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Development and Validation of a Prognostic Prediction Model for Postoperative Ovarian Sex Cord-Stromal Tumor Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: We developed a nomogram for prognostic prediction of overall survival (OS) in postoperative ovarian sex cord-stromal tumor (SCST) patients and discuss the effect of chemotherapy at various FIGO stages.

Material/Methods: SCST patients after surgery from 2004 to 2015 were enrolled from the Surveillance, Epidemiology and End-Results (SEER) database, matched into pairs by propensity score matching (PSM), and divided into a training set and a validation set. Univariate and multivariate Cox analyses were conducted to identify significant variables for the development of the nomogram. The nomogram model was validated by concordance index (C-index), receiver operating characteristics (ROCs) curve, calibration plot, and decision curve analysis (DCA). Survival curves showed the integrative ability of prognostic prediction and the efficacy of chemotherapy.

Results: A total of 913 SCST patients were initially enrolled, and after PSM, 506 patients were included. Age, marital status, CA125 levels, tumor size, FIGO stage, grade, and chemotherapy were indicators for building the OS nomogram. The C-index was 0.850 in the training set and 0.786 in the validation set. Calibration plots were satisfactory and the nomogram had relatively better clinical utility than FIGO stage. The survival analysis showed that the low-risk group had generally longer survival than the high-risk group based on the prognostic score, and chemotherapy had an overall reverse effect on OS.

Conclusions: The nomogram model displays the potential to provide individualized prognosis probability of SCSTs and to aid in clinical decision-making. The unfavorable results of chemotherapy in all stages shows the need for further exploration.

MeSH Keywords: Chemotherapy, Adjuvant • Nomograms • Prognosis • SEER Program • Sex Cord-Gonadal Stromal Tumors

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Background

Ovarian sex cord-stromal tumors (SCSTs) are rare ovarian tumors derived from sex cords and ovarian stroma or mesenchyme [1], accounting for approximately 7% of ovarian tumors, and the incidence rate is 2.1 per million women [2]. Sex cord-stromal tumors contain various histologic subtypes, mainly granulosa cell tumors (GCTs), Sertoli-Leydig cell tumors, thecomas, and gynandroblastomas, with GCTs accounting for nearly 90% of the malignancies [3]. SCSTs are mostly found in adults, including many perimenopausal and postmenopausal women. Although most cases present slow growth and good prognosis, about 20% relapse or metastasize, which can be fatal [4]. It was recently reported that mutations in FOXL2 are ubiquitous in adult GCTs, and DICER1 mutations are typically found in Sertoli-Leydig cell tumors, which could be potential therapeutic targets [5].

Debulking surgery, regardless of the cancer process, is always the most effective treatment for sex cord-stromal tumors [6]. Most SCSTs patients are diagnosed at an early stage for which no evidence supports postoperative adjuvant treatment due to the low risk of recurrence [7]. However, some researchers suggest chemotherapy be used after surgery for FIGO stage IC patients with larger tumor size or high mitotic index [8]. The small number of advanced patients makes it difficult to draw a firm conclusion, but the current clinical consensus is that adjuvant chemotherapy should be reserved for stage II–IV patients [6]. Therefore, whether chemotherapy is effective for patients at different stages remains controversial. Hormonal therapy is another reasonable treatment for advanced GCTs due to their dependence on estrogen, but at present no valid data support the effect of hormone treatment in the postoperative setting [9].

Prognostic prediction has been impeded by the rarity of patients and multiplicity of histologic and biologic behaviors [1]. International Federation of Gynecology and Obstetrics (FIGO) stage, age, tumor size, and absence of residual disease have been reported to be prognostic factors [10]. However, to the best of our knowledge, there has been no research on integrating the prediction model of SCSTs; therefore, individualized survival forecasting is imperative. In this study, we evaluated the prognostic value of chemotherapy in SCST patients based on the Surveillance, Epidemiology, and End-Results (SEER) database and established and validated a predictive nomogram incorporating chemotherapy and other clinically significant factors. We also compared the clinical performance of our nomogram with the FIGO staging system. We hypothesized that the prediction model developed in this study has better predictive value than the FIGO staging system. This research may provide valuable evidence for clinical decision-making, especially regarding chemotherapy.

Material and Methods

Patients and study design

The data of patients diagnosed as having SCST were obtained from the Surveillance, Epidemiology, and End-Results (SEER) 18 registry database (*http://seer.cancer.gov/*) using SEER*Stat 8.3.6 software. The SEER database was established by the National Cancer Institute and collects data on patient, disease, and survival outcomes, covering [11] nearly 35% of the US population. We initially retrieved a total of 70 225 individuals diagnosed with ovarian cancer from 2004 to 2015, with the site code "C56.9" according to the International classification of Diseases for Oncology, Third Edition (ICD-O-3). Morphology codes "8590/3-8671/3" were used to identify the malignant sex cord-stromal tumors. Treatment for stage IV patients varies between individuals and is not suitable for systematic analysis [12]. The inclusion criteria were as follows: (1) patients with confirmed I, II, or III FIGO stage determined by American Joint Committee on Cancer (AJCC); (2) patients with complete survival information including vital status, survival time, and cause of death; (3) patients who underwent surgery on the primary site; and (4) patients with positive histology. The exclusion criteria were as follows: (1) patients who underwent radiotherapy; and (2) surgery of primary site is tumor destruction, with no or unknown pathologic specimen. Finally, a total of 913 patients were included in our study (Figure 1). For data analysis, patients were grouped into 2 groups ≤50 years old and >50 years old based on the median age of the overall population. Tumor grade was classified into well differentiated (G1), moderately differentiated (G2), poorly differentiated (G3), undifferentiated (G4), and an unknown group. The maximum diameter of the tumor was used as tumor size, and was determined during surgery. Tumor size was divided into 3 subgroups by median value of 95 mm and an unknown group. Blood or serum CA125 levels were recorded before surgery, and the reference value was below 35 ug/ml. The histology types were simply divided as granulosa cell tumors (8620–8622) and non-granulosa cell tumors (8590, 8593, 8600, 8623, 8631, 8634, 8640, 8650, 8670) based on the pathological reports. The race included white, black, others (Asian, Pacific Islander, American Indian, and Alaska Native), or unknown. The marital status included married, unmarried ('single', 'separated', 'divorced' and 'widowed'), and unknown. The primary outcome was overall survival (OS), and survival time was defined as the time from diagnosis to death from any cause. This study followed the recommendations of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement [13].

Propensity score matching

To better assess the prognostic effect of chemotherapy, we performed propensity score matching (PSM) to reduce selection

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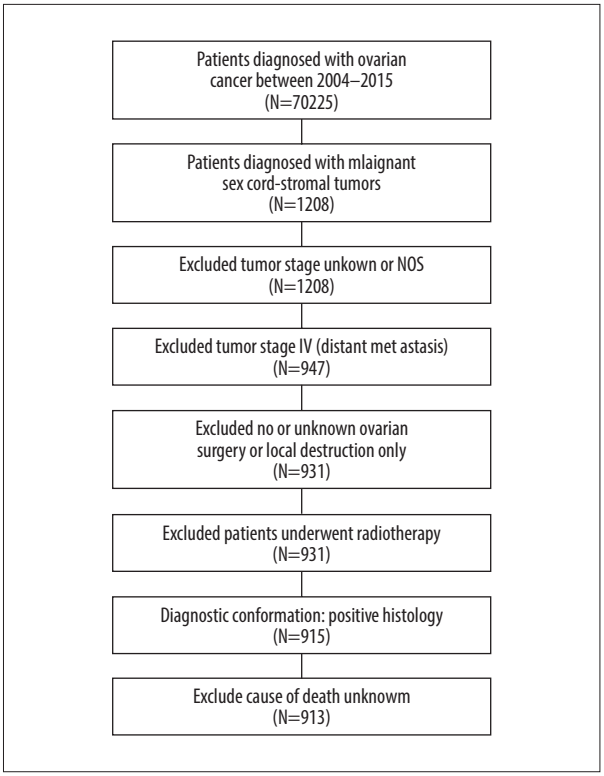

Figure 1. Flow chart for included patients of the SEER data cohort.

bias [14]. A 1: 1 match was calculated using propensity score logistic regression analysis within the caliper (0.1). PSM was conducted to adjust for age, race, grade, histology, marital status, FIGO stage, tumor size, and CA125. After PSM, 506 patients (253: 253) were randomly divided into the training set and validation set at a ratio of 7: 3 to establish and validate the model. The package 'nonrandom' of R 3.6.3 (Institute for Statistics and Mathematics, Vienna, Austria; *www.r-project.org*) was used for the analysis.

Development of the nomogram

Univariate Cox regression analysis determined the correlation between each variable and OS. Significant variables (P<0.10) in univariate analysis were then subjected into a full Cox regression multivariate analysis. The results of multivariate analysis were used to develop the nomogram for predicting 1-, 3-, and 5-year OS. According to the nomogram, we calculated the total points as the prognostic index (PI) for all patients and used the median value of 212 points to classify patients into a low-risk group and a high-risk group for later survival analysis. R package 'rms' and 'survival' and EmpowerStats 2.2 (*www.empowerstats.com*, X&Y solutions, Inc., Boston, MA) were applied to develop and validate the nomogram.

Validation of the nomogram

We assessed model performance by testing discrimination and calibration. Concordance index (C-index) and receiver operating characteristic (ROC) curves were utilized to determine the discrimination and predictive ability. Calibration plots graphically estimate the agreement between actual and predicted outcome probabilities, where a slope close to 1 indicates a well-calibrated predictor [15]. Bootstrapping with 1000 resamples was used to adjust for bias.

Survival analysis

Based on the median cut-off value of the prognostic index (212 points), the study population was divided into low-risk (<212 points) and high-risk (≥212 points) groups. Kaplan-Meier analysis was used to estimate the survival of patients in FIGO stage I, II, and III and overall population. The log-rank test was used to assess statistically significant differences between low- and high-risk groups.

Clinical performance

Decision curve analysis (DCA) was used to evaluate and compare the clinical usefulness of the nomogram [16]. DCA was carried out to assess the clinical benefit of the new nomogram in comparison with the FIGO staging system in the training and validation set and in the overall study population. The DCA was performed using R package 'Tableone' and 'Nonrandom'.

Results

Patients' baseline characteristics before and after propensity score matching

Before PSM

In total, 913 eligible SCST patients diagnosed from 2004 to 2015 in the SEER database were enrolled in the study. Patients' baseline characteristics before and after propensity score matching are summarized in Table 1. In the overall patients, the median age was 50 years old (range, 6–91 years). Patients were divided into binary groups according to whether they have received chemotherapy. The median follow-up time of patients was 50 (range, 3–154) months and 67 (range: 0–155) months in the chemotherapy and non-chemotherapy group, respectively. There were significant differences in age (P=0.001), grade (P<0.001), histology (P<0.001), marital status (P=0.013), FIGO stage (P<0.001), tumor size (P<0.001), and CA125 levels (P<0.001) between the 2 groups. Patients who underwent chemotherapy after surgery on primary sites had a larger proportion of characteristics such as poorly differentiated and

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Table 1. Correlations between chemotherapy and baseline characteristics of patients with sex cord-stromal tumors in the overall included population and propensity score-matched population.

Characteristic	Before PSM			After PSM		
	Surg only	Surg+chem	*p*-Value	Surg only	Surg+chem	*p*-Value
Number of patients	644	269		253	253	
Age (years)			*0.001*			0.652
≤50	314 (48.8)	165 (61.3)		144 (56.9)	150 (59.3)	
>50	330 (51.2)	104 (38.7)		109 (43.1)	103 (40.7)	
Race			*0.868*			0.059
White	437 (67.9)	187 (69.5)		175 (69.2)	179 (70.8)	
Black	149 (23.1)	60 (22.3)		45 (17.8)	56 (22.1)	
Others and unknown	58 (9.0)	22 (8.2)		33 (13.0)	18 (7.1)	
Marital status			*0.013*			0.335
Married	282 (43.8)	131 (48.7)		108 (42.7)	121 (47.8)	
Unmarried	321 (49.8)	133 (49.4)		136 (53.8)	127 (50.2)	
Unknown	41 (6.4)	5 (1.9)		9 (3.6)	5 (2.0)	
CA125 status			*<0.001*			0.066
Negative/normal	192 (29.8)	80 (29.7)		75 (29.6)	70 (27.7)	
Positive/elevated	116 (18.0)	85 (31.6)		58 (22.9)	81 (32.0)	
Borderline or unknown	336 (52.2)	104 (38.7)		120 (47.4)	102 (40.3)	
Tumor size (mm)			*<0.001*			0.187
≤95	311 (48.3)	86 (32.0)		80 (31.6)	82 (32.4)	
>95	253 (39.3)	146 (54.3)		131 (51.8)	143 (56.5)	
Unknown	80 (12.4)	37 (13.8)		42 (16.6)	28 (11.1)	
FIGO stage			*<0.001*			0.003
I	566 (87.9)	152 (56.5)		180 (71.1)	150 (59.3)	
II	39 (6.1)	68 (25.3)		34 (13.4)	63 (24.9)	
III	39 (6.1)	49 (18.2)		39 (15.4)	40 (15.8)	
Grade			*<0.001*			0.666
Well differentiated and moderately differentiated	113 (17.5)	41 (15.2)		38 (15.0)	38 (15.0)	
Poorly differentiated and undifferentiated	62 (9.6)	57 (21.2)		48 (19.0)	56 (22.1)	
Unknown	469 (72.8)	171 (63.6)		167 (66.0)	159 (62.8)	
Histology			*<0.001*			0.624
Granulosa	566 (87.9)	194 (72.1)		177 (70.0)	183 (72.3)	
Non-granulosa	78 (12.1)	75 (27.9)		76 (30.0)	70 (27.7)	

Non-granulosa includes Sertoli-Leydig cell tumor (n=94), Sertoli cell tumor (n=7), Leydig cell tumor (n=3), steroid cell tumor (n=21), thecoma (n=4), and sex cord-stromal NOS, not otherwise specified (n=24). Surg only, patients underwent surgery and did not or unknown if received chemotherapy. Surg+Chem, patients underwent surgery and received chemotherapy.

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Table 2. Patients demographics and clinicopathological characteristics of training set and validation set.

Factors	Training set		Validation set	
Number of patients	356		150	
Age (years)				
≤50	214	(60.11%)	80	(53.33%)
>50	142	(39.89%)	70	(46.67%)
Race				
White	254	(71.35%)	100	(66.67%)
Black	64	(17.98%)	37	(24.67%)
Others and unknown	38	(10.67%)	13	(8.67%)
Marital status				
Married	157	(44.10%)	72	(48.00%)
Unmarried	188	(52.81%)	75	(50.00%)
Unknown	11	(3.09%)	3	(2.00%)
CA125 status				
Negative/normal	93	(26.12%)	52	(34.67%)
Positive/elevated	102	(28.65%)	37	(24.67%)
Borderline or unknown	161	(45.22%)	61	(40.67%)
Tumor size (mm)				
≤95	115	(32.30%)	47	(31.33%)
>95	194	(54.49%)	80	(53.33%)
Unknown	47	(13.20%)	23	(15.33%)
FIGO stage				
I	227	(63.76%)	103	(68.67%)
II	65	(18.26%)	32	(21.33%)
III	64	(17.98%)	15	(10.00%)
Grade				
Well differentiated and moderately differentiated	51	(14.33%)	25	(16.67%)
Poorly differentiated and undifferentiated	74	(20.79%)	30	(20.00%)
Unknown	231	(64.89%)	95	(63.33%)
Histology				
Granulosa	260	(73.03%)	100	(66.67%)
Non-granulosa	96	(26.97%)	50	(33.33%)
Chemotherapy				
No/unknown	181	(50.84%)	72	(48.00%)
Yes	175	(49.16%)	78	(52.00%)
Survival months	61	(0–154)	54.5	(2–154)
Overall survival				
Alive	302	(84.83%)	124	(82.67%)
Dead	54	(15.17%)	26	(17.33%)

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undifferentiated, non-granulosa histology type, advanced FIGO stage, larger tumor size, and elevated CA125 levels. Table 1 displays the demographic and clinicopathologic characteristics of the 913 patients.

After PSM

Propensity score matching (1: 1) between the chemotherapy and non-chemotherapy groups was performed. After matching, 253 matched pairs were obtained. The median survival was 59 months (range, 0–154 months). The median follow-up time of patients was 52 (range, 3–154) months and 67 (range, 0–154) months in the chemotherapy and non-chemotherapy groups, respectively. FIGO stage was significantly different (P=0.003) between the 2 groups, while the other variables were not (Table 1). Then, the matched population were randomly divided into a training set (n=356) and a validation set (n=150). The baseline characteristics of the 2 groups are shown in Table 2.

Univariate and multivariate analysis

Univariate and multivariate analyses were carried out using the Cox proportional hazard model on the training set to explore the predicted variables (Table 3). To include sufficiently meaningful indicators, variables with P<0.10 were taken forward to multivariate analysis. Eventually, variables with P<0.05 in multivariate analysis were used as independent predictors of patient prognosis. The multivariate analyses revealed that chemotherapy worsened the OS (HR=1.86, CI=1.05–3.29, P=0.034). Older age (>50 years) (HR=3.49, 95% CI=1.93–6.30), advanced FIGO stage (stage II, HR=2.82, 95% CI=1.35–5.88 and stage III, HR=6.79, 95% CI=3.42–13.47), and positive CA125 levels (HR=6.94, 95% CI=2.35–20.50) were the most significant risk factors for OS (P<0.001). Tumor grade did not meet the requirement in univariate analysis (HR=2.32, 95% CI=0.76–7.13, P=0.14), whereas tumor grade was usually considered important for survival prediction and therefore was included in the multivariate analysis (HR=3.34, 95% CI=1.04–10.79, P=0.043). Unmarried status was also a risk factor for poor prognosis (HR=2.04, P=0.027). However, histology type had no effect on overall survival in the univariate analysis (HR=1.19, 95% CI=0.67–2.12, P=0.553) and race was not related to OS in the multivariate analysis.

Nomogram development

Age, grade, marital status, FIGO stage, chemotherapy, tumor size, and CA 125 levels were significantly associated with OS. The nomogram for predicting 1-, 3-, and 5-year OS was developed by incorporating these 7 independent prognostic factors (Figure 2). Each variable had a corresponding score in the nomogram (Table 3). For instance, a 55-year-old (63 points) divorced woman (34 points) underwent ovarian surgery for a 9-cm sex cord-stromal tumor (0 point). The preoperative CA125 was 35 ug/ml (60 points). Postoperative tumor grading was III (64 points) and staging was FIGO III (98 points). She received chemotherapy after surgery (34 points). In this case, there were 353total points, and the predicted 3- and 5-year survival rates were approximately 45% and 40%. The nomogram indicated that FIGO stage and CA125 levels contributed most to the outcome, followed by grade, tumor size, and age.

Nomogram validation

The C-indexes in the nomogram and FIGO staging system in the training set, validation set, and overall study population are listed in Table 4. The C-index for the OS prediction nomogram was 0.850 (95% CI=0.805–0.895) for the training group, 0.786 (95% CI=0.696–0.876) for the validation group, and 0.768 (95% CI=0.717–0.819) for the overall population, which were all higher than the corresponding C-indexes for the FIGO stage. ROC curves of the nomogram and FIGO stage for 1-, 3-, and 5-year OS also indicated that the nomogram had more accurate predictive and discriminative abilities than FIGO stage (Figure 3). The calibration curves demonstrated good agreement between the nomogram-predicted OS probability and the actual OS probability in both the training set and validation set (Figure 4A, 4B), indicating the reliability of our nomogram.

Survival analysis

Combining multiple prognostic predictors into a single score improves model assessment. The prognostic index of every patient was calculated according to each variable score, and the patients were divided into high-risk and low-risk groups using the median prognostic index (212 points) as the cut-off value. The overall survival time of the high-risk group was significantly shorter than that of the low-risk group in overall population (P<0.001), FIGO stage I patients (P<0.001), and FIGO stage III patients (P=0.041), proving the integral predictive capacity of the novel model. PI had a less significant function in FIGO stage II (P=0.081), probably due to the small population of patients included in this stage (Figure 5A). Chemotherapy showed a significantly worse effect in multivariate analysis of the matched population. To explore its function in different tumor stages, survival analyses based on FIGO stage I, II, and III patients were conducted. Chemotherapy showed a trend that approached significance in the overall population (P=0.067) and stage I (P=0.11) patients, but there was no effect on OS in stage II (P=0.95) and III (P=0.68) patients (Figure 5B). In stages IA and IB, in which chemotherapy is not recommended after surgery, patients who underwent postoperative chemotherapy had worse OS than those who did not (P=0.031). In stage IC, in which use of chemotherapy is controversial, the OS presented no significant difference (P=0.7) (Figure 5C).

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Table 3. Univariate and multivariate analysis for the training set.

Factors	Univariate analysis			Multivariate analysis			Score
	HR	95% CI	*P**	HR	95% CI	*P***	
Age (years)							
≤50	Ref			Ref			0
>50	3.09	(1.76–5.40)	*<0.0001*	3.49	(1.93–6.30)	*<0.0001*	63
Race							
White	Ref			Ref			
Black	0.77	(0.38–1.58)	*0.4821*	0.50	(0.24–1.07)	***0.0732***	
Others and unknown	0.15	(0.02–1.07)	*0.0581*	0.17	(0.02–1.30)	***0.0886***	
Marital status							
Married	Ref			Ref			0
Unmarried	2.22	(1.22–4.05)	*0.0092*	2.04	(1.08–3.85)	*0.0273*	34
Unknown	1.74	(0.40–7.63)	*0.4604*	1.64	(0.35–7.76)	*0.5344*	19
CA125 status							
Negative/normal	Ref			Ref			0
Positive/elevated	7.86	(2.75–22.41)	*0.0001*	6.94	(2.35–20.50)	*0.0005*	100
Borderline or unknown	3.23	(1.11–9.38)	*0.0309*	2.79	(0.95–8.19)	*0.0625*	60
Tumor size (mm)							
≤95	Ref			Ref			0
>95	5.06	(1.99–12.85)	*0.0007*	2.22	(0.83–5.92)	*0.1123*	43
Unknown	5.38	(1.87–15.48)	*0.0018*	3.36	(1.14–9.87)	*0.0275*	63
FIGO stage							
I	Ref			Ref			0
II	3.28	(1.64–6.57)	*0.0008*	2.82	(1.35–5.88)	*0.0059*	58
III	5.20	(2.76–9.79)	*<0.0001*	6.79	(3.42–13.47)	*<0.0001*	98
Grade							
Well differentiated and moderately differentiated	Ref			Ref			0
Poorly differentiated and undifferentiated	2.32	(0.76–7.13)	*0.1403*	3.34	(1.04–10.79)	*0.0434*	64
Unknown	2.22	(0.79–6.23)	*0.1299*	2.08	(0.72–6.04)	*0.1781*	36
Histology							
Granulosa	Ref						
Non-granulosa	1.19	(0.67–2.12)	*0.5526*				
Chemotherapy							
No/unknown	Ref			Ref			0
Yes	1.59	(0.93–2.73)	*0.0929*	1.86	(1.05–3.29)	*0.0343*	34

HR – hazard ratio; 95% CI – 95% confidence interval. * $P<0.10$ was considered significant in univariate Cox regression analysis; ** $P<0.05$ was considered significant in multivariate Cox regression analysis.

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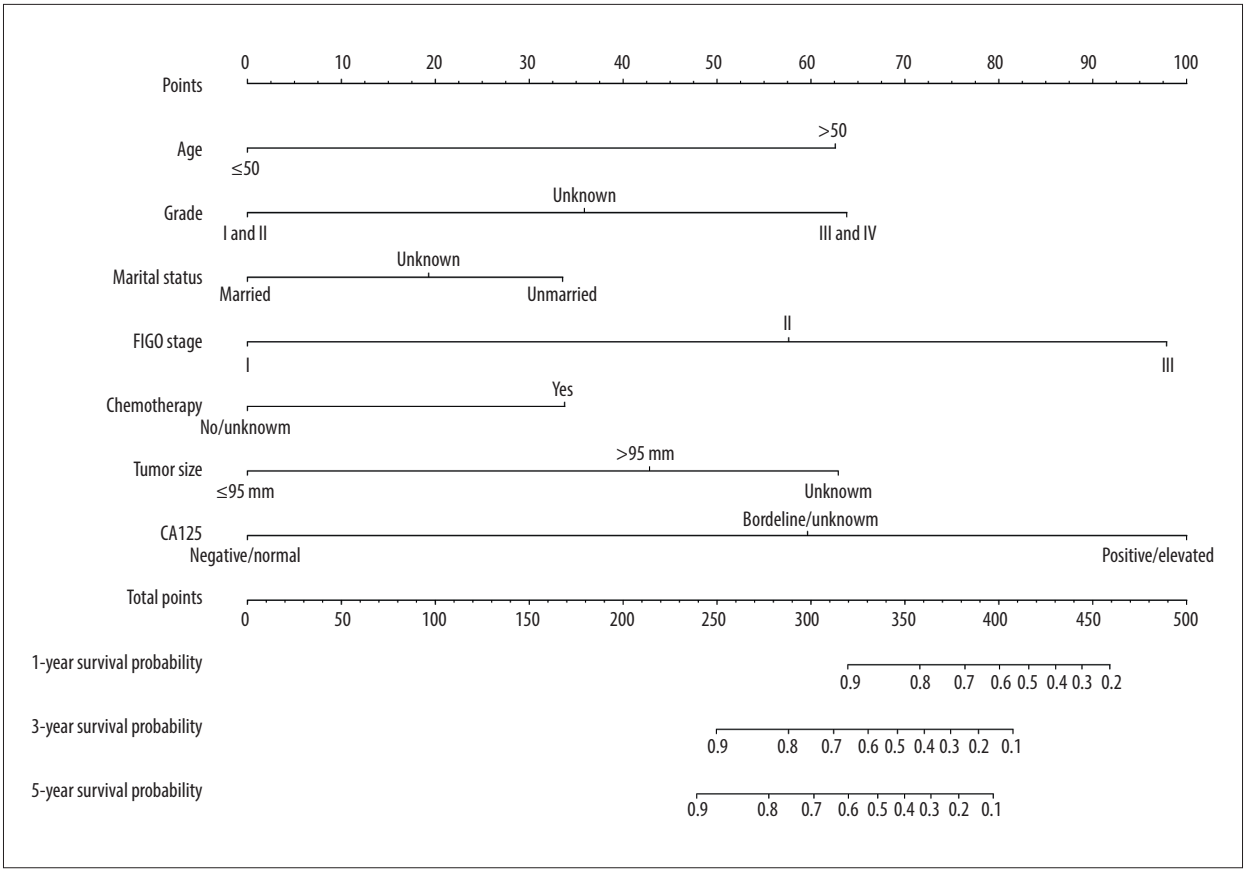

Figure 2. Nomogram predicting 1-, 3-, and 5-year overall survival for patients with sex cord-stromal cancer after surgery.

Table 4. Comparison of prognostic effect between nomogram and FIGO staging system.

Cox model	C-index* (95%CI)	C-index** (95%CI)	C-index*** (95%CI)
Nomogram	0.850 (0.805, 0.895)	0.786 (0.696, 0.876)	0.768 (0.717, 0.819)
FIGO	0.710 (0.644, 0.776)	0.583 (0.477, 0.689)	0.668 (0.610, 0.726)

* Comparison of C-index in the training set; ** comparison of C-index in the validation set; *** comparison of C-index in the overall population.

Clinical performance of the nomogram

DCA is a novel evaluation tool for clinical net benefit of prediction models. The DCA curves of the nomogram and FIGO staging system for 3- and 5-year OS are presented in Figure 6. The wider range of threshold probabilities of the nomogram suggest a superior net benefit in comparison to FIGO stage.

Discussion

SCSTs are uncommon and heterogeneous, with favorable prognosis, but slow progression of the tumor can cause relapse, and there is no accepted standard approach [17]. Due to its rarity, there is little information to guide clinical decision-making and prognosis prediction. In addition, the efficacy of chemotherapy for FIGO stage IC and advanced patients is controversial. Long-term chemotherapy can cause irreversible and severe toxicity resulting from the cumulative dose effect [18]. Hence, the present study was designed to build a more comprehensive prognostic model and to consider the effect of chemotherapy in different stages.

Currently, nomograms are broadly used as prognostic tools to generate individual probabilities by integrating multiple predictors, which connect biological and clinical characteristics [19]. To the best of our knowledge, no previous studies have established nomograms for postoperative sex cord-stromal tumors, probably due to the small number of patients. Our SEER-based nomogram includes parameters that are clinically practical and

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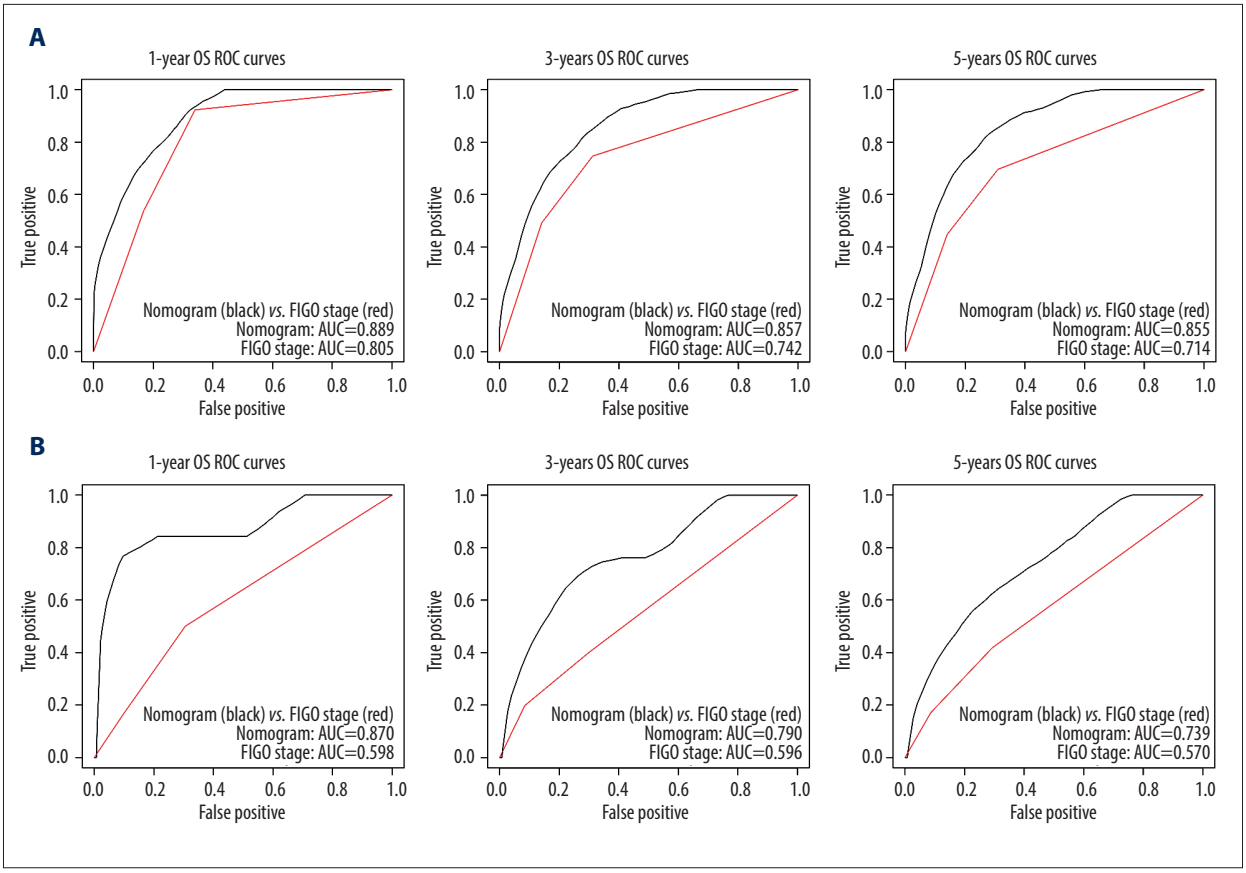

Figure 3. ROC curves of the nomogram and FIGO stage for 1-, 3-, and 5-year overall survival (OS) in (**A**) training set and (**B**) internal validation set. ROC – receiver operating characteristic; AUC – area under the curve.

readily available, consisting of age, grade, marital status, FIGO stage, chemotherapy, tumor size, and CA125 levels. The validation results show better discrimination and clinical utility than with the simpler FIGO stage, and calibration plots suggest excellent compatibility between predicted and observed OS. The external validation set also performed well in the above indicators.

The nomogram shows that advanced FIGO stage of disease and elevated CA125 levels are the most important factors contributing to poor prognosis. Multiple studies have shown that stage matters most [7,20,21], as stage I–II patients had 36% better survival than advanced patients [10]. CA125 is an established prognostic marker of epithelial ovarian cancer, regardless of disease stage, but its effect on SCSTs has not been elucidated. In the present study, the increased CA125 levels had a high hazard ratio of OS, which corroborates the results of Nasioudis, who first demonstrated the potential prognostic value of elevated CA125 among early-stage SCSTs patients [22]. Previous research has demonstrated that CA125 serum levels can be used to monitor response to chemotherapy and detect potential recurrence and disease progression in epithelial ovarian cancer [23]. Further studies on sex cord-stromal tumors are needed to verify our results.

We found that age ≤50 years, tumor size ≤95 mm, and high degree of differentiation are independent predictors for improved survival, in agreement with previous studies [10,24,25]. Younger age is usually associated with better physical status and intensive treatment, which may explain this difference [26]. Sex cord-stromal tumors can grow to large size, either because of their long duration or their high malignancy [27]. It has been reported that smaller tumor size indicates low probability of recurrence [28] and better survival [27]. Another SEER-based study, by Zhang et al., found that patients with well differentiated and moderately differentiated SCSTs had better 5-year survival than those with poorly differentiated tumors [10]. However, the large proportion of cases with unknown tumor grade, use of various grading systems, and underlying tumor misclassifications due to the lack of a central pathology review could also limit the reliability of this predictor.

We found that unmarried status was associated with worse overall survival in SCSTs patients. Although no previous study on SCSTs has investigated it, many studies on ovarian cancer have shown that unmarried women have an higher risk than married women, especially for those who are widowed or separated/divorced [29,30]. Although this predictive factor could

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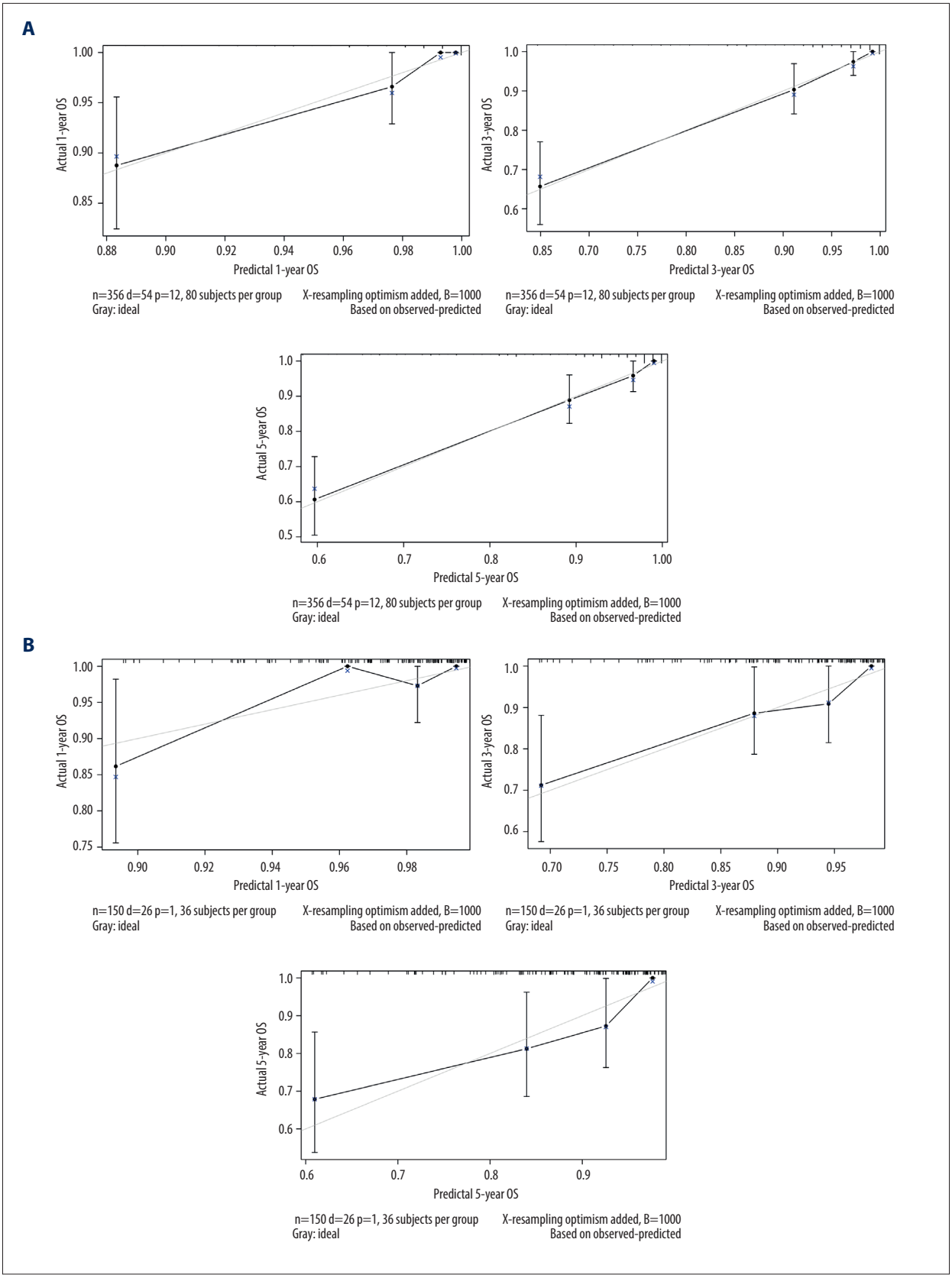

Figure 4. The calibration curves predicting 1-, 3-, and 5-year overall survival (OS) in (**A**) training set and (**B**) internal validation set.

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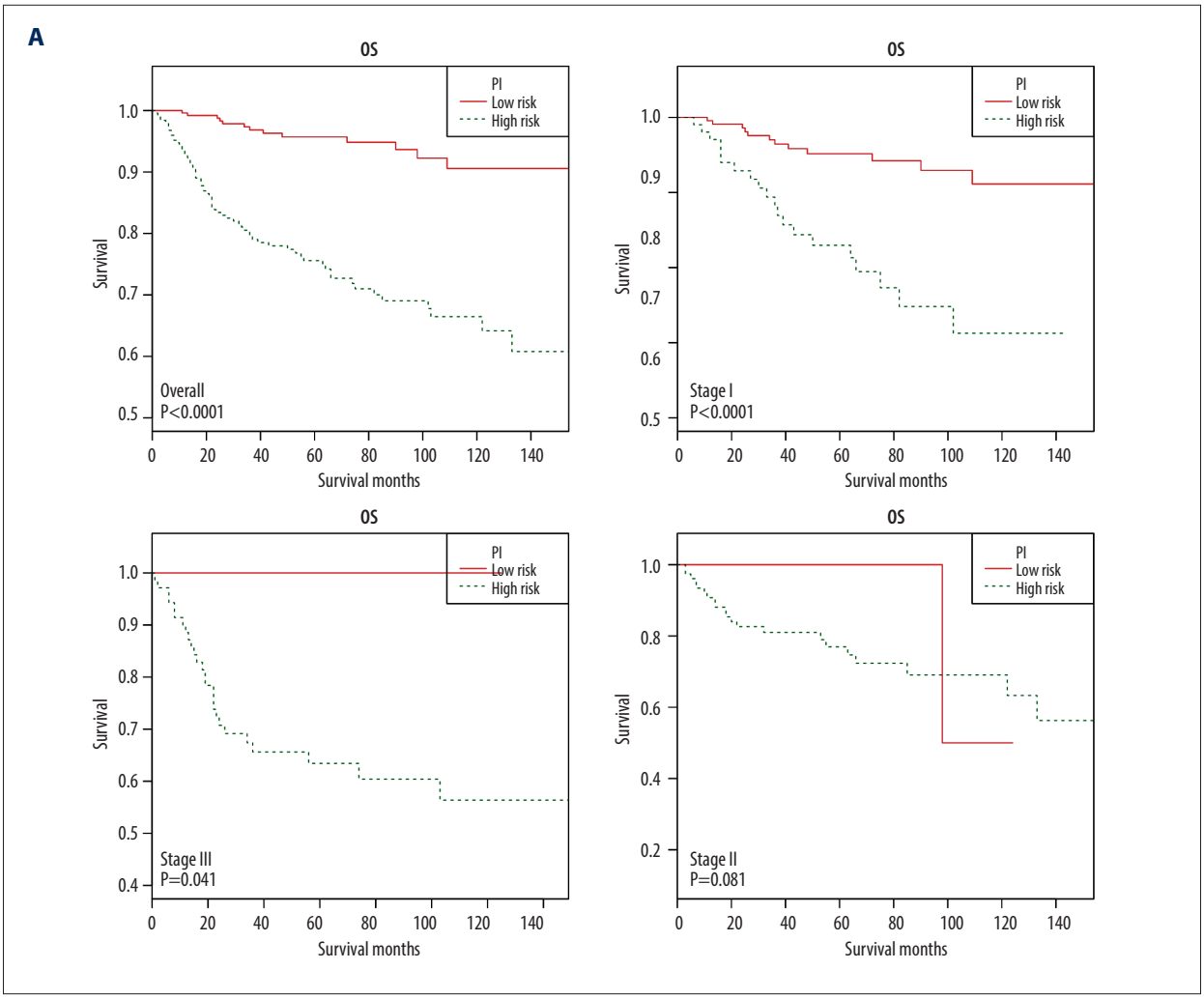
be confounded by emotional and economic support, it should still be considered in clinical practice.

At present, there is no consensus on use of adjuvant chemotherapy after surgery. Generally, it is suggested it be reserved for advanced-stage and recurrent disease [6]. Rupture of ovarian tumors has been identified as a negative prognostic predictor [31]; therefore, FIGO stage IC patients are also advised to receive chemotherapy. After using propensity score matching to control other confounders, multivariate analysis showed that the general effect of chemotherapy for the overall population was deleterious. Survival curves of specific stages displayed no difference in OS in FIGO stage III groups, which is consistent with the results of Badawi et al. [32] This is possibly because SCSTs tend to generate resistance to chemotherapy and have high recurrence rates. It may also due to the preselection of patients or ineffective chemotherapeutic regimens. In addition, multiple studies have found that patients with stage I and II disease did not benefit from postoperative chemotherapy, even if they had high-risk characteristics [34,35]. This finding suggests that surgery is sufficient for indolent early-stage cancer, and that chemotherapy can impair quality of life by serious adverse effects. Several single-nucleotide polymorphisms could be used to identify patients who are more likely to experience cisplatin-related toxicities [18]. Interestingly, even stage IA patients can experience relapse after administration of chemotherapy [36]. Since valid evidence on its benefit is still inadequate, individualized assessment and subsequent counseling should be provided before making clinical decisions.

Generally speaking, our study has several innovative advantages. This study is based on a large cohort of patients from 18 registries, and thus minimizes the selection and surveillance biases and allowed us to reach reliable conclusions. To better investigate the disputed effect of chemotherapy, we conducted propensity score matching to eliminate other confounding factors such as age, grade, histology, tumor size, and CA125 levels. Chemotherapy in current clinical practice is based on FIGO stages, so the stratification of chemotherapy is



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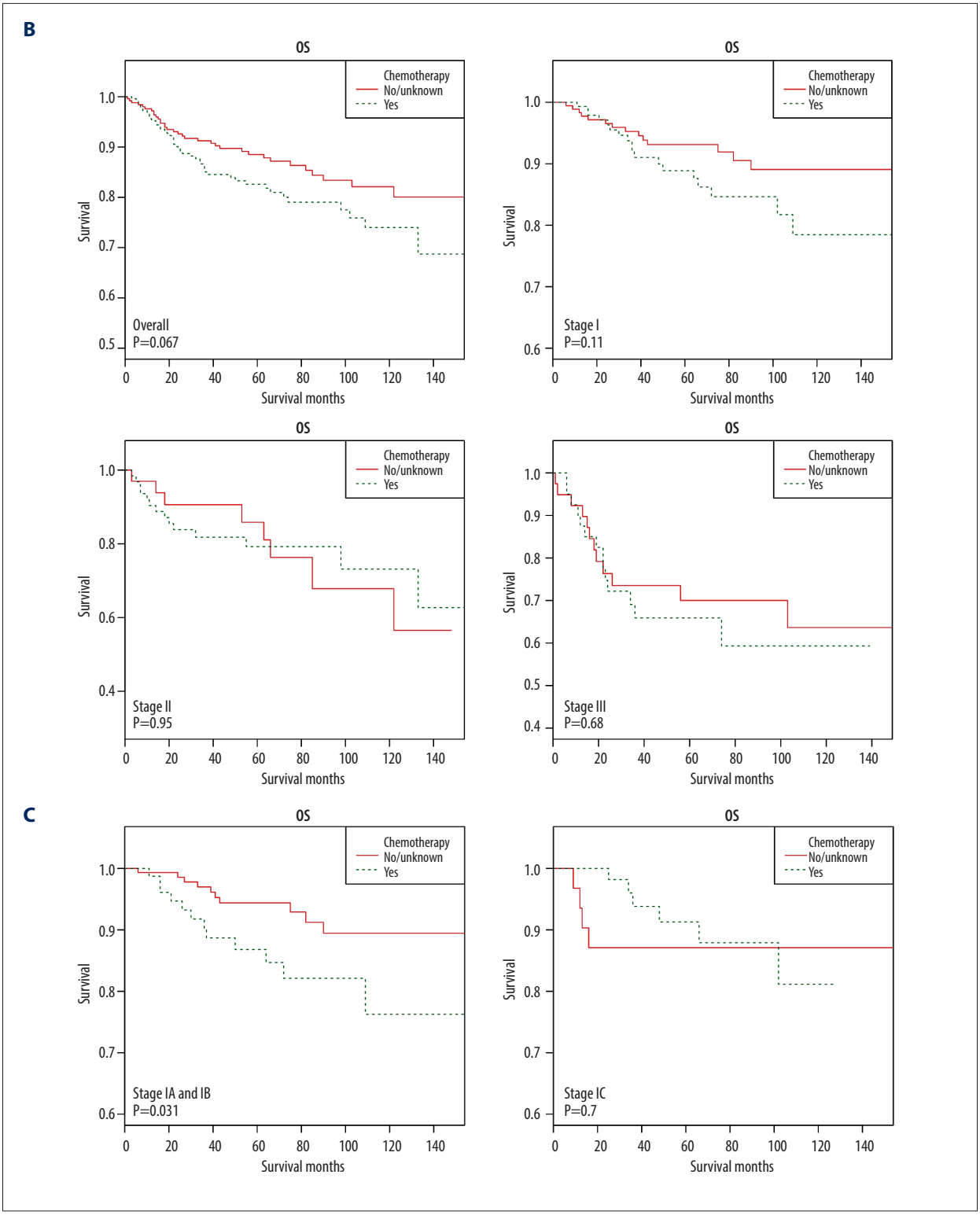

Figure 5. Overall survival (OS) of SCST patients who underwent surgery. Kaplan-Meier survival curve for patients with sex cord-stromal tumors. (**A**) Patients grouped by median value of prognostic index (PI) according to FIGO stages. Red lines represent low-risk groups, green lines represent high-risk groups. (**B, C**) Patients at different FIGO stages stratified by whether they received chemotherapy or not. Red lines represent patients without or unknown if received chemotherapy, green lines represent patients who received chemotherapy.

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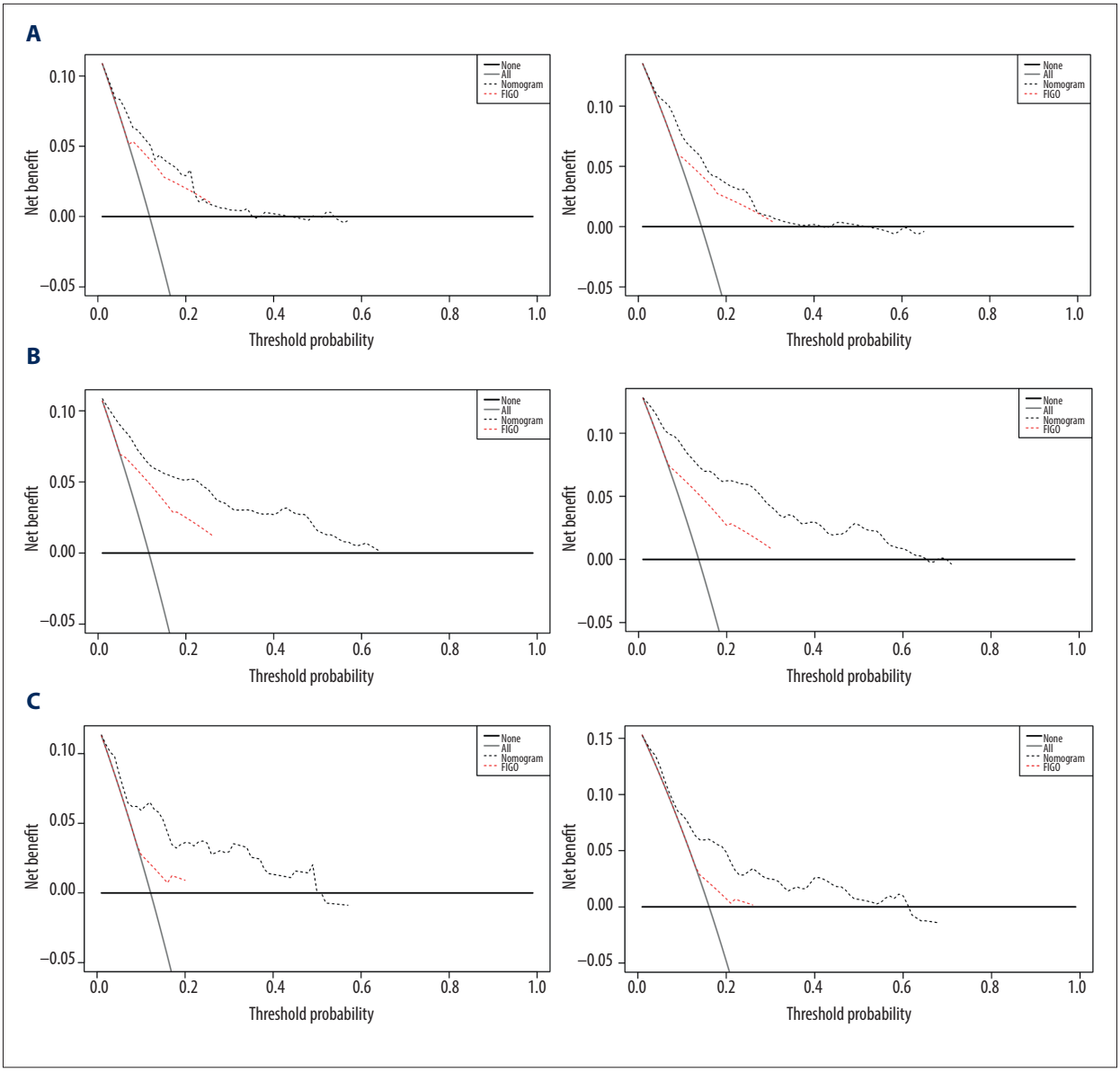

Figure 6. Decision curve analysis for nomogram and FIGO stage. The nomogram was compared to FIGO stage model in regard to 3- (**left**) and 5-year (**right**) overall survival (**A**) in the overall study population, (**B**) in the training set, and (**C**) in the validation set. The y-axis represents net benefit while the x-axis stands for the threshold probability. "All" refers to the assumption that all patients reached the endpoint and "none" to the hypothesis that no patients reached the endpoint.

naturally associated with significant difference in FIGO stages, even after PSM. To the best of our knowledge, this is the first study on sex cord-stromal tumors to provide a survival prediction model in the form of a nomogram, which has natural convenience in clinical application. The predictive factors in our study are practical and readily available. We also propose that CA125 levels and marital status should be taken into clinical consideration in subsequent SCST research. The results of DCA shows that our integrated nomogram has superior clinical utility compared to the FIGO staging system in prognosis prediction.

With regard to the research methods, some limitations need to be acknowledged. Firstly, our data was extracted from the SEER database, and the retrospective design has inherent deficiencies. The long span of study time entails changes in treatments and histopathologic evaluation. In addition, several important factors are unavailable from the SEER database, including gravidity, parity, chemotherapy regimen, extent of residual tumors, recurrence, performance status, and mitotic index. As chemotherapy protocols differ among different medical institutions, data from multi-institutional settings are required to determine the optimal scheme. Information on

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ascites is largely unavailable, although about half of patients with Sertoli-Leydig cell tumors present with abdominal symptoms due to ascites [37]. Further studies on external validation or reliable indicators are required to build a more accurate prediction model. The lack of clear benefit from chemotherapy also calls for the development of targeted medication for SCSTs.

Conclusions

We developed an individualized nomogram that can predict OS of postoperative patients with sex cord-stromal tumors. The training set and validation set exhibited good discrimination and calibration and better clinical utility than FIGO stage. We found that chemotherapy provided the reverse effect for overall stages, and further investigation should be carried out to confirm this finding. In spite of its limitations, this study offers some insights that may help prognosis evaluation and clinical decision-making.

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Conflict of interest

None.

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