



Establishment and validation of a novel nomogram for survival prediction of ovarian carcinosarcoma

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Background: Ovarian carcinosarcoma (OCS) is a rare and aggressive histological type of ovarian cancer. Current prognostic methods for OCS are insufficient. This study was undertaken to establish and validate a novel nomogram for predicting the overall survival (OS) of OCS patients.

Methods: We extracted 820 patients with OCS from the Surveillance, Epidemiology, and End Results (SEER) database and further randomly assigned them to a training set (n=574) and a validation set (n=246) at a ratio of 7-to-3. Univariate and multivariate regression analyses were utilized to verify independent prognostic factors, and a prognostic nomogram was constructed based on the results. The performance of the new model was compared with that of the AJCC staging system using the area under the receiver operating characteristic curve (AUC), net reclassification improvement (NRI), integrated discrimination improvement (IDI), calibration curve, and decision curve analysis (DCA).

Results: Cox regression analysis suggested that age, grade, tumor size, the American Joint Committee on Cancer (AJCC) stage, surgery, and chemotherapy were the independent prognostic factors. These factors were integrated into a prognostic nomogram to determine the 1-, 3-, and 5-year OS of OCS patients. The AUC, NRI, IDI, calibration curves, and DCA data demonstrated that our nomogram had better discriminative ability than the AJCC staging system alone. The calibration curves indicate that the nomogram was well-calibrated. The DCA verified the clinical applicability of the nomogram.

Conclusions: Our current study is the first to establish and internally validate a novel nomogram for predicting the 1-, 3-, and 5-year OS probabilities of OCS patients. Our prognostic nomogram was of good performance and can be an accurate tool to predict individualized survival time of OCS in clinical work.

Keywords: Ovarian carcinosarcoma (OCS); overall survival; prognostic model; nomogram; SEER database

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Introduction

Ovarian carcinosarcoma (OCS) is a rare and aggressive histologic type of ovarian cancer that accounts for approximately 1–4% of all cases (1). Histologically, OCS

is comprised of a carcinoma as well as a sarcoma. It is most prevalent in postmenopausal women, and many patients have a poor prognosis even at early-stage. The median survival of patients with OCS is less than two years (2,3). The prognostic factors remain controversial given the

condition's rarity in large clinical trials. Moreover, there is no standard treatment protocol for OCS, although surgical debulking followed by adjuvant chemotherapy seem to improve the outcomes (4,5).

The American Joint Committee on Cancer (AJCC) staging system is currently one of the staging systems for OCS (6), but the system lacks other important prognostic factors, such as demographic and pathologic characteristics, and often results in deviations from the predicted value when used alone (7). A more reliable prognostication model for OCS is needed to guide clinicians.

Nomograms have been widely used to assess the prognosis of diverse cancers, which quantifies risk by evaluating multiple prognostic factors in a visual chart (7-9). To our knowledge, the currently available nomogram for OCS is inadequate. Additionally, we screened and identified with relevant data in the Surveillance, Epidemiology, and End Results (SEER) database to obtain an adequate number of OCS cases.

Therefore, this study was undertaken to establish a novel nomogram based on multiple factors for OCS that were derived from the SEER database. We compared our nomogram with the traditional AJCC staging system to verify its predictive feasibility and validity. We present the following article in accordance with the TRIPOD reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-1796/rc>).

Methods

Data collection

The research data were obtained from the SEER database, which was established in 1973 by the American Cancer Institute. It is one of the most authoritative large tumor registration databases in the United States. The SEER database includes data on approximately 34.6% of the American population and provides large-scale data support for rare disease studies. All SEER research data are publicly available and de-identified, which exempted this study from the need for informed consent and ethical approval (10).

Patient and variable selection

We utilized the SEER*Stat version 8.3.9 (www.seer.cancer.gov) to download patient information from the SEER 18 database. The inclusion criteria were applied: (I) diagnosed between 1988 and 2015; (II) primary site in the ovary

[International Classification of Diseases for Oncology, third edition (ICD-O-3) code, C56.9]; (III) histologically proven malignant carcinosarcoma (ICD-O-3 codes 8950/3, 8951/3, and 8980/3). The exclusion criteria were applied: (I) not the primary tumor; (II) unknown information about race, marital status, tumor size, AJCC stage, tumor histological grade, or survival time. The following clinical pathologic variables were selected: age at diagnosis, race, marital status, year of diagnosis, histology, tumor histological grade, AJCC stage, tumor size, laterality, chemotherapy status, radiotherapy status, and surgery status. The tumor histological grade was defined according to the SEER database, and classified as grade I: well-differentiated; grade II: moderately differentiated; and grade III/IV: poorly differentiated, undifferentiated or anaplastic. All patients were staged according to the SEER stage: localized, regional, and distant. We employed the sixth edition of the Derived AJCC Stage Group. It is worth mentioning that the X-tile software (Rimm Lab, New Haven, CT, USA) converted three continuous variables (age at diagnosis, year at diagnosis, and tumor size) into categorical variables by determining the optimal cutoff points for each variable (11). We divided the age at diagnosis into the <68, 68–76, and >76-year categories using 68- and 76-year as the cutoff values. Tumor size was divided into the <195 and >195-mm categories using 195 mm as the cutoff. The year at diagnosis was divided into the 1988–2003, 2004–2013, and 2014–2015 categories with the year 2003 used as the cutoff. The main endpoint was overall survival (OS), which was calculated as the period from diagnosis to death from any cause. The survival time was measured in months.

Following the application of the inclusion and exclusion criteria, R software was utilized to identify 820 patients with OCS for further analysis. The patients were randomly assigned into a training set (70%, n=574) and a validation set (30%, n=246), and no significant intergroup differences between 2 sets by a log-rank test (P value >0.05). The specific steps for identifying and grouping patients are illustrated in *Figure 1*.

Statistical analysis

All statistical analyses were conducted using R version 3.6.1 (www.r-project.org). Univariate Cox regression analysis demonstrated potential prognostic factors with P values <0.10 and introduced them into multivariate analysis to verify the independent survival-related prognostic factors. Then, a novel nomogram associated with OS for OCS

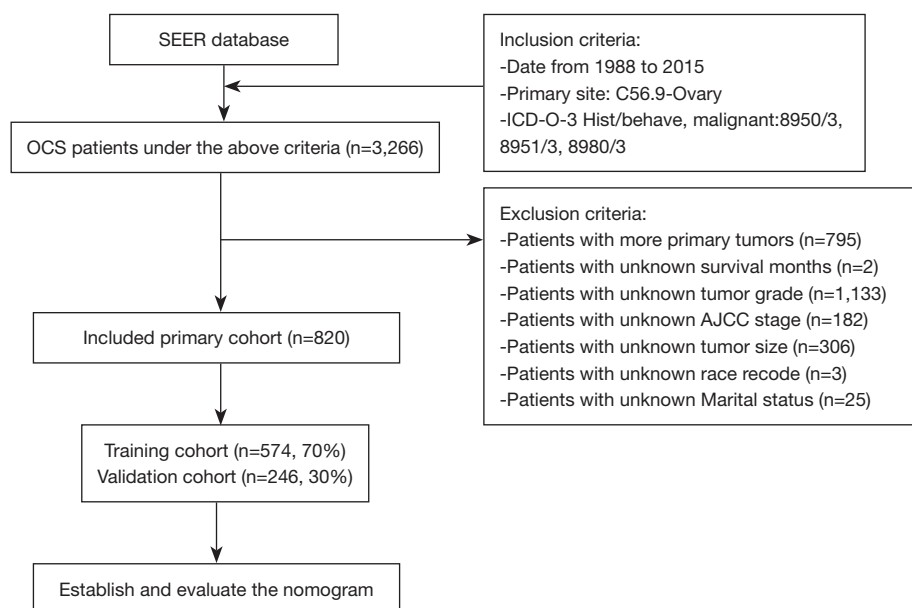


Figure 1 Flowchart of sample selection. SEER, surveillance, epidemiology and end results; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; AJCC, American Joint Committee on Cancer; OCS, Ovarian carcinosarcoma.

patients was developed base on the independent prognostic factors.

The performance of the nomogram was compared with that of the AJCC staging system utilizing several indicators. We first utilized the area under the time-dependent receiver operating characteristics (ROC) curve (AUC) to test the discrimination power of our nomogram, as well as 2 new indicators, net reclassification improvement (NRI) and integrated discrimination improvement (IDI), to further increase its predictive accuracy (12,13). The calibration curve was generated to estimate the calibration ability (14). Finally, we utilized decision-curve analysis (DCA) to test the clinical applicability of the new model (15). Statistical significance was set at a P value <0.05.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Baseline characteristics

Table 1 summarizes the baseline characteristics of the training and validation sets. All variables were similarly distributed between the two sets. Most of the patients in the training and validation sets were white (86.2% vs. 84.1%), under 68-year (55.9% vs. 59.3%), and married (52.3% vs.

60.6%). The clinical data demonstrated a relatively high degree of malignancy; approximately 94.6% and 95.5% of patients in the training and validation sets, respectively, had histological grades of III/IV. In comparison, approximately 51.2% and 56.1% of patients in the training and validation sets, respectively, were classified as AJCC stage III. Tumors in the training and validation sets were more likely unilateral (66.6% vs. 58.9%) and less than 195-mm in diameter (86.6% vs. 81.3%). In both sets, almost all patients received surgery and chemotherapy, whereas only a few received radiotherapy. The median survival time was 17 months.

Screening of model survival predictors

According to the results of univariate Cox regression analysis, we found that age at diagnosis, grade, size, AJCC stage, surgery, and chemotherapy status were potentially correlated with the OS of OCS (P<0.10). These potential prognostic factors were evaluated through multivariate regression analysis, which indicated that age at diagnosis [>76 vs. ≤ 68 years: hazard ratio (HR) =1.628, 95% confidence interval (CI): 1.283–2.067, P=0.000], size (>195 vs. ≤ 195 mm: HR =1.313, 95% CI: 1.029–1.777, P=0.000), histologic grade (III/IV vs. I: HR =4.794, 95% CI: 1.344–16.019, P=0.010), AJCC stage (IV vs. I: HR =4.003, 95%

Table 1 The basic characteristics of ovarian carcinosarcoma patients in the study

Variable	Training cohort (N, %)	Validation cohort (N, %)
Number of patients	574 [70]	246 [30]
Race		
White	495 (86.2)	207 (84.1)
Black	43 (7.5)	24 (9.8)
Other*	36 (6.3)	15 (6.1)
Marital status		
Married	300 (52.3)	149 (60.6)
Unmarried	86 (15.0)	25 (10.2)
Other*	188 (32.8)	72 (29.3)
Year of diagnosis		
1988–2003	169 (29.4)	76 (30.9)
2004–2013	291 (50.7)	120 (48.8)
2014–2015	114 (19.9)	50 (20.3)
Age of diagnosis		
≤68	321 (55.9)	146 (59.3)
68–76	126 (22.0)	57 (23.2)
>76	127 (22.1)	43 (17.5)
Grade		
I	13 (2.3)	3 (1.2)
II	18 (3.1)	8 (3.3)
III/IV	543 (94.6)	235 (95.5)
Historical stage		
Localized	53 (9.2)	27 (11.0)
Regional	89 (15.5)	28 (11.4)
Distant	432 (75.3)	191 (77.6)
Size		
≤195 mm	497 (86.6)	200 (81.3)
>195 mm	77 (13.4)	46 (18.7)
Laterality		
Unilateral	382 (66.6)	145 (58.9)
Bilateral	181 (31.5)	91 (37.0)
Paired	11 (1.9)	10 (4.1)

Table 1 (continued)

Table 1 (continued)

Variable	Training cohort (N, %)	Validation cohort (N, %)
AJCC stage*		
I	61 (10.6)	30 (12.2)
II	91 (15.9)	27 (11.0)
III	294 (51.2)	138 (56.1)
IV	128 (22.3)	51 (20.7)
Surgery		
Yes	556 (96.9)	243 (98.8)
No/unknown	18 (3.1)	3 (1.2)
Radiotherapy		
Yes	17 (3.0)	11 (4.5)
No/unknown	557 (97.0)	235 (95.5)
Chemotherapy		
Yes	437 (76.1)	184 (74.8)
No/unknown	137 (23.9)	62 (25.2)
Status		
Alive	144 (25.1)	70 (28.5)
Dead	430 (74.9)	176 (71.5)

*, American Indian/AK Native, Asian/Pacific Islander; Divorced/ Separated/Widowed; AJCC, American Joint Committee on Cancer.

CI: 2.482–6.458, P=0.000), surgical status (yes *vs.* no/ unknown: HR =2.840, 95% CI: 1.674–5.570, P=0.000), and chemotherapy status (yes *vs.* no/unknown: HR =2.036, 95% CI: 1.641–2.600, P=0.000) were independent prognostic factors for OCS (P<0.05). The results of the Cox regression analysis are listed in detail in *Table 2*.

Nomogram development

Based on the independent prognostic factors obtained from above, a novel nomogram was developed to predict the 1-, 3-, and 5-year OS of OCS patients (*Figure 2*). The nomogram showed that histologic grade contributed the most to prognosis, followed by the AJCC stage, surgery, chemotherapy status, age, and lastly tumor size. The total nomogram score, which was utilized to predict the

Table 2 Univariate and multivariate analyses Cox regression analysis in the training set

Variables	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Race				
White	Reference		–	–
Black	1.000 (0.699–1.430)	0.998		
Other*	1.004 (0.633–1.594)	0.986		
Marital status				
Married	Reference		–	–
Unmarried	1.149 (0.850–1.554)	0.366		
Other*	1.173 (0.941–1.462)	0.156		
Year of diagnosis				
1988–2003	Reference		–	–
2004–2013	0.851 (0.682–1.062)	0.152		
2014–2015	0.874 (0.641–1.192)	0.394		
Age of diagnosis				
≤68	Reference		Reference	
68–76	1.070 (0.835–1.371)	0.592	1.083 (0.860–1.378)	0.513
>76	1.560 (1.211–2.010)	0.001	1.628 (1.283–2.067)	0.000
Grade				
I	Reference		Reference	
II	3.451 (0.957–12.450)	0.058	3.900 (1.090–13.951)	0.036
III/IV	4.529 (1.338–15.328)	0.015	4.794 (1.344–16.019)	0.010
Historical stage				
Localized	Reference		–	–
Regional	1.561 (0.479–5.086)	0.460		
Distant	1.915 (0.636–5.771)	0.248		
Size				
≤195 mm	Reference		Reference	
>195 mm	1.313 (0.995–1.732)	0.054	1.313 (1.029–1.777)	0.000
Laterality				
Unilateral	Reference		–	–
Bilateral	1.023 (0.827–1.265)	0.834		
Paired	0.782 (0.363–1.683)	0.530		

Table 2 (continued)

Table 2 (continued)

Variables	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
AJCC stage*				
I	Reference		Reference	
II	1.315 (0.451–3.841)	0.616	1.938 (1.176–3.196)	0.009
III	2.053 (0.751–5.616)	0.161	3.444 (2.183–3.196)	0.000
IV	2.793 (0.823–6.313)	0.112	4.003 (2.482–6.458)	0.000
Surgery				
Yes	Reference		Reference	
No/unknown	3.054 (1.674–5.570)	0.000	2.840 (1.674–5.570)	0.000
Radiotherapy				
Yes	Reference		–	–
No/unknown	0.991 (0.551–1.780)	0.975		
Chemotherapy				
Yes	Reference		Reference	
No/unknown	2.065 (1.641–2.600)	0.000	2.036 (1.641–2.600)	0.000

*, American Indian/AK Native, Asian/Pacific Islander; Divorced/Separated/Widowed. HR, hazard ratio; CI, confidence intervals; AJCC, American Joint Committee on Cancer.

individual prognosis of OCS patients, was calculated as the sum of the scores of each of the factors above.

Nomogram validation

To analyze the feasibility and validity of the new model, we compared the prognostic performance of the novel nomogram with the AJCC staging system by applying AUC, NRI, IDI, calibration curves, and DCA analysis. In the training set, the AUCs for 1-, 3-, and 5-year OS of the novel nomogram were 0.704, 0.739, and 0.732, respectively, which were greater than of the AJCC staging systems (0.600, 0.661, and 0.700, respectively). In the validation set, the AUCs for 1-, 3-, and 5-year OS of the new model (0.761, 0.721, and 0.734, respectively) were also higher than the AJCC staging system (0.598, 0.644, and 0.679, respectively) (Figure 3). These results demonstrated the discriminative power of the novel nomogram performed superiorly compared to conventional staging.

The NRIs at 1-, 3-, and 5-year OS were 0.470 (95% CI: 0.295–0.620), 0.381 (95% CI: 0.213–0.590), and 0.186 (95% CI: 0.059–0.478), respectively, in the training sets, and

0.707 (95% CI: 0.387–0.966), 0.469 (95% CI: 0.049–0.70), and 0.435 (95% CI: 0.013–0.637) in the validation sets. Additionally, the IDIs at 1-, 3-, and 5-year OS were 0.053, 0.047, and 0.040, respectively ($P < 0.001$), in the training set, whereas the values for the validation set were 0.101, 0.100, and 0.059, respectively ($P < 0.001$). This further confirmed that our nomogram had better discriminative ability.

The calibration curves indicate that our nomogram was well-calibrated, because the 1-, 3-, and 5-year OS probabilities predicted of our model were much approximated to the actual observation (Figure 4). Finally, we utilized DCA curves to verify the clinical applicability of the nomogram. In both the training and verification sets, the curves for the 1-, 3-, and 5-year OS predictions of the nomogram model appeared above the corresponding curves for the AJCC model, which presented the net benefits of the former were superior to the latter (Figure 5).

Discussion

OCS is a rare but aggressive gynecological tumor. The majority of studies on OCS are based on individual case

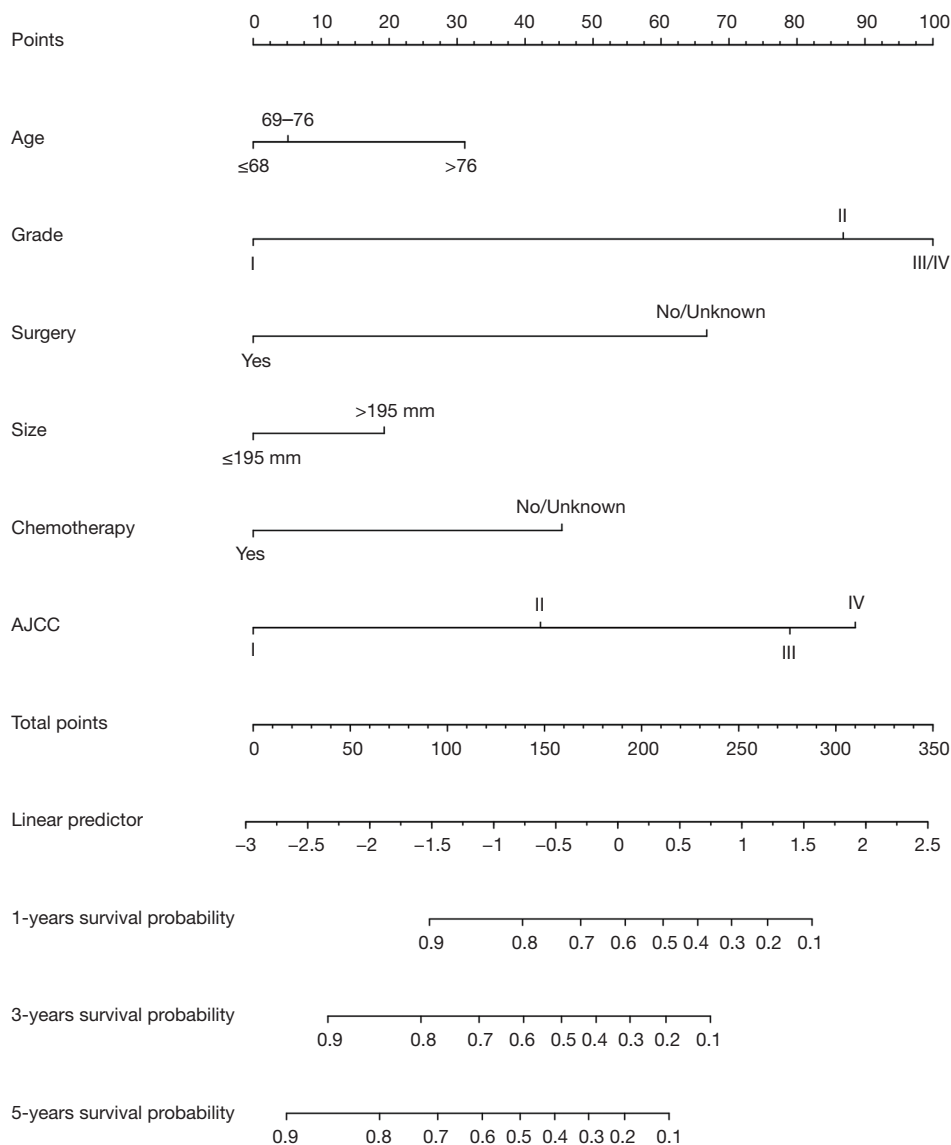


Figure 2 Nomogram predicting 1-, 3-, and 5-year overall survival of patients with ovarian carcinosarcoma.

reports or small retrospective case series. There is little consensus about the prognostic factors and treatment strategies for this disease, which prompted this study. Therefore, we examined the prognostic factors of demographic characteristics and clinicopathological features for OCS using the large volume of data in the SEER database and constructed an accurate prognostication model for individualized use.

Studies have shown that nomograms predict prognosis better than conventional staging systems and have important value in clinical practice (16). Through Cox

regression analysis, the present study identified age, grade, size, AJCC stage, surgery, and chemotherapy status as independent prognostic factors for OCS. Among the demographic characteristics, age was a significant prognostic factor for OCS, which correlated with the data from previous studies (1). In general, older patients had worse outcomes because of weaker immune responses. Race and marital status were not included in our model, which indicated that they did not affect the prognosis of OCS. Among the clinicopathologic features, the AJCC staging system influenced the treatment, outcome, and prognosis of

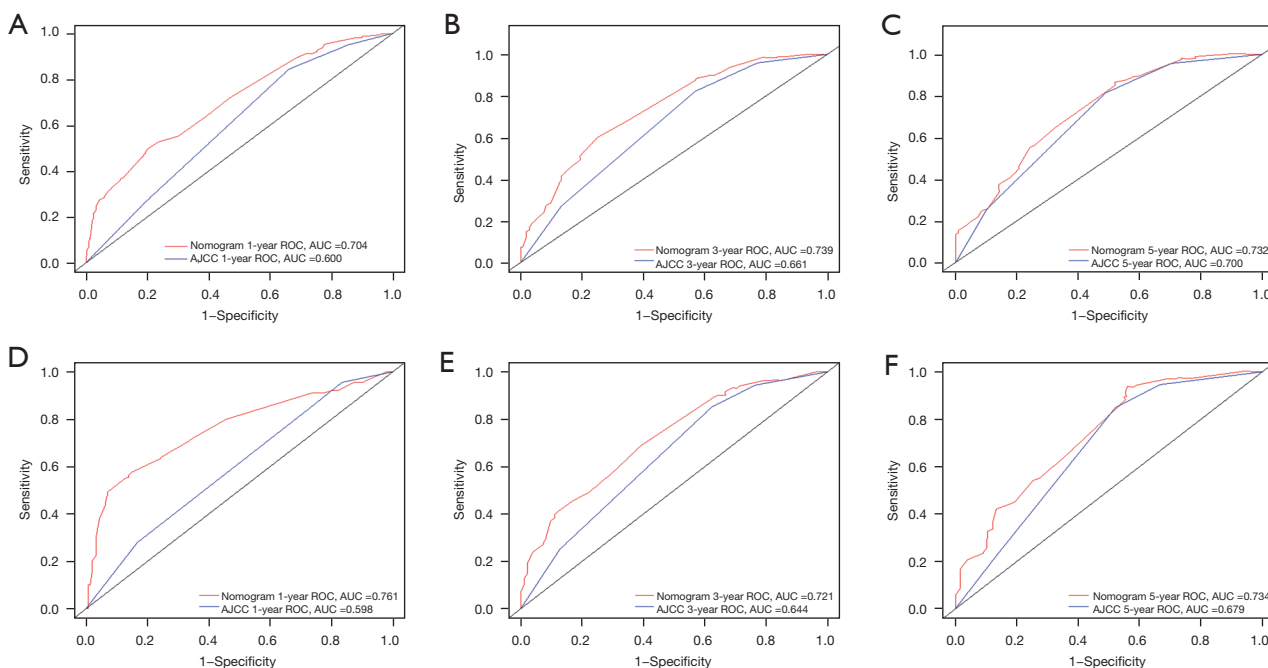


Figure 3 Receiver operating characteristic curves for nomogram of the 1-(A), 3-(B), 5-year (C) overall survival in training set. Receiver operating characteristic curves for nomogram of the 1-(D), 3-(E)-, 5-year (F) overall survival in validation set.

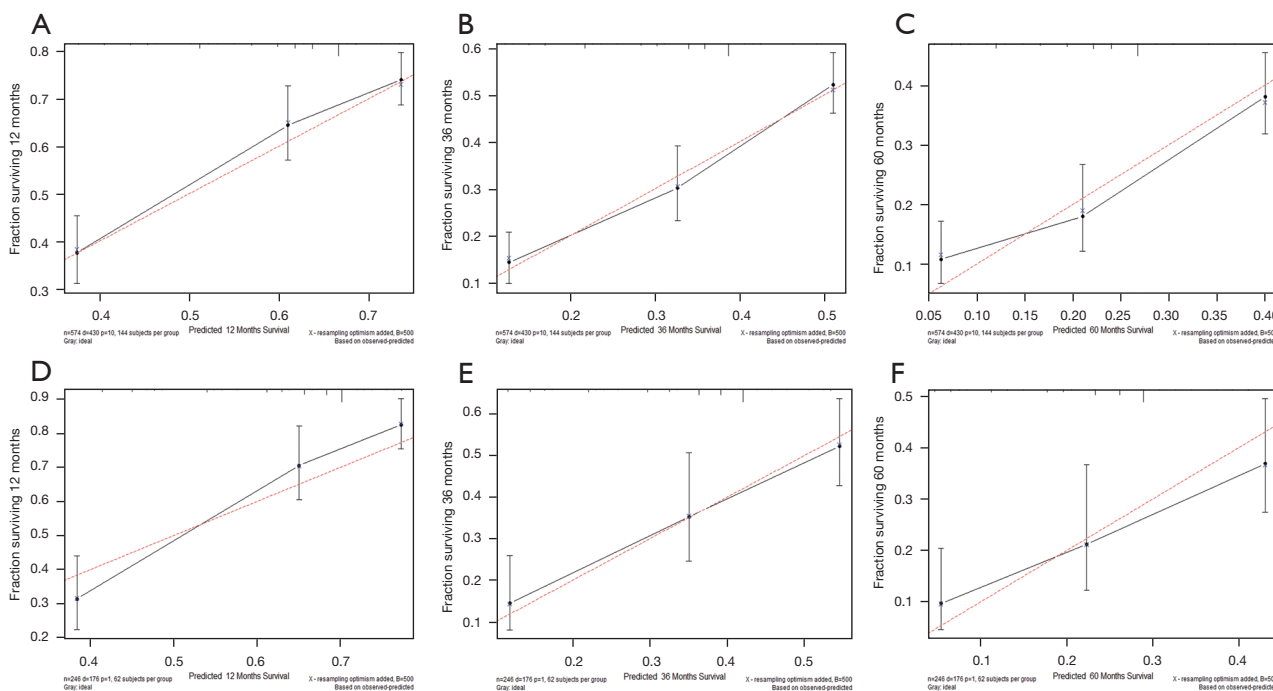


Figure 4 Calibration curves for nomogram of the 1-(A), 3-(B), 5-year (C) overall survival in training set. Calibration plots for nomogram of the 1-(D), 3-(E)-, 5-year (F) overall survival in validation set.

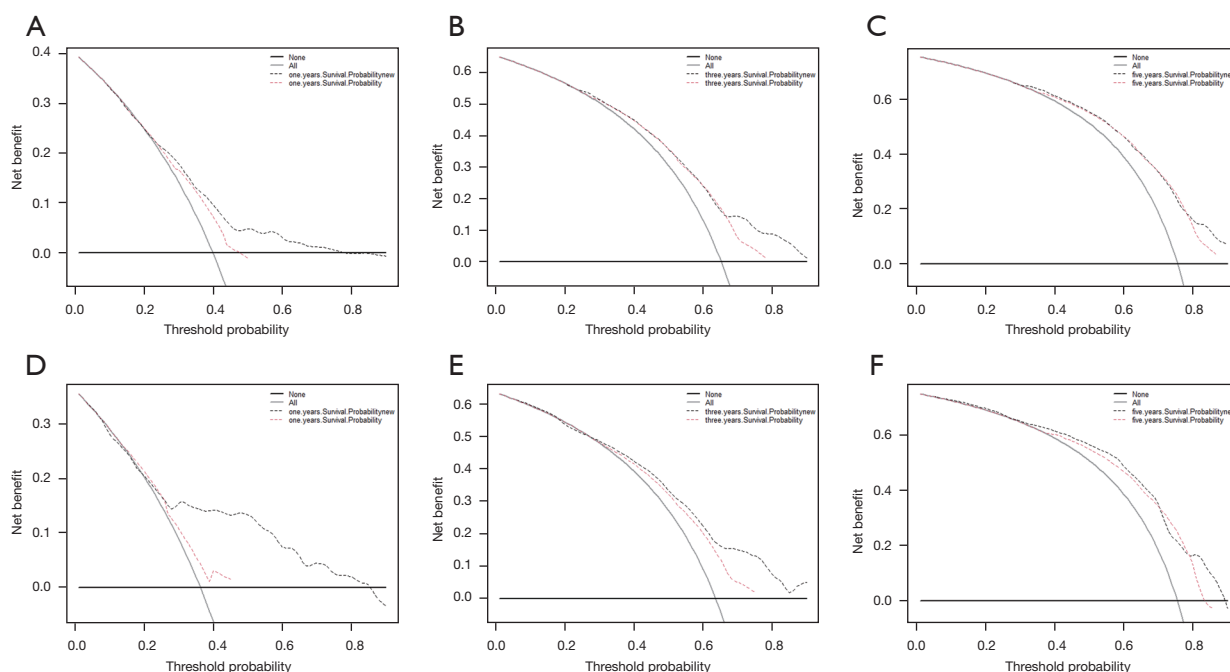


Figure 5 Decision curve analysis for the nomogram of the 1-(A), 3-(B), 5-year (C) overall survival in training set. Decision curve analysis for nomogram of the 1-(D), 3-(E)-, 5-year (F) overall survival in validation set.

OCS. *Figure 2* clearly demonstrates that small and poorly differentiated tumors had poor prognosis, whereas large and well-differentiated tumors had good prognosis.

Our study also demonstrated that surgery and chemotherapy status affected prognosis. The sarcomatous components of OCS are not sensitive to radiotherapy, which may explain why radiotherapy was not a prognostic factor in our model. The preferred treatment for OCS involves optimal cytoreductive surgery and platinum-based chemotherapy (17). Radiotherapy is recommended for patients with persistent disease that is restricted to the pelvis to decrease local recurrence. Few experimental studies have been done on radiotherapy alone; the impact of radiotherapy alone may be a significant topic for further investigation. This was a retrospective study, which was prone to selection biases. Further prospective studies are required to determine the exact relationship between radiotherapy and OCS prognosis.

The established nomogram was evaluated through a series of tests and compared with the AJCC staging system. These steps which are necessary for any clinical prognostic model before it is actually used. We first evaluated the discriminate ability of the nomogram using the AUC and demonstrated that the parameters of the training and

validation sets were higher than those of the AJCC staging system. NRI further compared the predictive ability of both models. NRI revealed that our model increased the likelihood of correct 1-, 3-, and 5-year OS predictions by 47%, 38.1%, and 18.6%, respectively, in the training set, and 70.7%, 46.9%, and 43.5%, respectively, in the validation set ($P < 0.05$). IDI was used as a supplementary assessment of the overall improvement of the prognostic model (18). IDI demonstrated that the new model improved the 1-, 3-, and 5-year OS predictive ability of the AJCC system by 5.3%, 4.7%, and 4%, respectively, in the training set and 10.1, 10%, and 5.9% in the validation set ($P < 0.05$). We further finetuned our model by assessing its fit with a calibration curve. The forecast lines of the nomogram corresponded well with the 45° reference lines (*Figure 4*), which indicated that our model was well-calibrated and could provide relatively accurate predictions (19). Finally, we utilized DCA curves to verify the clinical applicability of our model. DCA has received increasing attention as a prediction model evaluation tool, because it can calculate the net benefit of such models. As demonstrated in *Figure 4*, there was greater net benefit in the 1-, 3-, and 5-year DCA curves of our model compared to that of the AJCC staging system, which indicated that our model has better clinical use (20).

There were some limitations in the study. Firstly, the retrospective nature of the study may have resulted in selection bias. Secondly, the SEER database is not comprehensive, some prognostic factors such as the regimen of chemotherapy, results of debulking, lifestyle habits, and genetic markers were not recorded, which may decrease the accuracy of our model. Thirdly, the nomogram was not externally validated, which may result in overfitting of the model. To obtain more accurate results, further in-depth studies should examine a comprehensive list of prognostic factors and verify the validity of the model with external sets.

Conclusions

Above all, our study is the first to establish and internally validate a novel nomogram for predicting the 1-, 3-, and 5-year OS probabilities of OCS patients. Our prognostic nomogram was of good performance and can be an accurate tool to predict individualized survival time of OCS in clinical work.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://tcr.amegroupp.com/article/view/10.21037/tcr-21-1796/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroupp.com/article/view/10.21037/tcr-21-1796/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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