Prognostic Nomograms for Patients with Primary Sarcomatoid Carcinoma of The Urinary Bladder: Based on The SEER Database

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Purpose: The present study aimed to develop nomograms based on the SEER database to predict the prognosis for patients with primary sarcomatoid carcinoma of the urinary bladder (SCUB).

Materials and Methods: Patients with primary SCUB were identified in the Surveillance, Epidemiology, and End Results (SEER) database, between 1975 and 2017. Univariate and multivariable Cox analysis were conducted to identify the independent prognostic factors for developing the overall survival (OS) and cancer-specific survival (CSS) nomograms. Then, concordance index (C-index), receiver operating characteristic (ROC) curve and calibration curve were used to evaluate the accuracy of the nomogram model. In addition, the model was further compared with TNM staging system.

Results: A total of 238 eligible patients with primary SCUB were selected from the SEER database. As suggested by Cox-analysis, age, sex, T stage, M stage, tumor size, and surgery type of primary site were identified as the independent factors for predicting both OS and CSS. We developed OS and CSS nomograms with a favorable C-index by using these prognostic factors. The C-indexes of the OS and CSS nomogram in the present study were 0.738 (0.701-0.775) and 0.763 (0.724-0.802), which were superior to those of the AJCC TNM staging with 0.621 (0.576-0.666) and 0.637 (0.588-0.686) respectively, showing better discriminatory ability. Subsequently, the ROC curves showed that the 1-, 3- and 5-year AUCs (area under the curve) of OS nomogram (i.e., 0.793, 0.807 and 0.793) were higher than those of the TNM stage((i.e., 0.659, 0.676, 0.659). Similarly, as for CSS model, them ((i.e., 0.823, 0.804 and 0.804) were aslo exceed those of TNM stage((i.e., 0.683, 0.682, 0.682). Furthermore, the calibration curves indicated a good consistency between the predictive survival and the actual survival. Finally, patients were stratified by risk, and Kaplan-Meier survival curve suggested that the prognosis of the low-risk group was significantly better than that of the high-risk group.

Conclusion: We developed nomograms with the SEER database, which could help predict the prognosis of SCUB individuals more accurately.

Keywords: nomogram; sarcomatoid carcinoma; bladder cancer; SEER; prognostic analysis

INTRODUCTION

Bladder cancer is the 10th most commonly diagnosed cancer worldwide, with approximately 573,000 new cases and 213,000 deaths in 2020, and it ranks higher among men, for whom it is the 6th most common cancer and the 9th leading cause of cancer death.[1] Urothelial carcinoma is the most common type of bladder cancer, and urothelial carcinoma has a propensity for divergent differentiation, such as squamous, adenocarcinoma, plasmacytoid.[2] Sarcomatoid carcinoma of the urinary bladder(SCUB) is a rare and prominent variant of bladder urothelial carcinoma, which was initially described as carcinosarcoma by Dent.[3,4] Since SCUB has both epithelial and mesenchymal biphasic differentiation, different names have been used to name this biphasic tumor, such as sarcomatoid carcinoma, carcinosarcoma and pseudosarcomatoid carcinoma.[5] To avoid confusion in understanding and naming of this type of tumor, SCUB was first defined by the 2004 WHO classification as all bipolar malignant tumors with epithelial and mesenchymal differentiation.[6] It unifies the different names used for the same lesions in different literatures and avoids the confusion of understanding between pathologists and clinicians.

According to previous studies, SCUB accounts for only 0.1 % ~ 0.6 % of all bladder cancer, and the age-adjusted incidence is about 0.02 %, it typically showed high histologic grade, advanced-stage, and poor prognosis.[3,7-12] Since such cases are rare, only case reports and small case series are available, preclude full understanding clinical characteristics and prognostic factors of this disease.[7,9,12-14] Due to the lacking evidence, the optimal management for SCUB is not settled, and clinical management are mostly empirical and may vary in different institutions, often delay the treatment.[15] Additionally, it is unlikely to get a solution through large clinical trials due to its rarity. Surveillance, Epidemiology, and End Results(SEER) is one of the largest and highest authoritativeness cancer databases in the world, which collects data on cancer diagnoses, treatment, and survival for approximately 30% of the United States (US) population spans different geographic regions that can represent population diversity.[16,17] The SEER database provides clinical information on a variety of

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Table 1. Clinic characteristics of the primary SCUB patients in our study

Characteristics	N(%)
Total	238 (100)
Age (year)	
<60	49 (20.6)
60-82	132 (55.5)
≥83	57 (23.9)
Sex	
Male	162 (68.1)
Female	76 (31.9)
Race	
White	200 (84.0)
Black	27 (11.3)
Other[a]	11 (4.6)
Siteb	
C67.1	13 (5.5)
C67.2	46 (19.3)
C67.3	7 (2.9)
C67.4	13 (5.5)
C67.5	3 (1.3)
C67.6	3 (1.3)
C67.7	2 (0.8)
C67.8	38 (16.0)
C67.0	11 (4.6)
C67.9	102 (42.9)
Grade	
I/II	4 (1.7)
III	75 (31.5)
IV	98 (41.2)
Unknown	61 (25.6)
Histology	
Pseudosarcomatous carcinoma	134 (56.3)
Carcinosarcoma	104 (43.7)
Stage T	
T1	57 (23.9)
T2	76 (31.9)
T3	59 (24.8)
T4	44 (18.5)
Tis	2 (0.8)
Stage N	
N0	214 (89.9)
N1-N3	24 (10.1)
Stage M	
M0	212 (89.1)
M1	26 (10.9)
Tumor size(mm)	
< 50	57 (23.9)
50-99	72 (30.3)
≥100	30 (12.6)
Unknown	79 (33.2)
Surgery of primary site	
None[c]	7 (2.9)
Non-complete cystectomy	140 (58.8)
Complete cystectomy	91 (38.2)

[a] Other: American Indian/AK Native, Asian/Pacific Islander
[b] Site (primary tumor site): C67.0-Trigone of bladder, C67.1-Dome of bladder, C67.2-Lateral wall of bladder, C67.3-Anterior wall of bladder, C67.4-Posterior wall of bladder, C67.5-Bladder neck, C67.6-Ureteric orifice, C67.7-Urachus, C67.8-Overlapping lesion of bladder, C67.9-Bladder, NOS (unknow)
[c] None: none of surgery

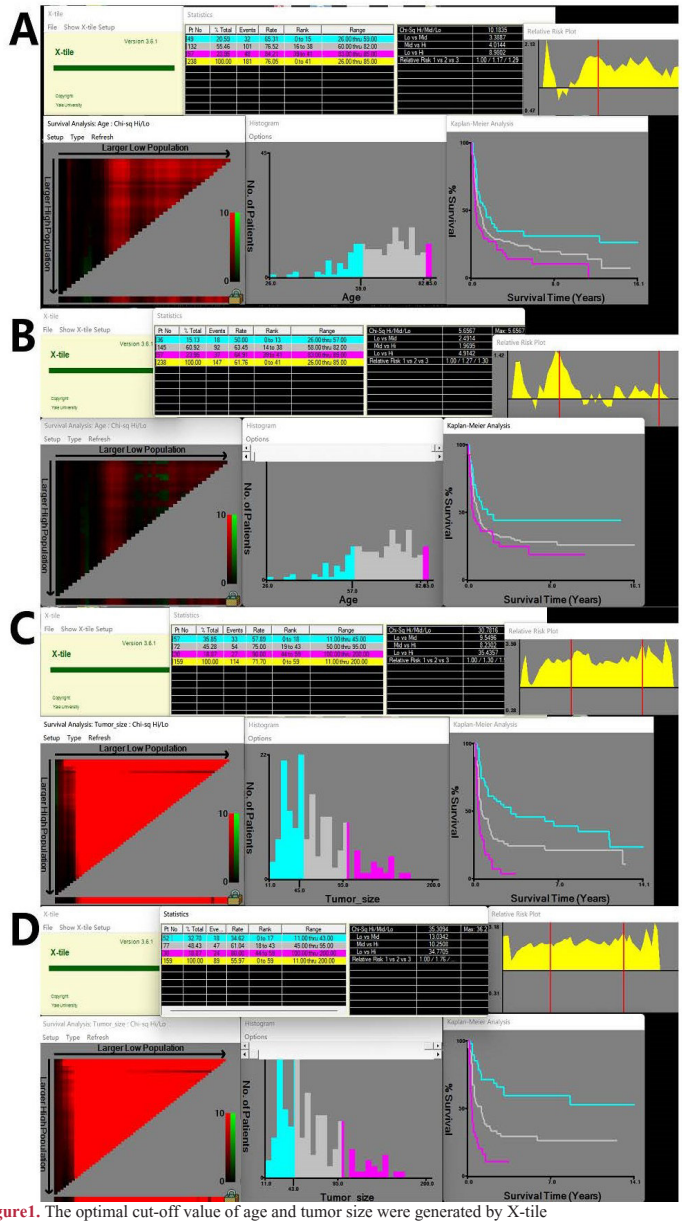

Figure1. The optimal cut-off value of age and tumor size were generated by X-tile The optimal cutoff value of age for OS. **(B)** The optimal cutoff value of age for CSS . **(C)** The optimal cutoff value of tumor size for OS. **(D)** The optimal cutoff value of tumor size for CSS.

tumors, which have high clinical value, especially for relative rare tumors.[18,19] In recent years, more and more research on tumor diseases has been carried out with the SEER database.[20,21]

Besides, the TNM (tumor node metastasis) staging system which was established by American Joint Committee for Cancer (AJCC), is a prevalent method in making prognostic estimates and therapeutic decisions for bladder cancer patients.[22,23] But, TNM classification is not a strong predictor that encompasses cancer biology as well as to accurately predict outcomes. Due to the various factors that may affect prognosis in bladder cancer patients, including sex, race, age, tumor grade, tumor site and therapy, the evaluation of cancer prognosis by AJCC TNM staging merely is irrational and unrealistic. [24-26] Thus, establishing a novel method involving tumor features and patient status is a pressing demand. Nomogram is a good approach for this purpose, which is widely used as prognostic devices in oncology.[27] Nomogram provide a risk of a particular event based on a variety of information integrated in a mathematical model, making it personalized and visual.[28] Compared to conventional staging, it performs rapid computation through a user-friendly digital interface, while improving accuracy and a more understandable prognosis to aid clinical decision-making.[27] In recent years, nomogram has been utilized as a handy and reliable tool for predicting the prognosis of various cancer patients by more and more studies.[17,29-34] Unfortunately, no nomogram has been reported to predict the prognosis of SCUB patients.

Table 2. Univariate and multivariable-Cox analysis of OS

Variables	Univariate Analysis HR (95%CI)	*P*-value	Multivariable Analysis HR (95%CI)	*P*-value
Age(year)				
<60	Reference		Reference	
60-82	1.47 [0.98;2.19]	.062	1.70 [1.10;2.63]	.018
≥83	2.09 [1.33;3.29]	.001	2.58 [1.54;4.33]	< 0.001
Sex				
Male	Reference		Reference	
Female	1.42 [1.04;1.94]	.029	1.811 [1.24;2.64]	.002
Race				
White	Reference			
Black	1.17 [0.75;1.83]	.49		
Other	0.91 [0.427;1.95]	.811		
Site				
C67.1	Reference		Reference	
C67.2	1.09 [0.58;2.05]	.781	0.95 [0.49;1.85]	.886
C67.3	0.81 [0.41;1.62]	.553	0.85 [0.41;1.73]	.645
C67.4	2.56 [0.99;6.64]	.053	1.71 [0.62;4.77]	.304
C67.5	0.93 [0.39;2.25]	.874	0.95 [0.38;2.36]	.904
C67.6	0.59 [0.13;2.66]	.49	0.26 [0.05;1.32]	.104
C67.7	0.54 [0.12;2.43]	.419	0.39 [0.08;1.88]	.239
C67.8	7.60 [1.63;35.37]	.01	1.83 [0.34;9.84]	.483
C67.0	0.69 [0.34;1.41]	.311	0.63 [0.29;1.33]	.222
C67.9	1.05 [0.45;2.48]	.913	1.18 [0.48;2.89]	.718
Grade				
I/II	Reference			
III	2.74 [0.67;11.23]	.161		
IV	1.92 [0.47;7.83]	.366		
Unknown	2.74 [0.66;11.29]	.163		
Histology				
Pseudosarcomatous carcinoma	Reference		Reference	
Carcinosarcoma	0.73 [0.54;0.98]	.038	0.97 [0.70;1.35]	.855
Stage-T				
T1	Reference		Reference	
T2	1.64 [1.07;2.52]	.023	1.99 [1.23;3.21]	.005
T3	1.69 [1.09;2.62]	.018	3.72 [2.16; 6.42]	< 0.001
T4	3.11 [1.96;4.94]	< 0.001	4.01 [2.25;7.14]	< 0.001
Tis	1.94 [0.47;8.09]	.363	1.14 [0.26;5.12]	.861
Stage-N				
N0	Reference		Reference	
N1-N3	1.71 [1.08;2.70]	.022	1.18 [0.69;2.03]	.552
Stage-M				
M0	Reference		Reference	
M1	2.79 [1.80;4.31]	< 0.001	1.92 [1.12;3.29]	.017
Tumor size (mm)				
< 50	Reference		Reference	
50-99	1.93 [1.25;2.99]	.003	1.96 [1.21;3.17]	.006
≥100	4.02 [2.39;6.76]	< 0.001	3.35 [1.84;6.10]	< 0.001
Unknown	2.24 [1.48;3.41]	< 0.001	2.73 [1.72; 4.34]	< 0.001
Surgery of primary site				
None	Reference		Reference	
Non-complete cystectomy	0.73 (0.34;1.56)	.414	0.42 [0.18;0.98]	.044
Complete cystectomy	0.37 (0.17;0.80)	.012	0.17 [0.07;0.41]	< 0.001

The purpose of the present study was to utilize the relatively large samples available in the SEER database to develop nomograms to help identity clinical features and predict the prognosis of primary SCUB patients more precisely, expected to promote the development of risk-based individualized treatment and optimal treatment strategies.

PATIENTS AND METHODS

The SEER database has been approved for public use by the local ethics committee. To collect related information from this database, the SEER Research Data Agreement (ID: 20358-Nov2019) was signed in this study, and the extracted data were publicly accessible and already de-identified. Hence, the present study is waived from ethical approval. Also, the study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Obtained information from the SEER Database

For the present study, the patient data of primary SCUB from 1975 to 2017 and whose tumor location and histological type codes were referenced in the ICD-O-3 (International Classification of Diseases for Oncology, 3rd), which were obtained from the SEER database (www.seer.cancer.gov) using the SEER*Stat software (SEER*Stat 8.3.9, released March 15, 2021).

The inclusion criteria were: 1)First primary malignant-bladder cancer, 2)Positive histology confirmation, 3)Histology type was “Sarcomatoid Carcinoma”: 8033/3-Pseudosarcomatous Carcinoma, 8980/3-Carcinosarcoma.

Patients were excluded if: 1) Bladder cancer was diagnosed at autopsy only or was found in the death certificate only, 2) With uncomplete or unknown T/N/M stage information, 3)Missing or unknown cause of death, 4) Unknown surgical status, 5)Unknown survival status, 6)Unknown survival time.

The following patient characteristics were analyzed, including:(1) age (age at diagnosis), (2) sex, (3) race,

Table3. Univariate and multivariable-Cox analysis of CSS

Variables		Univariate Analysis HR (95%CI)	*P*-value	Multivariable Analysis HR (95%CI)	*P*-value
Age					
	<58	Reference		Reference	
	58-82	1.49 [0.90;2.47]	.123	2.08 [1.18;3.65]	.011
	≥83	1.96 [1.12;3.46]	.019	3.10 [1.60;5.96]	.001
Sex					
	Male	Reference		Reference	
	Female	1.46 [1.03;2.06]	.032	2.25 [1.48;3.41]	< 0.001
Race					
	White	Reference			
	Black	1.04 [0.62;1.75]	.887		
	Other	1.08 [0.51;2.32]	.838		
Site					
	C67.1	Reference		Reference	
	C67.2	1.38 [0.63;3.00]	.419	1.16 [0.52;2.62]	.713
	C67.3	1.07 [0.47;2.47]	.865	1.18 [0.50;2.80]	.704
	C67.4	2.79 [0.88;8.81]	.081	1.82 [0.53;6.26]	.341
	C67.5	0.90 [0.30;2.68]	.852	0.93 [0.30;2.84]	.893
	C67.6	0.43[0.05;3.53]	.436	0.13 [0.02;1.17]	.069
	C67.7	0.93 [0.19;4.49	.93	0.77 [0.15;3.98]	.755
	C67.8	12.16 [2.44;60.75]	.002	2.44 [0.41;14.45]	.325
	C67.0	0.95 [0.41;2.24]	.91	0.88 [0.36;2.134]	.771
	C67.9	1.09 [0.38;3.10]	.877	1.30 [0.44;3.89]	.639
Grade					
	I/II	Reference			
	III	1.84 [0.45;7.59]	.397		
	IV	1.50 [0.37;6.16]	.571		
	Unknown	2.14 [0.52;8.87]	.292		
Histology					
	Pseudosarcomatous carcinoma	Reference			
	Carcinosarcoma	0.78 [0.57;1.09]	.141		
Stage T					
	T1	Reference		Reference	
	T2	1.76 [1.08;2.85]	.022	2.34 [1.37;4.00]	.002
	T3	1.69 [1.02;2.79]	.04	4.03 [2.19;7.42]	< 0.001
	T4	3.46 [2.08;5.75]	< 0.001	4.88 [2.59;9.21]	< 0.001
	Tis	1.18 [0.16;8.73]	.869	0.76 [0.10;5.88]	.789
Stage N					
	N0	Reference		Reference	
	N1-N3	1.80 [1.10;2.96]	.02	1.17 [0.65;2.10]	.611
Stage M					
	M0	Reference		Reference	
	M1	3.14 [1.98;4.97]	< 0.001	2.36 [1.31;4.23]	.004
Tumor size (mm)					
	<45	Reference		Reference	
	45-99	2.54 [1.47;4.38]	.001	2.49 [1.38;4.48]	.002
	≥100	5.74 [3.08;10.67]	< 0.001	4.27 [2.11;8.66]	< 0.001
	Unknown	3.30 [1.94;5.60]	< 0.001	4.15 [2.33;7.39]	< 0.001
Surgery of primary site					
	None	Reference		Reference	
	Non-complete cystectomy	0.66 [0.29;1.51]	.328	0.36 [0.15;0.90]	.029
	Complete cystectomy	0.33 [0.14;0.77]	.01	0.15 [0.06;0.40]	< 0.001

(4) site, (5) grade, (6) histology, (7) stage T, (8) stage N: (9) stage M, (10) tumor size(mm), (11) surgery of primary site.

As shown in Figure 1, age and tumor size were categorically divided based on the optimal cut-off value generated by X-tile software version 3.6.1 (Yale University School of Medicine, US). Based on the optimal cutoff value, the two continuous variables were converted into classification variables, age were divide into three groups (< 60, 60 –82, ≥ 83 years old for OS; < 58, 58-82, ≥ 83 years old for CSS), and tumor size divide into three groups(tumor size < 50, 50-99, ≥100 mm for OS; < 45,45-99, ≥100mm for CSS).

Race was classified into white, black and other (American Indian/AK Native, Asian/Pacific Islander). Site (primary tumor site) was divided accord to ICD-O-3: "C67.0-Trigone of bladder, C67.1-Dome of bladder, C67.2-Lateral wall of bladder, C67.3-Anterior wall of bladder, C67.4-Posterior wall of bladder, C67.5-Bladder neck, C67.6-Ureteric orifice, C67.7-Urachus, C67.8-Overlapping lesion of bladder, C67.9-Bladder, NOS". Grade was categorized into I, II, III, IV and unknown. Histology was classified into: "8033/3-Pseudosarcomatous Carcinoma, 8980/3-Carcinosarcoma". When defining T-N-M staging: Tis, T1, T2, T3, T4; N0, N1-3(N1, N2, N3); M0, M1. As for surgery of primary site, it was classified as: none of surgery, non-complete cystectomy, complete cystectomy. Details are presented in **Table 1**.

Overall survival (OS) was the first endpoint, defined as the time from diagnosis of SCUB to death due to any cause. Cancer-specific survival (CSS) was the second endpoint, defined as the time from diagnosis of SCUB to death due to this malignant disease. Survival time (in months) was set as the time from SCUB diagnosis to death or date of last follow-up time (the specific definition process of disease survival time in the SEER database can be obtained at: https://seer.cancer.gov/surviv-

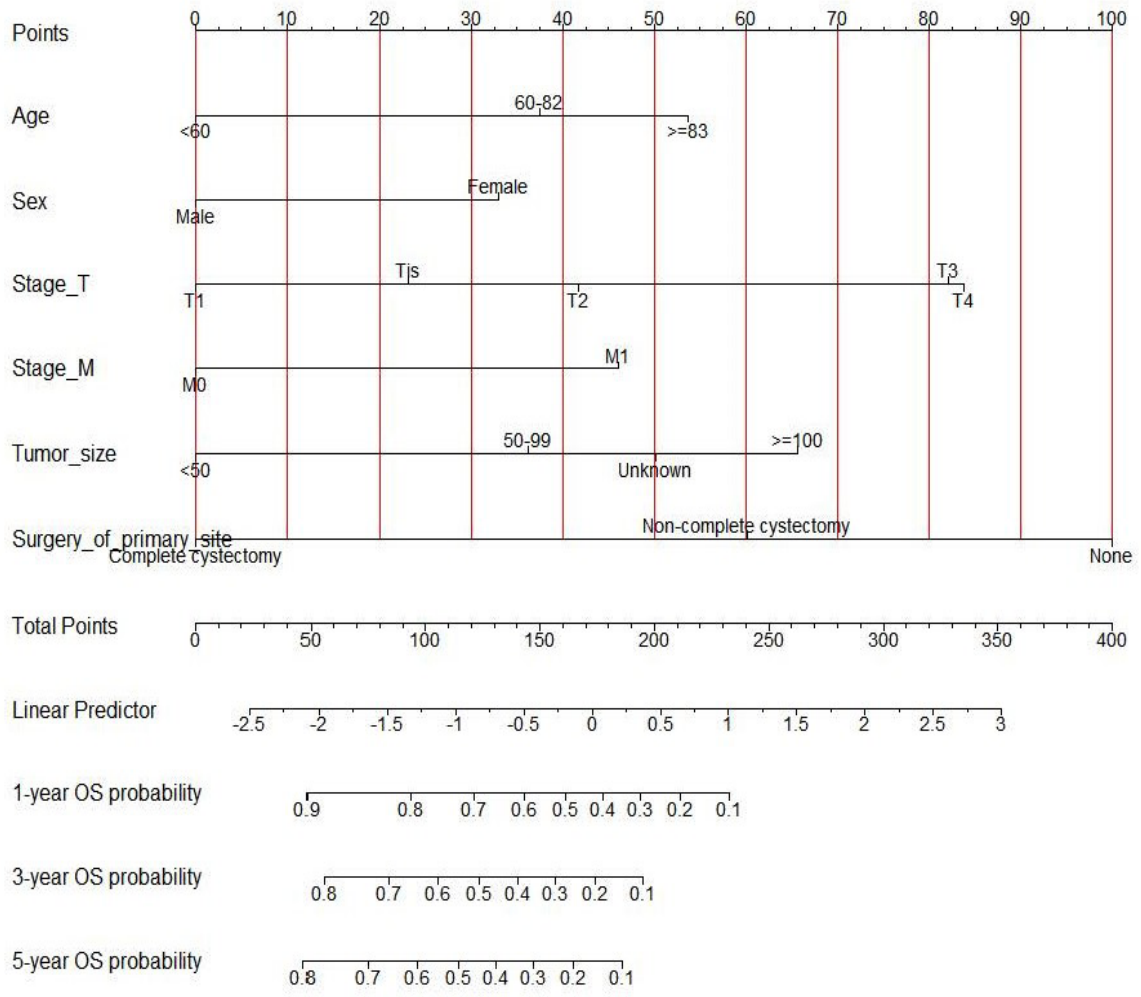

Figure 2. The nomogram for predicting 1- ,3- and 5-year OS of SCUB patients

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Statistical analysis

All statistical analyses in our research were performed by R Studio software (1.4.1106, based on R 4.0.5). Univariate Cox analysis was used to screen out significant variables ($P < 0.1$) for further multivariate analysis. Multivariable Cox regression analysis models were used to select out significant independent prognostic factors for the OS and CSS. The variables incorporated into the multivariable Cox models were checked whether they fit the proportional hazards (PH) assumption. Statistical significance was accepted at the $P < 0.05$ level, but only in univariate analysis it was accepted at the $P < 0.1$ level.

Specifically, potential prognostic factors with significant statistical significance were screened out by univariate-Cox regression, which was used to select out independent prognostic factors by multivariable-Cox regression afterwards. Then, these independent factors were used to develop the OS and CSS nomograms, and the TNM staging system was used to develop similar nomograms. Furthermore, the performance of the nomograms was evaluated by concordance-index (C-index), calibration plots and the area under curve (AUC) of the receiver operating characteristic (ROC) curve. Simultaneously, the C-indexs and AUCs of the nomograms in this study were compared with those of TNM staging system. Besides, patients were divided into high-risk and low-risk group with the cut-off value set at the median risk, estimated in the Kaplan-Meier method and drew the survival curves.

RESULTS

Population characteristics of the present study

By reviewing the SEER database, a total of 652 primary SUCB patients were identified based on inclusion criteria, accounting for approximately 0.19% of the total BC patients (341163 cases). Based upon the exclusion criteria, 238 primary SCUB patients were finally included in the present study. Overall clinical characteristics of these primary SUCB patients have been compiled in Table 1. The longest follow-up time was 193 months, the median of the follow-up time was 7 months (IQR 3-28). A total of 181 (76%) patients had died by the last follow-up date, of which 147 (81.2%) had died from SCUB and 34 (18.8%) from other causes. A total of 57 (24%) patients were alive by the last follow-up date.

Univariate and multivariable-Cox analysis of OS and CSS

The results of the univariate and multivariable-Cox

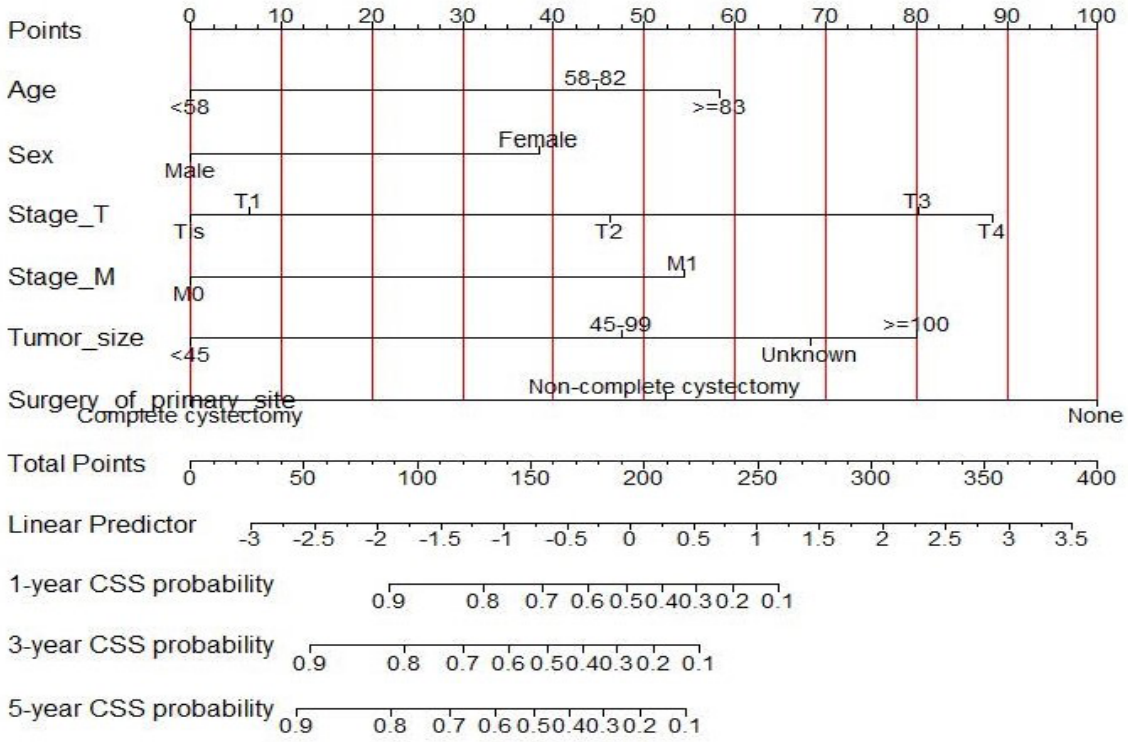


Figure 3. The nomogram for predicting 1- ,3- and 5-year CSS of SCUB patients

analysis of OS are shown in **Table 2**. First, nine potential factors were screened out by univariate Cox regression model of OS, including age, sex, site, histology, stage T, stage N, stage M, tumor size, surgery of primary site.

Then, multivariable Cox regression model screened out significant independent prognostic factors, including age, sex, stage T, stage M, tumor size, surgery of primary site.

As shown in **Table 3**, we screened out significant independent factors of CSS (including age, sex, stage T, stage M, tumor size, surgery of primary site) in the same method.

We found that several of these variables (including sex, histology, and stage T) violated the PH assumption in OS model and one of these variables (sex) violated the PH assumption in CSS model, which were incorporated into the multivariable Cox models. However, these variables are significant according to the univariate Cox analyses, and in consideration of their clinical significance and their presences improving the fit of the model, we included them in the multivariable Cox analyses. Both the OS and CSS multivariable-Cox models fitted the PH assumption. Continuous variables (age, tumor size) had been converted to categorical variables, so the linearity was not assessed.

Nomograms of OS and CSS

The results showed that age, sex, stage T, stage M, tumor size and surgery of primary site were significant independent prognostic factors of both OS and CSS for SCUB patients. We established nomograms of OS (**Figure 2**) and CSS (**Figure 3**). Each factor was scored through the model, the total score of each patient was determined according to the prognostic value of each prognostic factor, which was used to predict 1-, 3- and 5-year survival probability based on the fractional proportion at the bottom of the nomogram. The C-indexes of the OS and CSS nomogram in present study were 0.738 (0.701-0.775) and 0.763 (0.724 - 0.802) respectively, showing high accuracy.

If TNM staging system was used to develop the OS and CSS nomogram (Figure 4) only, their C-indexes were 0.621 (0.576-0.666) and 0.637 (0.588-0.686), respectively. Specifically, the C-indexes of our models were superior to those of TNM staging system only, showing better performance to predict the 1-, 3- and 5-year survival of SCUB patients.

Subsequently, the AUC of ROC curve and calibration plot were performed to evaluate the discrimination, calibration and clinic utility of the nomograms. The ROC curve (**Figure 5**) showed that the 1-, 3- and 5-year AUCs (area under curve) of OS nomogram (i.e., 0.793, 0.807 and 0.793) were higher than those of the TNM stage(i.e., 0.659, 0.676, 0.659). Similarly, as for CSS model, them ((i.e., 0.823, 0.804 and 0.804) were aslo exceed those of TNM stage(i.e., 0.683, 0.682, 0.682). The C-index combined with the AUCs reflected good discrimination ability of the models.

Meanwhile, high quality of calibration plots based on bootstrap resampling validation both in OS and CSS nomogram, showed excellent consistency between the observed and predicted values (**Figure 6**).

As shown in Figures 7, when all patients were divided into high-risk and low-risk groups, with medium risk as the cutoff point, the Kaplan-Meier survival curves of OS and CSS both showed significant differences in prognosis($P < 0.0001$). In other words, the prognosis of

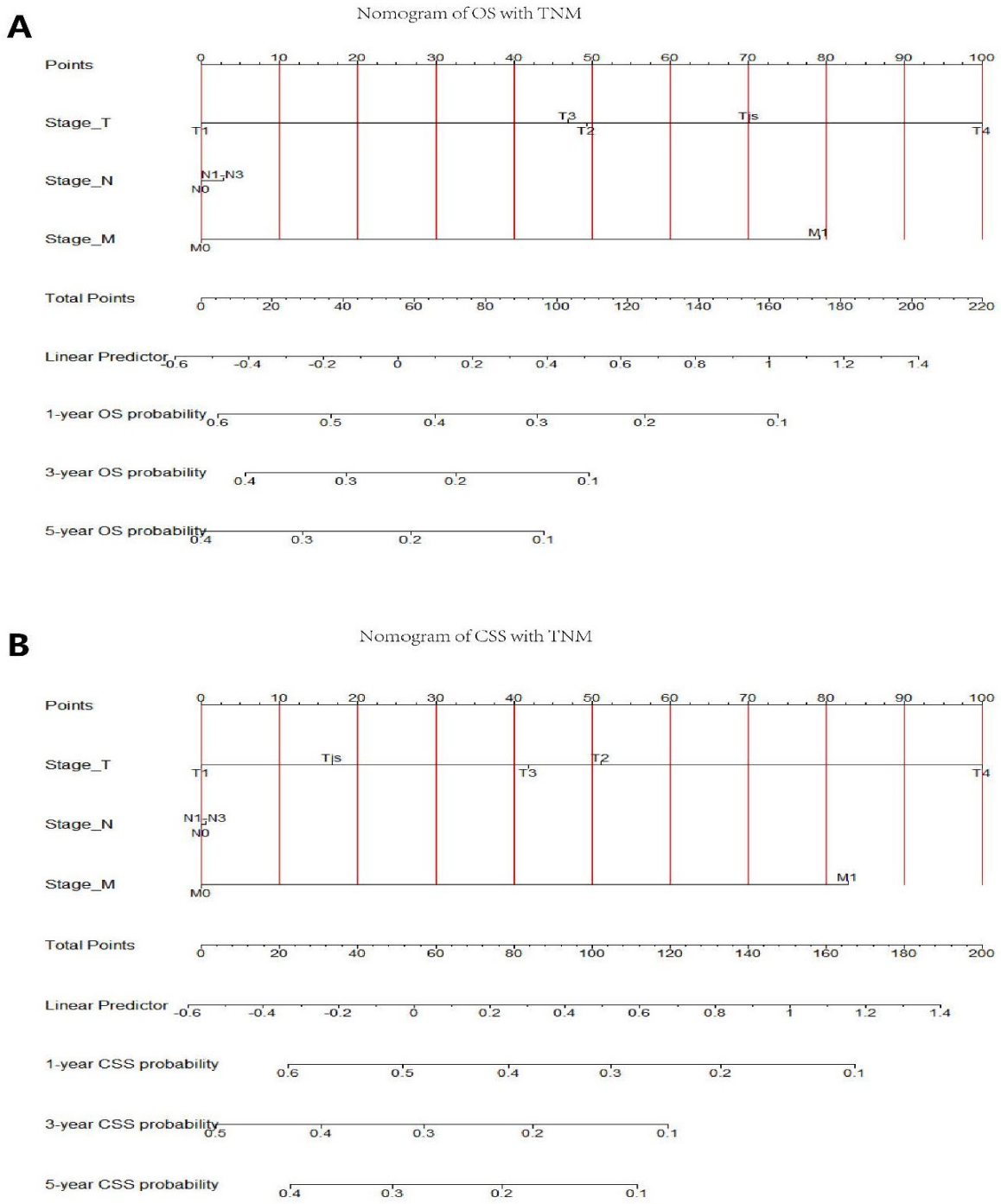


Figure 4. The nomograms with TNM staging system only
The nomogram for predicting 1- ,3- and 5-year OS of SCUB patients with TNM staging system only. **(B)** The nomogram for predicting 1- ,3- and 5-year CSS of SCUB patients with TNM staging system only.

the low-risk group was significantly better than that of the high-risk group.

DISCUSSION

SCUB is a rare and special type of bladder cancer, accounts for 0.1 % ~ 0.6 % of all such bladder cancer cases.[3,7-12] In line with these prior reports, we found that it was approximately 0.19% (652/341163) of primary bladder cancer patients in the SEER database from 1975-2017. Rare large-scale clinical studies of SCUB have been carried out as yet and case reports are the primary sources of information, the medical knowledge of it is very limited by now. Although few published studies have found that SCUB is a highly malignant disease with poor prognosis, the prognostic factors and the effectiveness of surgical treatment are still unclear. To better understand this disease, a comprehensive prognosis analysis of SCUB cases in the SEER database was conducted in our study.

Currently, the AJCC TNM staging is considered as an

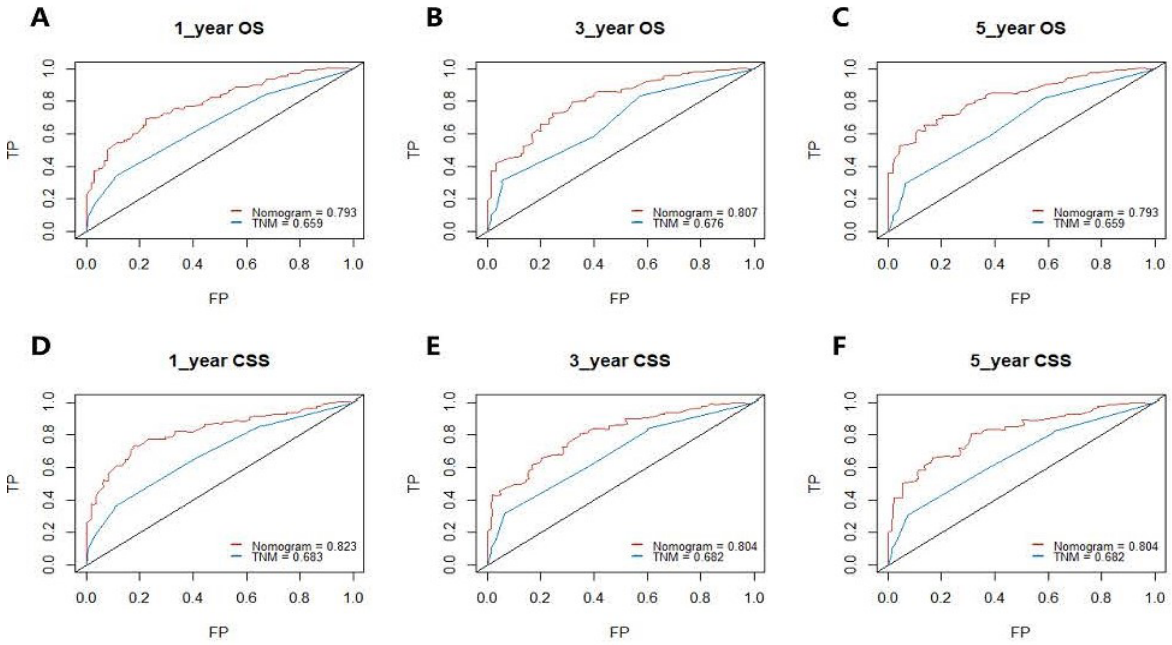
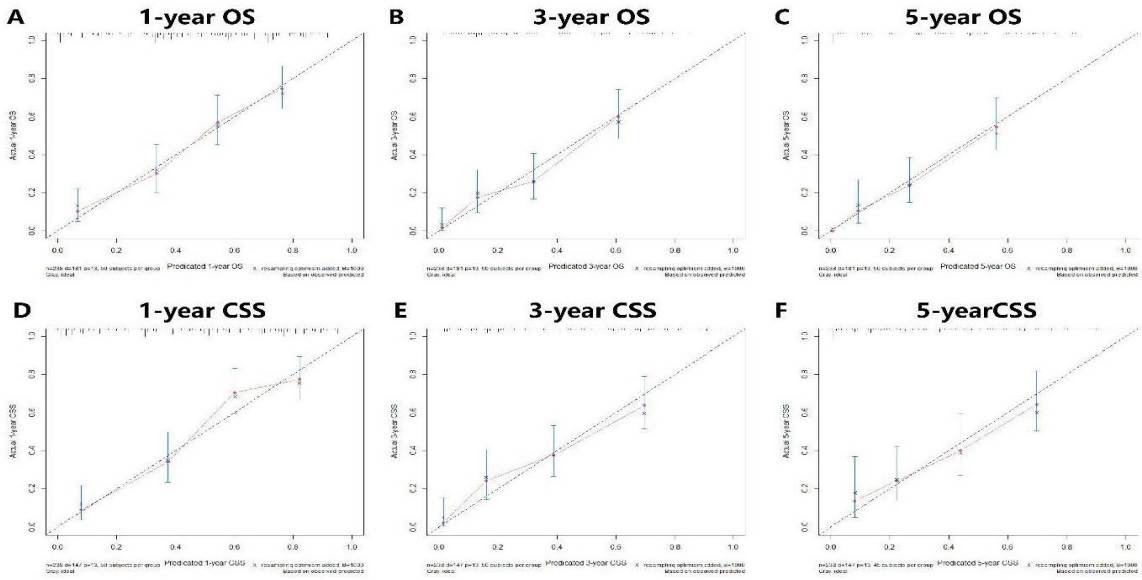


Figure 5. The ROC curves and AUC-values of our nomograms and TNM stage nomograms
(A-C) 1-, 3-, and 5- year OS. **(D-F)** 1-, 3-, and 5- year CSS.

excellent staging form of bladder cancer and is closely related to its prognosis, but it still cannot effectively predict the survival of the patients.[24,35] In a study of earlier data, TNM was not analyzed to draw conclusions, only summary stage (In situ, Localized, Regional, Distant) was found to be a significant prognostic factor for disease-specific survival.[10] But, according to the follow-up data of SEER, our study found that the prognosis of SCUB patients with the same TNM stage or summary stage were vastly different. For example, the survival time of T3N0M0 patients ranged from 1 month to 148 months after diagnosis, and the longest was still alive in 169 months. The survival time of each summary stage or other TNM stage also have similar situations.

In previous studies on bladder cancer, potential prognostic factors were found through the construction of novel nomograms, for example, age, gender, ethnicity, stage, grade, tumor size, surgery, variant histology have been identified using this approach.[34-36] In this study, 6 variables were identified as independent predictors of prognosis from 11 variables to construct our nom-



Figures 6. The calibration plots of our OS and CSS nomogram
(A-C) The calibration plots based on bootstrap resampling validation of 1-year, 3-year, and 5-year for OS nomogram. **(D-F)** The calibration plots based on bootstrap resampling validation of 1-year, 3-year , and 5-year for CSS nomogram. (B = 1000)

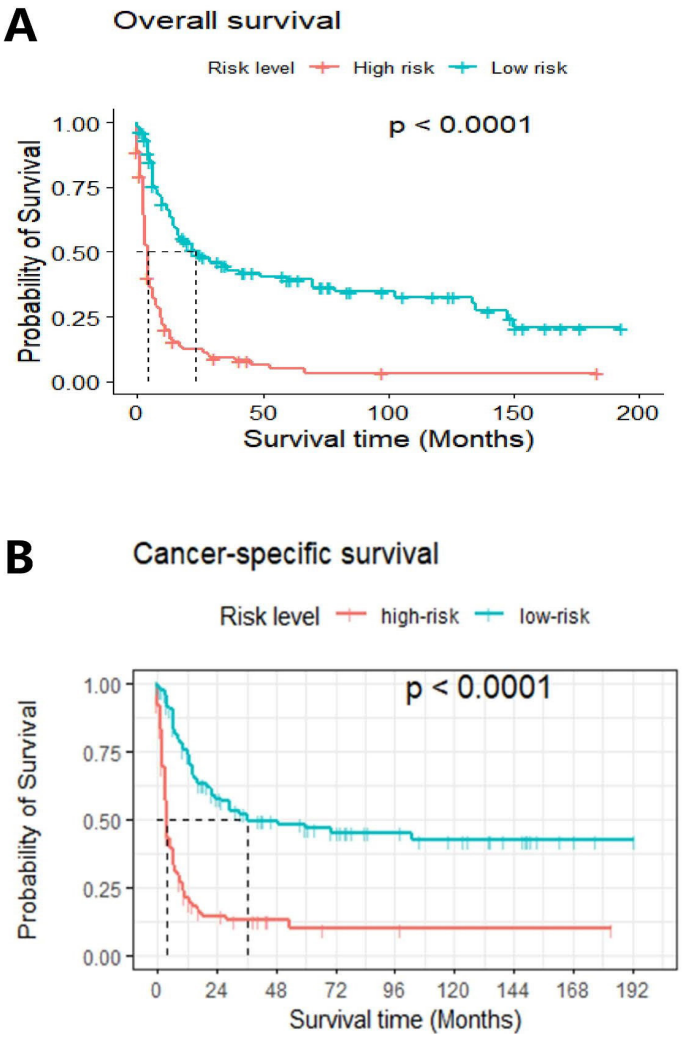


Figure 7. The KM survival curves when divided by risk
(A-B) When all patients were divided into high-risk and low-risk groups, the KM survival curves of OS and CSS. (both $P < .0001$)

ograms, including 2 personalized variables (age, sex), 3 variables about the tumor (tumor size, stage T, M), and 1 treatment variable (surgery of primary site). All 6 variables could be obtained easily, which facilitates the application of these nomograms in clinical practice. Clinicians could use these nomograms to predict 1-, 3- and 5- year survival rates of SCUB patients. For example, for an 85-year-old male patient presents with a 40-mm tumor, with T1 stage and with distant metastasis, with complete cystectomy primary tumor, the 1-, 3- and 5- year OS-rates will be over 70%, over 60%, below 60% respectively. the 1-, 3- and 5- year CSS-rates will be over 80%, about 70%, below 70% respectively.

Variant histologies (especially sarcomatoid carcinoma) in patients with bladder cancer have been associated with worse pathological stage at presentation[3,37]. We found that patients with SCUB who with deeper primary tumor invasion (higher T stage) and distant metastasis may have a worse prognosis, which is the same as previous studies on other types of bladder cancer and our general cognition. It implies the importance significance of early detection in improving the prognosis for patients with this kind of malignant tumor.

Among the variables included in these nomograms, we found the method used to treat the primary site was the most important prognostic factor for both OS and CSS. For example, for a 70-year-old female SCUB patient presents with a 45-mm tumor, with T2 stage and without distant metastasis, if these patients have undergone complete cystectomy, the 1-, 3-year, 5-year OS rates will be over 50%, according to our nomogram (the 1-year survival rate even more than 70%). If these patients undergone non-complete cystectomy, the 1-, 3-year, 5-year OS rates will be over 40%, roughly 20%, and below 20% respectively. However, if the patient refused any surgery, the 1- year survival rate will be below 20%, and it will be even both below 10% for the 3- and 5-year survival rates. It suggested that surgical intervention of primary tumor, especially radical resection, is an effective treatment for patients with this malignant disease, and emphasis on more active treatment of primary is needed. This phenomenon has an important reference value when we encounter the treatment choice of this kind of patients in clinic. A worse pathological stage at presentation potentially associated with positive surgical margins and residual disease after surgery with curative intent, may lead to a worse prognosis. It has been reported that positive surgical margins(PSMs) at radical cystectomy have a negative impact on survival disease-specific survival in patients with bladder cancer[38]. We speculate that the same phenomenon may occur in SUCB patients. Compared to negative surgical margins, PSMs may also have a negative impact on SUCB patients after surgical treatment. As far as we know, the current study is the first time to construct nomograms to predict the prognosis of SCUB patients, integrated personalized characteristics, AJCC TNM staging, tumor characteristics, and the treatment method. Although our nomograms were based on AJCC TNM staging, the C-indexes of these nomograms was higher than those of TNM staging system in both OS and CSS. Therefore, these nomograms showed improved power of discrimination. The C-index of these nomograms exceeded 0.7 for both OS and CSS, indicating the adequate power of discrimination[39]. Furthermore, the AUCs and the calibration curves of these nomograms indicated a good consistency between the actual survival and the predictive survival.

Nevertheless, several limitations of this study need to be pointed out. First, due to the rarity of SCUB, the sample capacity was still relatively insufficient, which may affect the quality of the results, and the internal or external validation was unable to be performed temporarily. Second, these nomograms only selected limited variables. Clinically, some patients with some patients with bladder cancer may accept a multimodal treatment potentially including neo- and adjuvant treatments[40,41], such as chemotherapy, targeted medicine and radiotherapy, which may also affect the prognosis. Regrettably, due to the lack of information on patient comorbidities, positive surgical margins, pathological data(e.g.percentage of sarcomatoid component, mitosis, necrosis), multimodal treatment, we were unable to assess the relationship between these variables and patient outcomes. When adding variables, the complexity of the nomograms may increase accordingly and may abate clinical utility. Whether it will improve the accuracy of these nomograms needs further study. Although

categorization of quantitative variables (e.g. age) may result in loss of power/inefficiency and residual confounding[42], there is no specific age values (85+) for those aged ≥ 85 years in SEER. so we could only convert it into categorical variable for statistical purposes. Moreover, being a retrospective study, it was thus susceptible to the potential selection bias and uncontrolled confounding factors.

Despite these limitations, this study provides a new perspective on SCUB, which will help future research pertaining to this rare disease and may offer valuable information for clinicians in the management and decision-making process of such patients. More high-quality and well-designed multi-institutional studies are needed, particularly in determining independent prognostic role and specifying optimal treatment. Additionally, more accurate pathological diagnosis, and more detailed available data from more countries are needed.

CONCLUSIONS

To summarize, we developed nomograms to predict 1-, 3- and 5-year overall and cancer-specific survival rates for SCUB patients. For SCUB patients, these nomograms are more practical and accurate for prognostic prediction compared with the AJCC staging system. We also anticipated it will improve awareness of this disease and help clinicians in the process of risk-based individualized management and decision-making for SCUB patients.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71: 209- 49.
2. Nigwekar P, Amin MB. The many faces of urothelial carcinoma: an update with an emphasis on recently described variants. Adv Anat Pathol. 2008;15:218-33.
3. Humphrey PA, Moch H, Cubilla AL, et al. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part B: Prostate and Bladder Tumours. Eur Urol. 2016;70:106-19.
4. DENT ED Jr. Carcinosarcoma (collision tumor) of the urinary bladder. J Urol.1955;74:104-8.
5. Sanfrancesco J, McKenney JK, Leivo MZ, Gupta S, Elson P, Hansel DE. Sarcomatoid Urothelial Carcinoma of the Bladder: Analysis of 28 Cases With Emphasis on Clinicopathologic Features and Markers of Epithelial-to-Mesenchymal Transition. Arch Pathol Lab Med. 2016;140:543-51.
6. Eble JN, Sauter G, Epstein JI, Sesterhen IA. World Health Organization Classification fo Tumour. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs.IARC Press. 2004.
7. Wright JL, Black PC, Brown GA, et al. Differences in survival among patients with sarcomatoid carcinoma, carcinosarcoma and urothelial carcinoma of the bladder. J Urol. 2007;178:2302-6; discussion 2307.
8. Cheng L, Zhang S, Alexander R, et al. Sarcomatoid carcinoma of the urinary bladder: the final common pathway of urothelial carcinoma dedifferentiation. Am J Surg Pathol. 2011;35:e34-46.
9. Fatima N, Canter DJ, Carthon BC, et al. Osunkoya AO. Sarcomatoid urothelial carcinoma of the bladder: a contemporary clinicopathologic analysis of 37 cases. Can J Urol. 2015;22:7783-7.
10. Wang J, Wang FW, Lagrange CA, Hemstreet Iii GP, Kessinger A. Clinical features of sarcomatoid carcinoma (carcinosarcoma) of the urinary bladder: analysis of 221 cases. Sarcoma, 2010;2010:454792.
11. Malla M, Wang JF, Trepeta R, Feng A, Wang J. Sarcomatoid Carcinoma of the Urinary Bladder. Clin Genitourin Canc. 2016;1:366-72.
12. Sui W, Matulay JT, Onyeji IC, et al. Contemporary treatment patterns and outcomes of sarcomatoid bladder cancer. World J Urol. 2017;35:1055-61.
13. Torenbeek R, Blomjous CE, de Bruin PC, Newling DW, Meijer CJ. Sarcomatoid carcinoma of the urinary bladder. Clinicopathologic analysis of 18 cases with immunohistochemical and electron microscopic findings. Am J Surg Pathol. 1994;18:241-9.
14. Robinson SP, Farooq A, Laniado M, Motiwala H. The demographic features, clinical outcomes, prognosis and treatment options for patients with sarcomatoid carcinoma of the urinary bladder: a single centre experience. Int Braz J Urol. 2018;44:45-52.
15. Amin MB. Histological variants of urothelial carcinoma: diagnostic, therapeutic and prognostic implications. Mod Pathol. 2009; 22:S96-118.
16. Duggan MA, Anderson WF, Altekruse S, Penberthy L, Sherman ME. The Surveillance, Epidemiology, and End Results (SEER) Program and Pathology: Toward Strengthening the Critical Relationship. Am J Surg Pathol. 2016;40:e94-102.
17. Diao JD, Ma LX, Wu CJ, et al. Construction and validation a nomogram to predict overall survival for colorectal signet ring cell carcinoma. Sci Rep. 2021;11:3382.
18. Xu Z, Wang L, Tu L, et al. Epidemiology of and prognostic factors for patients with sarcomatoid carcinoma: a large population-based study. Am J Cancer Res. 2020;10:3801-14.
19. Wagner MJ, Chau B, Loggers ET, et al. Long-term Outcomes for Extraskeletal Myxoid Chondrosarcoma: A SEER Database Analysis. Cancer Epidem Biomar. 2020;29:2351-7.
20. Leone JP, Graham N, Tolaney SM, et al.

Estimating long-term mortality in women with hormone receptor-positive breast cancer: The 'ESTIMATE' tool. Eur J Cancer. 2022;173:20-9.
21. Andrade KC, Khincha PP, Hatton JN, et al. Cancer incidence, patterns, and genotype-phenotype associations in individuals with pathogenic or likely pathogenic germline TP53 variants: an observational cohort study. Lancet Oncol. 2021;22:1787-98.
22. Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB. Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. Eur Urol. 2018;73:560-9.
23. Park JH, Moon KC. Tumor, Nodes, Metastases (TNM) Classification System for Bladder Cancer. Bladder Cancer. 2018;1:181-4.
24. Wang J, Wu Y, He W, Yang B, Gou X. Nomogram for predicting overall survival of patients with bladder cancer: A population-based study. Int J Biol Markers. 2020;35:29-39.
25. Hu MD, Chen SH, Liu Y, Jia LH. Development and validation of a nomogram to predict the prognosis of patients with squamous cell carcinoma of the bladder. Biosci Rep.2019;39:BSR20193459.
26. Megwalu II, Vlahiotis A, Radwan M, Piccirillo JF, Kibel AS. Prognostic impact of comorbidity in patients with bladder cancer. Eur Urol. 2008;53:581-9.
27. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16:e173-80.
28. Morlacco A, Modonutti D, Motterle G, Martino F, Dal Moro F, Novara G. Nomograms in Urologic Oncology: Lights and Shadows. J Clin Med. 2021;10:980.
29. Osawa T, Abe T, Takada N, Ito YM, Murai S, Shinohara N. Validation of the nomogram for predicting 90-day mortality after radical cystectomy in a Japanese cohort. Int J Urol. 2018;25:699-700.
30. Hirabayashi S, Kosugi S, Isobe Y, et al. Development and external validation of a nomogram for overall survival after curative resection in serosa-negative, locally advanced gastric cancer. Ann Oncol. 2014;25:1179-84.
31. Berardi G, Morise Z, Sposito C, et al. Development of a nomogram to predict outcome after liver resection for hepatocellular carcinoma in Child-Pugh B cirrhosis. J Hepatol. 2020;72:75-84.
32. Kim SY, Cho N, Choi Y, et al. Factors Affecting Pathologic Complete Response Following Neoadjuvant Chemotherapy in Breast Cancer: Development and Validation of a Predictive Nomogram. Radiology. 2021;299:290-300.
33. Fakhry C, Zhang Q, Nguyen-Tân PF, et al. Development and Validation of Nomograms Predictive of Overall and Progression-Free Survival in Patients With Oropharyngeal Cancer. J Clin Oncol. 2017;35:4057-65.
34. Zhang Y, Hong YK, Zhuang DW, He XJ, Lin ME. Bladder cancer survival nomogram: Development and validation of a prediction tool, using the SEER and TCGA databases. Medicine (Baltimore). 2019;98:e17725.
35. Aziz A, May M, Burger M, et al. Prediction of 90-day mortality after radical cystectomy for bladder cancer in a prospective European multicenter cohort. Eur Urol. 2014; 66:156-63.
36. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17:1471-4.
37. Mori K, Abufaraj M, Mostafaei H, et al. A Systematic Review and Meta-Analysis of Variant Histology in Urothelial Carcinoma of the Bladder Treated with Radical Cystectomy. J Urol. 2020;204:1129-40.
38. Claps F, Kamp MW, Mayr R, et al. Risk factors associated with positive surgical margins' location at radical cystectomy and their impact on bladder cancer survival. World J Urol. 2021;39:4363-71.
39. Lee YH, Bang H, Kim DJ. How to Establish Clinical Prediction Models. Endocrinol Metab (Seoul). 2016;31:38-44.
40. Claps F, Mir MC, Zargar H. Molecular markers of systemic therapy response in urothelial carcinoma. Asian J Urol. 2021;8:376-90.
41. Mir MC, Campi R, Loriot Y, et al. Adjuvant Systemic Therapy for High-risk Muscle-invasive Bladder Cancer After Radical Cystectomy: Current Options and Future Opportunities. Eur Urol Oncol. 2022;5:726-31.