Original Article

Nomograms to predict individual prognosis of patients with primary signet ring cell carcinoma of the urinary bladder

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Background: Signet ring cell carcinoma (SRCC) is a rare but highly malignant variant of bladder carcinoma. Nomograms have demonstrated good accuracy in predicting the prognosis and guiding the management of pure urothelial carcinoma (UC). However, no accurate and applicable nomogram has been formulated for primary SRCC cases. This study aimed to determine significant prognostic factors and to construct nomograms for predicting the survival outcomes of patients with primary SRCCs of the urinary bladder.

Methods: A total of 317 eligible patients diagnosed with SRCC were analyzed using the 2004–2016 data from the Surveillance, Epidemiology, and End Results database. Univariate and multivariate analyses were performed to explore the prognostic values. Nomograms were established to estimate the overall survival (OS) and cancer-specific survival (CSS) based on the Cox regression results. The performance of SRCC nomograms was evaluated using the concordance index and calibration curves. Survival curves were applied according to various surgical methods, lymph node status, and risk groups distinguished by nomograms.

Results: Two nomograms included common indicators that were significantly associated with OS and CSS, including T stage, M stage, tumor size, surgery, and the lymph node ratio (LNR). The nomograms indicated appreciable accuracy in predicting the OS and CSS, with concordance index of 0.723 [95% confidence interval (95% CI: 0.692–0.754] and 0.740 (95% CI: 0.701–0.779), respectively. The calibration curves revealed satisfactory consistency between the prediction of deviation correction and ideal reference line.

Conclusions: The two nomograms developed in this study showed high accuracy and reliability in predicting the survival outcomes of patients with SRCC and could be used to comprehensively assess the risk of SRCC. Moreover, they could assist in the optimal treatment selection for such patients.

Keywords: Signet ring cell carcinoma of the bladder; nomogram; prognosis; survival analysis

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Introduction

Bladder cancer (BCa) is among the most common types of cancer, with high mortality and steadily rising morbidity rates worldwide (1). Recent data have also indicated that BCa represents neoplasm with the fourth-highest incidence and eighth-highest mortality rates among men in the United States (US) in 2020 (2). Among the BCa types, the major histological type is urothelial carcinoma (UC), while primary signet ring cell carcinoma (SRCC) is rare, accounting for approximately <1% of cases (3,4). Compared with UC, SRCC tends to be associated with worse oncological outcomes, but the prevalent characteristics, treatment options, and prognosis are not comprehensively characterized because of their low occurrence rate (5-8).

Nomograms are visible tools based on statistical models that have demonstrated better accuracy in predicting the prognosis and guiding the management of pure UC (9,10). However, to the best of our knowledge, no accurate and applicable nomogram for patients with primary SRCCs has been formulated. Therefore, this study aimed to fully investigate the prognostic factors and to construct nomograms to predict the survival outcomes in patients with SRCC of the urinary bladder using data from the Surveillance, Epidemiology, and End Results (SEER) database. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-929).

Methods

Patients and variables

The SEER database collects data on cancer morbidity, survival, and mortality of patients with cancer encompassing ~28% of the US population. In this study, we identified adult patients (age: >18 years) diagnosed with primary SRCC of the bladder who were registered in the SEER database from 2004 to 2016. The primary cancer site was limited to the urinary bladder [International Classification of Diseases for Oncology third edition (ICD-O-3) side code: C67.0-67.9], and the histological type was confined to SRCC (ICD-O-3 code: 8490/3). The diagnosis was confirmed by positive histology and was their first or only cancer diagnosis (first positive indicator of malignancy). Patients without a positive pathologic diagnosis or complete survival data were excluded. Finally, 317 eligible patients were included in our analysis.

The patients were divided into four groups ("<50", "50–64", "65–79", and "≥80 years") according to their age at diagnosis. The lymph node ratio (LNR), which was calculated by dividing the number of positive nodes by the number of examined nodes, was stratified into the following three categories: "No LN removed", "Unknown", and "More than one LN removed". To properly assess the LNR prognostic value in patients with SRCC, a positive LNR ("More than one LN removed") was further divided into LNR =0, 0 <LNR ≤0.90 and LNR >0.90, according to the cut-off point of 0.90. The latter was estimated using the X-tile program, a practical tool for cut-point optimization, according to the minimal P value approach (11). Using the similar approach, we identified 5.5 cm as the cut-off point for patients with definite size of the tumor; ultimately, the tumor size was classified as "≤5.5 cm", ">5.5 cm", and "Unknown". The primary endpoints were the overall survival (OS) and cancer-specific survival (CSS). Survival time was defined as the interval from the first diagnosis to the date of death or last follow-up.

Statistical analyses

All categorical variables are presented as frequencies with respective proportions. Univariate analysis was first performed to identify the significant variables that were, then, used in the multivariable Cox proportional hazards models to explore the independent prognostic factors for survival outcomes. The OS and CSS were estimated and compared using the Kaplan-Meier curves and the log-rank test. We built nomograms based on significant information obtained from the multivariate Cox regression analyses. Meanwhile, the concordance index (C-index) was used to assess the predictive performance. Furthermore, calibration curves were established to evaluate the consistency between predicted and observed survival. All analyses were performed using SPSS v.25 (IBM Corp., Armonk, NY, USA) and R v.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and P<0.05 was considered statistically significant.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As data from the SEER program is available for the public and does not need patient informed consent, and ethical approval was waived by the local Ethics Committee of Beijing Hospital.

Results

Baseline characteristics of the overall cohort

Table 1 shows the demographic and clinicopathological characteristics of the included 317 patients. Generally, patients aged ≥50 years accounted for the greatest proportion (n=287; 90.54%). The majority of patients were men (n=231; 72.87%) and Caucasian (n=256; 80.76%). Of the 317 patients, 77.28%, 30.91%, 77.92%, and 21.14% had muscle invasive disease, lymph node metastasis, higher-grade disease, and distal metastasis, respectively. Most patients underwent surgery (n=267; 84.23%) and chemotherapy (n=140; 44.16%), while only a few patients (n=63; 19.87%) chose radiotherapy.

Univariable and multivariable Cox regression analysis

In univariable analysis, variables, such as the marital status, grade, T stage, M stage, surgery, radiation, tumor size, and LNR, showed statistical significance for OS. Furthermore, the marital status, T stage, M stage, surgery, tumor size, and LNR were significantly related to CSS (*Table 2*). Then, we incorporated these significant parameters into the multivariable Cox regression analysis. Besides, as important clinicopathological parameters, the primary site (P=0.060) and N stage (P=0.095) for OS and N stage (P=0.082) for CSS were also included in the multivariate analysis. The analysis demonstrated that T stage, M stage, surgery, tumor size, and LNR had significant relationships with the OS and CSS (*Table 3*). The Kaplan–Meier curves showed that patients without any surgery had the poorest OS and CSS. The median OS and CSS were only 6 [95% confidence interval (CI) =3.71–8.29] and 12 (95% CI: 7.44–16.56) months, respectively (both P<0.05). When surgery was classified into three groups—"no surgery," "radical cystectomy," and "other surgery"—radical cystectomy (RC) was found to prolong OS [hazard ratio (HR) =0.435, 95% CI: 0.303–0.624, P<0.001], whereas there were no significant differences in the CSS among patients undergoing RC or other surgery (P=0.24). In addition, lymph node dissection (LND) was found to have oncological advantages over no LND, with median survival times of 22 (95% CI: 16.84–27.16) *vs.* 10 months (95% CI: 8.13–11.89) and 33 (18.92–47.08) *vs.* 13 months (95% CI: 10.64–15.36) for the OS and CSS (both P<0.01), respectively (*Figure 1*).

Development and validations of predicting nomograms for OS and CSS

We plotted the nomograms for the 1-, 3-, and 5-year OS and CSS based on the independent predictors that were selected in the multivariable analysis (*Figure 2*). A certain point was generated for each covariate. Then, a total nomogram score was calculated for every patient, which was correlated with the probability of 1-, 3-, and 5-year survival outcomes. The nomograms showed favorable accuracy in predicting the OS and CSS, with C-index of 0.723 (95% CI: 0.692–0.754) and 0.740 (95% CI: 0.701–0.779), respectively. Moreover, the calibration curves revealed an appreciable accordance between the predictive outcome and actual survival (*Figure 3*). Furthermore, we calculated a specific OS and CSS risk score for each patient according to nomogram points and found that a higher nomogram score was associated with worse OS (HR =1.932, 95% CI: 1.542–2.422, P<0.001) and CSS (HR =2.051, 95% CI: 1.445–2.909, P<0.001) when considered as a continuous variable. Then, the risk score was stratified into two risk levels that were applied to regroup patients into low-risk and high-risk patients for OS (n=161, 50.79% *vs.* n=156, 49.21%) and CSS (n=170, 53.63% *vs.* n=147, 46.37%). *Figure 4* shows that the risk stratification enabled distinguishing between the OS and CSS among the risk subgroups, and low-risk patients apparently exhibited a better prognosis than the other patients (P<0.001).

Discussion

SRCC of the urinary bladder is a rare but aggressive histological variant with poor survival prognosis. Owing to the rarity of SRCC, it is often neglected, and most previous studies of the disease were case reports (6,12,13). To a certain extent, the American Joint Committee on Cancer staging system is regarded as a routine tool to predict prognosis, mainly based on T, N, and M information. Nevertheless, it is not specially designed for SRCC, and many individualized characteristics, such as lymph node metastasis, grade, and tumor size, that may be predictive are not involved (7,14). Nomograms are currently one of the most widely used prediction tools, owing to their ability to combine clinical characteristics in generating individual probabilities of clinical events, which could provide clinical decision-making and personalized medical therapy;

Table 1 Demographic and clinicopathological characteristics of patients with signet ring cell carcinoma

Variables	No.	%
Age at diagnosis (years)		
<50	30	9.46
50–64	103	32.49
65–79	127	40.06
≥80	57	17.98
Sex		
Male	231	72.87
Female	86	27.13
Race		
Caucasian	256	80.76
African	41	12.93
Other	20	6.31
Marital status		
Married	177	55.84
Single	121	38.17
Unknown	19	5.99
Primary site		
Trigone of bladder	19	5.99
Dome of bladder	26	8.20
Lateral wall of bladder	34	10.73
Anterior wall of bladder	6	1.89
Posterior wall of bladder	21	6.62
Bladder neck	10	3.15
Ureteric orifice	2	0.63
Urachus	13	4.10
Overlapping lesion of bladder	48	15.14
Bladder, NOS	138	43.53
Grade		
II	6	1.89
III	172	54.26
IV	75	23.66
Unknown	64	20.19
T stage		
Tis	3	0.95
T1	46	14.51
T2	79	24.92
T3	57	17.98
T4	109	34.38
Unknown	23	7.26
N stage		
N0	197	61.15
N1	41	12.93
N2	54	17.03
N3	3	0.95
Unknown	22	6.94
M stage		
M0	238	75.08
M1	67	21.14
Unknown	12	3.79
Surgery		
No surgery	50	15.77
TURBT	95	29.97
Partial cystectomy	26	8.20
Radical cystectomy	125	39.43
Other surgery	21	6.62
Radiation		
No/unknown	254	80.13
Yes	63	19.87
Chemotherapy		
No/unknown	177	55.84
Yes	140	44.16
Size (cm)		
≤5.5	109	34.38
>5.5	39	12.30
Unknown	169	53.31

Table 1 (*continued*)

Table 1 (*continued*)

Variables	No.	%
LNR		
No LN removed	176	55.52
More than one LN removed	128	40.38
LNR =0	57	17.98
≤0.90	60	18.93
>0.90	11	3.47
Unknown	13	4.10

NOS, not otherwise specified; TURBT, transurethral resection of bladder tumor; LNR, lymph node ratio; LN, lymph node.

however, there has been no nomogram for SRCC to date. In this study, we conducted a large-scale, population-based, retrospective, prognostic, and predictive survival analysis; interestingly, we identified several independent features, including T stage, M stage, surgery, tumor size, and LNR, that could affect the oncological outcomes of patients with SRCC. Additionally, we generalized these independent risk factors into two nomograms to predict the prognosis of SRCC, which showed reliable and accurate performance.

Recent studies have confirmed that patients with SRCC are more likely to experience a worse prognosis than those with pure UC (6-8,14,15). Wang *et al.* analyzed the data of 103 patients with SRCC and those of 14,648 patients with

Table 2 Univariate Cox regression model analysis for OS and CSS in nomogram cohort

Characteristics	Overall survival (OS)		Cancer-specific survival (CSS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis (years)				
<50	1 (reference)		1 (reference)	
50–64	0.945 (0.598–1.494)	0.808	1.024 (0.597–1.754)	0.932
64–79	0.999 (0.638–1.563)	0.995	0.895 (0.522–1.533)	0.686
≥80	1.375 (0.839–2.253)	0.207	1.146 (0.625–2.104)	0.659
Sex				
Male	1 (reference)		1 (reference)	
Female	1.191 (0.899–1.578)	0.224	1.178 (0.835–1.660)	0.350
Race				
Caucasian	1 (reference)		1 (reference)	
African	1.323 (0.918–1.907)	0.133	1.370 (0.886–2.119)	0.157
Other	1.067 (0.649–1.754)	0.797	0.994 (0.537–1.841)	0.986
Marital status				
Married	1 (reference)		1 (reference)	
Single	1.512 (1.161–1.970)	0.002	1.341 (0.972–1.850)	0.074
Unknown	0.884 (0.509–1.534)	0.660	0.604 (0.280–1.302)	0.198
Primary site				
Trigone of bladder	1 (reference)		1 (reference)	
Dome of bladder	0.729 (0.359–1.479)	0.381	0.799 (0.315–2.027)	0.637
Lateral wall of bladder	0.956 (0.496–1.841)	0.892	1.049 (0.445–2.476)	0.912
Anterior wall of bladder	1.101 (0.396–3.060)	0.854	1.574 (0.473–5.234)	0.459
Posterior wall of bladder	1.202 (0.597–2.420)	0.606	1.333 (0.536–3.318)	0.536

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Overall survival (OS)		Cancer-specific survival (CSS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Bladder neck	0.742 (0.299–1.842)	0.520	1.187 (0.411–3.426)	0.751
Ureteric orifice	0.291 (0.037–2.287)	0.241	0.708 (0.088–5.675)	0.745
Urachus	0.439 (0.168–1.145)	0.092	0.538 (0.162–1.789)	0.312
Overlapping lesion of bladder	1.116 (0.601–2.071)	0.729	1.597 (0.727–3.506)	0.244
Bladder, NOS	1.265 (0.726–2.205)	0.407	1.537 (0.742–3.183)	0.248
Grade				
II	1 (reference)		1 (reference)	
III	4.183 (1.031–16.972)	0.045	2.612 (0.643–10.608)	0.179
IV	3.290 (0.799–13.552)	0.099	2.115 (0.510–8.764)	0.302
Unknown	3.810 (0.924–15.712)	0.064	2.034 (0.485–8.530)	0.332
T stage				
Tis	0.347 (0.047–2.543)	0.298	0.001 (0.0001–2.520)	0.949
T1	1 (reference)		1 (reference)	
T2	1.003 (0.650–1.548)	0.990	1.542 (0.854–2.787)	0.151
T3	1.142 (0.723–1.803)	0.569	1.692 (0.912–3.136)	0.095
T4	1.615 (1.076–2.425)	0.021	2.463 (1.405–4.138)	0.002
Unknown	1.386 (0.778–2.471)	0.268	1.302 (0.552–3.072)	0.547
N stage				
N0	1 (reference)		1 (reference)	
N1	1.306 (0.909–1.877)	0.149	1.227 (0.784–1.921)	0.370
N2	1.610 (1.145–2.264)	0.006	1.781 (1.202–2.637)	0.004
N3	1.098 (0.272–4.440)	0.895	0.777 (0.108–5.578)	0.802
Unknown	1.244 (0.741–2.087)	0.409	0.912 (0.443–1.877)	0.803
M stage				
M0	1 (reference)		1 (reference)	
M1	2.613 (1.939–3.521)	<0.001	2.940 (2.076–4.163)	<0.001
Unknown	1.026 (0.524–2.008)	0.941	0.693 (0.255–1.879)	0.471
Surgery				
No surgery	1 (reference)		1 (reference)	
TURBT	0.662 (0.457–0.958)	0.029	1.055 (0.638–1.743)	0.836
Partial cystectomy	0.271 (0.146–0.504)	<0.001	0.320 (0.136–0.755)	0.009
Radical cystectomy	0.433 (0.302–0.621)	<0.001	0.701 (0.428–1.146)	0.157
Other	0.781 (0.460–1.324)	0.359	1.118 (0.559–2.233)	0.753

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Overall survival (OS)		Cancer-specific survival (CSS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Radiation				
No/unknown	1 (reference)		1 (reference)	
Yes	1.512 (1.110–2.059)	0.009	1.367 (0.931–2.007)	0.111
Chemotherapy				
No/unknown	1 (reference)		1 (reference)	
Yes	1.092 (0.846–1.410)	0.497	1.230 (0.903–1.675)	0.189
Size (cm)				
≤5.5	1 (reference)		1 (reference)	
>5.5	2.390 (1.567–3.646)	<0.001	2.714 (1.663–4.428)	<0.001
Unknown	1.864 (1.397–2.485)	<0.001	1.795 (1.261–2.554)	0.001
LNR				
No LN removed	1 (reference)		1 (reference)	
More than one LN removed		<0.001		0.007
LNR =0	0.340 (0.226–0.510)	<0.001	0.402 (0.250–0.647)	<0.001
≤0.90	0.789 (0.569–1.094)	0.155	0.836 (0.564–1.238)	0.371
>0.90	1.451 (0.737–2.857)	0.282	1.660 (0.767–3.594)	0.198
Unknown	0.603 (0.326–1.115)	0.107	0.578 (0.268–1.249)	0.163

OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; TURBT, transurethral resection of bladder tumor; LNR, lymph node ratio; LN, lymph node.

pure UC and concluded that SRCC was an independent predictor of inferior CSS in contrast to pure UC (16). Similarly, Jin *et al.* reported that compared with pure UC, SRCC was significantly associated with a higher risk of overall and cancer-specific mortality (8). The highly aggressive behaviors and uncertain efficacy of multimodality treatments may result in poor SRCC prognosis. Our study confirmed that patients with SRCC presented with a higher frequency of higher histological grade and advanced stage disease; these findings are in line with the outcomes of prior studies and could induce a poor prognosis (5,8,16). Besides, we found that the tumor size could also influence the prognosis of SRCC. Notably, the N stage was not significantly associated with the OS and CSS and was not present in the nomograms; thus, we focused on the LNR, which has been an excellent indicator in BCa (17,18). Multivariate Cox regression analysis in our study indicated that patients in the LNR =0 group exhibited significantly improved OS and CSS than those in the other groups, suggesting its applicability in SRCC. Thus, we included T stage, M stage, tumor size, and LNR into the final nomograms. Apart from that, many other variables are also involved in our analysis [i.e., demographic characteristics, clinicopathological parameters (primary site, grade, and N stage), and therapy strategies], and the surgery type is finally determined in the nomogram.

Some investigators have suggested that the percentage of signet ring cell components is related to an advanced stage and worse oncological outcomes (6,19). Signet ring cells can rapidly invade the submucosa in a diffuse manner without distinct mucosal lesions at an early stage, which could cause only edematous, bullous, or erythematous mucosa to be revealed by cystoscopy, making early diagnosis difficult unless a full-thickness biopsy is performed (20,21). However, the mechanism of this aggressive pattern remains unclear. Thomas *et al.* reported that the extent of

Table 3 Multivariate Cox regression model analysis for OS and CSS in nomogram cohort

Characteristics	Overall survival (OS)		Cancer-specific survival (CSS)	
	HR (95% CI)	P value	HR (95% CI)	P value
Marital status				
Married	1 (reference)		1 (reference)	
Single	1.276 (0.950–1.713)	0.105	1.178 (0.839–1.654)	0.345
Unknown	0.720 (0.387–1.337)	0.298	0.561 (0.247–1.279)	0.169
Primary site			Not selected	
Trigone of bladder	1 (reference)			
Dome of bladder	1.218 (0.528–2.810)	0.645		
Lateral wall of bladder	1.249 (0.621–2.516)	0.533		
Anterior wall of bladder	2.049 (0.632–6.647)	0.232		
Posterior wall of bladder	1.290 (0.610–2.727)	0.505		
Bladder neck	0.954 (0.372–2.446)	0.922		
Ureteric orifice	0.767 (0.094–6.245)	0.804		
Urachus	0.518 (0.172–1.558)	0.242		
Overlapping lesion of bladder	1.096 (0.570–2.107)	0.785		
Bladder, NOS	1.113 (0.613–2.020)	0.725		
Grade			Not selected	
II	1 (reference)			
III	5.963 (1.211–29.368)	0.028		
IV	5.220 (1.040–26.210)	0.045		
Unknown	4.485 (0.881–22.833)	0.071		
T stage				
Tis	0.479 (0.063–3.660)	0.478	0.001 (0.001–2.307)	0.951
T1	1 (reference)		1 (reference)	
T2	1.358 (0.865–2.130)	0.183	2.082 (1.134–3.822)	0.018
T3	3.479 (1.998–6.059)	<0.001	5.566 (2.718–11.398)	<0.001
T4	2.871 (1.742–4.732)	<0.001	4.322 (2.233–8.366)	<0.001
Unknown	0.704 (0.365–1.357)	0.295	0.781 (0.302–2.020)	0.611
N stage				
N0	1 (reference)		1 (reference)	
N1	1.187 (0.659–2.138)	0.569	1.069 (0.535–2.139)	0.849
N2	1.623 (0.979–2.691)	0.061	1.873 (1.043–3.362)	0.036
N3	1.004 (0.224–4.512)	0.995	0.931 (0.119–7.263)	0.946
Unknown	0.714 (0.332–1.536)	0.388	0.882 (0.343–2.270)	0.794

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Overall survival (OS)		Cancer-specific survival (CSS)	
	HR (95% CI)	P value	HR (95% CI)	P value
M stage				
M0	1 (reference)		1 (reference)	
M1	1.931 (1.355–2.752)	<0.001	2.528 (1.661–3.848)	<0.001
Unknown	0.852 (0.397–1.825)	0.680	0.945 (0.313–2.854)	0.921
Surgery				
No surgery	1 (reference)		1 (reference)	
TURBT	0.656 (0.424–1.014)	0.058	1.119 (0.627–1.998)	0.703
Partial cystectomy	0.239 (0.115–0.497)	<0.001	0.273 (0.104–0.716)	0.008
Radical cystectomy	0.351 (0.209–0.588)	<0.001	0.536 (0.277–1.034)	0.063
Other	0.673 (0.381–1.189)	0.173	0.984 (0.468–2.072)	0.967
Radiation			Not selected	
No/unknown	1 (reference)			
Yes	1.096 (0.762–1.576)	0.621		
Size (cm)				
≤5.5	1 (reference)		1 (reference)	
>5.5	2.188 (1.398–3.424)	0.001	2.378 (1.419–3.987)	0.001
Unknown	1.359 (0.978–1.890)	0.068	1.322 (0.885–1.976)	0.173
LNR				
No LN removed	1 (reference)		1 (reference)	
More than one LN removed	–		–	
LNR =0	0.366 (0.222–0.603)	<0.001	0.401 (0.224–0.719)	0.002
≤0.90	0.577 (0.361–0.922)	0.021	0.498 (0.287–0.862)	0.013
>0.90	0.849 (0.411–1.757)	0.660	0.814 (0.349–1.896)	0.633
Unknown	0.482 (0.250–0.930)	0.029	0.437 (0.192–0.993)	0.048

OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified; TURBT, transurethral resection of bladder tumor; LNR, lymph node ratio; LN, lymph node.

signet ring differentiation was correlated with infiltrative invasion using immunohistochemical analysis in bladder adenocarcinoma cases with signet ring morphology (19). It has been hypothesized that the ErbB2/ErbB3 pathway is constitutively activated via interaction with mucin 4 (MUC4), which contributes to the loss of tight junctions and cell-cell interactions, ultimately increasing cell growth and forming the SRCC (22). Hamilton *et al.* reported a mutation in the E-cadherin gene in a gastric SRCC case and indicated a similar hypothesis to that stated above (23). Moreover, Foda *et al.* reported negative/low expressions of epidermal growth factor receptor, matrix metalloproteinase-13, and E-cadherin, which could result in the aggressive biological behavior of SRCC (24). Nam *et al.* conducted whole-exome and RNA sequencing of colorectal SRCCs and determined that the accumulation of mucin in signet ring cells could be attributed to the overexpression of MUC2 (25). We suppose that similar mechanisms might be observed in other SRCCs.

The optimal treatment option for SRCC of the

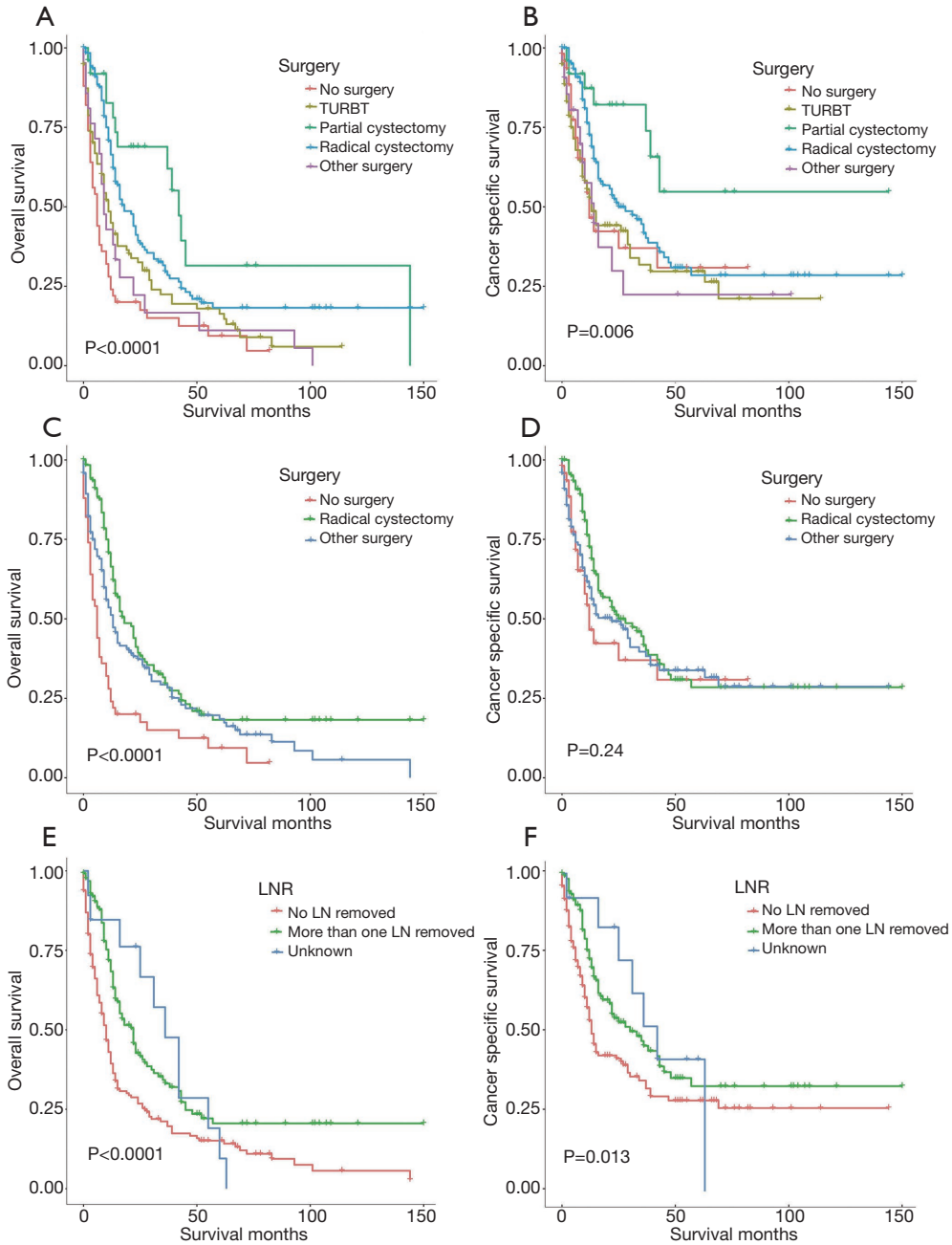

Figure 1 Kaplan-Meier survival curves of patients with primary SRCC. (A,B) The OS and CSS in patients stratified by surgery; (C,D) The OS and CSS in patients stratified by RC; (E,F) The OS and CSS in patients stratified by LNR. SRCC, signet ring cell carcinoma; OS, overall survival; CSS, cancer-specific survival; TURBT, transurethral resection of bladder tumor; RC, radical cystectomy; LNR, lymph node ratio.

bladder is not yet well confirmed. Our two nomograms included only one treatment variable, the surgery type, which was satisfactory in estimating the prognosis of patients with SRCC. Surgery was assumed to be the most common therapeutic method, differing from transurethral resection of bladder tumor (TURBT) to RC with pelvic lymphadenectomy (5,6,19). Wang *et al.* compared different surgical options and suggested that RC could be more

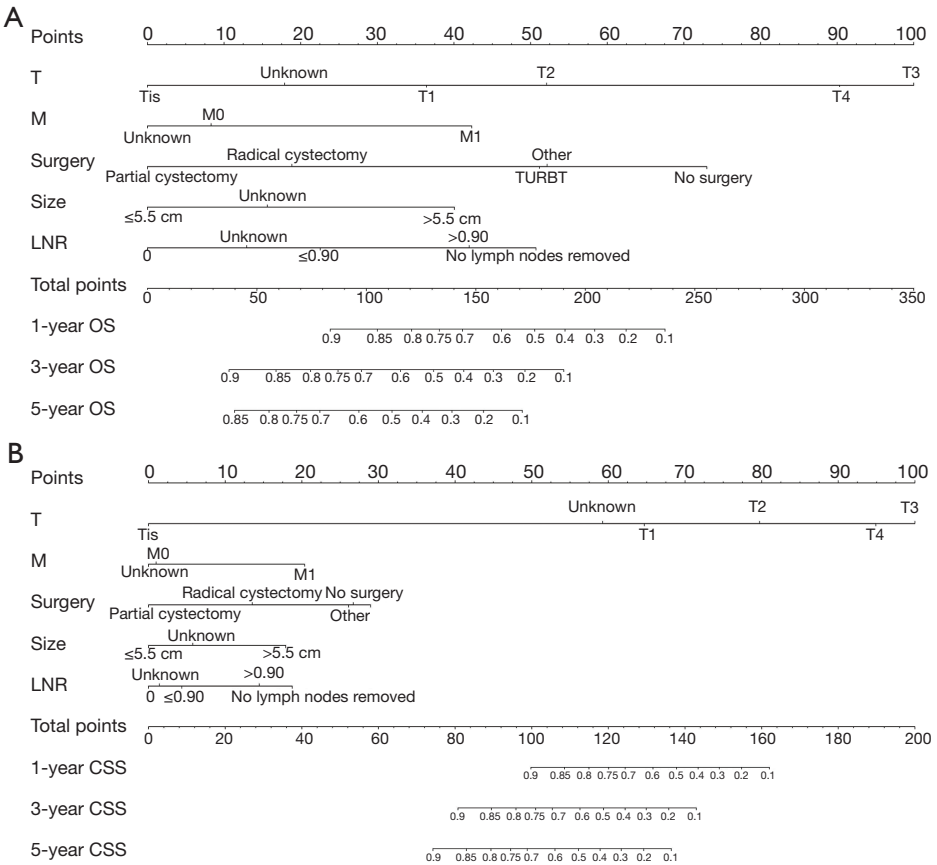

Figure 2 Nomograms to predict the 1-, 3-, and 5-year (A) OS and (B) CSS of patients with primary SRCC. Points are obtained according to the predictive contributions of the variables, including the T stage, M stage, surgery, tumor size, and LNR. Then, the total points are calculated to estimate the probability of OS and CSS at 1-, 3-, and 5-year. SRCC, signet ring cell carcinoma; TURBT, transurethral resection of bladder tumor; LNR, lymph node ratio; OS, overall survival; CSS, cancer-specific survival.

effective than some other bladder-preserving methods (5). A recent systematic review of 41 studies concluded that all patients with muscle invasive BCa simultaneously accompanied with histological variants, including SRCC, should receive RC (7). Meanwhile, Guo *et al.* found that when compared with RC alone, RC with lymphadenectomy was associated with improved OS in patients with SRCC (26). Consistent with those findings, our nomograms also supported that the performance of RC is significantly superior to some other surgical methods, such as TURBT, for the survival of patients with SRCC, while RC with LND possessed oncological advantages than no LND. Moreover, patients without any surgery had the most dismal outcomes. However, in this study, only 39.43% of patients were treated with RC, whereas many patients underwent TURBT (95/317) or no surgery (50/317), which might account for their worse prognosis. We suspect that a higher frequency of metastasis, delayed diagnosis, socioeconomic status, and the physicians' tendency to perform radical treatment for older patients might be responsible for the surgical options. Furthermore, in consistency with our findings, previous studies have reported the resistance of SRCCs to chemotherapy and lack of response to radiotherapy (5-7). Nevertheless, some researchers have suggested that patients with SRCC would benefit from adjuvant chemotherapy (27,28). Immune checkpoint inhibitor drugs are also a potential treatment choice (29). In summary, multi-institutional clinical trials should be further explored to assist in the treatment of SRCC. Above all, our prognosis models are proposed to be innovative and rational enough to be useful in clinical practice.

This study had some limitations. First, the observational

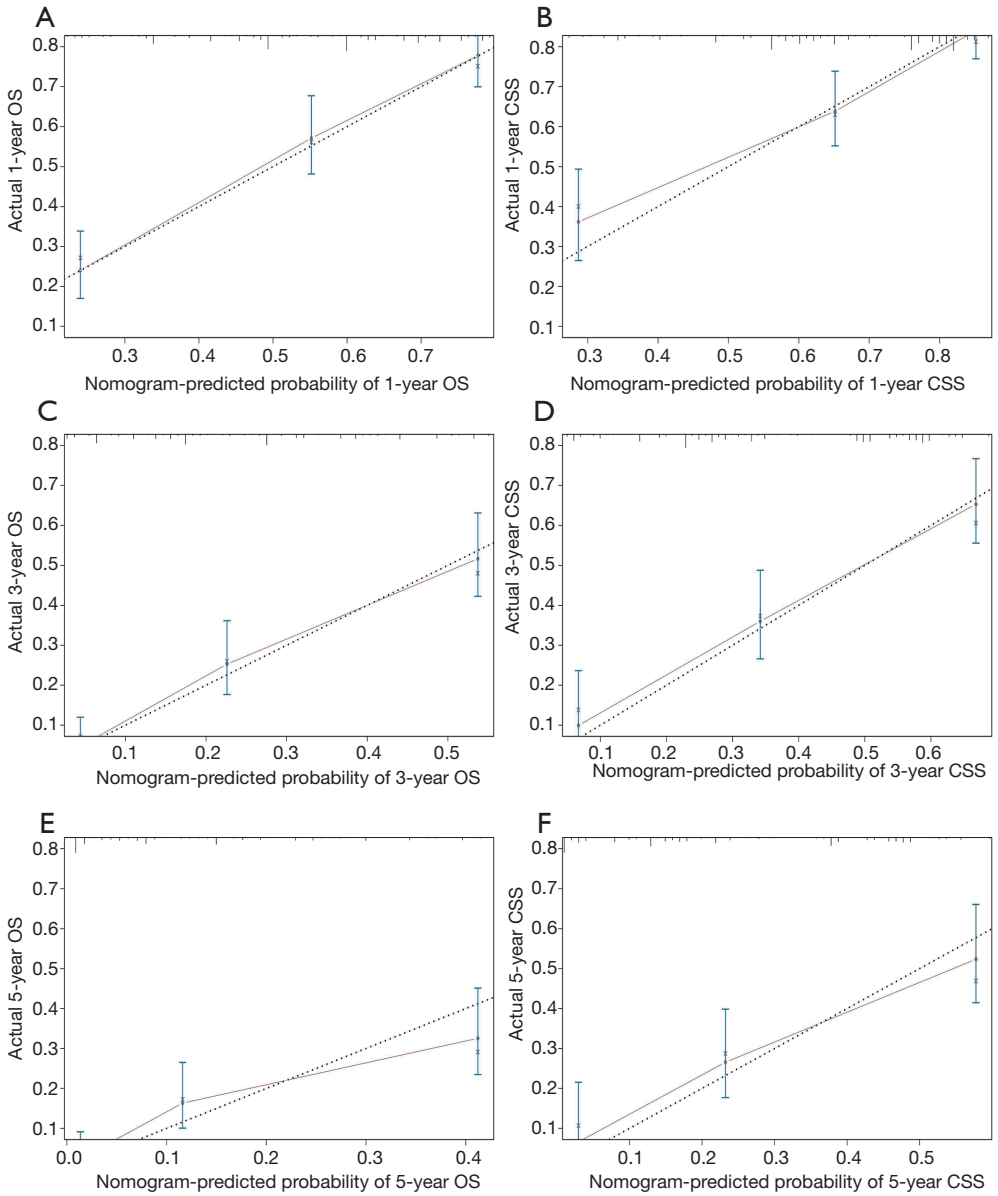

Figure 3 Nomogram model calibration curves. The calibration curves of the 1-year OS (A) and CSS (B); 3-year OS (C) and CSS (D); and 5-year OS (E) and CSS (F). (bootstrap method, 1,000 repetitions). X-axis: predicted probability of survival derived from nomogram; Y-axis: actual probability of survival. The calibration curves demonstrated that the predicted outcome shows appreciable accordance with the actual survival. OS, overall survival; CSS, cancer-specific survival.

and retrospective study design allows for the existence of confounding factors. In addition, some important data (e.g., lymphovascular invasion, adjuvant intravesical therapy, chemotherapy or radiotherapy type, and the use of new drugs) that may have affected the oncological outcomes were not available in this study. At the same time, some accurate information is missing. For example, the category "Unknown" was assigned to the tumor size and LNR, which might have led to information bias and could have influenced the HR of the variables. Furthermore, despite the nomograms reflecting satisfactory predictive efficacy, because of the limited number of patients in the cohort and retrospective nature of the study, external verification should be performed before being formally applied in

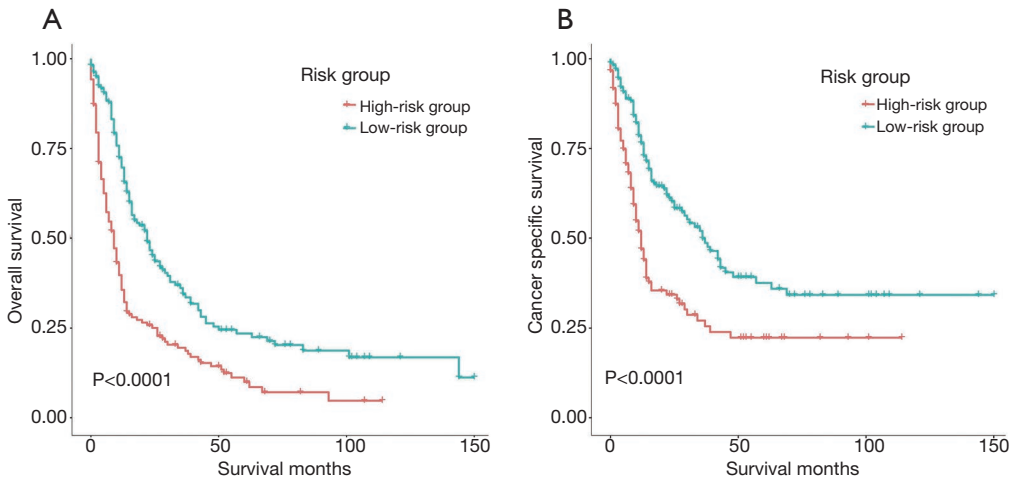

Figure 4 Kaplan-Meier survival curves of patients with primary SRCC stratified by different risk groups based on the nomogram. (A) Overall survival; (B) cancer-specific survival. SRCC, signet ring cell carcinoma.

clinical practice to further verify the results. Finally, the data were derived only from the population covered by the SEER, and our findings may not be generalizable to other geographic locations.

Conclusions

Our analysis demonstrated several clinicopathological factors and cancer therapy strategies that could predict survival outcomes in patients with SRCC. Based on these predictive parameters, we plotted the quantitative nomograms and identified their high accuracy and reliability in estimating the survival of individuals. Thus, these nomograms can help clinicians assess the risk of SRCC and provide personalized treatment plans.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-929). 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). As data from the SEER program is available for the public and does not need patient informed consent, and ethical approval was waived by the local Ethics Committee of Beijing Hospital.

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