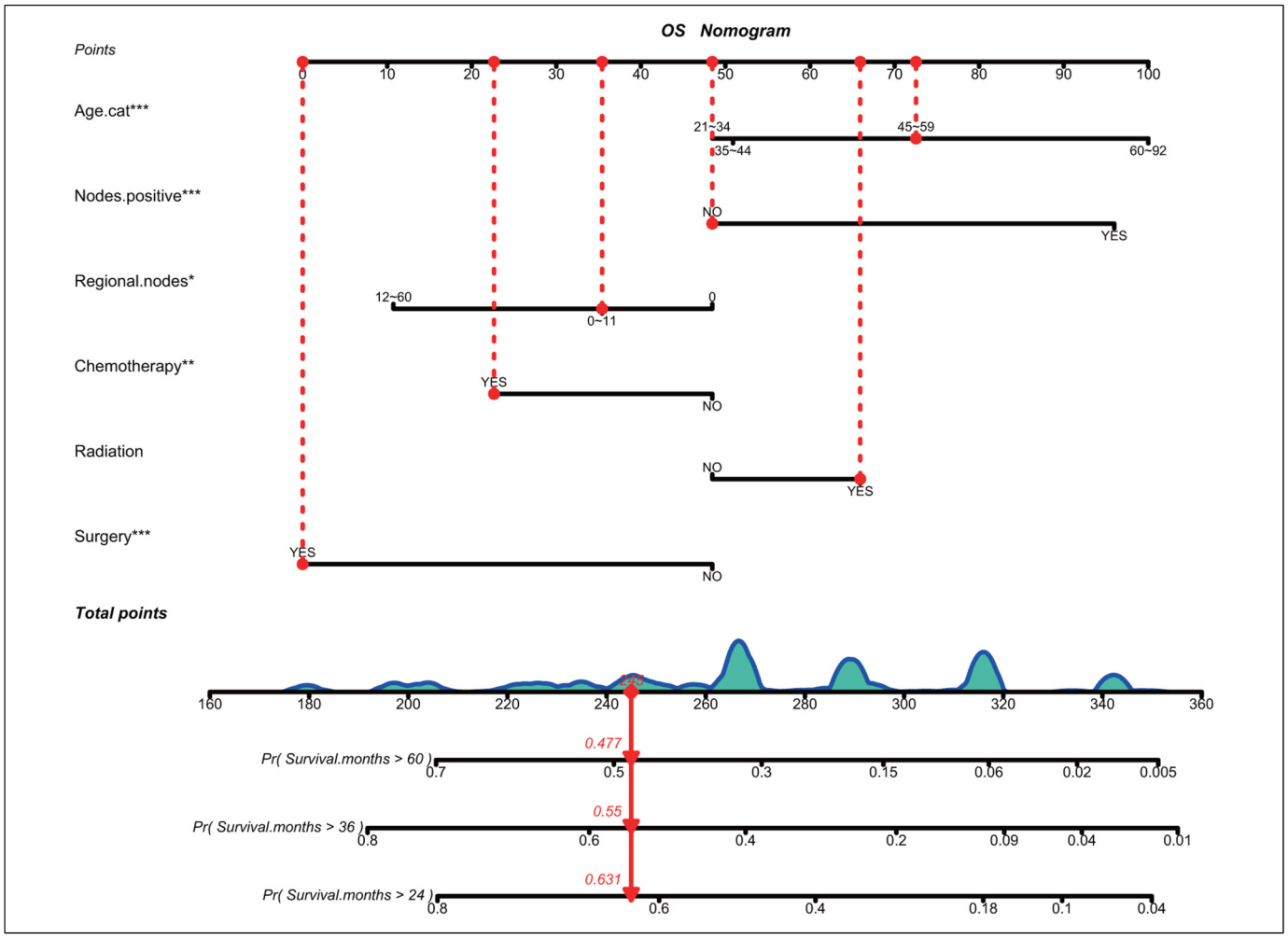

Figure 3. The nomogram for predicting 24-, 36-, and 60 months OS in SmCC patients.
Abbreviations: OS, overall survival; SmCC, small cell carcinoma of the uterine cervix.

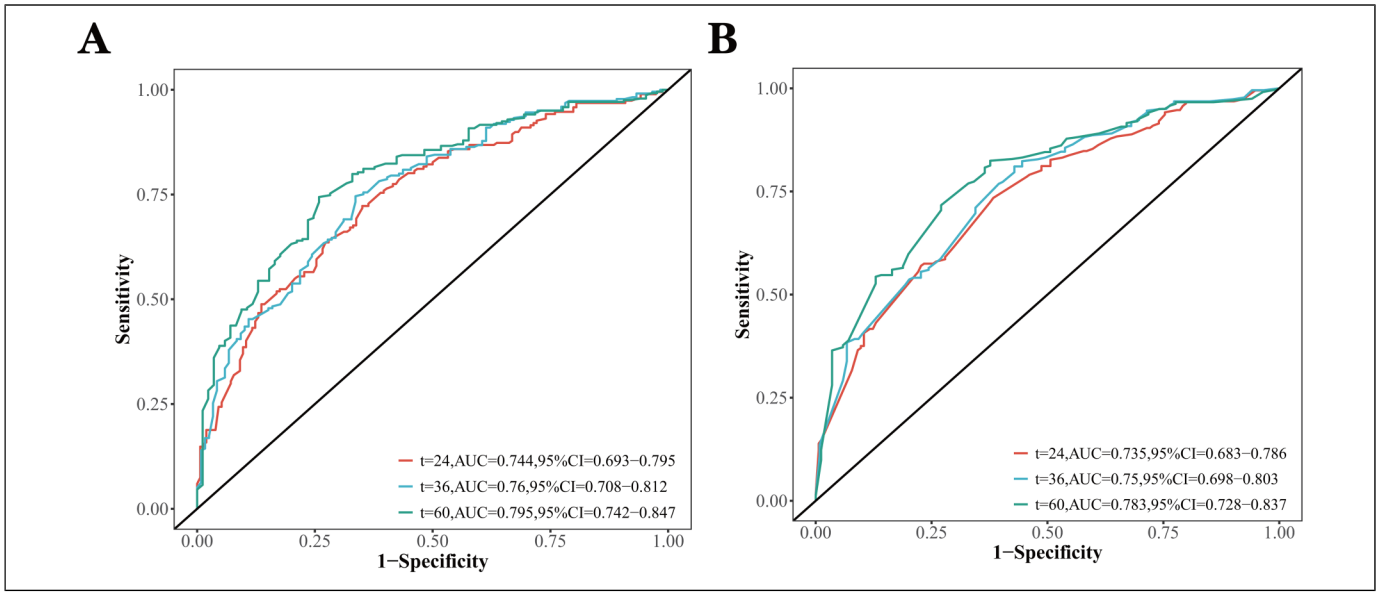

Figure 4. The ROC curve for 24-, 36-, 60 months OS prediction in all models (A) and the stepwise model (B).
Abbreviations: OS, overall survival; ROC, receiver operating characteristic.

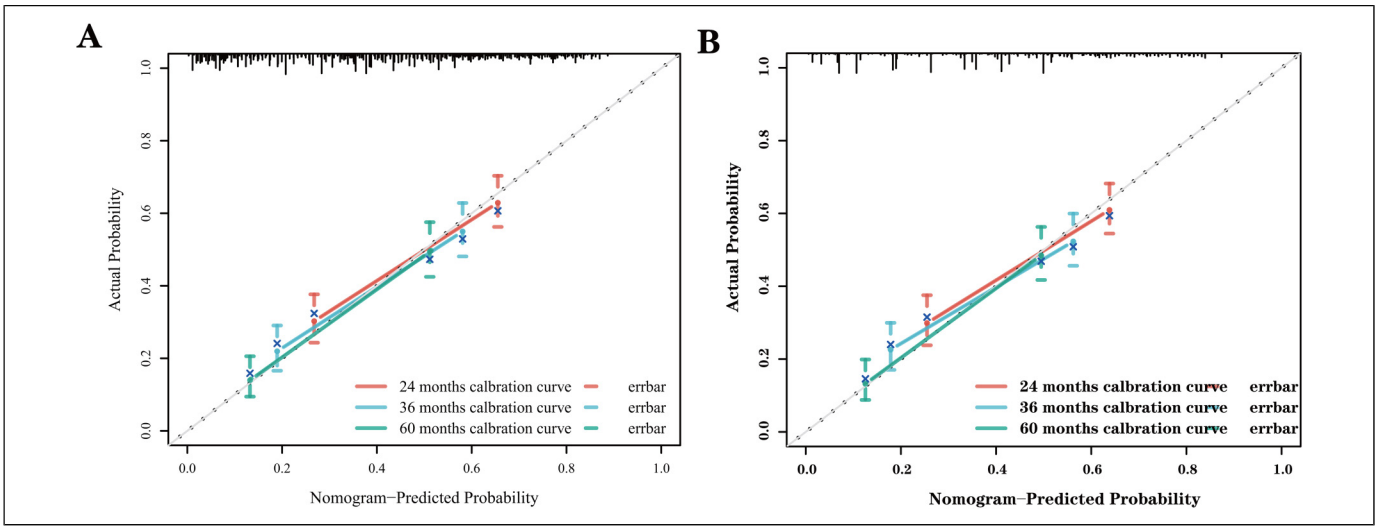

Figure 5. The calibration plots for predicting 24-, 36-, and 60 months OS in SmCC patients in all models (A) and the stepwise model (B).
Abbreviations: OS, overall survival; SmCC, small cell carcinoma of the uterine cervix.

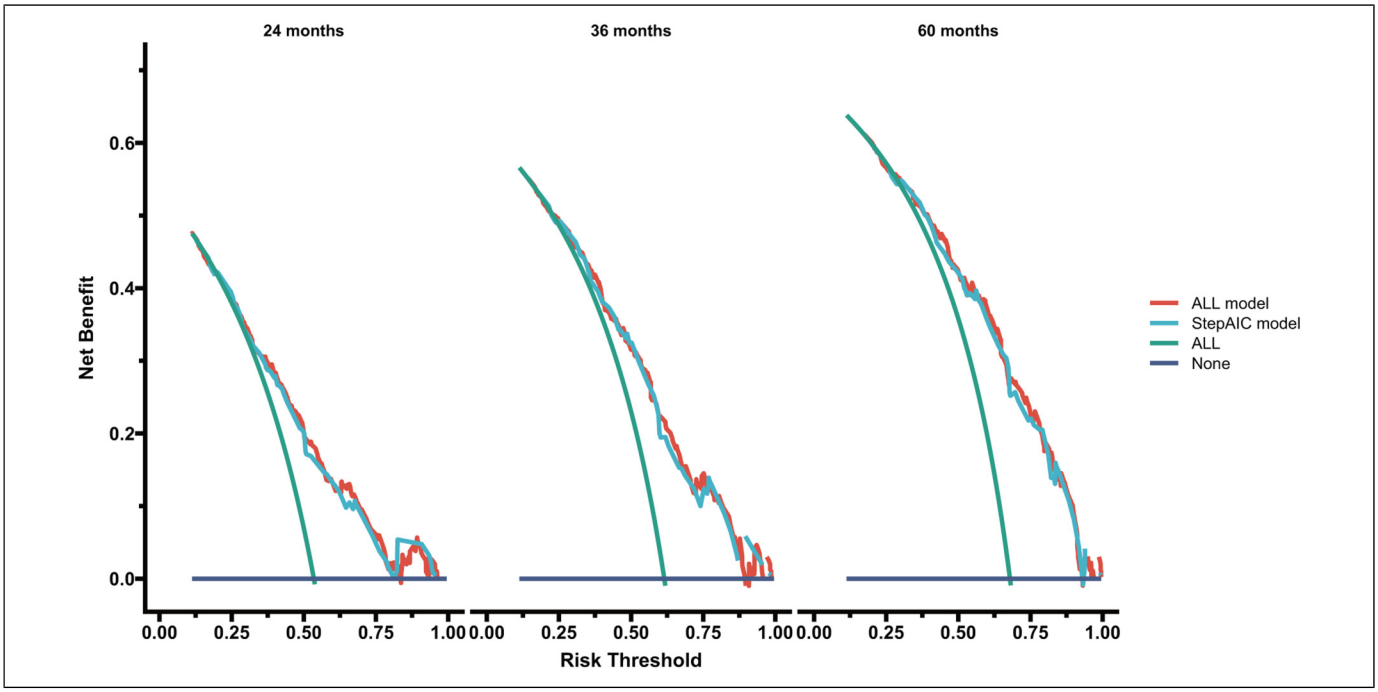

Figure 6. DCA plots of the all model and stepwise model for OS prediction at 24-, 36-, and 60 months.
Abbreviations: DCA, decision curve analysis; OS, overall survival.

A multicenter study in Korea found that systemic chemotherapy may improve SmCC prognosis even in the early stages.[16] Surgery combined with adjuvant chemotherapy have been shown to have better survival outcomes than either surgery or chemotherapy alone.[8,10,14] Postoperative chemotherapy has been shown to improve the prognosis of SmCC patients.[17] The present study findings confirmed the favorable impact of surgery and chemotherapy on OS. Although radiotherapy is also recommended in the guidelines for the management of SmCC, its effect on SmCC prognosis is controversial. This study found that radiotherapy did not improve the OS of SmCC patients, which is consistent with some previous studies. Shen et al showed that adjuvant radiotherapy after radical surgery and adjuvant chemotherapy significantly improved disease-free survival (DFS), although this effect was not significant for FIGO stages I to II SmCC patients.[18] A Chinese study found that radiotherapy had a detrimental impact on the OS of SmCC patients with negative lymph

node metastasis.[19] Furthermore, patients who underwent surgery as a primary treatment had a greater OS than those who underwent radiotherapy as their primary treatment. Additionally, postoperative radiotherapy had no discernible impact on cause-specific survival (CCS), DFS, or OS of FIGO stages I to II SmCC patients.[20,21] Another study found that radiotherapy was associated with poor OS of SmCC.[22] In contrast, Chen et al found that patients in stages IB2 to II who received primary radiotherapy had the same survival outcomes as patients in stages IA to IB2 who underwent primary surgery and that primary radiotherapy had a better prognosis than primary surgery for patients in stages IB2 to II. Furthermore, for most stages I to II patients, combination primary radiotherapy and chemotherapy showed better outcomes than other therapeutic regimens.[23] However, in the previous studies, the majority of the patients were in stages I to II. Alexander et al found that brachytherapy may significantly improve the OS of stages II to IVA SmCC but not stage I and stage IVB SmCC.[24] A previous study using SEER data found that external beam radiotherapy combined with brachytherapy improved the OS of stage III patients.[25] The effect of radiotherapy on prognosis was thought to be related to the stage of SmCC. Due to the lack of FIGO stage information in the SEER database since 2010, as well as the rarity of SmCC, stage variables were not included in the analyses to ensure sufficient sample size, and therefore the impact of radiotherapy on OS may not have been adequately evaluated.

The present study demonstrates some advantages. First, this study was based on the SEER database, which has a large population coverage. Second, in addition to clinicopathological features, social demographical data such as race and marital status were included, thereby reducing possible confounding effects. Lastly, we performed a comprehensive assessment of the nomogram to demonstrate its good predictive ability.

Apart from the absence of FIGO staging, this study had other limitations, including the lack of specific information on treatment modalities, such as specific chemotherapy or radiotherapy regimens, as well as the range of surgical excision. Additionally, since the SEER database primarily includes data on Americans, it is deficient in data on other races, particularly Asians, limiting its use. Finally, as is the case with all retrospective studies, there is a risk of selection bias in this study.

Conclusion

In conclusion, a novel prognostic nomogram model was established using a large population sample to predict the OS of patients with SmCC. Surgery and chemotherapy were found to be effective therapeutic modalities of SmCC patients.

Acknowledgements

The authors would like to thank the SEER database for providing clinical information.

Author's Contribution

Yusha Chen and Jiancui Chen were involved in the design of the study. Xiaoqian Lin carried out data collection and analysis. Yusha Chen assisted in drafting the manuscript. Xiangqin Zheng and Suyu Li revised the manuscript. All the authors reviewed and approved the final manuscript.

Data Availability

The data of this study are available in the SEER database (https://seer.cancer.gov/). Data downloading and processing are as described in Materials and Methods.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The data analyzed in this study are publicly available and do not include the identification of patients. Therefore, consent and approval by the ethics committee are not required.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research study was supported by the grants from Fujian Provincial Health Technology Project (2019-ZQN-25), Fujian Science and Technology Project (2019J05138), Young and Middle-Aged Key Talents Training Project in Fujian Province (2019-ZQN-23), and Fujian Maternity and Child Health Hospital (YCXQ 18-17).

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